

Prescribing smoked cannabis for chronic noncancer pain

Preliminary recommendations

Meldon Kahan MD MHS_c FRCPC FCFP Anita Srivastava MSc MD CCFP Sheryl Spithoff MD CCFP Lisa Bromley MD CCFP

Abstract

Objective To offer preliminary guidance on prescribing smoked cannabis for chronic pain before the release of formal guidelines.

Quality of evidence We reviewed the literature on the analgesic effectiveness of smoked cannabis and the harms of medical and recreational cannabis use. We developed recommendations on indications, contraindications, precautions, and dosing of smoked cannabis, and categorized the recommendations based on levels of evidence. Evidence is mostly level II (well conducted observational studies) and III (expert opinion).

Main message Smoked cannabis might be indicated for patients with severe neuropathic pain conditions who have not responded to adequate trials of pharmaceutical cannabinoids and standard analgesics (level II evidence). Smoked cannabis is contraindicated in patients who are 25 years of age or younger (level II evidence); who have a current, past, or strong family history of psychosis (level II evidence); who have a current or past cannabis use disorder (level III evidence); who have a current substance use disorder (level III evidence); who have cardiovascular or respiratory

disease (level III evidence); or who are pregnant or planning to become pregnant (level II evidence). It should be used with caution in patients who smoke tobacco (level II evidence), who are at increased risk of cardiovascular disease (level III evidence), who have anxiety or mood disorders (level II evidence), or who are taking higher doses of opioids or benzodiazepines (level III evidence). Cannabis users should be advised not to drive for at least 3 to 4 hours after smoking, for at least 6 hours after oral ingestion, and for at least 8 hours if they experience a subjective “high” (level II evidence). The maximum recommended dose is 1 inhalation 4 times per day (approximately 400 mg per day) of dried cannabis containing 9% delta-9-tetrahydrocannabinol (level III evidence). Physicians should avoid referring patients to “cannabinoid” clinics (level III evidence).

Conclusion Future guidelines should be based on systematic review of the literature on the safety and effectiveness of smoked cannabis. Further research is needed on the effectiveness and long-term safety of smoked cannabis compared with pharmaceutical cannabinoids, opioids, and other standard analgesics.

The new Health Canada regulations on medical marijuana permit physicians to prescribe dried cannabis to patients who can then purchase the cannabis directly from licensed distributors.¹ The prescription must specify the dose to be used per day and the amount to be dispensed per month (to a maximum of 150 g per 30 days, or 5 g per day). Unlike all other prescribed medications, Health Canada has not reviewed data on the safety or effectiveness of medical cannabis and has not approved cannabis for therapeutic use.

This review offers preliminary guidance on the indications, contraindications, and dosing of smoked cannabis in the

EDITOR'S KEY POINTS

- New Health Canada regulations on medical marijuana allow patients with physicians' prescriptions to purchase dried cannabis from licensed distributors. Unlike all other prescribed medications, Health Canada has not reviewed data on the safety or effectiveness of medical cannabis and has not approved cannabis for therapeutic use.
- The evidence supporting smoked cannabis is limited and weak. Pain is the most common reason for using medical cannabis. This review offers preliminary guidance on the indications, contraindications, and dosing of smoked cannabis in the treatment of chronic noncancer pain to assist physicians until formal guidelines are produced. Readers are encouraged to review the preliminary guidance document on dried cannabis recently released by the College of Family Physicians of Canada.



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treatment of chronic noncancer pain, pending the development of formal guidelines. Pain is the most common reason for using medical cannabis.²⁻⁶

Quality of evidence

We searched PubMed from 2007 to 2014 using the search term *medical marijuana*. We also used search terms combining *cannabis* or *marijuana* with its therapeutic or harmful effects, including the terms *pain*, *analgesia*, *cardiovascular*, *respiratory*, *anxiety*, *psychosis*, *substance use disorders*, and *motor vehicle accidents*. We reviewed the abstracts of 301 studies and reviews, selecting those articles we thought most relevant to prescribing in primary care (102 articles in total). Our review was not systematic, and we did not employ explicit inclusion or exclusion criteria. Recommendations were graded as level I (based on well conducted controlled trials or meta-analyses), level II (well conducted observational studies), or level III (expert opinion). When relevant, level III recommendations were based on opioid research, as summarized in the Canadian guideline on opioid prescribing.⁷ We relied on the Health Canada monograph on cannabis⁸ for information on pharmacokinetics and dosing.

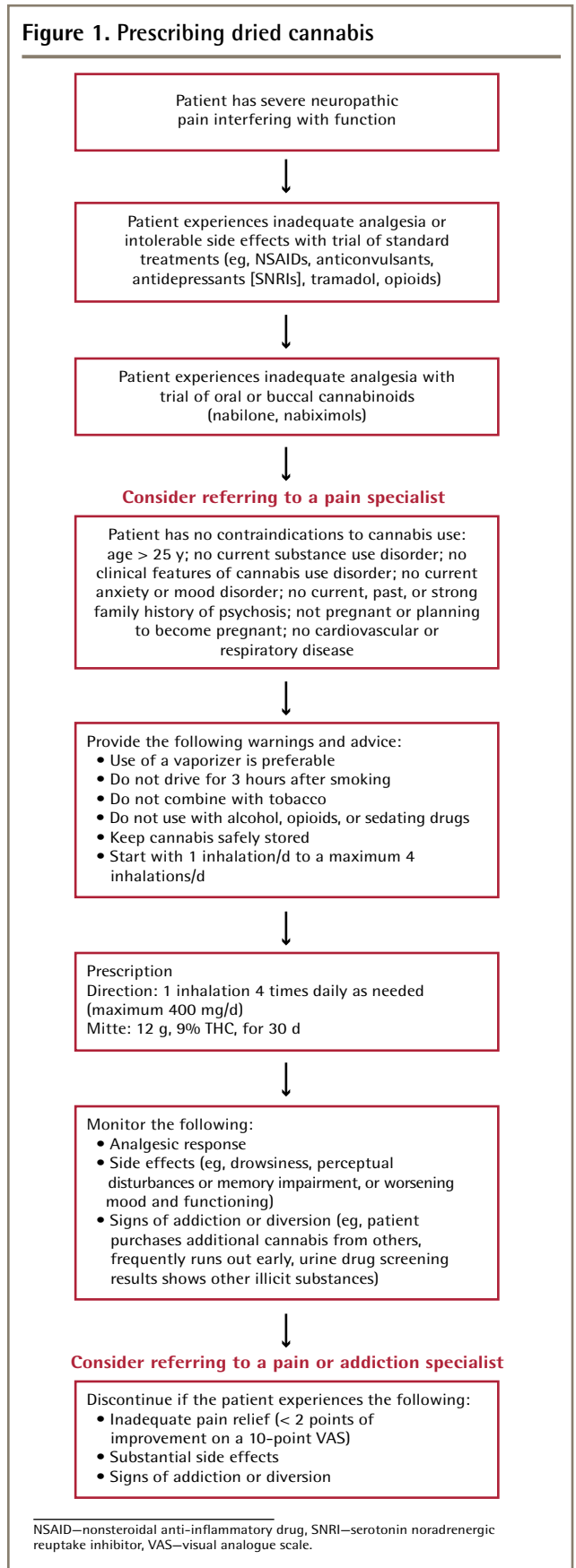
Main message

Figure 1 outlines recommendations for prescribing dried cannabis. Indications, contraindications, and other considerations are detailed below.

Smoked cannabis is indicated for severe neuropathic pain that has failed to respond to standard treatments (level II evidence). The evidence supporting smoked cannabis is limited and weak. To date, 5 controlled trials have examined smoked cannabis for the treatment of chronic pain.⁹⁻¹³ The trials found that smoked cannabis was superior to placebo for neuropathic pain from HIV, multiple sclerosis, and other causes. The trials had small sample sizes and only lasted between 1 and 15 days. Other important outcomes including functional status or quality of life were not measured because the trials were only a few days' duration. We could not find any clinical trial that compared smoked cannabis to standard analgesics. Therefore, we recommend that smoked cannabis be prescribed only for severe neuropathic pain syndromes that have not responded to adequate trials of pharmaceutical cannabinoids and other analgesics.

Smoked cannabis is not indicated for patients with pain conditions commonly seen in primary care (level III evidence). Most medical cannabis users have common pain conditions such as fibromyalgia or low back pain.¹⁴ We advise against prescribing smoked cannabis for these conditions because the safety and effectiveness of smoked cannabis have not been studied, and

Figure 1. Prescribing dried cannabis



because better and more evidence-based treatments are available.

Cannabinoids have important acute and chronic cognitive effects (level II evidence). Acutely, smoked cannabis can cause perceptual distortions, cognitive impairment, and euphoria.⁸ Chronic cannabis use is associated with persistent neuropsychological deficits, even after a period of abstinence.¹⁵ As long-term studies have been observational, causality cannot be definitively established. Nonetheless, these studies indicate that cannabis can have clinically important adverse effects; therefore, long-term prescribing should be undertaken with caution.

Smoked cannabis is contraindicated in some patient groups (levels II and III evidence). Smoked cannabis is contraindicated in patients younger than 25 years of age; those with a current, past, or strong family history of psychosis; those with a current or past cannabis use disorder (CUD); those with a current substance use disorder; those with cardiovascular or respiratory disease; or those who are pregnant or planning to become pregnant (**Box 1**).

Patients younger than 25 years of age (level II evidence): Youth who smoke cannabis are at greater risk than older adults of cannabis-related psychosocial harms, including crime, suicidal thoughts, illicit drug use, CUD, and long-term cognitive impairment.¹⁶⁻²¹

Cannabis use disorder (level III evidence): The prevalence of CUD among medical marijuana smokers is the same as that among regular recreational smokers.²² Patients with CUD should be counseled to discontinue their cannabis use and attend treatment, even if they claim that the cannabis is helping their pain. Research has demonstrated that pain patients who are addicted to prescription opioids experience marked improvements in pain, mood, and function when they discontinue

opioids and receive addiction treatment.²³ While research on CUD and pain is lacking, we would expect similarly positive outcomes in pain patients who are successfully treated for CUD.

Current substance use disorder (level II evidence): Cannabis should not be prescribed to patients with current problematic use of alcohol, opioids, or other drugs. There are potentially dangerous drug interactions between cannabis and high doses of opioids, alcohol, and other sedating drugs. Although causality has not been established, patients who use cannabis are more likely to misuse prescription opioids²⁴ and to have a higher severity of problematic alcohol and cocaine use.²⁵⁻²⁷ Finally, substance users are more likely to divert prescribed cannabis to support their drug use. In a study of adolescents attending an addiction treatment program in the United States, 47% reported using medical marijuana supplied to them by a registered marijuana patient.²⁸

Current, past, or strong family history of psychosis (level II evidence): Observational studies have demonstrated an association between cannabis use in adolescence and persistent psychosis. Cohort studies suggest that cannabis is a dose-related risk factor for the later development of psychosis.²⁹⁻³⁵

Cardiovascular disease (level III evidence): Cannabis smoking causes acute physiologic effects including elevations in blood pressure and heart rate, catecholamine release, elevations in carboxyhemoglobin levels, postural hypotension, and reversible cerebral vascular syndrome.^{36,37} There have been reports of young people suffering cardiac events shortly after smoking cannabis.³⁸⁻⁴⁰ We therefore recommend against prescribing cannabis to patients with known cardiovascular disease.

Respiratory disease (level II evidence): Although it is difficult to control for the confounding effects of tobacco smoke, evidence suggests that heavy cannabis smoking might be an independent risk factor for impaired respiratory function and chronic obstructive pulmonary disease.^{41,42}

Pregnant or planning to become pregnant (level II evidence): Preliminary evidence links cannabis use during pregnancy to subtle neurodevelopmental abnormalities in infants.⁴³

Cannabis should be prescribed with caution in certain patients (levels II and III evidence). Patients who have current, active mood or anxiety disorders, those who smoke tobacco, those with risk factors for cardiovascular disease, and those who use high doses of alcohol, opioids, or benzodiazepines should be prescribed smoked cannabis with caution (**Box 1**).

Current mood and anxiety disorders (level II evidence): Although a causal relationship has not been

Box 1. Smoked cannabis prescription: Contraindications and precautions.

Contraindications

- Current, past, or strong family history of psychosis
- Pregnant or planning to become pregnant
- Younger than 25 y of age
- Current or past cannabis use disorder
- Current substance use disorder
- Respiratory disease
- Cardiovascular disease

Precautions

- Current mood or anxiety disorder
- Tobacco smoking
- High risk of cardiovascular disease
- Taking higher doses of opioids or benzodiazepines

confirmed, there is a strong relationship between cannabis use and anxiety and mood disorders, as well as suicidal thoughts.^{16,44-54} Acute cannabis use can trigger anxiety and panic attacks, especially at high doses.^{55,56} Cannabis use might worsen psychiatric impairment in patients with anxiety disorders.^{52,57,58} Heavy cannabis smokers who report relief of anxiety with cannabis might be experiencing early symptoms of cannabis withdrawal when they abstain; withdrawal symptoms can be resolved through cannabis cessation.⁵⁹ If cannabis is prescribed to patients with underlying anxiety disorders, it should be prescribed at low doses and discontinued if it worsens anxiety or triggers panic attacks.

Tobacco smokers (level II evidence): Even after controlling for tobacco exposure, cannabis smoking has been associated with lung cancer⁶⁰ and chronic bronchitis.^{61,62} Patients who smoke tobacco should be strongly encouraged not to use cannabis or to use it via oral or vaporized routes.

Risk factors for cardiovascular disease (level III evidence): Physicians should prescribe cannabis with considerable caution in patients with risk factors for cardiovascular disease. Only a low dose should be prescribed, and the patient should be encouraged to use a vaporizer or to ingest it orally rather than smoking it.

Use of alcohol, opioids, or benzodiazepines in high doses (level III evidence): Cannabis use could worsen the cognitive impairment caused by high doses of alcohol, opioids, and benzodiazepines. Combining alcohol with cannabis increases the risk of motor vehicle accidents to a greater extent than if either drug is used alone.⁶³ If cannabis is prescribed, it should be prescribed at a low dose and should be discontinued if it affects patients' memory, mood, or function. Patients should be advised to use alcohol in moderation, and physicians should consider tapering high opioid or benzodiazepine doses.⁷

Cannabis users should be advised not to drive after use (levels II evidence). Cannabis use before driving is a risk factor for motor vehicle accidents. Those using cannabis should not drive for at least 3 to 4 hours after smoking, for at least 6 hours after oral ingestion, and for at least 8 hours if they experience a subjective "high" (level II evidence).⁶⁴⁻⁶⁸

Physicians should always prescribe an adequate trial of pharmaceutical cannabinoids before prescribing smoked cannabis (level II evidence). Oral or buccal cannabinoids have far greater evidence of efficacy than smoked cannabis does for the treatment of neuropathic pain,⁶⁹⁻⁷⁴ and there is no evidence that smoked cannabis is a more effective analgesic than pharmaceutical cannabinoids.⁷⁵ Pharmaceutical cannabinoids are also safer, with fewer cognitive effects. The inhalation route delivers a higher peak level more quickly than the oral route, and the total bioavailable dose of delta-9-tetrahydrocannabinol

(THC) is higher in a smoked cannabis cigarette than in oral or buccal cannabinoids. Experimental and clinical studies have confirmed that the acute cognitive effects of oral or buccal cannabinoids are milder and their effects on driving and memory are less strong than with smoked cannabis.^{8,73,75-80} A database review found that nabilone is associated with very low rates of misuse.⁸¹

Physicians should follow the regulations of their provincial college when prescribing dried cannabis (level III evidence). Physicians should review the complete policies of their provincial colleges of physicians and surgeons before prescribing cannabis (**Box 2**).

Physicians should advise cannabis smokers about harm-reduction strategies (level III evidence). Patients should be advised about ways to mitigate the potential harms of smoked cannabis (**Box 3**). Exposure to the toxic by-products of combustion can be avoided by vaporizing cannabis (heating the dried plant until the cannabis on the plant's surface vaporizes). This produces much lower concentrations of exhaled carbon monoxide (and probably other toxins) than smoking does.⁸² Physicians should advise patients not to use cannabis with alcohol or other sedating drugs, and not to put tobacco into marijuana joints. Patients should be warned not to give or sell their cannabis to others, as this is both dangerous and illegal. Patients with adolescent children at home should let the physician know how they intend to safely store the cannabis. Patients should be advised not to hold their breath after inhalation.

Box 2. Prescribing policies that have been recommended by at least 1 provincial college of physicians and surgeons

The following have been recommended by at least 1 provincial college:

- State the patient's medical condition on the prescription
- Register with the college as a marijuana prescriber
- Send the college a copy of the prescription
- Keep all prescriptions on a separate record for possible inspection by the college
- Only the physician who manages the patient's condition may prescribe cannabis for that condition
- Do not prescribe cannabis through telemedicine
- Have the patient sign a written treatment agreement
- Document that other treatments have been tried and that the patient is aware of the risks of dried cannabis
- Use a standardized tool to assess the patient's risk of addiction
- Have a procedure or protocol for identifying cannabis misuse
- Do not charge the patient fees

Box 3. Harm-reduction strategies

Patient warnings

- Do not drink or use sedating drugs while using cannabis
- Do not to drive for at least 3 h after smoking cannabis, 6 h after oral ingestion of cannabis, and 8 h if you experience a "high"

Avoiding medical harms

- Do not mix cannabis with tobacco
- Use a vaporizer or ingest the cannabis orally
- Stop cannabis if pregnant or planning to become pregnant

Avoiding drug diversion

- Do not give or sell your cannabis to others or buy it from anyone other than a licensed distributor
- Keep the cannabis in a safe, secret location, particularly if adolescents live at home

Before prescribing cannabis, physicians should conduct a pain assessment and assess the patient for substance use disorders and anxiety or mood disorders; after cannabis is prescribed, physicians should monitor the analgesic response to cannabis (level III evidence). The assessment outlined in the Canadian guideline for opioid prescribing is useful for cannabis prescribing as well.⁸³ The physician should ask the patient to rate his or her pain on a 10-point scale, and to describe the effect of the pain on daily activities. The physician should take a careful history of current and past mood and substance use (cannabis, tobacco, alcohol, opioids, benzodiazepines, and cocaine). A urine drug screening test is suggested; cannabis prescribing should be avoided in patients whose urine drug screening results are positive for cocaine or other illicit drugs. Several colleges recommend use of a standardized tool to identify problematic use. The CAGE-AID (CAGE Adapted to Include Drugs) might be the easiest (**Box 4**).⁸⁴ At each office visit, the physician should inquire about the effects of cannabis on pain and function. The physician should also ask about psychoactive effects of cannabis, compliance with the dosing recommendations, and use of any other substances.

Physicians should discontinue cannabis prescriptions if they are ineffective or cause harm (level III evidence). Smoked cannabis should be discontinued in the following circumstances.

- The patient experiences insufficient analgesia (less than 2 points improvement on a 10-point scale and no improvement in function). As with opioids, patients whose pain has rendered them unable to work or engage in productive activities should be considered to have experienced treatment failure if the cannabis use does not result in improved functioning, even if the patient reports subjective pain relief (level III evidence). Smoked cannabis can cause fatigue and

Box 4. The CAGE Adapted to Include Drugs: One or more positive responses indicate the need for further assessment. A urine drug screening test is also recommended.

Have you ever felt you ought to Cut down on your drinking or drug use?

Have people Annoyed you by criticizing your drinking or drug use?

Have you ever felt bad or Guilty about your drinking or drug use?

Have you ever had a drink or used drugs first thing in the morning (Eye-opener) to steady your nerves, get rid of a hangover, or get the day started?

Data from Brown and Rounds.⁸⁴

cognitive impairment, which might worsen function in patients who are already disabled by pain.

- The patient experiences side effects such as drowsiness, perceptual disturbances, memory impairment, or worsening mood and functioning.
- The patient shows clinical features of CUD (**Box 5**). Physicians should consider referring patients with a suspected CUD to an addiction medicine physician for assessment and management.

Dried cannabis should be prescribed to a patient only by the physician who manages that patient's pain. Physicians should avoid referring patients to "cannabinoid" clinics (level III evidence). Experience from the United States suggests that medical marijuana practices tend to prescribe to large volumes of patients. In Colorado, 49% of more than 36 000 medical recommendations for medical marijuana were written by only 15 physicians.⁸⁵ We believe that this could lead to potentially unsafe prescribing, given the risks of smoked cannabis and its uncertain evidence of effectiveness. Therefore, before referring a patient for an opinion on prescribing dried cannabis, the family physician should first ensure that the consultant is an expert in pain management who routinely conducts a complete assessment, who has an unbiased and comprehensive understanding of the evidence on the risks and benefits of smoked cannabis, and who does not charge patients fees and does not have any financial involvement with licensed cannabis distributors.

Several provincial colleges specify that only the physician who manages the patient's pain condition may prescribe dried cannabis for that patient. In effect, this restricts cannabis prescribing to the patient's primary care physician or, in patients with complex neuropathic pain conditions, the patient's neurologist or pain specialist. This is a sound policy because it reduces the risk of dangerous drug interactions (for example, the cannabinoid clinic prescribes high-dose, potent THC

Box 5. Clinical features of cannabis use disorder in patients with chronic pain

The following are indicative of cannabis use disorder:

- Patient insists on cannabis prescriptions despite having a pain condition that is amenable to treatments other than smoked cannabis
- Patient uses cannabis daily or almost daily, spending a considerable amount of nonproductive time on this activity
- Patient has poor school, work, and social functioning
- Patient is currently addicted to or misusing other substances (other than tobacco)
- Patient has risk factors for cannabis use disorder: is young, has a current mood or anxiety disorder, or has a past history of addiction or misuse
- Patient reports having difficulty stopping or reducing use
- Friends or family members have expressed concern

while the primary care physician prescribes high-dose opioids). Also, the primary care physician is much more likely than a high-volume specialized clinic to identify cannabis-related problems, such as CUD, anxiety, or cognitive impairment.

Physicians should prescribe no more than 400 mg per day of 9% THC, which is a dose that is effective for pain but which causes minimal cognitive impairment (level III evidence). This optimal dose should be effective for pain, while causing minimal euphoria or cognitive impairment. Subjects in a controlled trial¹³ experienced relief of pain with 1 inhalation 3 times per day of 9.4% smoked cannabis. The single inhalation produced a serum level of 45 µg/L, which is slightly lower than the level associated with euphoria (50 to 100 µg/L). The subjects in this trial did not experience serious cognitive effects such as confusion and disorientation, whereas these effects were observed in subjects using higher doses.⁸ Patients should be advised to hold their breath after inhalation for no more than a few seconds. If they notice that a dose causes cognitive impairment, they should take smaller or less frequent inhalations and hold their breath for shorter periods of time.

Treatment should be initiated with 1 inhalation per day. Smoked cannabis has a duration of action of about 2 to 4 hours.⁸ We suggest a dose of no more than 1 inhalation 4 times per day to avoid cannabis intoxication and cognitive impairment. Four inhalations per day for 30 days can be provided with a prescription of 400 mg per day (half of a joint per day), or 12 g per month. The prescription should specify “maximum 9% THC,” as the concentration of THC produced by distributors varies widely (less than 1% to 30%). Lower doses are suggested for heavy drinkers, those taking opioids or benzodiazepines, and patients with mood or anxiety disorders.

Oral ingestion of dried cannabis: Because THC has 2.5 times greater bioavailability through smoking than through oral ingestion,⁸ for patients who only ingest dried cannabis mixed in food, we recommend a dose of no more than 1 g per day.

Physicians should be prepared to manage patient disagreements over cannabis prescriptions (level III evidence). The indications, precautions, and contraindications outlined in this paper will exclude many current medical cannabis users. Medical cannabis users tend to be young with the same types of pain as the general pain population but with higher rates of substance use disorders and mental illness.⁸⁶⁻⁸⁸ Further, our suggested maximum dose (400 mg per day) is lower than the average dose smoked by medical cannabis users (1 to 3 g per day).⁸ The best strategy for managing disagreements with patients is to offer clear explanatory statements. These are outlined in more detail in **Box 6**.

Box 6. Messages to patients who disagree with your decision not to prescribe cannabis

The following messages might be useful for explaining your decision not to prescribe cannabis:

- Smoked cannabis has serious risks and minimal evidence of benefit
 - Neither Health Canada nor any national medical organization has endorsed smoked cannabis as a medicine, and physicians are bound to comply with the standards of our profession
 - As your physician, I suggest we work together to devise an individualized treatment plan for you. Safe and effective treatments are available for your condition
- If the patient is at high risk of cannabis-related harms (eg, young, concurrent anxiety, substance use disorder):
- As your physician, I cannot prescribe any medication that might harm you

If the patient claims that oral cannabinoids are ineffective:

- Explore the possibility that the patient is using smoked cannabis for its effects on mood

If the patient remains dissatisfied:

- I will not prescribe cannabis, but I will refer you to a comprehensive pain physician who might prescribe it if he or she feels it is appropriate

If cannabis use disorder is suspected:

- In my opinion, your use of cannabis could be causing you harm. We need to talk about ways to reduce or stop your cannabis use

If the patient says that your refusal forces him or her to purchase cannabis illegally:

- I would advise you not to buy cannabis or any other drug from the street. In my opinion, using street cannabis is not benefiting your health and could be causing you harm

Conclusion

Readers are encouraged to review the preliminary guidance document on dried cannabis recently released by the College of Family Physicians of Canada.⁸⁹ Future guidelines should be based on systematic review of the literature on the safety and effectiveness of smoked cannabis. The guideline's recommendations should be based on a consensus of clinicians and researchers who do not have important conflicts of interest. Further research is needed on the effectiveness and long-term safety of smoked cannabis compared with pharmaceutical cannabinoids, opioids, and other standard analgesics. Smoked cannabis should be prescribed only for patients with severe neuropathic pain conditions that have not responded to standard analgesics and synthetic cannabinoids. It should not be prescribed to those younger than 25 years of age; pregnant women; those with cannabis or other substance use disorders; those with current, past, or strong family history of psychosis; or patients with cardiovascular or respiratory disease. The maximum recommended dose is 400 mg per day or 12 g per month.

Dr Kahan is Associate Professor in the Department of Family and Community Medicine at the University of Toronto in Ontario and Medical Director of the Substance Use Service at Women's College Hospital. **Dr Srivastava** is Assistant Professor and Research Scholar in the Department of Family and Community Medicine at the University of Toronto and a staff physician with the St Joseph's Health Centre Family Health Team. **Dr Spithoff** is a staff physician with the Women's College Hospital Family Health Team. **Dr Bromley** is a staff physician at Sandy Hill Community Health Centre in Ottawa, Ont.

Contributors

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Competing interests

None declared.

Correspondence

Dr Meldon Kahan, Substance Use Service, Women's College Hospital, 76 Grenville St, Toronto, ON M5S 1B1; telephone 416 323-7559, extension 7; e-mail meldon.kahan@wchospital.ca

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