THE COLLEGE OF FAMILY PHYSICIANS OF CANADA

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Guidance in Authorizing Cannabis Products Within Primary Care

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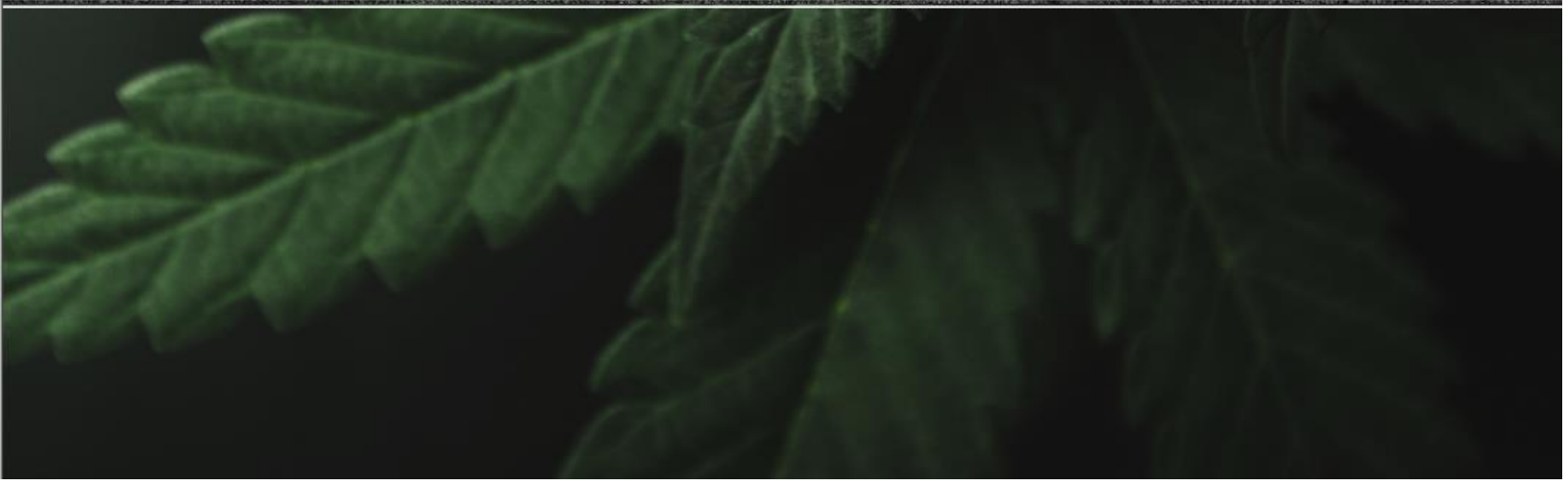

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Contents

Introduction

Under the Access to Cannabis for Medical Purposes (ACMPR)[1] section of Canada's cannabis regulations, which came into effect with the Cannabis Act on October 17, 2018, access to medical cannabis is authorized by a physician who signs a medical document. Authorized patients may purchase cannabis from a federally licensed producer, designate another person to produce it for them, or register to produce it themselves.[2] Physicians do not prescribe cannabis since it is not a Health Canada–registered medication with a Drug Identification Number. The ACMPR medical document is an authorization for the use of cannabis for medical purposes, and, while the authorizing physician is encouraged to offer guidance on the form, strength, and dose, the dispensed form, dose, and titration are ultimately determined by the licensed producer.

Under the Cannabis Act 2018, the use of cannabis for recreational purposes became legal (except for edible cannabis, cannabis extracts, and cannabis topicals, which became lawfully produced and sold as of October 17, 2019; see Table 1). Cannabis for recreational purposes differs from cannabis for medical purposes in that Health Canada does not regulate recreational cannabis production, possession, and distribution in the same way it does for cannabis for medical purposes. The basic facts and advice on safe consumption of recreational cannabis are summarized in the Government of Canada fact sheet.[3]

Provinces differ in their guidance and regulatory oversight for cannabis use.[4] Provincial medical colleges, in the absence of regulatory oversight and approval, issued statements and guidance to comply with federal and provincial regulations (see the list of regulators provided under Recommendation 6). The Cannabis Act legalized recreational cannabis use and proposed a framework for the use of medical cannabis in Canada. However, it remains illegal to carry any cannabis with you when entering or leaving Canada, whether it is for medical or recreational purposes.

Before cannabis use legalization, little research had been conducted on its therapeutic use, safety, or efficacy. This situation puts family physicians in a difficult position, as they are asked to authorize their patients' access to a product with little evidence to support its use.

To address this predicament, this document offers family physicians guidance on authorizing cannabis use for some specific conditions. Although the old Access to Cannabis for Medical Purposes regulations spoke only of use for medical purposes without specifying any diagnoses, the writing group chose chronic pain and anxiety as the original clinical areas of focus because they are the most common conditions for which a patient requests authorization. Since the original 2014 version was released, we have updated the document, added content, and broadened the scope of discussion beyond chronic pain and anxiety.

Cannabis is the raw plant material, composed of hundreds of different compounds, that serves as the source for non-pharmaceutically produced medical cannabis, including material for smoking and vaping as well as for edibles and concentrates. The two chemicals from the cannabis plant discussed are tetrahydrocannabinol (THC) and cannabidiol (CBD).

Research shows that cannabis could be a potent psychoactive substance with a risk of acute and chronic adverse effects of varying severity. Its most common acute effects include perceptual distortions, cognitive impairment, euphoria, and anxiety.[5] Chronic use of cannabis may be associated with persistent neuropsychological deficits, even after a period of abstinence.[6,7] The frequency and intensity vary based on the proportional content of psychoactive ingredients and on other factors including extent of use, age of first use, and length of abstinence.[8]

Medium- and long-term therapeutic and adverse effects of medical and recreational cannabis have not been sufficiently studied. Products containing THC have a known abuse and dependence potential (liability). It is recommended that family physicians consider the anticipated therapeutic benefits versus potential harms for a patient's health condition before authorizing initial or continuing cannabis use. As with any other therapeutic approach, continuing cannabis use is warranted only if the authorizing physician is satisfied that there has been improvement in the patient's presenting symptoms (e.g., pain level), function, and/or quality of life; the risk of cannabis use disorder has been reassessed; and the benefits outweigh potential harms.

Table 1. Timeline of the legalization of cannabis for medical purposes in Canada[9,10,11,12]

Date	Development
1999	Under the Controlled Drugs and Substances Act (CDSA), exemptions under Section 56 made accessing dried marijuana for medical purposes legal in Canada for the first time.
2000	In the case of R. v. Parker, the Ontario Court of Appeal ruled that it was unconstitutional to prohibit the possession of marijuana for medical purposes.
2001	Under the 2001 Marihuana Medical Access Regulations, patients authorized by a health care practitioner to access marijuana for medical purposes could legally acquire it by: • Growing their own supply of marijuana • Designating someone to grow marijuana for them • Purchasing marijuana through Health Canada's licensed supplier
2013	The Marihuana for Medical Purposes Regulations (MMPR) implemented a licensing system that enabled commercial growers to produce and distribute marijuana for medical purposes. With medical authorization from a health care provider, individuals could access quality-controlled dried marijuana from licensed producers.
2015	The Supreme Court of Canada's decision in R. v. Smith expanded the types of cannabis products available to authorized medical users. In R. v. Smith, the court ruled it was unconstitutional to restrict medical users' legal access only to dried marijuana. Licensed producers were then permitted to make and sell other forms of cannabis, such as cannabis oil, and authorized users could legally possess and use these products.

2016	In Allard v. Canada, the Federal Court of Canada ruled that authorized users' Charter rights were violated by requiring them to acquire marijuana for medical purposes only through licenced suppliers. The court found that authorized users did not have "reasonable access" to marijuana for medical purposes.
August 24, 2016	The Access to Cannabis for Medical Purposes Regulations (ACMPR), which replaced the MMPR, provided options other than licensed suppliers for authorized users to legally acquire marijuana from for medical purposes. Under the ACMPR, individuals could register to produce cannabis for their own medical use or designate someone to produce it for them.
June 21, 2018	The Cannabis Act was implemented, amending the CDSA and the Criminal Code, as well as other Acts.
October 17, 2018	The Cannabis Act took effect, replacing the ACMPR.
October 17, 2019	The amended Cannabis Regulations permitted the legal sale of edible cannabis, cannabis extracts, and cannabis topicals in accordance with the requirements of the Cannabis Act.

Methods

The original 2014 document was written by members of the Addiction Medicine and Chronic Pain member interest groups of the Member Interest Groups Section (MIGS) of the College of Family Physicians of Canada (CFPC) in collaboration with other individuals and the following member interest groups: Child and Adolescent Health, Maternity and Newborn Care, Mental Health, Palliative Care, and Respiratory Medicine. The MIGS is made up of members with special interests, and often enhanced expertise, in specific clinical domains that are relevant to the practice of family medicine. The 2020 update of this document was completed with the help of members of the Addiction Medicine and Chronic Pain member interest groups, other family physicians, and CFPC staff.

The writing team based the document's updates on a literature search and review of evidence on specific topics related to cannabis effectiveness, safety, and adverse effects. The team acknowledges the research of Dr. Meldon Kahan and colleagues[13] and Dr. Michael Allan and colleagues (the simplified guideline[14] and the associated systematic review[15]), which was adapted in the preparation of this document. The material appears with the permission of the publisher, *Canadian Family Physician*.

For the 2014 document, members of the participating program committees collaborated to prepare a succession of drafts, which then underwent an editorial team review followed by expert peer reviews. A subgroup of the editorial team wrote the final document on behalf of the participants. The final document was taken to the entire group for its consensus before publication.

For the 2020 update participants were asked independently to identify chapters that required substantial updating. Chapters were selected for updating if a minimum of 50 per cent of the members identified that chapter for updating. We then asked participants to

identify additional areas or topics for new chapters independently. The results were pooled and participants were asked to rank topics for inclusion. The seven highest-ranked topics were then selected and first and second authors were assigned to work on the new topics. This guidance document is intended to support family physicians who may authorize medical cannabis. It is not a clinical practice guideline and did not follow a formal method such as the Grading of Recommendations Assessment, Development and Evaluation (GRADE framework). The committee represents a broad sample of family physicians without financial conflicts of interest.

Recommendations were broadly graded as level i (based on well-conducted controlled trials or meta-analyses), level ii (well-conducted observational studies), or level iii (expert opinion; for the purposes of this document, consensus among the committee members drafting this document).

Terminology

Medical marijuana: This term is in popular use but is imprecise, referring broadly to cannabis dispensed or otherwise obtained and used either for supervised medical purposes or for self-medication. In a scientific context we prefer to use the term cannabis.

Cannabis: We use this term to refer to the substance under discussion in this paper; when used medically, it is the product that a patient may purchase through a licensed producer if they have a medical document authorizing its dispensing.

Pharmaceutical cannabinoids: This term refers to the prescription drugs nabilone (capsules, racemic mixture of THC isomers) and nabiximols (buccal spray, plant extract, 27 mg/mL of THC, 25 mg/mL of CBD, other cannabinoids, flavonoids, and terpenes). Dronabinol (capsules, (–)-trans-Δ^9- tetrahydrocannabinol only) was previously available but has been removed from the Canadian market by the manufacturer.

Cannabinoids: The broader term encompassing both cannabis and pharmaceutical cannabinoids.

Medical document: Health Canada uses this term to denote the prescription-like form that physicians complete and sign to authorize patients' access to cannabis for medical purposes from a licensed producer. Health Canada provides a sample medical document on its website.[16]

How to navigate this document

This document is organized into two parts. The first, "A. Summary of Recommendations," outlines the recommendations in brief, sketching in point form the still-developing landscape within which family physicians find themselves regarding medical cannabis:

- The federal regulations that give the physician the responsibility for granting access to this regulated substance
- The as-yet limited evidence regarding effects and efficacy of cannabis in clinical use
- The degree to which evidence derived from studies of pharmaceutical cannabinoids can be applied to cannabis

- The provincial medical regulatory authorities' requirements of physicians regarding signing medical documents for cannabis
- The issues and questions that arise between physicians and patients in the sometimes-challenging conversations surrounding cannabis use

The second part, "B. Discussion and Supporting Evidence," provides a fuller discussion of these topics. It describes:

- What we know to date about the potential harms and benefits of cannabis use in various populations and about the treatment of various conditions
- Regulations and suggested best practices to follow before authorizing and continuing a patient's access to cannabis

Section B also provides practical resources to use in clinical practice, including:

- Messages for patients
- Tools to use when screening patients for misuse or addiction risk
- A sample treatment agreement
- Information about the strains available from licensed producers
- Calculations for dosing

In sections A and B the recommendations are grouped under the following headings:

- General principles (recommendations 1 to 6)
- Assessment, monitoring, and discontinuation (recommendations 7 to 10)
- Misuse prevention and intervention (recommendations 11 and 12)
- Strategies to prevent harm (recommendations 13 and 14)
- Communication with patients and consultants (recommendation 15)
- Dosing (recommendation 16)

A. Summary of Recommendations

General principles

Recommendation 1

There is little research evidence to support the authorization of cannabis as a treatment for pain conditions commonly seen in primary care, such as fibromyalgia or low back pain (level iii).

We suggest authorizations for cannabis can be considered for patients with chronic neuropathic pain or palliative cancer pain that has failed to respond to standard treatments (level i).

Additional conditions that may warrant potential authorization include:

- Spasticity (due to multiple sclerosis or spinal cord injury), after failure to respond to standard therapies and preferably a trial of nabiximols or other pharmaceutical cannabinoids (level i)
- Nausea/vomiting due to chemotherapy, after failure to respond to standard therapies and a trial of the pharmaceutical cannabinoid nabilone (level i)

Recommendation 2

Prior to authorizing cannabis for therapeutic purposes, we recommend the clinician first consider two steps:

- An adequate trial of appropriate pharmacologic and non-pharmacologic therapies
- Where appropriate, an adequate trial of pharmaceutical cannabinoids (level i)

Recommendation 3

When authorizing THC-containing cannabis products for appropriate medical indications, we suggest the cannabis product should likely also contain CBD (level ii).

Recommendation 4

We recommend that until further research clarifies the effectiveness and harms in treating anxiety, post-traumatic stress disorder (PTSD), or insomnia, cannabis is not an appropriate therapy for these conditions (level ii).

Recommendation 5

We recommend particular care is required in authorizing and advising patients on the appropriate use of cannabis for special populations (generally level iii). These include:

- Older adults
- Adolescents and youth patients
- Pregnant patients
- Patients experiencing mental health challenges or substance use disorders
- Patients with concurrent medical conditions or risk factors, such as risk factors for cardiovascular disease
- Patients who smoke tobacco
- Patients who are heavy users of alcohol or are taking high doses of opioids (prescribed or non-prescribed), benzodiazepines, or other sedating medications prescribed or available over the counter

Recommendation 6
We recommend physicians follow the regulations of their provincial or territorial medical regulators when authorizing cannabis (level iii), including requirements for documentation, consent, assessment, and monitoring.

Assessment, monitoring, and discontinuation

Recommendation 7
When considering the initiation of cannabis for medical purposes, we recommend physicians start with a history and physical examination, including detailed mental health, substance use, and, if applicable, pain histories (level iii).

Recommendation 8
We suggest using the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) criteria[17] to assess for cannabis use disorder before initiating therapy and as appropriate while on therapy (level iii).

Recommendation 9
We recommend physicians regularly monitor patients' responses to treatment with cannabis (level iii). We recommend physicians discontinue authorization if the therapy is not clearly effective or if harms outweigh benefits (level iii).

Recommendation 10
We suggest physicians record patients' use of cannabinoid edibles, topicals, and oils/extracts and their doses (if known). Caution is advised when authorizing, as individual effects are unclear and lower doses are recommended, at least initially. If possible, educate patients about potential side effects and inform them that data on their use are still lacking (level iii).

Misuse prevention and intervention

Recommendation 11
We recommend physicians assess and monitor all patients on cannabis therapy to identify the potential for problematic use and emerging toxicities using harm-reduction and harm-prevention approaches and, when warranted, attempting individualized tapers (level iii).

Recommendation 12
We recommend physicians screen for, assess, and treat cannabis withdrawal syndrome when it is identified (level iii).

Strategies to prevent harm

Recommendation 13
We recommend that patients using cannabis for medical purposes be advised (level iii):

- Wait at least six hours before driving if using via the inhalational route
- Wait at least eight hours before driving if using via the oral route
- If using daily, their serum THC level may be higher than legal allowable limits, even if they do not feel impaired
- Combining cannabis and alcohol seriously increases risk and should be avoided

- The recommendations above apply to typical driving with a Class 5 licence, and limitations/times can increase with other licence classes or additional safety-sensitive work

Recommendation 14

We suggest using harm-reduction strategies when authorizing cannabis therapy for patients. Physicians are advised to discuss these strategies with patients (level iii).

Communication with patients and consultants

Recommendation 15

We recommend that the physician who is authorizing cannabis for a particular clinical indication should be primarily responsible for managing the care for that condition and following up with the patient regularly (level iii).

Dosing

Recommendation 16

Given the weak evidence for benefit, the known risks of using cannabis, and the potential for unknown risks, it is recommended that physicians involved with authorizing cannabis "start low and go slow." (level iii).

B. Discussion and Supporting Evidence

General principles

Recommendation 1

There is little research evidence to support the authorization of cannabis as a treatment for pain conditions commonly seen in primary care, such as fibromyalgia or low back pain (level iii).

We suggest authorizations for cannabis can be considered for patients with chronic neuropathic pain or palliative cancer pain that has failed to respond to standard treatments (level i).

Additional conditions that may warrant potential authorization include:

- **Spasticity (due to multiple sclerosis or spinal cord injury), after failure to respond to standard therapies and preferably a trial of nabiximols or other pharmaceutical cannabinoids (level i)**
- **Nausea/vomiting due to chemotherapy, after failure to respond to standard therapies and a trial of the pharmaceutical cannabinoid nabilone (level i)**

To date, five controlled trials have examined cannabis in the treatment of chronic neuropathic pain.[18,19,20, 21, 22] The trials were small, included patients who had previously smoked cannabis, and lasted from one to 15 days. Functional status, quality of life, and other important outcomes were not measured. No head-to-head comparisons of therapeutic benefits or adverse effects were made with other standard treatments for these conditions or with pharmaceutical cannabinoid preparations.

There is very limited research on cannabis for most medical conditions (See Appendix 1. Summary of Available Evidence). No controlled studies have been conducted on cannabis for osteoarthritis, and the Canadian Rheumatology Association does not endorse the use of cannabis for either fibromyalgia or osteoarthritis.[23] Pharmaceutical cannabinoids have some evidence of benefit for conditions such as nausea/vomiting due to chemotherapy, but the evidence is frequently weaker than for first-line treatments.[14,15,24,25] Family physicians are advised to recommend other treatments with more evidence of safety and efficacy for these conditions.

Recommendation 2

Prior to authorizing cannabis for therapeutic purposes, we recommend the physician first consider two steps:

- **An adequate trial of appropriate pharmacologic and nonpharmacologic therapies**
- **Where appropriate, an adequate trial of pharmaceutical cannabinoids (level i)**

There are many pharmacologic and nonpharmacologic treatments that have been documented as being effective in the treatment of neuropathic pain, and these established therapies should be tried before moving on to trials of cannabinoids. The same is true for other potential indications such as palliative cancer pain, nausea/vomiting due to chemotherapy, and spasticity due to multiple sclerosis or spinal cord injury. Oral and buccal pharmaceutical cannabinoids have a larger body of evidence of efficacy than cannabis has in the treatment of neuropathic pain,[26,27,28,29,30,31] although, apart from

nabiximols (which is indicated for neuropathic pain associated with multiple sclerosis or cancer), these drugs' use for this treatment is off label.

However, until further research is conducted, the same contraindications and precautions that apply to cannabis apply to pharmaceutical cannabinoids.

Recommendation 3

When authorizing THC-containing cannabis products for appropriate medical indications, we suggest the cannabis product should likely also contain CBD (level ii).

Natural cannabis products may contain more than 500 chemical compounds, but the two primary active components are THC and CBD. THC is often viewed as the more psychoactive component, while CBD provides a moderating effect on the psychological effects of THC. Teasing out which component or combination of components provides active management for each varying medical condition is challenging, but that is the key focus for clinicians.

Background

The majority of the work investigating the various effects of cannabis components has been done in healthy subjects. Some of the initial work regarding THC and CBD involved a study of 40 healthy individuals given eight different interventions: placebo, 30 mg THC, 15/30/60 mg CBD, and combinations of 30 mg THC with 15/30/60 mg CBD.[32] THC alone caused strong psychological effects which CBD alone did not. When CBD was added to THC, it dampened the psychological effects.[32] Subsequent studies have shown that THC can cause anxiety and/psychotic features while CBD is less likely to do so.[33] Other studies have shown that CBD reduces psychotic features induced by THC.[34,35] A systematic review of 29 studies further supports the protective effects of CBD on the psychotic effects that can be seen from THC and cannabis.[36] It should be stated that not all studies find that CBD reduces the psychotic or anxiety effects of THC, but it is postulated that this may be due to regular users having a blunted CBD response.[37]

Overall, low-risk guidelines generally recommend that if cannabis is to be used, the products used should have lower THC and higher CBD proportions.[38,39] Note that the majority of this research has been in healthy subjects. Older patients are generally not studied. Moreover, the potentially toxic effects of higher CBD levels have not been adequately investigated. For smoked cannabis, original doses should be at most 9 per cent THC (with appropriate CBD), at doses of 0.4 g to 0.7 g per day. If the THC percentage increases, the gram dosing should be decreased appropriately.

When considering the medical use of cannabis, research is required to evaluate its use as therapy for medical conditions to determine which component or proportions of components results in the best clinical outcomes, balancing benefits and adverse events.

Evidence of medical effects of varying cannabinoid components

Characteristics and key findings of five randomized controlled trials (RCTs) that compared THC, CBD, or a combination of THC and CBD in the treatment of specific medical conditions or symptoms are summarized in Table 2. While each RCT had a placebo arm, Table 2 focuses on the comparisons between the components of cannabis. In the study of patients with fibromyalgia,[40] the number attaining at least a 30 per cent reduction in pain was high (between 40 per cent and 90 per cent) for all groups, but it must be stated that the trial duration was only three hours and shorter trials generally have better pain responses.[15]

Additionally, while 40 per cent of patients in the CBD arm reported pain relief of at least 30 per cent, 55 per cent using placebo did.[40] Lastly, the researchers measured the perception of being "high" during the trial and found it was linked to THC levels and correlated with improved pain response.[40]

Table 2. Randomized controlled trials comparing THC, CBD, or THC/CBD (* denotes statistically significant differences)

Study	Number of Patients	Condition	Interventions	Duration	Finding
Strasser 2006[42]	243	Terminal cancer and weight loss	THC/CBD, THC	6 weeks	No difference in appetite
Johnson 2010[43]	177	Refractory cancer pain (on ~270 mg morphine)	THC/CBD, THC	2 weeks	Percentage of patients experiencing ≥ 30% pain reduction: THC/CBD 38% versus THC 21%*
Berman 2004[41]	48	Brachial plexus injury	THC/CBD, THC	2 weeks	No difference in pain reduction
Notcutt 2004[44]	24	Chronic pain	THC/CBD, THC, CBD	8 weeks	Percentage of patients reporting pain relief: 38% while taking THC/CBD, 33% with THC, 17% with CBD
van de Donk 2019[40]	20	Fibromyalgia	THC/CBD, THC, CBD	3 hours	Percentage of patients experiencing ≥ 30% pain reduction: THC/CBD 90%, THC 65%, CBD 40% (Note: Placebo 55%)*

In summary, the one trial examining appetite stimulation did not find a difference between THC/CBD compared with THC.[42] Two of the four pain studies found THC/CBD to be superior to THC alone or CBD alone.[40,43] Of the remaining two studies, in the chronic pain study there was no statistical difference in the number of patients attaining pain relief (as defined by response to open-label THC/CBD cannabis) but there was a numerical trend for THC/CBD to be preferred over THC followed by CBD.[44] From these very limited data, CBD alone appears to be the least effective for pain (and perhaps no better than placebo). Given these results, and recognizing the very limited nature of the RCT evidence base, it is likely

preferable to use a combination product of THC/CBD (and not CBD alone) for the treatment of pain.

Adverse events of varying cannabinoid components

Most of the adverse event data are drawn from the "Simplified guideline for prescribing cannabinoids in primary care."[14] For the most part, RCTs have not shown differences in adverse events when comparing THC and THC/CBD use.[14] However, drowsiness was seen in 83 per cent of patients with THC, 58 per cent with THC/CBD, and 38 per cent with CBD, with a statistically significant difference between THC and CBD (Fisher test P = 0.003).[44] Dysphoria/euphoria was seen in about 50 per cent of patients with either THC or THC/CBD and 17 per cent of patients assigned to CBD, a statistically significant difference (Fisher test P = 0.03).[44] In the study of fibromyalgia patients, THC or THC/CBD led to feeling high in 80 per cent of patients versus 40 per cent with CBD, a statistically significant difference (Fisher test, P = 0.02).[40] While CBD is often considered safer, it is not without adverse events. For available evidence on medical cannabinoids, see Appendix 1. Summary of Available Evidence, which shows CBD is more likely to cause the following adverse events over placebo (with number needed to harm): somnolence (6), decreased appetite (7), and diarrhea (12).

Conclusions

CBD may help moderate some of the psychological effects (such as features of psychosis) seen with THC use. When THC is required for symptom management (such as in pain control), it should likely be combined with CBD. The evidence suggests that the addition of CBD will not reduce pain reduction benefits, and it may in fact improve the effect.

Recommendation 4

We recommend that until further research clarifies effectiveness/harms in treating anxiety, PTSD, or insomnia, cannabis is not an appropriate therapy for these conditions (level ii).

A literature review identified only two small RCTs on the use of cannabis in the treatment of anxiety disorders, which are described in detail in Appendix 1. Observational data indicate a strong and consistent association between cannabis use and anxiety and mood disorders, although causality has not been established.[45,46,47,48,49,50,51,52,53,54] Acute cannabis use can trigger anxiety and panic attacks,[55] and studies on animals and human volunteers suggest that high doses of cannabis actually worsen anxiety.[56] Cannabis use may worsen psychiatric impairment in patients with anxiety disorders.[53, 57,58] However, a review of observational studies identified that cannabis may have anxiolytic effects in addition to the anxiogenic ones.[59] The paper goes on to suggest that products lower in THC and higher in CBD may have anxiolytic effects.

In other research, the THC content of cannabis has been associated with anxiety, though this relationship appears to be bidirectional.[57,60,61] Physicians should consider the THC content of available cannabis and consider authorizing, if at all, only lower-strength strains for patients with anxiety.[62] Regular users of cannabis might experience early symptoms of cannabis withdrawal when they abstain, including an exacerbation of anxiety, creating a challenge in distinguishing withdrawal from an anxiety disorder; withdrawal symptoms can ultimately be resolved through cannabis cessation.[63]

The evidence for using pharmaceutical cannabinoids in the treatment of anxiety and insomnia is stronger than the evidence for using cannabis. Small trials have demonstrated

that oral nabilone improves sleep in patients with fibromyalgia or PTSD.[24,64] Two small studies (with 10 and 24 patients) examined oral cannabidiol extract for patients with social anxiety disorder and reported some minor benefits in the first one to three hours but nothing beyond three hours (see Appendix 1. Summary of Available Evidence).[65]

Recommendation 5

We recommend particular care is required in authorizing and advising patients on the appropriate use of cannabis for special populations (generally level iii). These include:

- **Older adults**
- **Adolescents and youth patients**
- **Pregnant patients**
- **Patients experiencing mental health challenges or substance use disorder**
- **Patients with concurrent medical conditions or risk factors, such as risk factors for cardiovascular disease**
- **Patients who smoke tobacco**
- **Patients who are heavy users of alcohol or taking high doses of opioids (prescribed or non-prescribed), benzodiazepines, or other sedating medications prescribed or available over the counter**

The use of cannabis in some populations is worthy of special consideration. Adolescents, youth, and older adults require such consideration because of their vulnerabilities related to age, while the care of pregnant patients should take into consideration effects on a developing fetus. The vulnerability of patients with mental health issues should be also considered when prescribing cannabis.

Patients under age 25

Until about 25 years of age, adolescents and youth are undergoing neurodevelopment that can be affected by the consumption of cannabis, whether for medical or recreational purposes.[66,67] The medical literature is still evolving on how cannabis affects brain development in young persons. However, there is a growing body of evidence of harmful effects, including short- and longer-term cognitive impairment.[6,7]

There are very few medical indications for prescribing cannabis in young patients. Treatment-resistant epilepsy and nausea and vomiting associated with chemotherapy are both potential medical considerations for authorizing,[68] but there are important caveats. The treatments studied were not cannabis but rather cannabidiol for the treatment of resistant seizures and nabilone (or dronabinol) for nausea and vomiting associated with chemotherapy. Additionally, patients in this age group with these unusual conditions are usually under the care of pediatric specialists. These specialists should either be the authorizers or be consulted before cannabinoids are authorized for these indications.

Some adolescents and young adults under the age of 25 may be candidates for having cannabis prescribed for neuropathic pain, but in this age group at least three other options should be explored first.[14] Additionally, it would be reasonable to involve a pain team or consultant prior to considering prescribing cannabis in this special population. If the above criteria have been addressed and a family physician is considering cannabis as an option in a child, adolescent, or young adult, the clinician is advised to weigh the benefits and harms while collaborating with the patient and family, where appropriate, to develop a treatment plan

Patients who are pregnant or breastfeeding

Screening for cannabis use during prenatal care is strongly recommended, as is counselling about the potential adverse health outcomes associated with cannabis use during pregnancy and lactation. A patient who is pregnant can be advised and supported to avoid cannabis use on the basis of possible harms to their developing child. The earlier 2014 version of this CFPC guidance document on authorizing cannabis states that "preliminary evidence links cannabis use during pregnancy to neurodevelopmental abnormalities in infants."[69, 70] The document advises pregnancy as a contraindication to prescribing cannabis. This was further supported by the "Simplified guideline for prescribing medical cannabinoids in primary care."[14] The medical literature is conflicting and still evolving with respect to the risks of cannabis use during lactation. Advising patients against the use of cannabis during lactation is recommended.

Older adults

There is limited medical literature but increasing media coverage of cannabis use by older adults, including both recreational and medical use.[71] Many adults access cannabis for medical purposes through their own sources and some seek medical providers to prescribe cannabis. As a starting point, the indications for older patients should overlap with those for other adult patients as identified in Appendix 1. Summary of Available Evidence and listed in the "Simplified guideline for prescribing cannabinoids in primary care."[14] Additionally, this population requires specific considerations for increased risks of adverse events that are common with cannabinoid use. A recent systematic review of controlled trials in older patients reported that while there may be hope that THC might be useful in treating conditions such as anorexia or behavioural symptoms in dementia, there is a general lack of research to support use specifically in this population.[72]

The relatively common side effects of sedation, dizziness, disorientation, confusion, and ataxia pose considerable concern for this population. In one systematic review, adverse events were more common during cannabinoid treatment compared with the control treatment, and they were most frequently sedation-like symptoms.[72] Some studies have found a potential association between cannabis use and acute physiological effects such as hypertension, tachycardia, catecholamine release, and vascular constriction.[73,74] While there are studies that suggest the increased risk and development of respiratory symptoms and lung effects from smoking cannabis,[75,76] particularly if mixed with tobacco, it remains to be confirmed that smoking cannabis alone leads to the development of chronic lung disease. In the context of some presumed risk of lung disease from smoking combusted cannabis, patients could consider vaping as an alternative to smoking but it should be clear that vaping could also have health risks.

When reviewing an older patient's request for prescribed cannabis, physicians are advised to perform a review of relevant systems, including a review of fall risk, engagement in activities of daily living, and their need for support in the home and in public spaces and to consult with family members or members of their support network for third party information on the patient's level of functioning. Recent literature suggests that—given scant clinical evidence—an individual assessment of risks and benefits and a discussion of those factors with the patient may provide a reasonable approach to shared decision-making regarding treatment in these patients.[77] The patient should be advised of the side-effect profile of cannabis use and to avoid cannabis use if the risk/benefit profile raises concerns and is not in the best interest of the patient.

In older patients with evidence-based medical indications for cannabis use (including adequate trials of other therapies with a lower risk profile for harms), family physicians may consider a trial of cannabinoids. If a trial of prescribing is offered, the family physician is advised to start with the lowest dose, delivered by the lowest-risk route, with close monitoring for benefits and harms.

Patients with risk factors for cardiovascular disease
Physicians are advised to use considerable caution when authorizing cannabis for use by patients with risk factors for cardiovascular disease. The dose should be kept low and the patient should be encouraged to avoid smoking cannabis, particularly with tobacco. If cannabis is being considered, pharmaceutical preparations should be advocated first.

Patients with psychiatric diagnoses, mental health challenges, or substance use issues
Patients with mental health challenges and/or psychiatric diagnoses also warrant special consideration. Many people anecdotally endorse cannabis use for mood and anxiety issues and PTSD. However, support for its use for these indications is sparse in the medical literature.[14,69,78,79] In fact, some studies and even patients themselves suggest that some mental health symptoms may worsen or be exacerbated by cannabis use.[14] There is substantial medical literature on the risks of cannabis use and the exacerbation of psychosis in persons with psychotic illnesses or at risk of developing psychotic illnesses.[80,81]

Patients with mental health symptoms may be seeking prescribed cannabis for physical symptoms, such as pain, or for mental health symptoms, such as anxiety, insomnia, or depression. Whatever the reason for the request, careful consideration is recommended, including an understanding of the patient's perceptions and expectations of cannabis use, a review of systems, a screening for mental health symptoms, and a review of their previous experiences with cannabis, including side effects and harms. A review of any previous history of physiologic dependence on cannabis, cannabis use disorder, and alcohol or other substance use disorder should be included. Other recommendations include patient education about medical evidence supporting or not supporting cannabis use and about evidence in the literature of side effects and harms.

When authorizing cannabis treatment for patients with co-existing anxiety and neuropathic pain, it is recommended that the physician:

- Keeps the dose low to avoid triggering anxiety
- Considers indicating low THC content or CBD-only strains on the medical document
- Discontinue cannabis if the patient's anxiety or mood worsens

Prescribing cannabis should be considered with great caution in cases where cannabis use may destabilize mental health symptoms or pose a risk to a patient's wellness. Prescribing cannabis is inadvisable where there is evidence of previous harms from cannabis.

Advising patients with psychosis or at risk for psychosis to avoid THC products is strongly recommended. There is some evidence that CBD may be protective for psychosis;[82] however, the data in this area are very preliminary.

For patients who use recreational drugs, drink alcohol, or are on psychoactive prescribed medications, family physicians can consider adjusting doses and advising patients of the risks of co-consumption of cannabis and substances that can cause sedation and other side effects. Cannabis use can worsen the cognitive impairment caused by opioids,

benzodiazepines, other sedatives, and alcohol. Patients taking cannabis should be advised to use alcohol in moderation, and physicians should consider tapering patients on high doses of opioids or benzodiazepines.

Where there are issues of previous addiction with cannabis or other substances, providers are advised to collaborate with the patient, consider risk stratification of prescribing, and consider other alternative therapies.

For patients with active substance use disorders, it is advisable to avoid prescribing cannabis. However, physicians may consider prescribing cannabis for harm reduction. In some individuals with progressed substance use disorders, physicians may ask to develop treatment plans that involve the use of cannabis as a route to reduce the patient's use of other more harmful substances or to avoid their buying contaminated street marijuana. Evidence in the literature for cannabis use for harm reduction in severe addiction disorders is fairly recent and supports possible positive outcomes.[83] However, more recent ecological evidence has shown that opioid-related mortality is likely not improved with cannabis.[84] Physicians are advised to consider very specific populations of patients and the support available in their environment that would promote the goal of harm reduction and whether a closely monitored trial of a cannabis product may be undertaken.

Tobacco smokers
Even after controlling for tobacco smoking, some studies have found cannabis smoking was associated with lung cancer[85] and chronic bronchitis.[86] Patients who smoke tobacco should be strongly advised not to also smoke cannabis.

Patients who are heavy users of alcohol or are taking high doses of opioids or benzodiazepines
Cannabis use can worsen the cognitive impairment caused by opioids, benzodiazepines, other sedatives, and alcohol.[87] Patients taking cannabis should be advised to use alcohol in moderation, and physicians should consider tapering patients on high doses of opioids or benzodiazepines.[88,89]

Recommendation 6

We recommend physicians follow the regulations of their provincial or territorial medical regulators when authorizing cannabis (level iii), including requirements for documentation, consent, assessment, and monitoring.

Many of the provincial/territorial regulatory bodies have released policies on the authorization of cannabis.[90] These regulators advise physicians to conduct a thorough assessment and to try conventional alternatives before providing a medical document for cannabis. Additional requirements vary considerably from one jurisdiction to another. Physicians should review the complete policy of their provincial or territorial regulator before signing a medical document for cannabis. The regulatory bodies in Canada are:

- College of Physicians and Surgeons of Alberta (http://www.cpsa.ca/)
- College of Physicians and Surgeons of British Columbia (https://www.cpsbc.ca/)
- College of Physicians and Surgeons of Manitoba (http://www.cpsm.mb.ca/)
- College of Physicians and Surgeons of New Brunswick (http://www.cpsnb.org/)
- College of Physicians and Surgeons of Newfoundland and Labrador (https://www.cpsnl.ca/)
- College of Physicians and Surgeons of Nova Scotia (https://cpsns.ns.ca/)

- College of Physicians and Surgeons of Ontario (https://www.cpso.on.ca/)
- College of Physicians and Surgeons of Prince Edward Island (https://cpspei.ca/)
- Collège des médecins du Québec (http://www.cmq.org/)
- College of Physicians and Surgeons of Saskatchewan (https://cps.sk.ca/)
- Yukon Medical Council (http://www.yukonmedicalcouncil.ca/)

Conflict of interest
Physicians must not have a financial interest in a company that produces cannabis products, and they should follow their provincial regulatory authority's code of ethics regarding potential conflicts of interest. Patients often receive cannabis from licensed producers via courier or delivery. Under extraordinary circumstances (if, for example, the patient does not have a postal address), a physician may receive and store cannabis for their patient. Consultation with provincial regulatory authorities about all such arrangements is advised.

Authorizations
Several provinces require physicians to:

- State the patient's medical condition on the medical document
- Register with the regulator as a cannabis authorizer
- Send the regulator a copy of the medical document and/or keep the medical document in a separate record for possible inspection

Some provinces specify that only the physician who manages the patient's condition may write a medical document authorizing cannabis so the therapy occurs in the most potentially beneficial context of continuous and comprehensive care. An ongoing doctor-patient relationship is similarly important when visits are conducted using telemedicine, where the patient and physician must communicate via a technological interface rather than face to face. The COVID-19 pandemic provided an opportunity to demonstrate that telemedicine is an effective, viable option for authorizing physicians to monitor responses to treatment, the emergence of adverse effects, and any signs and symptoms of addiction without being physically present with their patients. Standards and guidelines should be restructured at timely intervals to account for changes in the medical landscape.

Documentation and consent
Several regulators recommend that each patient should sign a written treatment agreement (see Box 1), that their physician should document that other treatments have been tried, and that the patient should acknowledge that they are aware of the risks of cannabis. They also recommend that the patient be reassessed at least every three months.

Assessment and monitoring for cannabis use disorder
Several provincial regulators advise physicians to use a standardized tool to assess the patient's risk of addiction and to have a procedure or protocol for identifying cannabis use disorder. Physicians should consult their regulatory bodies for information about specific procedures.

Box 1. Sample treatment agreement between a doctor and patient

Treatment Agreement Regarding the Medical Use of Cannabis

Because we take our responsibilities to authorize and supervise the medical use of cannabis very seriously, we ask you to read, understand, and sign this form.

1. I request Dr._____ to sign a medical document for me under the Cannabis Act's regulations on Access to Cannabis for Medical Purposes, so that I may use cannabis to treat my medical condition.
2. I agree to receive a medical document for cannabis from only one physician, Dr. _____.
3. I agree to consume no more cannabis than the doses authorized for me by Dr._____. I will not request a refill before the agreed-upon refill date.
4. I agree to not distribute my cannabis to any other person, for personal use or for sale.
5. I am aware that using cannabis can be associated with psychosis in some people, including persons who are still undergoing neurodevelopment (brain growth). Therefore, I will ensure that no person under the age of 25 years and no person at risk of psychosis has access to my cannabis.
6. I agree to the safe storage of my cannabis (in a locked cabinet is advised).
7. I am aware that taking cannabis with other substances, especially sedating substances, may cause harm and possibly even death. I will not use illegal drugs (e.g., cocaine, heroin) or controlled substances (e.g., narcotics, stimulants, anxiety pills) that were not prescribed for me.
8. I will not use controlled substances that were prescribed by another doctor unless Dr._____ is aware of this.
9. I agree to testing (e.g., urine drug screening) when and as requested by my physician.
10. I agree to have an office visit and medical assessment at least every__(months or weeks).
11. I understand that Health Canada has provided access to cannabis by signed medical document from a physician for the treatment of certain medical conditions but, despite this, Health Canada has not approved cannabis as a registered medication in Canada.
12. I understand that my physician may not be knowledgeable about all the risks associated with the use of a substance that lacks Health Canada approval, such as cannabis. Short-term adverse events of cannabis include sedation, dizziness, impaired short-term memory, impaired motor coordination, altered judgment, and paranoia or psychosis at high doses. Long-term effects may include cannabis use disorder (addiction), amotivational syndrome, cycling vomiting, mental health concerns (e.g., anxiety or schizophrenia), vascular or respiratory disease, impaired thinking, and reduced life satisfaction.
13. I agree to communicate to my physician, Dr. _____, any experiences of altered mental status or possible medical side effects of the use of cannabis.
14. I accept full responsibility for any and all risks associated with the use of cannabis, including theft, altered mental status, and side effects of the product.
15. I am aware that cannabis use is not advisable during pregnancy and breastfeeding. I agree to inform my physician, Dr._____, if I am pregnant.
16. I am aware that smoking any substance can cause harm and medical complications to my breathing and respiratory status. I will avoid smoking cannabis. I will avoid mixing cannabis with tobacco.
17. I am aware that my physician may discontinue authorizing cannabis for my condition if they assess that the medical or mental health risks or side effects are too high.
18. I agree to see other specialists or therapists about my condition at my physician's request.
19. I agree to avoid driving a vehicle or operating heavy machinery for at least six hours after inhalation use of cannabis and eight hours after oral use.
20. As per the Access to Cannabis for Medical Purposes regulations, I agree to purchase my cannabis only from a licensed producer (or personal supply if authorized for home growth).
21. I am aware that any possible criminal activity related to my cannabis use may be investigated by legal authorities and criminal charges may be laid. During the course of an investigation, legal authorities have the right to access my medical information with a warrant.
22. I am aware that if cannabis is discovered on a urine drug screen and I am not permitted to have cannabis on a urine drug screen, legal arguments to keep my job do not exist (or are very unlikely).
23. Following the terms of this contract is one of the conditions I must meet to access cannabis for treatment. I understand that if I violate any of this agreement's terms, my physician may stop authorizing my use of cannabis.
24. Dr. _____ has the right to discuss my health care issues with other health care professionals or family members if it is felt, on balance, that safety concerns outweighs my right to confidentiality.

Patient's printed name Patient's signature
Date Practitioner's signature

Assessment, monitoring, and discontinuation

Recommendation 7

When considering the initiation of cannabis for medical purposes, we recommend physicians start with a history and physical examination, including detailed mental health, substance use, and, if applicable, pain histories (level iii).

Tools that may be helpful in assessing substance use disorder and/or cannabis use disorder include the Cannabis Use Disorder Identification Test – Revised (CUDIT-R),[91] the Severity of Dependence Scale (SDS),[91] and the Cannabis Use Screening Test (CAST).[92] The diagnostic and screening tools for cannabis use disorder are described in more detail under Recommendation 8. A medication management agreement, with informed consent, may also be useful; key aspects are provided below.

By combining practical experience and a reasonable understanding of the available literature, family physicians are well positioned to have a comprehensive, patient-centred conversation about cannabis. While the legalization of recreational cannabis use may reduce the number of patients seeking cannabis through medical authorization, understanding cannabis's role as a potential medical therapy for a select list of conditions is still appropriate. The provision of high-quality care and shared decision-making can be accomplished through dialogue during a clinic visit and, if the physician elects, a written treatment agreement. The following tips may be helpful:

- Assess the patient's condition, ensuring it is one of the conditions with adequate evidence of benefit and that other criteria are met for the consideration of cannabinoids (such as reasonable trials of conventional therapies). Also consider the route of administration of cannabis.
- Screen for substance use disorder and cannabis use disorder.
- Assess for psychiatric disorders where cannabinoids (cannabis, oils, or synthetics) can result in adverse effects.
- Use tools to assess pain and response, as appropriate.
- Discuss side effects and potential acute and chronic adverse events before initiating therapy.
- Provide advice on cross-border and international travel and cannabinoid use.
- Outline contraindications during pregnancy and breastfeeding.
- Remind the patient about safety concerns related to consumption and use (such as occupational use of heavy machinery).
- Document functional goals and agree on a timeframe for assessing whether the therapy has resulted in progress toward those goals.

Informed consent is required by most regulatory colleges as a standard of practice. It is important to consider the patient's point of view and their expectations.

The patient's medication history should be reviewed prior to their starting cannabis, and any potential interactions should be explained (see Recommendation 11). Patients requesting cannabis therapy may be taking either over-the-counter or prescription medication for other conditions. In recreational users, cannabis is sometimes combined with other drugs of abuse. Given the indications for considering cannabis therapy, patients may have chronic pain, neurological conditions, or psychiatric disorders, and they may be taking medication for those conditions that could potentially interact with cannabinoids.[93]

THC and CBD are both metabolized through the cytochrome P450 pathway and may interact with other medications metabolized by that pathway, or with cytochrome P450 modulators. Interaction with other sedatives can amplify the effects of cannabis, which include sedation, impaired psychomotor performance, and increased blood pressure and heart rate.[93]

A review of interactions between cannabinoids and alcohol, other drugs of abuse, and prescription medicines is available.[93]

The patient medical agreement should include their history and physical examination, with an investigation of common substances of abuse (this includes their age at first use, the first drug they used, why they started, why they maintained use, amount, number of slips, reasons around the relapse, and current consumption of substances). A psychiatric screen for depression, ADHD, bipolar disorder, schizophrenia, and psychotic symptoms is important. A physical examination and history may identify additional characteristics of cannabis use or cannabis use disorder, such as a strong smell of cannabis, stained fingers, and amotivation syndrome.[94] Ideally, the patient's medication history can be revisited periodically (every three months is suggested).

Each initiation of cannabis is a trial and should be evaluated for benefits, risks, and harms after the trial period. When considering a trial for the treatment of chronic pain, a 10-point scale may provide rapid reassessment, but the simplicity provides limited details. The use of a scale such as the Brief Pain Inventory (BPI) may be more helpful in determining whether the trial has been worthwhile.[95] The BPI has been validated in many countries and can be used as a self-reported tool. It can help in the three-factor representation (pain intensity, activity interference, and affective interference) of pain. It may also be useful to use another tool, such as the Short-Form McGill Pain Questionnaire, concurrently with the BPI.[96]

Clinicians should also inquire about sleep and activities of daily living. Instruments from other disciplines can be useful; the Lawton Instrumental Activities of Daily Living Scale[97] and the Daily Living Activities Scale[98] are good methods of capturing the day-to-day abilities of the patient. Combined with the BPI and McGill short form, these tools can give a helpful representation of the capabilities of the individual, although it is challenging to add all of them to a primary care visit.

The use of urine drug screens is also advised by many provincial licensing authorities. A discussion of urine drug screens is beyond the scope of this section, but these screens should not be used punitively. They are an additional tool to be used with conversation and a recovery plan. Care is required in interpretating the results of these tests, as urine drug screens can be altered. But they can alert the authorizing physician to safety issues that require monitoring. THC-negative urine from a person authorized for cannabis suggests the possibility of diversion. While witnessed urine samples can help ensure authenticity, some patients see witnessed urination as degrading. An alternative might be to use the presence of biological agents to prove the authenticity of a urine sample (for example, assessing for the presence of other known prescribed medications apart from cannabis, nabilone, and other cannabinoids will not trigger a positive point-of-care test). Note that synthetic THC (e.g., nabilone) and other cannabinoids such as CBD will not trigger a positive THC result on a urine drug screen.

In general, guidelines suggest cannabinoids should not be offered as first- or second-line therapies.[14,99] Non-cannabinoid therapies should be used first. At least three trials of medication for neuropathic pain should be undertaken before cannabis is recommended. For symptoms in a palliative care context, two or more therapies should be tried before cannabis authorization.[14] Driving is a concern, as both fatal and non-fatal crashes occur with greater frequency among people taking cannabinoids.[100] Many experts advocate for pharmaceutically derived cannabinoids to be tried prior to the use of natural cannabis, but with the legalization of cannabis, patient engagement may be more difficult. Additionally, nabilone has limited evidence for pain management and is off label for that indication. Nabiximols is quite costly and rarely covered.[14]

As with all medications, authorizing should be done with caution. Follow similar procedures you might use when considering opioids as a treatment option. It is reasonable to notify the patient's primary pharmacist about the authorization of medical cannabis. A baseline urine drug screen may provide beneficial substance use details. Monitor for substance use disorders, including cannabis use disorder. Consider each initiation as a trial for a three- to four-month period. A treatment agreement expressing the rights of the patient and the physician can be helpful. Such agreements are not meant to be punitive but rather to provide starting points for conversation.

Recommendation 8

We suggest using the DSM-5 criteria to assess for cannabis use disorder before initiating therapy and as appropriate while on therapy (level iii).

The identification and treatment of substance use disorders are essential parts of medical care. Substance use disorder is the term used in the DSM-5, which amalgamates the definition of substance abuse and dependence into a single diagnosis, with variable severity. Cannabis is a substance with the potential for disordered use. See Box 2 for the DSM-5 definition of cannabis use disorder.

Box 2. DSM-5 diagnostic criteria for cannabis use disorder

A problematic pattern of cannabis use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. Cannabis is often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control cannabis use.
3. A great deal of time is spent in activities necessary to obtain cannabis, use cannabis, or recover from its effects.
4. Craving, or a strong desire or urge to use cannabis.
5. Recurrent cannabis use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued cannabis use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of cannabis.
7. Important social, occupational, or recreational activities are given up or reduced because of cannabis use.
8. Recurrent cannabis use in situations in which it is physically hazardous.
9. Cannabis use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by cannabis.
10. Tolerance, as defined by either of the following:
    a. A need for markedly increased amounts of cannabis to achieve intoxication or desired effect.
    b. Markedly diminished effect with continued use of the same amount of cannabis.
11. Withdrawal, as manifested by either of the following:
    a. The characteristic withdrawal syndrome for cannabis (refer to Criteria A and B of the criteria set for cannabis withdrawal, pp. 517–518).
    b. Cannabis (or a closely related substance) is taken to relieve or avoid withdrawal symptoms.

The presence of at least two of the above symptoms indicates cannabis use disorder. The number of criteria fulfilled determines the severity of the disorder:

- Mild: presence of two to three symptoms
- Moderate: presence of four to five symptoms
- Severe: presence of six or more symptoms

Those who are using cannabis for medical purposes may fulfill criteria #10 and/or #11 but not necessarily have cannabis use disorder, as tolerance and withdrawal can be normal physiological adaptations when a substance is appropriately used under medical

supervision.[101] Thus, if only two criteria are met and they are #10 and #11 in patients who are appropriately using cannabis under medical supervision, then cannabis use disorder may not necessarily be diagnosed.

The DSM-5 criteria are considered the gold-standard definition of cannabis use disorder. At this time, there have been no trials comparing shorter tools for identifying cannabis use disorder against the gold-standard DSM-5 definition in the primary care setting. There are some screening tools for cannabis dependence that have been tested and compared with the DSM-IV criteria, though these tools were not developed for use in patients using cannabis for medical purposes. Three of them are:

- The Cannabis Use Disorder Identification Test - Revised (CUDIT-R): an eight-item tool, modified from the Alcohol Use Disorders Identification Test (AUDIT), which has been tested against a Structured Clinical Interview for the DSM (SCID)[91]
- The Severity of Dependence Scale (SDS): a five-item tool, also used to identify cannabis dependence, but, there is no standardized diagnostic cut-off, which limits its functionality as a tool[91]
- The Cannabis Use Screening Test (CAST), developed for use in adolescents, which is a six-item tool tested against the DSM-IV criteria[92]

The rate of cannabis use disorder has not been identified among those authorized to use cannabis for medical purposes. Part of the difficulty is the newer definition of cannabis use disorder in DSM-5 and the variability of tools used in older studies.

Recommendation 9

We recommend physicians regularly monitor patients' responses to treatment with cannabis (level iii). We recommend physicians discontinue authorization if the therapy is not clearly effective or if harms outweigh benefits (level iii).

At follow-up office visits, the physician should reassess the effects of cannabis on the patient's pain ratings and function.

Many psychoactive drugs with abuse liability will temporarily blunt the patient's perception of pain without improving function. All centrally acting analgesics can also cause sedation, euphoria, or cognitive impairment. To authorize or continue to authorize cannabis for the purpose of analgesia, physicians should be as certain as they would need to be in prescribing any other analgesic that its potential benefits are greater than its potential risks.

Cannabis therapy should be reassessed and possibly stopped in the following circumstances:

- The patient experiences insufficient analgesia and/or no improvement in function (note that some pain patients continue to complain of severe pain even as their function improves)
- The treatment is not improving sleep, mood, function, and/or quality of life
- The patient experiences side effects such as memory impairment, sedation, fatigue, and worsening functioning
- The patient shows clinical features of cannabis use disorder (see Box 2)

Recommendation 10

We suggest physicians record patients' use of cannabinoid edibles, topicals, and oils/extracts and their doses (if known). Caution is advised when authorizing, as individual effects are unclear and lower doses are recommended, at least initially. If possible, educate patients about potential side effects and inform them that data on their use are still lacking (level iii).

In December 2018 Health Canada published its *Backgrounder: Consultation on the strict regulation of additional cannabis products*.[102] The draft backgrounder was open to 60 days of public consultations on the proposed framework to regulate legal sales of edible cannabis, topical cannabis, and cannabis extracts. The final version of the Cannabis Act includes regulations on edibles, topicals, and oils/extracts and became available October 2019. The regulations are concerned with the use of recreational products and recommend that producers be prohibited from making any potential health claims. The scientific evidence on the health benefits of edibles or topicals is limited. Most studies are small and are funded by cannabis manufacturers. The topical and edible products vary from one producer to another, and the outcome reporting has not yet been standardized.

Cannabinoids are lipophilic, and therefore the absorption of topicals, unless prepared with an effective delivery system, will only minimally penetrate beyond the stratum corneum of the skin. Studies in both Europe and North America have reported inaccuracy in the labelling of CBD products.[103,104,105] When 84 commercial CBD products were analyzed, only 30 per cent were accurately labelled, with 21 per cent of the products identified as containing THC.[104] The mislabelling of vaporization CBD liquid occurred for 88 per cent and oils for 55 per cent of the products. Under-labelling of CBD content is less concerning, whereas THC presence poses risks, especially for children.[106] Since 2016 the United States' Food and Drug Administration has issued numerous warning letters to companies marketing CBD products for inaccurate labelling and marketing products as treatments for illnesses.[107]

In the broadest sense, cannabinoid-derived pharmaceuticals may be seen as alternative methods for cannabis use. There are currently two cannabinoid-derived pharmaceutical products available in Canada. Nabilone (an oral capsule) is approved to treat nausea caused by chemotherapy and to increase appetite in patients with extreme weight loss caused by AIDS. Nabiximols, the second product, is a buccal spray used to treat spasticity associated with multiple sclerosis. While these products have been studied in multiple RCTs, they are pharmaceuticals and do not reflect the use of cannabis-derived topicals, edibles, and oils/extracts that became commercially available in late 2019.

CBD has been prepared in oral liquid and capsule formulations for clinical trials, including for the treatment of seizures[108,109,110] and anxiety,[111] respectively. The best researched of these is in refractory pediatric seizure disorders such as Dravet syndrome and Lennox-Gastaut syndrome.[108,109,110] These RCTs are summarized in the evidence section of this guidance document. While the CBD treatments generally reduced seizure frequency, there were also adverse events such as sedation, decreased appetite, and liver enzyme abnormalities. It is important to note that the seizure disorders studied are very rare and complex, meaning other specialists such as pediatricians and/or neurologists would be involved in the patient's care. Family physicians would not initiate this treatment for this subpopulation.

The "Simplified guideline for prescribing medical cannabinoids in primary care" suggested that "clinicians could consider medical cannabinoids for refractory neuropathic pain and refractory pain in palliative care, chemotherapy-induced nausea and vomiting, and spasticity in multiple sclerosis and spinal cord injury after reasonable trials of standard therapies have failed. If considering medical cannabinoids and criteria are met, the guideline recommends nabilone or nabiximols be tried first."[14] The data on the use of medical cannabis-based edibles, topicals, oils/extracts have not changed significantly since.

While some observational studies are being reported, there is a profound lack of research on the use of edibles, oils, and topicals. Observational studies lack control groups, blinding, intention-to-treat analysis, and other measures to control confounding and bias. For example, an observational study of 188 children with autism in Israel reports 84 per cent had moderate or significant improvement.[112] These findings seem impressive and suggest considerable benefit in a hard-to-treat population. However, these patients already had licences to receive cannabis therapy, resulting in a selection bias. Additionally, the study is non-randomized and lacks a control/placebo, making it impossible to verify that cannabis oil is the cause of any benefit. Furthermore, there was no blinding of patients or assessor, the data were analyzed retrospectively, and the analysis was based on 49 per cent of the original patient group. Also, the study was funded by the cannabis manufacturer and the first author works for the manufacturer.

There is clearly a need for high-quality RCTs to truly assess the benefits and at least short-term harms of cannabis edibles, topicals, and oils/extracts. For many conditions these formulations have not been studied with RCTs at all. This profoundly limits the ability to make recommendations around therapeutic use. In light of the almost complete lack of reliable research, some guidance groups, such as the Canadian Centre on Substance Use and Addiction, provide some high-level advice on non-medical cannabis use.[113] When this document was written, topical products in particular seemed to be gaining in popularity and were perceived as being safe. Patients might be using them for their purported/advertised analgesic and anti-inflammatory properties. However, as of today, no high-quality RCTs or observational studies have been conducted. This is a crucial area for future research.

Harms

After the 2013 legalization of cannabis sales in Colorado, the state reported a significant increase in emergency department visits and cannabis-related calls for all ages to the poison control centre.[114] The rate of cannabis-related hospital visits almost doubled in the year post-legalization, with hospitalizations rising to 28 per 100,000 from 15 per 100,000, and emergency visits increasing to 38 per 100,000 from 22 per 100,000 previously.[114] A retrospective study in Denver, Colorado, found that emergency visits for edible cannabis, as opposed to inhaled, were more likely to be associated with acute psychiatric symptoms (18 per cent versus 11 per cent) and intoxication (48 per cent versus 28 per cent).[115] The same study reported that edibles accounted for approximately 11 per cent of the visits, although they represented only 0.3 per cent of cannabis sales.[116] A number of the presentations were related to toxicity, likely from too high a dose. It is quite possible users are unaware of how long edibles can take to have their effect. Counselling on this is important to mitigate harms.

To summarize, there is a lack of high-quality evidence to support the use of edibles, topicals, and oils/extracts. A belief in improved safety is not supported by the limited

available evidence, particularly among edible products. Recommendations focus on broad safety-related issues and good standards of care. It is hoped that more evidence will be available soon to refine recommendations around the use of cannabis edibles, topicals, and oils/extracts as medical therapy.

Additional recommendations for edibles, topicals, and oils/extracts:

- Discuss a patient's use of edibles, topicals, and oils/extracts in a non-judgmental way, and assume a harm-reduction and shared decision-making approach.
- A trial of cannabis edibles, topicals, and oils/extracts is not recommended prior to a trial of nabiximols.
- Encourage "starting low and continuing slow" with the use of edibles, topicals, and oils/extracts. Remind patients of the slower onset of effect to avoid unintentional overdoses and of the extended length of time over which effects might last.
- Keep all cannabis-based products in a safe, locked cabinet away from children. Avoid using cannabis products in potentially appealing packaging or forms (candies, muffins, cookies, etc.) that could increase their attractiveness to children and adolescents.

Harms prevention and intervention

Recommendation 11

We recommend physicians assess and monitor all patients on cannabis therapy to identify the potential for problematic use and emerging toxicities using harm-reduction and harm-prevention approaches and, when warranted, attempting individualized tapers (level iii).

Some patients report their perception of cannabis and cannabis-plant-derived products as a safe alternative to many medications, especially opioids, probably due to the absent risk of respiratory arrest and fatal overdose with medicinal cannabis in therapeutic doses. However, the literature on associated long-term adverse effects remains limited. Results are frequently mixed and difficult to synthesize due to observational study design, non-standardized reporting, non-comparable populations, lack of controls, multiple routes of administration, and changes over time in the chemical composition of existing natural and synthetic products. As with other similar questions, causality cannot be claimed as most studies are observational in nature, have multiple biases such as significant confounding, and have broad confidence intervals or small/inconsistent effects. Specific important confounders to long-term harms of cannabis include co-existing tobacco smoking and other comorbid medications and recreational substance use.

All patients using cannabis should be monitored carefully and assessed routinely for cannabis use disorder. The clinical features of cannabis use disorder are listed in Box 2.

Patients with suspected cannabis use disorder should be advised that they could experience improved mood and better function if they stop or reduce their use. Patients who are unable to stop or reduce may be considered for referral for formal addiction treatment. Cannabis should not be authorized for patients with current problematic use of cannabis, alcohol, or other drugs (see Recommendation 5).

Before authorizing cannabis use for the patient, the physician should take a careful history of current and past substance use, including cannabis, alcohol, tobacco, prescription opioids, and benzodiazepines and illicit drugs such as heroin and cocaine. Several medical

regulatory authorities recommend using a standardized tool to assess the risk of addiction. The CAGE Adapted to Include Drugs (CAGE-AID) Questionnaire is one such simple tool.[117,118] It has four simple questions that ask a patient how they and those around them perceive their substance use and how dependent they are on substances to start their day; the patient's responses can be used to determine whether further assessment is needed. A urine drug screen may also be included in the initial assessment. It should be noted that synthetic cannabinoids such as Spice and pharmaceutical cannabinoids such as nabilone will not show on urine drug screens.

Statistics Canada's National Cannabis Survey reported that at the end of 2018, 11 per cent of females and 19 per cent of males older than 15 were cannabis users. Almost half of them used cannabis for therapeutic purposes, and 70 per cent of medical users reported daily consumption.[119] The high proportion of daily users among Canadians consuming cannabis for medical purposes underscores the need for primary care practitioners to become comfortable with discussing potential long-term cannabis toxicities, harm reduction, and adverse effect prevention strategies with their patients. Such discussions should translate into informed decision making with further consideration of minimizing negative individual and societal consequences.

For the moment, the best approach appears to be keeping a high index of suspicion for the most commonly reported chronic toxicities of cannabis and advising patients about potential long-term effects of cannabis toxicity. Screening of all regular users of cannabis who are at higher risk (elderly, people younger than 25, those who are pregnant, those using high doses, and those reporting unsafe practices) for the most pertinent toxic effects of cannabis is recommended on an individual basis. Discussing the potential risks of different products and different methods of use may be helpful. Some formulations, such as "shatter" and other concentrated extracts, can have a very high THC content. They are also associated with "dabbing," a method of use that may have higher potential risks than methods such as vaping or ingestion.

A brief, per system summary of the most recent systematic and non-systematic reviews looking at the prolonged use of cannabis and cannabinoids is presented below. Some special situations, such as cannabis-induced hyperemesis syndrome, are also highlighted to facilitate discussions with regular cannabis users and assist in their recognition in regular practice.

Cancer

Clinical data suggestive of anti-cancer benefits do not exist. On the other hand, some studies have shown small associations with the induced cancer risk. For example, one small case-control (403 patients) study found that each joint-year of marijuana smoking is associated with a relative risk (RR) increase of 1.08 (95%CI 1.02 to 1.15).[120] However, the effects are inconsistent and small and/or based on research at very high risk of bias, making the effects of smoked cannabis on cancer development unclear.[121]

Pulmonary

Five systematic reviews were evaluated to determine the impact of cannabis on pulmonary health.[121,122,123,124,125] The results are generally presented descriptively without pooling.[121,122,123,125] While prospective cohort studies would be preferred, some reviews included studies down to case reports/series.[121,122,123,125]

One systematic review pooled data and included observational studies of at least cross-sectional design or higher, and it thus provides the most reliable basis for recommendations.[124] Low-level evidence suggests an association between cannabis use and cough (RR 2.0), sputum production (RR 3.8), and wheezing (RR 2.8). While there is a potential increased risk of COPD (RR 2.28, 95%CI 0.68 to 7.72) it is not statistically significant, and the evidence is considered insufficient. The other systematic reviews were inconsistent but often reported similar potential concerns.

Cardiovascular

Cannabis smoking appears to be associated with more acute hemodynamic cardiovascular changes, including an increase in heart rate and/or palpitations that might be followed by orthostatic hypotension. Association with an increased risk of cardiac ischemia, arrhythmia, or sudden death remains questionable.[126] Another review raised various concerns,[77] especially for cannabis use in unstable heart disease, while another reports the evidence is insufficient to determine whether cannabis increases cardiovascular risk.[121] The Canadian Cardiovascular Society recommends future heart transplant recipients abstain from smoking, inhaling, and vaping cannabis for six months.[127] We recommend that physicians err on the side of caution in the presence of unstable angina, congestive heart failure, post-surgical hemodynamic instability, and other hemodynamically challenging clinical situations that should be considered temporary contraindications for any cannabis use.

Neuropsychiatric

There are multiple observed structural, functional, and chemical changes in the brain[122] associated with cannabis use.

More frequent use and younger age of cannabis initiation are associated with more profound neuropsychiatric adverse effects. Effects include a reduced ability to learn and remember new information (less so in therapeutic doses and at adult ages), decreased attention and alertness, and some effects on memory and cognitive function. A 2016 review reported that even when not intoxicated, individuals who are heavy cannabis users scored lower than nonusers on tests of neuropsychological function, including executive function, attention, learning and memory, motor skills, and verbal ability. However, these differences in performance between heavy cannabis users and nonusers were no longer present after the cannabis users abstained for one month or more. The extent of cannabis use, age at first use, and length of abstinence may influence the severity of the adverse neuropsychological effects of heavy cannabis use and the duration of these effects following abstinence.[8] Multiple persistent neurotoxic effects are the most concerning in adolescent cannabis use.[128]

The presence of CBD may be protective against some negative neuropsychiatric effects of THC, as noted in Recommendation 3. Regular high-dose THC cannabis use is associated with an increased risk of depression and anxiety disorders, suicidal ideations, and mania.[116,121,129]

Motivation

The phenomenon of cannabis amotivational syndrome was noted as far back as the 19th century.[8] The literature describes a constellation of symptoms including apathy, anhedonia, decrease in goal-oriented activities, poor overall functioning, and learning difficulties. Frequency, duration of use, and younger age of onset of use are the main predictors.

Presently, there are sufficient pathophysiological data supporting this description in heavy and/or regular users. The rate of cannabis use disorder among all users is around 9 per cent, and it appears to be related to decreased motivation for non–drug-related activities such as graduating from high school or college studies.[8,122]

Psychosis and schizophrenia

Several cohort studies have examined the association between cannabis use and schizophrenia/psychosis. One review included 12 cohort studies with 591 to 50,053 patients followed for one to 35 years. The authors reported that people who used cannabis 50 times or more were six times more likely to develop schizophrenia.[130] Examining the largest cohort study in that group, the absolute risk of developing schizophrenia over about 30 years was 0.7 per cent in people who had never used cannabis, 1.5 per cent in people who had used it at least once, and 4.2 per cent in those who used cannabis 50 or more times.[131] Two systematic reviews found similar results, with regular users having an increased risk with an adjusted odds ratio of 2.09 (95%CI 1.54 to 2.84)[80] or an unadjusted odds ratio of 3.90 (95%CI 2.84 to 5.34).[132] In patients with a history of psychosis, ongoing use is associated with an increased risk of relapse and extended hospital stays.[133] These results are observational, and the effects are reduced (but not eliminated) by adjustment of confounders.[134] While the causes of schizophrenia and psychosis are typically multifactorial, cannabis is associated with these conditions and may play some role.

Cannabis-induced hyperemesis syndrome

Although cannabis-induced hyperemesis syndrome (CES) appears frequently in the literature of the past two decades, it still represents a significant diagnostic and management challenge. Physicians are advised to maintain a high level of suspicion for CES in regular or almost-regular cannabis users presenting with recurrent vomiting.

A systematic review identified 14 main characteristics of CES, including seven most frequently reported: "history of regular cannabis for any duration of time (100%), cyclic nausea and vomiting (100%), resolution of symptoms after stopping cannabis (96.8%), compulsive hot baths with symptom relief (92.3%), male predominance (72.9%) abdominal pain (85.1%), and at least weekly cannabis use (97.4%)."[135] Severe CES could lead to dehydration, acute renal failure, and serious electrolyte imbalance. The care is mostly supportive and depends on severity (intravenous fluids, dopamine antagonists, capsaicin cream applications to abdomen, and hot baths). The best treatment is the cessation of cannabis use, which results in CES resolution in most, but not all, cases. Restarting cannabis use frequently leads to the recurrence of CES.[135]

Drug-drug interactions

In regular cannabis users taking multiple medications, routine screening for potential drug-substance interactions is recommended, as are attempts to deprescribe or taper medications with neurosuppressant, analgesic, and hypnotic properties. Other medications with psychoactive properties should be used with much caution if patients already use or are about to initiate cannabis use, as THC drug-drug interactions could be especially important.[136]

Both THC and CBD are metabolized via the cytochrome P450 system, and metabolites are excreted in feces and urine. There are several potential drug-drug interactions with the inducers and inhibitors of the system.

The potential cytochrome P450 inducers (lowering THC effect) include azole antifungals (e.g., ketoconazole, fluconazole), calcium channel blockers (e.g., verapamil, diltiazem), cimetidine, ciprofloxacin, grapefruit juice, macrolide antimicrobials (e.g., erythromycin, clarithromycin), protease inhibitors, rifampicin, selective serotonin re-uptake inhibitors (SSRIs; e.g., fluoxetine, paroxetine), and, for CBD, tobacco.[137]

The potential inhibitors of the cytochrome P450 system (increasing THC levels) include amiodarone, carbamazepine, cimetidine, fluconazole, fluoxetine, fluvoxamine, ketoconazole, omeprazole, and phenytoin. Note that different isoenzymes of cytochrome P450 can have differing effects, so some drugs can potentially increase or decrease the THC effect.

Those that increase levels of CBD include cimetidine, ciprofloxacin, diltiazem, estradiol, fluoxetine, fluvoxamine, grapefruit juice, levonorgestrel, omeprazole, quinidine, SSRIs (e.g., fluoxetine), verapamil, and others.[137]

THC may decrease serum concentrations of some medications, such as chlorpromazine, clozapine, cyclobenzaprine, duloxetine, haloperidol, naproxen, and olanzapine. For CBD there may be an increase in serum concentrations of antihistamines, antipsychotics, antiretrovirals, atorvastatin and simvastatin, benzodiazepines, beta blockers, calcium channel blockers, cyclosporine, haloperidol, macrolides, opioids, PDE5 inhibitors, SSRIs, and tricyclic antidepressants. Cannabis has central nervous system depressant effects additive to those of alcohol, barbiturates, and benzodiazepines. THC and CBD increase warfarin levels and international normalized ratios.[138]

Synthetic cannabinoids and dangerous use

The number of synthetic cannabinoids, initially invented as research ligands and later modified for illicit use, continues to grow. In the United States, synthetic cannabinoids could be co-used with regularly acquired cannabis in 30 per cent to 35 per cent of cases. The most common clinically relevant toxicities include tachycardia (~40 per cent), agitation (~20 per cent), drowsiness, vomiting/nausea, hallucinations, confusion, hypertension, chest pain, diaphoresis, dizziness/vertigo, headaches, paresthesia, tremor, and seizures (less than 5 per cent). Psychotomimetic, cardiovascular, pulmonary, renal, and other cannabis-specific effects have been reported. In addition, hyperthermia, rhabdomyolysis, hyperglycemia, acidosis, and hypokalemia were noted in hospitalized patients using synthetic cannabinoids. There are more than 30 case reports of synthetic cannabinoid–suspected deaths (sudden cardiac dysrhythmia, seizures, hypothermia, self-injury).[139,140] Withdrawal or intoxication could occur quickly, within 15 minutes of initiation. No standardized toxicology screens are available. Diagnosis is clinical. Physicians are advised to ask cannabis users periodically about synthetic cannabis co-use and to counsel against it.

Recommendation 12

We recommend physicians screen, assess, and treat cannabis withdrawal syndrome when it is identified (level iii).

Cannabis withdrawal syndrome (CWS) is a recognized clinical entity in DSM-5 that occurs within seven days of abrupt cessation of cannabis use (see Box 3).[17] The amount of cannabis consumed, potency of THC, and duration of consumption prior to discontinuation correlate with the severity of the CWS.[141, 142, 143] By day 45 sleep patterns and dreams return to normal.[63,141,143]

As DSM-5 does not define the intensity of withdrawal, clinical judgment can be used to determine severity, though proposed scales to define severity of CWS have been published.[142, 144] The combination of cannabis with gambling disorders, comorbid medical/psychiatric disease, and the use of tobacco or other substances, such as cocaine, stimulants, and alcohol, results in a more challenging syndrome of withdrawal and is associated with poorer outcomes.[141,142,144,145, 146] The majority of patients with CWS have mild cases and can be managed as outpatients.[144]

Box 3. DSM-5 cannabis withdrawal syndrome diagnostic criteria

Criterion A: Cessation of cannabis use that has been heavy and prolonged

Criterion B: Three or more of the following develop within several days after Criterion A:

a) Irritability, anger, or aggression
b) Nervousness or anxiety
c) Sleep difficulty
d) Decreased appetite or weight loss
e) Restlessness
f) Depressed mood
g) At least one of the following physical symptoms causing significant distress: stomach pain, shakiness/tremors, sweating, fever, chills, and headache.

Criterion C: The symptoms of Criterion B cause clinically significant distress or impairment in social, occupational, or other areas of functioning.

Criterion D: The symptoms are not due to a general medical condition and are not better accounted for by another disorder.

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American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5.* American Psychiatric Publishing, Inc. 2013.[17]

Generally, CWS is not associated with cannabis hyperemesis syndrome. There is no correlation between CWS and nausea.[144] If more severe symptoms such as seizures, hypertension, or persistent vomiting occur, then a synthetic cannabinoid may be the etiological agent.[147]

Gender, health issues, frequency of cannabis use, extent of cannabis use, and potency of THC are recognized as factors affecting the severity of CWS.[63,142,144,146,148,149,150,151] However, conditions such as ADHD do not increase risk.[152]

Cannabis withdrawal typically falls into two different courses: Type A and Type B.[141,144,146] In Type A, symptoms peak between day two and day six of abstinence and then decrease. In Type B, symptoms decrease from abstinence without a later peak.

Treatment of CWS

Most cannabis users who are consuming high-potency cannabis and those who have tried repeatedly to discontinue tend to have more difficult withdrawal symptoms.[151,153] Tailoring treatments to target withdrawal symptoms may improve treatment outcomes.[154]

The treatment of cannabis withdrawal has been primarily symptomatic. A Cochrane review presents reasonable evidence to support psychological intervention.[155] Those who work

clinically with patients with CWS often use group therapy, cognitive behavioural therapy, 12-step programs, dialectic behavioural therapy, and similar approaches. Withdrawal symptoms, negative affect, and peer use are associated with relapse.[156] Yoga and aerobic exercise training may reduce cannabis cravings, but further study is needed.[156,157]

Medications

Cannabis withdrawal has many symptoms in common with nicotine withdrawal.[142,158] There is incomplete evidence for all of the pharmacotherapies investigated for CWS, and for many outcomes the quality of the evidence was low or very low. Findings indicate that SSRI antidepressants, mixed action antidepressants, atomoxetine, bupropion, and buspirone are probably of little value in the treatment of cannabis dependence. Pharmaceutical cannabinoids may help with CWS.[158] However, given the limited evidence of efficacy, THC preparations should be considered still experimental, with some positive effects on withdrawal symptoms and craving. The evidence base for the anticonvulsant gabapentin[159] (1,200 mg per 24 hours), N-acetylcysteine, and oxytocin is weak, but these medications are also worth further investigation.[160] Sleep disruption is common during withdrawal;[161] mirtazapine can be used for depressive symptoms and sleep[162] but Z-drugs should be avoided because of their risk of dependency. See Appendix 2.

Strategies to prevent harm

Recommendation 13

We recommend that patients using cannabis for medical purposes be advised (level iii):

- **Wait at least six hours before driving if using via the inhalational route**
- **Wait at least eight hours before driving if using via the oral route**
- **If using daily, their serum THC level may be higher than legal allowable limits, even if they do not feel impaired**
- **Combining cannabis and alcohol seriously increases risk and should be avoided**
- **The recommendations above apply to typical driving with a Class 5 licence, and limitations/times can increase with other licence classes or additional safety-sensitive work**

Two driving-related risks are important for patients to understand: the risk of motor vehicle collision and the risk of legal consequences. Cannabis has been shown to impair driving-related tasks in intermittent users at least five hours following use.[163] There is likely some tolerance to these effects that develops over time, but there is a high degree of variability in impairment among chronic users.[164] At the same time, chronic use will cause blood levels of THC to be positive longer than in intermittent use, and therefore blood levels may exceed allowable limits under federal legislation.[165]

Recommendation 13 required modification in this edition for three reasons. First, evidence is evolving and indicates impairment may last longer than previously understood. Second, past recommendations (e.g., “waiting eight hours to drive if the patient experienced euphoria”) depended on patients’ ability to self-assess euphoria and, in turn, their capacity to drive. No evidence was found to suggest that users of any substance can accurately assess their own impairment, so that recommendation is not supported. Finally, there is now an allowable legal limit that should be reflected in the recommendations (see Box 4).

The problem

Driving after using medical cannabis may be quite common. In one study of 790 patients who use medical cannabis, 56 per cent reported driving within two hours after using, 50 per cent reported driving while "a little high," and 21 per cent reported driving while "very high."[166]

A meta-analysis of nine observational studies estimates that cannabis use is associated with an almost doubling of the risk of injury or death from motor vehicle crashes, with an odds ratio of 1.92 (95%CI 1.35 to 2.73).[167] Other researchers have found similar risk estimates with cannabis.[168,169,170] Others have also identified a dangerous synergistic risk when combined with alcohol.[169,170] When looking specifically at the combination of cannabis and alcohol, risk was increased with an odds ratio of 6.4 (95%CI 5.2 to 7.9).[170]

Evidence of impairment

Laboratory studies have demonstrated that cognition and attention can be impaired with even small amounts of THC. Doses of 12 mg to 20 mg (1 per cent to 3 per cent THC) led to worsened reaction time, reduced motor coordination, reduced short-term memory, temporal distortion, poor divided attention, and poor decision making in rapidly changing situations.[171] There is a suggestion of a dose-dependent relationship between serum concentration and generally worsening driving cognitive/motor function and deteriorating driving safety in intermittent users. In a simulator study, impairment lasted at least five hours after inhalation of 100 mg of cannabis at 12.9 per cent THC by young, healthy volunteers, but the assessment ended at five hours, making it difficult to determine when impairment was resolved.[163,172]

There are multiple factors that influence impairment, including pattern of use, age, and use in combination with alcohol. For example, one study documented a greater chronic impact on executive function among users between the ages 35 and 50.[173] A degree of tolerance is known to develop in frequent users (defined as four or more times per week),[174] but impairment is highly variable among regular users.[175]

A recent simulator study of 15 chronic and 15 occasional cannabis users showed that the time to maximal impairment after inhalation was the same in chronic versus occasional users: approximately five hours. Effects were more marked and lasted longer in occasional users, with a 50 per cent improvement from maximal impairment occurring at eight hours in chronic users and 13 hours in occasional users.[176] Another similar study concluded that between two and six hours after inhalation, THC caused the same degree of impairment as a blood alcohol concentration above 0.5 mg/mL.[172]

It is clear that combining cannabis and alcohol results in a significantly higher degree of impairment than with either alone. In a placebo-controlled driving simulator study of 18 occasional cannabis users, combining a low dose of approximately 14 mg of THC with 0.04 per cent blood alcohol concentration resulted in severe impairment.[177]

Several authors emphasize that the greatest degree of impairment, the greatest risk of driving while impaired, and the greatest risk of injury from motor vehicle crashes exist when cannabis is combined with alcohol.[166,171] There is therefore an urgent need for prevention efforts regarding the use of cannabis and alcohol concurrently.[178]

Method of use

Most studies of impairment examine users who smoke or vaporize cannabis, leaving very few data to guide decisions about edibles. One study attempted to address this gap by measuring serum and oral fluid levels, subjective cognitive effects, and objective cognitive performance in 18 subjects who consumed standardized-dose (up to 50 mg THC) cannabis brownies (after a standard low-fat breakfast and no snacks to limit variability in absorption). Peak serum levels were lower with oral use compared with what would be expected via the inhalational route (less than 5 ng/mL), but return to baseline did not occur until up to 20 hours post-ingestion. Despite the low serum levels, participants reported marked subjective effects of cannabis, and impairment resolved slowly—up to eight hours following ingestion. Testing ceased before the complete resolution of cognitive and mood-related effects.[179]

Assessment of serum levels

Although serum THC levels are not precise markers for impairment at a given point in time, there is an interest in associating impairment with THC levels for legal purposes. A number of researchers have noted that serum levels/concentrations of THC are often not correlated with impairment,[171] with the duration of subjective effects in some studies lasting beyond the point when serum levels fall, while other studies have demonstrated minimal impairment while serum levels remain elevated. Based on a review of the often-conflicting literature, the Canadian Drug Policy Coalition concluded that a serum level of 7 ng/mL to 10 ng/mL was the threshold for impairment.[180] However, it is notable that other researchers have found serum levels of 2 ng/mL to 5 ng/mL to cause significant impairment.[172] THC remains detectable in the blood of chronic users at least 24 hours after inhalation.[176]

It is notable that Canadian federal legislation sets an allowable limit of 2 ng/mL of serum THC before penalties are applied (see Box 4). For a serum THC level between 2 ng/mL and 5 ng/mL, a fine of up to $1,000 applies. At THC levels beyond 5 ng/mL (or 2.5 ng/mL when combined with 0.05 per cent blood alcohol concentration), the first offence involves a minimum fine of $1,000, and subsequent offences involve jail terms.[181] Although not all jurisdictions across Canada are currently using serum THC levels to prosecute cannabis-impaired driving, it is notable that studies have shown that the use of low doses of THC (500 mg of cannabis containing 6.7 per cent THC) results in serum levels in excess of 50 ng/mL (higher if combined with alcohol).[177]

Box 4. Penalties for impaired driving under federal legislation

Cannabis alone
Serum THC 2 ng/mL to 5 ng/mL = maximum $1,000 fine
Serum THC > 5 ng/mL = same as combined with alcohol

Cannabis (>2.5 ng/mL) and alcohol (> 0.05% blood alcohol concentration)
First offence: minimum $1,000 fine
Second offence: minimum 30 days in jail
Further offences: minimum 120 days in jail

Some jurisdictions plan to use oral fluid testing as a proxy measure for serum level. Although oral fluid is a reliable marker of recent cannabis use, it does not correlate well with serum levels, and there are no good studies linking oral fluid levels with impairment.[139] No studies were identified that attempted to directly correlate impairment from cannabis, serum levels of THC, or oral fluid results with culpability in motor vehicle

collisions.

Limitations
As with other facets of cannabis research, limitations here include small sample sizes and heterogeneity of study populations.

Many studies assessed impairment within a limited time period (e.g., five hours),[163] and in many cases impairment was seen up to the last assessed time point. Future studies should plan to assess users until resolution of impairment (12 hours or more).

It is clear that many users of cannabis prefer the oral route (edibles), but evidence is sparse regarding the degree and duration of impairment and the value of serum or oral fluid measurement. Further study is required to provide better guidance regarding driving after oral use of cannabis.

Finally, there is limited evidence to demonstrate whether the results of simulator studies of cannabis use correlate with real-world driving studies or with culpability in motor vehicle collisions. These are important questions that remain to be answered.

Recommendation 14

We suggest using harm-reduction strategies when authorizing cannabis therapy for patients. Physicians are advised to discuss these strategies with patients (level iii).

Patients may be unaware that it is as important to follow dosing recommendations with cannabis as with any other course of treatment. Some forms of cannabis, such as shatter and other cannabis extracts, may have significantly higher THC concentrations than others. In addition, different modes of delivery are safer or more precise than others.

For example, vaping may be safer than smoking (combustion), as the vapour contains fewer toxic elements.[175] However, new data are emerging that suggest vaping might not be as safe as had been hoped. In a summary of recent Electronic cigarette or Vaping product Associated Lung Injury (EVALI) data that included 48 deaths, THC (or THC-containing products) was associated with 80 per cent of the lung injuries that led to hospitalization. Vitamin E acetate may be the toxicant in THC-related cases.[182] Vaporized cannabis has been evaluated in clinical trials.[183] Regardless, it is important to advise patients that sedation and cognitive impairment are among the potential side effects of cannabis, and that these side effects can affect their safety.[184]

Recommendation 13 discusses safety with activities involving alertness and coordination. It is important to go slowly with the treatment until a stable, effective dose is reached.

Physicians are advised to share patient education materials with those who are interested in cannabis treatment. The general approach to harm-reduction strategies applies to cannabis, as well. There are several important principles adapted from a 2019 Canadian Rheumatology Association position statement on medical cannabis[185] and *Canada's Lower-risk Cannabis Use Guidelines*.[39] The adapted recommendations are listed below in Box 5.

Using a non-stigmatizing harm-reduction approach is recommended whenever possible. If a physician estimates the risks of medical cannabis outweigh its benefits, they should feel comfortable refusing the authorization.

Box 5. Harm-reduction strategies

1. We recommend acknowledging and documenting patients' requests for authorization of medicinal cannabis and self-medicating practices.
2. We suggest shared decision making as an approach to initiating medicinal cannabis use. Patients might be advised that there is some support in the literature for the use of medicinal cannabis in conjunction with the mainstream therapies; however, the data to support its use as a sole therapeutic approach in any condition are lacking.
3. When initiating medicinal cannabis, we recommend establishing specific and realistic treatment objectives. An increase in daily function and a decrease in polypharmacy (especially opioids and central nervous system suppressants) are examples of such goals.
4. We recommend documenting:
    a) An adequate assessment of the condition(s) being treated.
    b) Presence/absence of any substance use disorder.
    c) Risk factors such as individual/family history of psychosis, schizophrenia, bipolar disorder, cardiac, pulmonary conditions, immunosuppressed state, pregnancy/risk of pregnancy, concurrent medications, and the type of regular activities (operation of machinery, driving etc.)
5. We suggest discussing the risks of potential adverse effects and benefits based on the individual patient's goals and vulnerabilities.
6. Drug preparations, routes of administration, and dosing could be negotiated based on their relative safety profile (topical > ingested > inhaled > smoked—acknowledging the limited evidence base for administration by some routes, particularly topical). Whenever possible, higher CBD proportional content should be prioritized, especially during the waking hours.
7. We recommend that initial total daily dose for oil consumption does not exceed 2 g/day. Inhaled (and smoked) cannabis could be started at 0.5 g/day. We recommend using the smallest effective dose and keeping the total maximum daily dose at 5 g/day or lower.
8. Medicinal cannabis can be used regularly and/or on demand.
9. We recommend scheduling follow-up visits every four to eight weeks after initiating the treatment and as needed, or every three months when the dose is stable.
10. With regular cannabis users, we recommend planning for periodic re-assessments of cannabis therapy effectiveness and possibility of tapers.
11. We suggest assessing for and documenting potential drug-drug or drug-substance interactions at each visit.
12. Medical cannabis should not be used in patients under the age of 25 years or if pregnant. We recommend caution while using it in elderly patients.
13. Recreational cannabis use should be minimized and/or discontinued, if possible. The use of synthetic cannabis should be avoided.
14. We recommend educating patients to avoid/minimize risky practices such as smoking, mixing with tobacco or alcohol (and other psychotropic substances), deep inhalation and breath holding, high THC (including concentrates), dabbing, etc.

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Fitzcharles M et al. *J Rheumatol.* 2019;46:532.
CAMH. *Canada's Lower-Risk Cannabis Use Guidelines (LRCUG)*. Centre for Addiction and Mental Health; 2017.

Communication with patients and consultants

Recommendation 15

We recommend that the physician who is authorizing cannabis for a particular clinical indication should be primarily responsible for managing the care for that condition and following up with the patient regularly (level iii).

The fragmentation of patient care is never advisable. Several regulatory authorities (see Recommendation 6) have advised that the authorization of cannabis and care for a clinical condition that includes cannabis therapy should be managed by the most responsible health care provider for that patient.

Before referring a patient, the physician should first ensure that the clinic:

- Has expertise in the patient's medical or psychiatric condition
- Conducts a careful patient assessment routinely prior to recommending any therapeutic intervention
- Provides an explicit statement on the clinic's policies on the indications, contraindications, and dosing for cannabis
- Does not have any financial conflicts of interest, such as charging patients fees or financial involvement with licensed cannabis producers

The referring physician should send the consultant all clinically relevant information on the patient's substance use, mental health, and pain history. The consultant should correspond with the referring doctor regarding the management of and recommendations for the patient.

Dosing

Recommendation 16

Given the weak evidence for benefit, the known risks of using cannabis, and the potential for unknown risks, it is recommended that physicians involved with authorizing cannabis "start low and go slow." (level iii)

The optimal cannabis dose should improve pain relief and function while causing minimal euphoria or cognitive impairment. Gradual dose titration is needed to establish the dose's effectiveness and safety. This is of critical importance because, as Health Canada has stated, even low doses of low-THC cannabis can cause cognitive impairment lasting as long as 24 hours in some individuals.[5,25]

What follows is a synthesis of what is known from the few controlled trials on cannabis available and the medical literature on pharmaceutical cannabinoids. In the absence of rigorous evidence, it is important to stress the trialling of other possible therapies before embarking on a trial of cannabis therapy, as well as the necessity to start low and go slow, while continually monitoring the patient's response to the treatment.

Suggested dosing: Start low

Determining a safe and effective dose for herbal cannabis is much more difficult than for pharmaceutical products because individuals vary in their mode of administration (e.g., inhaled versus oral), so there can be a wide variation in the dose delivered. Wide interpatient dose variability is also noted for pharmaceutical cannabinoids.[171,186]

Subjects in one trial experienced relief of pain with one inhalation of 9.4 per cent THC cannabis smoked three times per day. The single inhalation produced a serum level of 45 µg/L, a level slightly lower than the level associated with euphoria (50 µg/L to100 µg/L).[22]

Patients initiating cannabis therapy in an inhaled form (smoked or vaporized) should start with very small amounts of herbal cannabis. Patients often measure their "dose" in terms of puffs; a single inhalation therefore represents a meaningful and intuitive dose form. Since the products available to the patient vary in the amount of cannabinoid they contain (cannabis strains have different cannabinoid profiles), by starting with a single inhalation of a new strain the patient may slowly explore their response to the product. Starting with strains with lower THC levels is wise, because the lower percentage minimizes potential unwanted cognitive effects; also, higher doses of THC do not necessarily lead to better pain control.

Since medical documents need to specify 30-day quantities and authorization takes effect on the date of signing, patients may order several grams over a one-month period; they may choose to purchase only a few grams of a given strain for two weeks and then ask for a different strain. As long as they do not exceed the allowable 30-day limit, and they are able to work with the licensed producer, patients may explore different THC and CBD profiles.

The licensed producer may call the authorizing physician to confirm details of the authorization. Requesting notification from the licensed producer whenever changes are made to what the physician has authorized is recommended (see Recommendation 1).

There are many reports of patients having to use larger quantities of herbal cannabis when juicing (i.e., macerating cannabis in a blender with liquids) or when preparing oral products; however, there is simply not enough information to support these claims.

The following calculations are offered as preliminary pharmacokinetic considerations, based on several assumptions as outlined.

The amount of active cannabinoids delivered to the patient using herbal cannabis will depend on several factors, including the cannabinoid content of the source material and the mode of administration, as well as genetic and metabolic patient factors. Clearly the first two factors may be amenable to adjustment; the THC and CBD levels of the herbal material are standardized by the licensed producers, and physicians should suggest that patients begin with lower THC levels. The Access to Cannabis for Medical Purposes regulations refer only to dried herbal cannabis, and not any form of extract or oral edible product, so patients must also choose the mode of administration.[9] Here the physician faces difficult choices; the inhaled route may be by vaporization, about which limited information is available, or by smoking, which is clearly not ideal but remains the most common means of cannabis self-administration.

It is useful to contemplate some broad considerations of these cannabis inhalation techniques to guide these discussions and decisions:

- Based on World Health Organization estimates, an average "joint" contains 500 mg (0.5 g) of herbal cannabis. A typical tobacco cigarette, by comparison, weighs 1.0 g.[187]

- Studies of smoked cannabis for neuropathic pain conditions suggest effective doses ranging from one single inhalation from 25 mg of herbal cannabis containing 9.4 per cent THC three times daily using a pipe[22] to nine inhalations from a 900 mg joint of herbal cannabis containing 7 per cent THC.[18,19] This translates into current evidence for a daily inhaled dose of 100 mg to 700 mg of up to 9 per cent THC–content cannabis.
- It is worth noting that the incidence of adverse events increases with increasing THC levels.[22]

In one study of vaporized cannabis for neuropathic pain, the amount of herbal material placed in the vaporizer was 800 mg, and subjects took between eight and 12 inhalations from the vaporizer balloon over a two-hour period.[183] Once again, analgesic effects were noted at low THC levels and side effects increased with the THC level of administered cannabis.

Most studies of smoked or vaporized cannabis use a standardized inhalation procedure: inhale slowly over five seconds, hold breath for 10 seconds, then gently exhale.

Until further dose and delivery system information becomes available, these data may be crudely fashioned to provide patients with the following guidance and information for ideal safe dosing/use:

1. Although the safety of vaporized cannabis is being clarified, the patient may be advised to consider vaporized cannabis over smoked cannabis.
2. They should use inhaled cannabis in a well-ventilated, private, and calm environment.
3. The authorization for cannabis will be for the lowest effective level of THC available.
4. They should start any new cannabis product with a slow, single inhalation and then wait to appreciate the effects fully.
5. They should allow for several single inhalation trials of a product to observe the effects and then discuss their responses with their physician before either increasing the number of inhalations or changing their order with the producer.
6. As with all psychoactive drugs, patients must be informed of and alert to cannabis's potential mood-altering, euphoric, or sedative effects, which can occur and present risk even at very low doses.
7. They should keep notes on effects and experiences throughout the therapy to facilitate discussions with their authorizing physician and other health professionals.

Increasing dosage: Go slow

The Access to Cannabis for Medical Purposes regulations allow physicians to authorize as much as 5.0 g of cannabis per patient per day. However, it is expected that analgesic benefit will occur for most patients at considerably lower doses, and that the upper level to the safe use of cannabis will be on the order of 3.0 g per day.[5] Even this level of use should be considered only in very circumscribed conditions:

- This dosing level would apply to experienced users of cannabis only, never to cannabis-naive patients.

- It must be arrived at only through a careful process of assessing the patient's response as dosage is slowly increased, weighing analgesic benefit, improvement in function, and presence or absence of adverse effects.

Furthermore, physicians considering authorizing cannabis at doses higher than the current evidence supports (an inhaled dose of 100 mg to 700 mg of no more than 9 per cent THC cannabis daily) are strongly advised to:

- Discuss the decision to increase the dosage, either approaching or exceeding a 3.0 g/day level, with a trusted and experienced colleague.
- Document in the patient's record the reasons that support the increased dosage.

Although it is not required by the Access to Cannabis for Medical Purposes regulations, physicians should specify the percentage of THC on all medical documents authorizing cannabis, just as they would specify dosing when prescribing any other analgesic (level iii).

The THC concentrations used in most controlled trials on neuropathic pain (see Recommendation 1) ranged from 1 per cent to 9 per cent. Physicians should be aware that many commercial strains have THC concentrations as high as 15 per cent to 30 per cent; these concentrations may increase the risk of cognitive impairment, addiction, motor vehicle accidents, and psychosis.

Therefore, the physician should note on the medical document to "Supply cannabis containing 9 per cent THC or less. Send information on percentage THC composition directly to the physician's office. Notify the physician of any change in the THC concentration of the product given to the patient."

The medical cannabis authorization document also requires indication of a daily quantity of cannabis. As indicated above, at present, the medical literature supports a daily dose of dried cannabis leaves/buds of a maximum of 100 mg to 700 mg.

Note that federal legislation requires you to **specify the weight of dried cannabis product** on the authorization (medical) form rather than the dose of THC or CBD. While 2.5 g to 3.0 g a day is considered an appropriate upper limit of individual dosing, larger amounts might be required when using oils. To approximate, 1.0 g (or 1 mL or 1 cc) of cannabis oil could require approximately 3.0 g to 3.5 g of dried cannabis.

So, if your patient is taking approximately 0.3 mL of cannabis oil of a specific type from one licensed producer three times a day, you will need to authorize approximately 3.0 g a day. It is rare that patients need 5.0 g to 7.0 g a day unless they are using oils topically or order from different licensed producers.

Many bottles come with droppers that hold approximately 1 mL of oil. Along the side of the dropper there are usually marks showing increments of 0.1 mL. Use Table 3 to approximate the single-dose weight in milligrams (mg) to record in the patient's chart and, if required by your medical regulatory authority, in a medical document. Using milligrams clarifies the actual dose of CBD and/or THC your patient is taking.

Table 3. Dosing of cannabis oils: Using the percentage of THC or CBD and volume to determine the milligrams dosage (1 millilitre = 1 gram = 1,000 milligrams of oil)

Volume in mL or cc of Oil (mg of CBD or THC)	1% THC or CBD	5% THC or CBD	10% THC or CBD	15% THC or CBD	20% THC or CBD	25% THC or CBD
0.2 (200)	2 mg	10 mg	20 mg	30 mg	40 mg	50 mg
0.3 (300)	3 mg	15 mg	30 mg	45 mg	60 mg	75 mg
0.5 (500)	5 mg	25 mg	50 mg	75 mg	100 mg	125 mg
1 (1,000)	10 mg	50 mg	100 mg	150 mg	200 mg	250 mg
10 (10,000)	100 mg	500 mg	1,000 mg	1,500 mg	2,000 mg	2,500 mg
20 (20,000)	200 mg	1,000 mg	2,000 mg	3,000 mg	4,000 mg	5,000 mg
30 (30,000)	300 mg	1,500 mg	3,000 mg	4,500 mg	6,000 mg	7,500 mg
40 (40,000)	400 mg	2,000 mg	4,000 mg	6,000 mg	8,000 mg	10,000 mg
50 (50,000)	500 mg	2,500 mg	5,000 mg	7,500 mg	10,000 mg	12,500 mg
100 (100,000)	1,000 mg	5,000 mg	10,000 mg	15,000 mg	20,000 mg	25,000 mg

Conventionally, patients are advised to start at a very low volume of medicinal cannabis oil at night: 0.1 mL to 0.2 mL. Using cannabis at night helps the patient deal with some temporary effects such as somnolence and impaired balance, if they occur. Medicinal cannabis oil therapeutic effect is usually appreciated between 45 minutes and 90 minutes after its ingestion and lasts for up to six to eight hours.

The dose in milligrams should be titrated up slowly, based on the patient's goals and their tolerance to initial side effects, for example by adding 0.1 mL every two to three days until a therapeutic effect is reached. Titration and dose adjustment might take up to a few weeks.

For a non-experienced prescriber, starting with "pure CBD" or 1:1 (THC:CBD) oils will be easier. Depending on the balance of the therapeutic effect versus side effects (both may be more pronounced with THC), adjusting THC dose/proportion would be advisable. Generally, if patients have achieved no improvement in their symptoms after three months of stable dosing, the therapy should be revised.

Initial authorization should be given for a maximum of three months. When the dose is stable, the medical document can be signed authorizing a patient to use the same daily amount (in grams of dried material) for one year, unless your medical regulatory body dictates otherwise. All licensed producers accept the federal (Health Canada) medical documen[188] in addition to their own forms. However, be aware that some provincial regulatory bodies require additional details. For example, in Alberta you must also report the indications for treatment with medical cannabis, the dose of THC and CBD in milligrams, and the dosage form (oils/smoked/vaporized), and the form must be submitted directly to the

College of Physicians and Surgeons of Alberta in addition to the licensed producer.[189] It is important to be familiar with the requirements of your own regulatory body.

Conclusions

The CFPC developed this guidance document in response to a clearly expressed need from members for assistance in navigating an extraordinary practice situation. They have been caught between their desire and obligation to provide evidence-informed care for their patients and regulations that appear, to patients at least, to compel them to deal with cannabis as if it were a medicine.

We are confident in the practical expertise and judgment of those members who participated in the creation of this document; at the same time, we recognize that the clinical conditions it deals with and the lack of solid evidence for most of the recommendations make giving clear-cut advice difficult. We have tried, nonetheless, to provide guidance that is as definitive as possible because we recognize that family physicians often feel unprepared to engage in these essential conversations with their patients.

The CFPC will continue to support efforts by Health Canada and other bodies to generate additional research evidence on the place of cannabis in the treatment of chronic pain, anxiety, and the various other conditions for which its use has been suggested. We encourage CFPC members to contact us to add their input and share their experiences as we move forward safely and compassionately in this new and challenging area of therapeutics.

Appendix 1. Summary of Available Evidence

Cannabis is advocated as a treatment for a long list of conditions and ailments.[190] It is most commonly requested for treating pain, followed by for sleep and mental health issues such as anxiety and depression.[174] While there are commonly held beliefs that there is a substantial body of evidence for most indications, high-level evidence is sparse in many cases.[14,190]

Methods

We drew the majority of the evidence from the article "Systematic review of systematic reviews for medical cannabinoids" published in 2018 in *Canadian Family Physician*.[15] The literature search for that systematic review included publications up to April 2017. To update the evidence review we searched the terms cannabis or cannabinoid with chronic pain or anxiety from January 2017 to April 2019, with the results limited to systematic reviews. As the evidence for anxiety is much more limited, we also searched for RCTs over the same time frame.

We focused on RCTs and systematic reviews of RCTs because the standard to attain marketing authority and recommend therapeutics in Canada is evidence of benefit demonstrated in RCTs. This evidence is supplemented by the authors' files on this topic.

Results

Summary of search results

For chronic pain the new search identified 15 systematic reviews, of which nine were selected for inclusion in the evidence base. For anxiety the new search identified 15 studies, of which five were selected for inclusion in the evidence base. A further search of controlled trials of cannabinoids for anxiety identified nine studies, with zero being relevant for inclusion.

Most medical conditions

Evidence for seizures, pain, mental health (including sleep), nausea and vomiting due to chemotherapy, and spasticity are outlined below. For other conditions the evidence is sparse, poor, or both. For example, there is only one RCT related to glaucoma; it had six patients and did not find a benefit for intra-ocular pressure.[191] Four RCTs have examined the use of cannabinoids for appetite stimulation in HIV, with two finding no difference between cannabinoids and placebo, one finding a 2 kg greater improvement with cannabinoids over placebo, and one finding megestrol resulted in an 8.5 kg greater weight gain compared with cannabinoids.[15]

Seizures

A 2014 systematic review of cannabinoids for epilepsy included four RCTs of between nine and 15 patients.[192] In all cases, patients were given cannabidiol (from 100 mg to 300 mg per day). No benefit was seen, but the trials were underpowered.

Three large RCTs were published between 2017 and 2018, primarily looking at treatment-resistant, mostly pediatric patients. The studies demonstrated a 17 per cent to 23 per cent

reduction in seizures and reported the number needed to treat for a seizure reduction of at least 50 per cent with 10 mg/kg to 20 mg/kg of oral cannabidiol (see Table 4).[108,109,110]

Table 4. Epilepsy RCTs of cannabidiol oral solution versus placebo (14 weeks' duration)

Epilepsy Syndrome	Patients	Cannabidiol Dose	Median Seizure Reduction Compared With Placebo*	≥ 50% Seizure Reduction‡
Treatment-Resistant Dravet Syndrome[108]	120 (ages 2 to 18 years, median 9)	20 mg/kg	23% better	43% versus 27%
Treatment-Resistant Lennox-Gastaut Syndrome[109]	171 (ages 2 to 45 years, median 14)	20 mg/kg	17% better	44% versus 24%
Treatment-Resistant Lennox-Gastaut Syndrome[110]	225 (ages 2 to 48 years, mean 16)	10 mg/kg to 20 mg/kg	10 mg: 19% better 20 mg: 22% better	38% (20 mg) and 36% (10 mg) versus 19% (placebo)

‡ All results statistically significant (except Dravet syndrome ≥ 50 per cent seizure reduction, which was $P = 0.08$).

Adverse events were relatively consistent across studies and were pooled for the following (meta-analysis performed by author): somnolence in 25 per cent with cannabidiol versus 8 per cent with placebo (number needed to harm [NNH] = 6, $P = 0.001$); decreased appetite in 20 per cent with cannabidiol versus 5 per cent with placebo (NNH = 7, $P < 0.0001$); and diarrhea in 18 per cent versus 9 per cent with placebo (NNH = 12, $P = 0.001$). Elevation of liver enzymes occurs in approximately 16 per cent of cannabidiol users versus approximately 1 per cent of those assigned to placebo (Fisher test, $P < 0.001$). It is important to note that cannabidiol was not adverse event–free as had been hoped.

Bottom line
Cannabidiol can be helpful in treatment-resistant, primarily pediatric seizure disorders. Common adverse events include somnolence, decreased appetite, diarrhea, and elevated liver enzymes. This niche of therapy is more applicable to neurologists and pediatric neurologists and is far less applicable to comprehensive primary care clinicians.

Mental health

Anxiety

For anxiety, two comprehensive reviews[190,191] identified only one RCT mentioned in the simplified guideline.[14] This one RCT included 24 patients over one simulated speaking exercise and reported improvement in a mood visual analogue scale.[65] The five new systematic reviews that were identified added little. Two were systematic reviews of observational studies that found associations of general worsening of anxiety/depression in cannabis users,[193,194] but this adds little to the question of therapeutic utility. Another

systematic review[195] identified only the same anxiety trial already covered[65] and another systematic review that focused on PTSD,[196] which is covered below. The last systematic review included five studies,[79] which were presented descriptively (not as a meta-analysis). Three older studies were not considered because two from 1981 did not indicate if randomization occurred,[197,198] and one from 1982 involved patients with anxiety induced by THC and then treated with CBD.[199] The only other newly identified study was an RCT of 10 patients with social anxiety who were randomized to CBD or placebo and then received SPECT scans.[111] At 140 minutes after dosing, scores on the Visual Analogue Mood Scale (0 to 100) were significantly lower in the CBD group[200] compared with patients who received placebo.[162]

Depression

No RCTs have specifically examined depression.[14]

Insomnia

While sleep has been investigated as a secondary outcome in a number of pain studies (and one sleep apnea study), it has been the primary outcome in only one study of patients with insomnia.[190,191] The RCT recruited 32 fibromyalgia patients with self-reported insomnia, and 29 finished the two treatment intervals of two weeks each.[18] Each person received nabilone 0.5 mg at bedtime (increased to 1.0 mg at one week if needed) or amitriptyline 10 mg at bedtime (increased to 20 mg at one week if needed). There were no statistical differences on sleep scale or preference, with 41 per cent preferring nabilone versus 32 per cent preferring amitriptyline. The Insomnia Severity Index (scale 0 to 28, with higher scores worse) started around 18 (moderate insomnia) and improved about 5 points with amitriptyline and about three more with nabilone (a statistically significant difference). Adverse events related to treatment were more common with nabilone (91 total) versus amitriptyline (53 total), with dizziness, nausea, and drowsiness being common.[24]

Post-traumatic stress disorder

PTSD was a focus of a 2017 systematic review, but the authors identified only two observational studies that did not show benefit, and they did not find any RCTs.[196] A separate comprehensive systematic review[190] identified one RCT of 10 Canadian military patients randomized to nabilone or placebo for two seven-week treatment intervals.[201] In general, nabilone resulted in greater improvement on PTSD measurement scales and did not have more adverse events. The clinical relevance of the scale changes is somewhat unclear and the size of the trial was quite limited.

Bottom line

The evidence base for cannabinoids in primary care psychiatric issues is sparse. For example, for anxiety there are two RCTs with total of 35 patients with social anxiety who were followed for 2.5 hours or less. In general, the evidence base is too sparse to reliably guide the management of psychiatric conditions such as anxiety, depression, sleep, and PTSD.

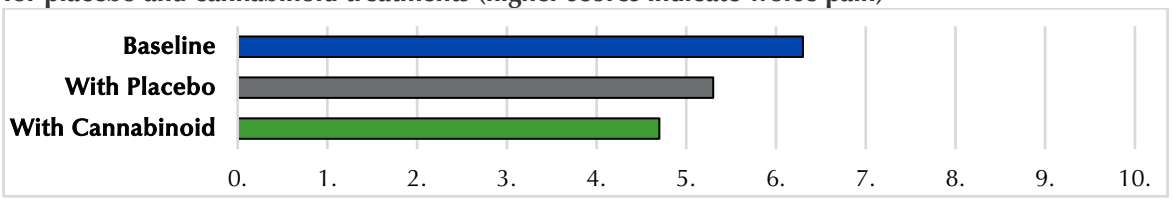
Pain

The 2018 systematic review provides the largest summary of usable data for cannabinoids in chronic pain, including mean differences in pain scales and those attaining a meaningful difference (at least a 30 per cent improvement) in pain.[15] The updated search identified nine new systematic reviews.[121,196,202,203,204,205,206,207,208] Four will not be considered further: One

was a systematic review of systematic reviews (reporting results already captured),[208] one[205] is a summary of a comprehensive review[190] that was included in the systematic review of systematic reviews that was published in *Canadian Family Physician*,[15] one duplicated[196] the pain results of another publication,[121] and another[202] presented only standard mean difference summaries, which are not clinically interpretable.

When describing the effect of cannabinoids on pain, first consider the effects on the traditional pain score of 0 to 10, with higher scores being worse. A study mentioned in the systematic review of systematic reviews in *Canadian Family Physician* noted that a baseline level of pain of 6.3 improved by 0.8 points with placebo versus 1.6 points with cannabinoids.[15] Another meta-analysis reported a baseline level around 6.5, and pain levels improved approximately 1 point with placebo versus 0.65 with cannabinoids.[204] Taking the results together, the expected effects are depicted in Figure 1.

Figure 1
Graphic portrayal of a typical baseline pain score in neuropathic pain studies and final pain scores for placebo and cannabinoid treatments (higher scores indicate worse pain)



Changes in pain scales can seem small, particularly when compared with effects related to placebo. It is also helpful to know what proportion of patients attain a clinically meaningful (at least 30 per cent) improvement in pain in both the placebo and the treatment groups, which is called the responder analysis.

Table 5 provides details of the proportion of patients attaining clinically meaningful improvement. The largest meta-analysis included 15 RCTs (mostly neuropathic) and 1,985 patients, with 30 per cent of patients given placebo attaining a meaningful improvement in pain compared with 39 per cent of patients given cannabinoids.[14] One meta-analysis did not find statistical significance, but it was also the smallest.[203] Otherwise, the other studies found similar results, although one found less benefit[207] and another found more.[121]

Table 5. Summary of 2017–18 systematic reviews reporting the percentage of patients with clinically meaningful (at least 30 per cent) improvement in pain

Study	Number of Trials	Number of Patients	Type of Pain	Percentage Attaining ≥ 30% Pain Reduction With Placebo	Percentage Attaining ≥ 30% Pain Reduction With Cannabinoid	Number Needed to Treat
Allan 2018a[14]	15	1,985	Chronic	30%	39%	11
Stockings 2018[207]	9	1,734	Non-cancer	26%	29%	24
Mucke 2018[206]	10	1,586	Neuropathic	33%	39%	11[§]
Amato 2017[203]	4	455	Neuropathic	19%	26%	NSS
Nugent 2017[121]	9	1,042	Neuropathic	31%	43%	9

[§] Different meta-analysis, calculating risk difference (absolute risk) slightly different.
NSS = not statistically significant

It is important to note that there is concern that the estimate of the benefit may be exaggerated, as sensitivity analyses reveal that larger and longer trials (with a generally lower risk of bias) found no statistically or clinically significant effect.[15] Additionally, there is evidence that the benefit with inhaled cannabis is not different from that of other cannabinoids—specifically nabiximols, which were the most commonly studied. Lastly, it must be stated that most of the evidence is for neuropathic pain. There is some evidence that patients with palliative cancer pain may benefit from cannabinoids. For other conditions, the evidence is limited or negative. For example, a 2017 RCT of 65 patients with chronic abdominal pain who were followed for seven weeks found the effect of THC to be no different from that of placebo.[209]

Bottom line
Cannabinoids improve chronic neuropathic pain for about 39 per cent of patients (compared with 30 per cent using placebo) and likely improve palliative cancer pain. The evidence for other chronic pain conditions is limited.

Nausea and vomiting in chemotherapy

Five systematic reviews were identified in the systematic review of systematic reviews.[15] By pooling RCTs in the varying systematic reviews, cannabinoids were found to be effective in controlling nausea and vomiting due to chemotherapy. Control of nausea and vomiting occurred in 47 per cent of cannabinoid users versus 13 per cent on placebo (NNT = 3), from a meta-analysis of seven RCTs with 500 patients. Compared with neuroleptics, control of nausea and vomiting occurred in 31 per cent of cannabinoid users versus 16 per cent of patients on placebo (NNT = 7) from a meta-analysis of 14 RCTs with 1,022 patients. Most studies lasted one day (after chemotherapy) and involved nabilone or dronabinol (with nabilone alone available in Canada). The RCTs were often quite old (e.g., four of seven in the placebo meta-analysis were more than 35 years old) and treatment regimens have changed considerably. Given these concerns, the recommendation is that cannabinoids (specifically nabilone) could be considered for nausea and vomiting due to chemotherapy that is refractory to standard therapies.[14]

There is a lack of evidence to support the use of cannabinoids in other types of nausea and vomiting. In particular, guidelines strongly recommend against their use in pregnancy.[14]

Bottom line
Cannabinoids (particularly nabilone) are effective and reasonable for refractory nausea and vomiting due to chemotherapy. They have not been adequately studied in other types of nausea and vomiting and use in pregnancy is strongly recommended against.

Spasticity

Three systematic reviews that addressed spasticity were identified in the systematic review of systematic reviews.[15] Similar to how pain was looked at, spasticity was considered on a scale from 0 to 10, with higher scores being worse. Spasticity scores started around 6.2 and improved by approximately 1 point with placebo versus improvements of approximately 1.3 to 1.8 with cannabinoids.[15] The proportion attaining a clinical meaningful (at least 30 per cent) improvement in spasticity was 25 per cent for those using placebo compared with 35 per cent using cannabinoids (NNT = 10, based on a meta-analysis of three RCTs of 652 patients). Most of the results are from multiple sclerosis patients (with a few spinal cord injury patients) using nabiximols.

Bottom line
Cannabinoids (specifically nabiximols) provide clinically meaningful improvement in spasticity for 35 per cent of multiple sclerosis and spinal cord patients compared with 25 per cent taking placebo.

Adverse events

Adverse events were pulled from the systematic review of systematic reviews,[15] focusing on statistically significant meta-analyses of included systematic reviews. The summary shown in Table 6 is from the "Simplified guideline for prescribing medical cannabinoids in primary care."[14] As they are pulled from meta-analyses of RCTs, some of the pooled event rates (for example, blurred vision and visual hallucination) represent symptoms that are potentially different in meaningful ways. That said, the adverse events are common and concerning (for example, dizziness NNH = 5). It should be noted that features of trial

design (such as the enrolment of regular users) have likely led to an underestimation of adverse event rates. Additionally, these adverse events come from RCTs and so are causally related to cannabinoid use. Adverse event frequency was not statistically different between the different types of cannabinoids. Rarer events, such as hyperemesis syndrome or schizophrenia, generally require large numbers and longer follow-up and so are typically identified through observational studies. These are not reported here.

Table 6. Estimated adverse event rates related to medical cannabinoids compared with placebo

Type of Adverse Event	Cannabinoid Event Rate	Placebo Event Rate	Number Needed to Harm
Overall	81%	62%	6
Withdrawal Due to Adverse Events	11%	~3%	14
Ataxia/Muscle Twitching	30%	11%	6
Blurred Vision/ Visual Hallucination	6%	0%	17
Central Nervous System	60%	27%	4
Disorientation/Confusion	9%	2%	15
Dissociation/ Acute Psychosis	5%	0%	20
Disturbance Attention/ Disconnected Thought	17%	2%	7
Dizziness	32%	11%	5
Dysphoria	13%	0.3%	8
Euphoria	15%	2%	9
“Feeling High”	35%	3%	4
Hypotension	25%	11%	8
Numbness	21%	4%	6
Psychiatric	17%	5%	9
Sedation	50%	30%	5
Speech Disorders	32%	7%	5

Bottom line

Compared with placebo, medical cannabinoids cause multiple different adverse events in patients, from visual disturbance or hypotension (for one additional patient in every three to 10 patients) to hallucination or paranoia (for perhaps one in 20 patients). Approximately 8 per cent more will quit due to adverse events than would with placebo. Adverse events are common with medical cannabinoids and likely underestimated.

Appendix 2. Medications Trialled to Treat Cannabis Use Disorder

Medications	Results
Gabapentin	Encouraging for use in withdrawal, reductions in use, craving, improvements in cognitive functioning, and in problems secondary to marijuana use
Mirtazapine	Helped with insomnia and food-related symptoms of withdrawal
N-acetylcysteine	Encouraging in reducing cannabis use
Nabilone	Beneficial in reducing cannabis withdrawal syndrome, cannabis use
Nabilone and zolpidem	Encouraging results in both cannabis use and withdrawal
Nabiximols	Encouraging for use in withdrawal
Naltrexone	Encouraging when used chronically to reduce cannabis use
Oxytocin	Encouraging in psychosocial treatment
Quetiapine	Helped with specific withdrawal symptoms, including sleep, food intake, and weight loss; concerns about increases in craving need to be considered
THC and lofexidine	Encouraging results in reducing cannabis use and withdrawal
Topiramate	Encouraging for reduced cannabis use in adolescents; not well tolerated; slower titration may help
Venlafaxine	May exacerbate cannabis use
Zolpidem	May help with withdrawal sleep-related issues only

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