Can J Anesth/J Can Anesth (2016) 63:608–624
DOI 10.1007/s12630-016-0598-x

REVIEW ARTICLE/BRIEF REVIEW

# Medical cannabis: considerations for the anesthesiologist and pain physician

# Marijuana à des fins médicales: réflexions pour l'anesthésiologiste et le médecin spécialiste de la douleur

**Pierre Beaulieu, MD, PhD · Aline Boulanger, MD · Julie Desroches, PhD · Alexander J. Clark, MD**

Received: 27 October 2015 / Revised: 21 December 2015 / Accepted: 25 January 2016 / Published online: 5 February 2016


**Abstract**

**Purpose** *New regulations are in place at the federal and provincial levels in Canada regarding the way medical cannabis is to be controlled. We present them together with guidance for the safe use of medical cannabis and recent clinical trials on cannabis and pain.*

**Source** *The new Canadian regulations on the use of medical cannabis, the provincial regulations, and the various cannabis products available from the Canadian Licensed Producers were reviewed from Health Canada, provincial licensing authorities, and the licensed producers website, respectively. Recent clinical trials on cannabis and pain were reviewed from the existing literature.*

**Principal findings** *Health Canada has approved a new regulation on medical marijuana/cannabis, the Marihuana for Medical Purposes Regulations: The production of medical cannabis by individuals is illegal. Health Canada, however, has licensed authorized producers across the country, limiting the production to specific licenses of certain cannabis products. There are currently 26 authorized licensed producers from seven Canadian provinces offering more than 200 strains of marijuana. We provide guidance for the safe use of medical cannabis. The recent literature indicates that currently available cannabinoids are modestly effective analgesics that provide a safe, reasonable therapeutic option for managing chronic non-cancer-related pain.*

**Conclusion** *The science of medical cannabis and the need for education of healthcare professionals and patients require continued effort. Although cannabinoids work to decrease pain, there is still a need to confirm these beneficial effects clinically and to exploit them with acceptable benefit-to-risk ratios.*

**Résumé**

**Objectif** *De nouvelles réglementations sont misent en place au Canada, à la fois au niveau fédéral et provincial, concernant le contrôle de la marijuana à des fins médicales. Nous les présentons conjointement avec un guide pour une utilisation sécuritaire de la marijuana à des fins médicales et des essais cliniques récents avec la marijuana dans le traitement de la douleur.*

**Source** *Les nouvelles réglementations canadienne sur l'utilisation de la marijuana à des fins médicales, les réglementations provinciales et les différents produits du cannabis proposés par les producteurs canadiens autorisés ont été analysées à partir, respectivement, de Santé Canada, des services chargés d'accorder les licences et des sites Web des producteurs autorisés. Les essais cliniques récents sur le cannabis et le traitement de la douleur ont été recherchés dans la littérature actuelle disponible.*

**Constatations principales** *Santé Canada a approuvé une nouvelle réglementation sur l'utilisation de la*

P. Beaulieu, MD, PhD · A. Boulanger, MD
Department of Anesthesiology, Faculty of Medicine, Université de Montréal, Montréal, QC, Canada

P. Beaulieu, MD, PhD (✉) · J. Desroches, PhD
Department of Anesthesiology, CHUM, 3840 rue St Urbain, Montreal, QC H2W 1T8, Canada
e-mail: pierre.beaulieu@umontreal.ca

A. Boulanger, MD
Pain Clinic, CHUM, Montréal, QC, Canada

A. J. Clark, MD
Department of Anesthesia, Pain Management and Perioperative Medicine, Dalhousie University and Central Zone, Nova Scotia Health Authority - QEII HSC, Halifax, NS, Canada

*marijuana/cannabis, le règlement sur la marijuana à des fins médicales (RMFM) : La production de marijuana à des fins médicales par des individus est illégale. Toutefois, Santé Canada a délivré des licences à des producteurs autorisés sur l'ensemble du pays en limitant l'autorisation à certains produits spécifiques du cannabis. Il y a actuellement 26 fabricants autorisés détenteurs de licences dans sept provinces canadiennes offrant plus de 200 souches de marijuana. Nous fournissons un guide pour l'utilisation sécuritaire de la marijuana à des fins médicales. Les études récentes indiquent que les cannabinoïdes actuellement disponibles sont des analgésiques d'efficacité modeste qui procurent une option thérapeutique raisonnable et sécuritaire pour la gestion de la douleur chronique non liée au cancer.*

**Conclusion** *La recherche scientifique sur l'utilisation de la marijuana à des fins médicales et le besoin d'éducation des professionnels de la santé et des patients demandent des efforts continus. Même si les cannabinoïdes diminuent la douleur, il reste nécessaire de confirmer cliniquement ces effets bénéfiques et de les exploiter avec des rapports bénéfices-risques acceptables.*

## Introduction: medical cannabis and pain

The cannabis plant, also known as hemp or marijuana, is one of the oldest documented medicines in history. Various strains of cannabis exist, but there is no consensus on whether *Sativa*, *Indica*, *and Ruderalis* are three separate species or subspecies of *Cannabis sativa*. Cannabis contains 545 chemical compounds, 104 of which are cannabinoids, the rest being flavonoids, terpenes, fatty acids, among others - all with potential medical uses.[1] The best-characterized constituent is $\Delta^9$-tetrahydrocannabinol (THC), the principal psychoactive component of cannabis. Other important constituents include cannabidiol (CBD) and cannabinol. The former lacks psychoactive capa bilities, whereas the latter is a mildly psychoactive chemical.[1,2] Cannabinoids produce their effects through the activation of two distinct G-protein-coupled receptors termed cannabinoid $CB_1$ and $CB_2$. The $CB_1$ receptor is expressed at high levels in the central nervous system (CNS) and along pain pathways. In contrast, the $CB_2$ receptor is found predominantly, although not exclusively, outside the CNS, where it is most densely expressed in peripheral tissues with immune functions. The isolation of endogenous ligands (endocannabinoids, mainly anan damide and 2-arachidonoylglycerol) suggests that cannabinoids may play an important role in mediating a variety of neurophysiological processes including nociception.

These major pharmacological discoveries of the 1990s sparked interest in the possible medical uses for cannabinoids as potential analgesics. To date, 26 randomized clinical trials (and also some follow-up studies) are looking at the efficacy of various cannabinoids for treating various chronic pain conditions.[3-5] In this paper, we present the new Canadian regulations on medical cannabis and the current provincial licensing authorities regulations in Canada, identify marijuana available on the Canadian market (companies, plants and drugs, mode of deliveries), give an update on clinical studies published during the last five years on cannabis and pain, and finally provide guidance on the use of medical cannabis in 2016 in Canada.

## New Canadian regulation on medical cannabis

In 2001, the Canadian government enacted regulations for access to dried marijuana for medical purposes through the Marihuana Medical Access Regulations (MMAR).[6] It came about after a decision by the Ontario Court of Appeal that allowed Terrance Parker, an epileptic patient, to use marijuana to treat his severe epilepsy.[7] Under MMAR, patients were allowed to submit applications to Health Canada to obtain authorization to possess marijuana. These applications required validation by one or two physicians that the patient was suffering from medical conditions for which medical marijuana use was approved. Authorized patients were able to purchase marijuana from Health Canada, grow their own marijuana, or obtain marijuana from a designated grower.[8] Health Canada, through a contracted grower, provided the strain *Cannabis sativa*, containing approximately 12% THC with no CBD content.

Concerns about this program were expressed during the following years. Patients disliked the application process and that only one strain of marijuana was available for purchase from Health Canada.[9] Other expressed concerns about hazards (humidity, mold, poor air quality), safety (fire hazards due to faulty or overloaded electricity installations), and security (an illicit market, risk of home invasion by criminals) related to the production of marijuana by individuals. Furthermore, rapid growth in the number of authorized users had a significant impact on the administration of the program, leading to long application processing times and high costs. Finally, Canadian courts found parts of the MMAR to be invalid.[9]

To address these concerns, in 2013 the Canadian Government enacted the Marihuana for Medical Purposes Regulations (MMPR).[10] Under the MMPR, Health Canada no longer issues authorizations to possess marijuana for medical purposes to patients. It does, however, licence qualified applicants to produce and distribute marijuana.

Licensed producers are required to establish strict regulatory measures relating to good production practices, quality assurance, testing, standardization, security, and distribution. To monitor the use of marijuana, Health Canada requires licensed producers to provide reports to provincial licensing authorities. These reports contain information on the patient, the prescribing heath professional, and the quantity of marijuana authorized.[8]

Under the MMPR, healthcare practitioners (physicians and nurses) must sign a medical document indicating the daily dose of marijuana and the length of time for which this document is valid.[10] Patients should not be asked to pay for this medical document as it is considered similar to a prescription. After obtaining the document, patients can register with the licensed producer of their choice. The licensed producer then must verify with the healthcare professional that the document is legitimate and accurate. The regulations state that patients may not possess more than one month's amount of marijuana, or a maximum of 150 g, at one time.[8] The licensed producer couriers the marijuana to the patient. Since June 2015,[11] producers have been allowed to supply marijuana for medical purposes in three forms: fresh, dried, oil (see section 4).

The MMAR and MMPR operated in parallel for a transition period from June 2013 until the end of March 2014. Thus, the MMPR replaced the MMAR as of 1 April 2014 and is in operation today.[12] Following this transition period, individuals were not supposed to produce their own marijuana. This part of the regulation, however, was suspended by a British Columbia Court of Appeal to allow patients who were unable to afford marijuana from a licensed producer to continue to grow their own.[8] Until another decision is rendered, patients who had valid authorization to possess marijuana as of 31 March 2014, as well as authorization for personal-use production or designated-person production, have had their authorizations extended.[8]

## Provincial licensing authorities guidelines and policies

Based on the absence of scientific evidence, provincial and territorial licensing authorities recommend caution when prescribing a substance without knowing its risk and benefit. Specific provincial regulations are listed in Table 1.[13-24]

## Marijuana available on Canadian market (companies, plants, mode of delivery)

Under the current MMPR, production of medical marijuana by individuals is illegal. Health Canada has licensed authorized producers across the country, limiting the production to specific license types, such as "Cultivation Only," "Sale Only," or "Cultivation and Sale" of the various marijuana products, including dried marijuana plant material, fresh marijuana, and cannabis oil. There are 26 authorized licensed producers (as of October 23, 2015) located in seven provinces in Canada who hold a valid license from Health Canada and are supplying dried medical marijuana to the Canadian population[25] (Table 2). These licensed producers offer more than 200 strains of dried marijuana (with additional strains coming soon), including various strains of cannabis such as *Cannabis sativa*, *Cannabis indica*, or hybrid forms. In addition, they offer dried marijuana with diverse THC/CBD content ratios and mixed strains. Thus, the government's decision to transfer marijuana production to licensed producers has increased the diversity of products available for patients because the current MMPR does not limit the marijuana strains that can be cultivated or their THC/CBD content ratio.

With such a diversity of products, patients may be challenged when choosing the best product for their particular medical condition. Although some authorized producers offer a customer service line to help patients select the appropriate strain based on the THC/CBD content ratio, patients may prefer to select a local authorized producer or strains they can afford (licensed producers have the liberty to set their own price). The price for the dried marijuana plant material is currently in the range of $5 to $15 per gram.

There is little information to guide physicians and patients as to the appropriate product and/or THC/CBD ratio to use for a specific medical condition. Most patients therefore select their strain based on their symptoms and disease and the benefits they want to experience as well as the time of the day they are using the marijuana. For example, some strains of marijuana present a very high CBD but low THC content ratio, which is associated with little or no psychoactive effects. These products may be suitable for symptom relief in patients who prefer to avoid the psychoactive effect to maintain their daily routine.

Currently, Health Canada has not provided any precise dose or established a uniform dosing schedule for medical cannabis because it is not an approved therapeutic drug in Canada. However, to help physicians and nurse practitioners (authorized by provincial licensing authorities) to prescribe medical cannabis, they provide a *Daily Amount Fact Sheet (Dosage)* document to assist the practitioner determine a safe, effective dose.[26] This document clearly states that "dosing remains highly individualized and relies to a great extent on titration (i.e., finding the right dose where potential therapeutic effects are maximized while adverse effects are

minimized)." It is also noted that "various surveys published in peer-reviewed scientific literature suggest that the majority of people using smoked or orally ingested medical cannabis reported using approximately 1-3 g of dried marijuana per day." Dried marijuana can be inhaled through smoking, vaporizing, or oral administration. Smoking cannabis results in a more rapid onset of action, higher blood levels of cannabinoids, and a shorter duration of pharmacodynamic effects compared to oral administration. Vaporization presents several advantages, such as formation of a smaller quantity of toxic by-products and more efficient extraction of THC from the dried material.[27,28]

In addition to dried marijuana, Health Canada has authorized some of the licensed producers to produce fresh marijuana buds and leaves and/or cannabis oil with the intention of permitting their sale in the future. Furthermore, patients who already have a prescription to purchase dried medical marijuana will be permitted to buy fresh marijuana or cannabis oil without an additional prescription. These new forms of cannabis, which will be available for purchase in a few months, will allow patients who do not want to, or are not able to, inhale or vaporize the dried herb to relieve their symptoms using these alternative products.

Currently, with more than 200 strains of dried marijuana available, and fresh marijuana and cannabis oil products becoming available soon, Canadian patients will be, more than ever, able to find a good fit from the diversity of products offered. In turn, their symptoms will be managed and the burden of their disease eased.

## Update on clinical studies on cannabis and pain

Recent advances in cannabinoid pharmacology have resulted in increasing attention to the therapeutic potential of cannabinoids. A number of preparations have been or are being developed and investigated in randomized clinical trials. The difficulties encountered when conducting a clinical trial on pain include the fact that pain is a subjective experience. Patients with pain comprise a heterogeneous group with different syndromes and a variety of physical, psychological, and social problems.[29]

It would be outside the scope of this article to review all the trials published on medical cannabis and pain, but some excellent recent reviews have been published.[2-5] We now summarize these recent reports to consolidate our current understanding of the effects of cannabinoids in pain management. To do so, we update two published reviews of acute[2] and chronic[3] pain trials and comment on cancer-related pain.

### Acute pain

A variety of compounds were used in these acute pain studies, including marijuana, cannabis extracts, THC, nabilone, dronabinol, and levonantradol. These cannabinoids are not very effective in alleviating acute pain. This conclusion is based on studies conducted in the postoperative setting (five studies) and in human volunteers (13 studies) between 1977 and 2008.[2] In addition, in some cases, administration of cannabinoids, especially in high doses, is associated with increased pain.[30-33] However, small numbers of patients have been studied, and the doses used may not have been adequate in postoperative patients. No new study on this particular subject has been published since 2008. However, a prospective, randomized study published in 2013[34] was carried out in 73 patients undergoing elective operations. The authors focussed on postoperative analgesia in Jamaican cannabis users ($n = 42$) compared to non-users ($n = 31$). They showed that cannabis users required significantly more opioid rescue analgesia and had higher pain scores during the immediate postoperative period than non-users. Also, female cannabis users required significantly more analgesia than male users.

The combination of THC and CBD administered in an oromucosal spray (nabiximols) in postoperative patients who cannot take oral medications after abdominal or major surgery has never been tested. Hence, it is unknown whether it has therapeutic potential. A large multicenter study of patients undergoing surgery with a reproducible painful condition and using THC/CBD spray is needed before any conclusion can be drawn regarding the effect of cannabinoids in postoperative pain management.[2]

### Chronic non-cancer-related pain

Cannabinoids are, on the whole, effective for treating chronic pain conditions.[3-5] Up to 2010, a total of 18 trials were reported in a systematic review by Lynch and Campbell.[3] Their review showed a modest analgesic effect in patients with chronic non-cancer-related pain. Overall, 13 of the trials focussed on neuropathic pain and the other five trials on other types of pain. Several trials reported significant improvements in sleep, and there were no serious adverse events reported.[3]

Since 2010, eight new studies have been published[35-42] (Table 3). Seven of them were performed on patients with neuropathic pain and one on patients with chronic headache. Only one clinical study showed negative results.[35] It was on patients with painful diabetic neuropathy treated with nabiximols for ten weeks. Depression, however, was identified as a major

**Table 1** Provincial licensing authorities' regulations on medical cannabis

| Province | Requirements of the physician |
|---|---|
| British Columbia[13] | Document that conventional therapies have not successfully helped the patient |
| | Assess the patient for addiction and/or risk of addiction using a validated addiction risk tool and retain a copy in the patient record |
| | Discuss and document that patient was informed of the risks |
| | Review the patient's PharmaNet information prior to issuing an authorization for marijuana for medical purposes and in any reassessment of the patient |
| | Retain a copy of the document provided for the authorization of marijuana for medical purposes in the patient's medical record |
| | Include processes to identify any misuse/abuse/diversion by the patient in any reassessment of patients receiving marijuana for medical purposes |
| | Do not sell or dispense marijuana for medical purposes |
| | Do not complete a document for the authorization of marijuana for medical purposes for a patient unless a) have a longitudinal treating relationship with the patient or b) are in direct communication with another physician or nurse practitioner who has a longitudinal treating relationship with the patient and both are in well-documented agreement with the issuance of a document for the authorization of marijuana for medical purposes |
| | Have patient sign a written consent form |
| | Reassess patient at least once every three to six months |
| Alberta[14] | Register with the College as a authorizer of marijuana for medical purposes |
| | Attempt and find conventional therapies ineffective in treating the patient's medical condition |
| | Assess the patient risk of addiction using standard addiction risk tool |
| | Receive informed consent |
| | Review available prescription databases to obtain the patient medication profile |
| | Comply with provincial and federal regulations |
| | Complete a patient's medical document |
| | Evaluate the patient on a regular basis to determine the benefits and risks and every three months following stabilization |
| | Identify misuse and abuse |
| | Provide ongoing care to the patient for the underlying medical condition |
| | Provide the College a copy of the medical document (within 1 week) |
| | Must not apply to become a licensed producer |
| | Must not store, provide, or dispense marijuana |
| Saskatchewan[15] | Have to be the treating physician for the condition for which the patient is authorized to use marihuana |
| | Review the patient's medical history, review relevant records, and conduct an appropriate physical examination |
| | Have the patient sign a written agreement |
| | Record in the file of the patient: the treatment agreement, the diagnosis, the list of other treatments attempted and the effect of such treatments, a statement that the patient has been advised about the risks and the possible benefits from the use of marihuana |
| | Keep a separate record containing the names, quantities, medical conditions, and licensed producer (if known). Provide the College with this information every 12 months if fewer than 20 patients, or every 6 months if the physician has 20 or more patients on medical marijuana |
| | Do not store or dispense marijuana |
| | Do not have any financial or management interest in a licensed producer |

**Table 1** continued

| Province | Requirements of the physician |
|---|---|
| Manitoba[16] | Make a diagnosis and discuss all potential treatment options with the patient |
| | Try conventional therapies prior to authorizing the use of medical marijuana |
| | Discuss with the patient all potential risks and benefits and the lack of clear scientific evidence |
| | Document the discussions with the patient and the medical reasons for which the marijuana is authorized |
| | Be the treating physician for the condition for which the patient is authorized to use marijuana |
| | The patient examination may not occur at premises of a licensed producer or a location provided by or subsidized by a licensed producer |
| | Must not dispense or provide marijuana |
| | May not be legally or beneficially involved in any way with a licensed producer and may not apply to become a licensed producer |
| | Keep a separate log available for inspection by the College at any time that includes: patient's name, medical condition, quantity and dosages of marijuana authorized |
| | Have a process to report any misuse or abuse of medical marijuana by the patient |
| Ontario[17] | Have to consider if marijuana is the most appropriate treatment for the patient and the risks |
| | Must not prescribe marijuana to patients under the age of 25 unless all other conventional therapeutic options have failed |
| | Advise patient about effects, interactions, side effects, contraindications, precautions; obtain informed consent |
| | Initiate treatment with a low quantity of marijuana and strains that are low in THC; if the initial prescription proves ineffective, increase the quantity or prescribe higher strains of THC |
| | Require patients to sign a written treatment agreement |
| Quebec[18] | Prescribe marijuana for medical condition identified in the document information for Health Care Professionals available on Health Canada's Web site and only within a research framework |
| | Before prescribing marijuana, consider other therapeutic options, including other forms of cannabinoids |
| | Read literature, inform patient that marijuana is not a recognized treatment, ask the patient to read the patient information document and inform the patient about any research projects underway |
| | Collaborate in a research project and obtain the research participant's consent |
| | Specify the type of product and the quantity and frequency of the use on the prescription |
| | Assess the patient at least every three months |
| | Keep a register of all patients and, on request, make it available to an officer of the College |
| | May not supply the patient |
| | May not become or apply to become a cannabis producer |
| | Must collaborate with the College and its partners in the collection of scientific data to improve knowledge and practices |
| New Brunswick[19] | The patient's primary physician may write the prescription, but if hesitant to prescribe, the physician may assist the patient in having marijuana prescribed by another New Brunswick physician |
| | Prescribe the daily amount of marijuana |
| | Warn patient regarding cautions and risks, about obtaining marijuana from another source, and about redirecting the drug to another individual as well as maintaining their supply of marijuana in a secure place |
| | Warn the patient about what circumstances would result in a discontinuation of marijuana |
| | Obtain informed consent |
| | Must not have any personal gain from providing a non-medical service |
| Nova Scotia[20] | Must not bill patients directly for services related to the authorization of marijuana for medical purposes, which includes completion of any required forms |
| | Authorize the use of marijuana in the context of a bona fide patient-doctor relationship |
| | Authorize the use of marijuana for medical purposes when in direct, in-person contact with their patients |

**Table 1** continued

| Province | Requirements of the physician |
|---|---|
| Prince Edward Island[21] | Be familiar with the relevant Acts and Regulations, be aware of any changes of prescribing information (medical and legal), and be aware of the CMPA and CMA's positions on this matter |
| | Be engaged in a physician-patient relationship and prescribe only for those potential indications listed on Health Canada's website |
| | Prescribe to residents of PEI and never via telehealth technology |
| | Document in patient medical records: that all the conventional therapies and other therapeutic options have been attempted; that the patient has been informed that marijuana has not been scientifically verified; the discussion with regard to report to the registrar if impairment with respect to driving; the discussion with regard to risks/benefits; the quantity of marijuana and length of prescription; details of any reassessment done on renewing a prescription, including the process to identify any misuse/abuse/diversion |
| | Complete a written consent form and informed the patients that their name and other relevant details will be provided to the College and any irregularities will be reported |
| | Shall not accept delivery of marijuana on a patient's behalf or dispense to the patient |
| Newfoundland and Labrador[22] | Be familiar with the MMPR and the materials identified in the reference section in the guideline |
| | Educate himself or herself about the risks, benefits, potential complications, and drug interactions associated with the use of marijuana |
| | Document in the patient record the conventional therapies used and whether these therapies have been effective |
| | Assess the patient for risk of addiction using a standardized addiction tool and retain a copy in the patient record |
| | Establish an individualized written protocol for the periodic reassessment of a patient, including a process to identify any misuse/abuse/diversion and keep the information in the patient record |
| | Discuss risks, benefits, potential complications, and drug interactions with the patient |
| | Adhere strictly to the requirements of MMPR with respect to the issuance of a "medical document" for access to marijuana and keep a copy in the patient record |
| | Must be the treating physician for the condition for which the patient is authorized to use marijuana |
| | Should not charge any fee to, or accept any compensation from, a licensed producer for providing prescription |
| | Should not operate, be a partner in, or benefit financially from operation of a licensed production facility |
| Yukon[23] | Must register with the Yukon Medical Council as an authorizer of marijuana for medical purposes |
| | Attempt to find conventional therapies effective in treating the patient's medical condition of symptom(s) |
| | Assess the patient's risk of addiction using a standard addiction risk tool |
| | Receive informed consent in accordance with standard informed consent |
| | Review available prescription databases to obtain a patient medication profile |
| | Comply with federal regulation |
| | Complete the patient medical document including the daily quantity of dried marijuana to be used by the patients (in grams) and the period of use specified as the number of weeks or months |
| | Evaluate the patient on a regular basis (minimum every three months following stabilization) to determine the benefits and risks (including misuse or abuse) of marijuana |
| | If requested, provide to the Council a copy of the patient's medical document |
| | Must not dispense or provide marijuana directly to any patient |
| | Must not apply to become a licensed producer of marijuana |
| Northwest Territories and Nunavut[24] | Watch for new information or policies that may be provided by their medical regulatory bodies |
| | Contact their College directly to enquire about specific practices that must be followed when issuing a medical document. |

CMA = Canadian Medical Association; CMPA = Canadian Medical Protective Association; MMPR = Marihuana for Medical Purposes Regulations; THC = tetrahydrocannabinol

confounder of the study's outcomes. Patients with depression had higher baseline pain scores and were also more likely to respond favorably to intervention, regardless of whether it was nabiximols or placebo administration. Another study looked at cannabinoid-opioid interaction in 21 patients with mixed chronic pain admitted for a five-day inpatient stay.[43] Participants were asked to inhale vaporized cannabis three times a day. The vaporized cannabis augmented the analgesic effects of opioids without significantly altering plasma opioid levels. This combination may allow opioid treatment at lower doses with fewer side effects.

In conclusion, 26 clinical trials of good or excellent quality have been published, half of them in patients with neuropathic

**Table 2** Dried marijuana products available for purchase from the Canadian Licensed Producers approved by Health Canada

| Province/Territory | Licensed Producer | Available Products (plants/dried) and their THC/CBD content ratio | | | |
|---|---|---|---|---|---|
| | | | THC/< 1% CBD | THC/CBD | < 1% THC/CBD |
| BC | Broken Coast Cannabis Ltd. | Cultivation and Sale | 5 | 0 | 0 |
| | Canna Farms Ltd. | Cultivation and Sale | 10 | 2 | 0 |
| | Emerald Health Botanicals Inc. | Cultivation and Sale | 7 | 2 | 0 |
| | In The Zone Produce Ltd. | Cultivation Only | NA | NA | NA |
| | Tilray | Cultivation and Sale | 18 | 5 | 0 |
| | Whistler Medical Marijuana Corp. | Cultivation and Sale | 8 | 2 | 0 |
| AB | Aurora Cannabis Enterprises Inc. | Cultivation Only | NA | NA | NA |
| SK | CanniMed Ltd. | Sale Only | 3 | 3 | 1 |
| | Prairie Plant Systems Inc.* | Cultivation Only | NA | NA | NA |
| MB | Delta 9 Bio-Tech Inc. | Cultivation and Sale | 28 | 2 | 0 |
| ON | ABcann Medicinals Inc. | Cultivation Only | NA | NA | NA |
| | Agripharm Corp. | Cultivation and Sale | NA | NA | NA |
| | Aphria | Cultivation and Sale | 8 | 4 | 0 |
| | Bedrocan Canada Inc. | Sale Only | 4 | 1 | 1 |
| | Bedrocan Canada Inc. (2nd site) ** | Cultivation and Sale | 4** | 1** | 1** |
| | CannTrust Inc. | Cultivation and Sale | 8 | 3 | 0 |
| | KindCann Ltd. | Cultivation Only | NA | NA | NA |
| | MariCann Inc. | Cultivation and Sale | 8 | 2 | 0 |
| | MedReleaf Corp. | Cultivation and Sale | 13 | 2 | 1 |
| | Mettrum Ltd. | Cultivation and Sale | 1 | 2 | 1 |
| | RedeCan Pharm | Cultivation and Sale | 10 | 1 | 0 |
| | Peace Naturals Project Inc. | Cultivation and Sale | 1 | 0 | 0 |
| | Tweed Farms Inc.*** | Cultivation and Sale | 16*** | 5*** | 3*** |
| | Tweed Inc. | Cultivation and Sale | 16 | 5 | 3 |
| QC | Hydropothecary | Cultivation and Sale | 3 | 1 | 0 |
| NB | OrganiGram Inc. | Cultivation and Sale | 10 | 3 | 0 |

* Prairie Plant System Inc. products are available at CanniMed Ltd

** Bedrocan Canada Inc. second site products are sold at Bedrocan Canada Inc

*** Tweed Farms Inc. products are sold only at Tweed Inc

CBD = cannabidiol; THC = tetrahydrocannabinol

pain. In all, 11 trials used nabiximols, six used inhaled cannabis (either smoked or vaporized), six used nabilone, two used dronabinol, and one used ajulemic acid (CT-3). Almost of all of these studies, including a substantial number of patients (1,364 patients completed the studies), showed that cannabinoids were effective in alleviating pain, especially neuropathic pain. In other treatment outcome assessments of chronic pain, cannabinoids were effective in relieving pain in patients with musculoskeletal disorders, fibromyalgia, pain associated with human immunodeficiency virus (HIV) infection, and other chronic pain conditions. It should be noted that, overall, drug-related adverse effects were generally well tolerated. They were transient or mild to moderate and most commonly consisted of sedation, dizziness, dry mouth, nausea, and disturbances in concentration. Ware *et al.* (2015)[44] conducted a prospective cohort study to describe safety issues among subjects with chronic non-cancer-related pain who were given a standardized herbal cannabis product (12.5% THC) for a one-year period. Their controls were subjects with chronic pain from the same clinics but who were not cannabis users. The authors showed that 215 individuals with chronic pain recruited to the cannabis group and 216 controls showed no difference in the risk of serious adverse events. Medical cannabis users were at increased risk of non-serious adverse events, most of which were mild to moderate. Finally, there were no differences in secondary safety assessments including pulmonary and neurocognitive function and standard hematology, biochemistry, renal, liver, and endocrine function.

## Cancer-related pain

Cancer-related pain is a common problem, and 70-90% of patients with advanced cancer experience significant

pain.[45] Cannabinoids have been tested in this difficult clinical situation. Four studies that were performed more than 35 years ago evaluated the role of cannabinoids in relieving pain associated with cancer using THC or a nitrogen analogue of THC.[46-49] Three of these trials demonstrated that THC was analgesic and well tolerated despite its sedative side effect.[46-48]

Two clinical trials have been recently published in patients with cancer-related pain.[50,51] One study compared the efficacy of THC-CBD and THC oromucosal spray with placebo in regard to relieving the pain of patients with advanced cancer.[50] In 177 patients with cancer-related pain who experienced inadequate analgesia despite chronic opioid dosing, the mean pain score was significantly in favor of THC-CBD compared with placebo, whereas the THC group showed no change. Twice as many patients taking THC-CBD showed a reduction of more than 30% from the baseline pain scores when compared with placebo. Furthermore, no significant group differences were found in sleep quality or nausea scores. An open-label extension study investigated the long-term safety and tolerability of THC-CBD oromucosal spray in patients with cancer-related pain.[52] This study showed that the long-term use of THC-CBD spray (median duration of treatment 25 days, minimum two days, maximum 579 days) was generally well tolerated, with no evidence of a loss of effect for the relief of cancer-related pain with long-term use. Furthermore, patients who kept using the study medication did not seek to increase the dose of the THC-CBD spray or other pain-relieving medication over time.[52]

In another randomized, double blind, placebo-controlled, graded-dose study of 360 patients (263 completed the study), nabiximols was found to be a useful add-on analgesic for patients with opioid-refractory cancer-related pain.[51] The authors verified the efficacy and safety at a low dose (1-4 sprays/day) and a medium dose (6-10 sprays/day) but not at a high dose (11-16 sprays/day), at which point it was not well tolerated.

In conclusion, chronic and unrelieved pain associated with cancer can cause significant distress and disability. The available literature has been valuable in providing insight into the long-term benefit, safety, and tolerability of oral THC and THC-CBD spray in these patients.

## Guidance (a practical approach) for the use of medical cannabis

### Evaluating a patient for a trial of cannabis for medical purposes

Prudent medical practice incorporates comprehensive evaluation of a patient when new therapies are considered. The following recommendations concerning evaluation and management are similar to those published by the College of Family Physicians of Canada titled Authorizing Dried Cannabis for Chronic Pain or Anxiety,[53] the Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain published by the National Opioid Use Guideline Group,[54] and the Canadian Pain Society's Guidelines for the Use of Cannabinoid Compounds in Chronic Pain.[55]

Essential elements of the evaluation and management include the following.

1. Medical history and physical examination
2. Assessment of pain or other symptoms to be treated, identification of any active diagnoses, and ensuring that they are under optimal management
3. Assessment of psychological contributors and risk of addiction or substance abuse
4. Documentation of any history or current use of illicit or non-prescribed drugs, including cannabis and synthetic cannabinoids
5. Determining the effect of previous use of cannabinoids for medical purposes
6. Consideration of urinary drug screening to assess current use of prescribed and non-prescribed medication
7. Setting goals of treatment with cannabis - e.g., pain reduction, increased functional abilities, improved sleep quality, increased quality of life, reduced use of other medications[56]
8. Development of a treatment plan incorporating these goals
9. Discussion of possible side effects that might be experienced with cannabinoid use (e.g., CNS, cardiovascular, respiratory)
10. Discussion of the risks of addiction
11. Development of a follow-up schedule to review the patient periodically
12. Determining whether the goals of treatment are being achieved and the appropriateness of the response
13. Monitoring for potential misuse or abuse (being aware of clinical features of cannabis dependence[57]
14. Development of a treatment strategy, particularly for a patient at risk
15. Maintaining an ongoing relationship with the patient

### Provincial licensing authorities and professional societies

At all times, the practitioner should be familiar with, and follow the regulations of, the provincial licensing authority.[24,53] As a general rule, authorization of medical cannabis is considered a medical act. Examples are as follows.

**Table 3** Clinical trials (2010-2015) on the treatment of chronic non-cancer-related pain with cannabinoids

| Main author (date) | Cannabinoid and dosage (control group) | Type of pain (number of patients who completed) | Primary outcome(s) (method) | Duration of the trial | Results | Adverse events | Outcome |
|---|---|---|---|---|---|---|---|
| Selvarajah *et al.* (2010)[35] | Nabiximols (up to four times a day) *vs* placebo | Diabetic neuropathy ($n$ = 29) | Change in mean daily total pain scores (sum of superficial, deep, and muscular pain) (Parallel groups) | 2 weeks titration then 10 weeks | Significant improvement in pain scores in both groups, but mean change between groups was not significant. Patients with depression had greater baseline pain scores that improved regardless of intervention. | 6 withdrew because of AEs | − |
| Pini *et al.* (2012)[38] | Nabilone (0.5 mg/day) *vs* ibuprofen (400 $mg{\cdot}day^{-1}$) | Medication overuse headache ($n$ = 26) | Reduction of headache frequency, duration and intensity of headache pain and amount of daily analgesic consumption (Crossover) | 8 weeks for each treatment | Improvement of all primary outcomes with both drugs compared to baseline. Nabilone directly superior to ibuprofen in pain intensity, analgesic intake and level of dependence. | All AEs were mild except 2 moderate ones : one man with loss of concentration and memory on nabilone and one woman with gastric discomfort on ibuprofen. | + |
| Langford *et al.* (2013)[36] | Nabiximols (maximum of 12 sprays per day) *vs* placebo | Central neuropathic pain in patients with multiple sclerosis (Phase A : n = 297; Phase B : $n$ = 42) | Phase A : improvement of 30 % or more in mean pain NRS score from baseline to the last week of treatment; Phase B : time to treatment failure during the withdrawal period (NRS) (Parallel groups) | Phase A: Parallel-group phase of 14-week treatment; Phase B : 18-week randomized withdrawal study (14-week open-label treatment period + a double-blind 4-week randomized-withdrawal phase) | Phase A : THC/CBD spray showed a high response rate, statistically different to placebo at week 10 but not at the week 14 primary endpoint Phase B : significant difference in favor of THC/CBD spray | THC/CBD spray well tolerated, with the majority of mild to moderate AEs in severity. Three patients in the THC/CBD spray arm and two in the placebo arm experienced a treatment-related serious AE. No evidence of a withdrawal syndrome when THC/CBD stopped. | +/- |
| Wilsey *et al.* (2013)[37] | Vaporized cannabis (4 puffs at 1h and 4-8 puffs at 4 h) at medium-dose (3.53%), low-dose (1.29%), or placebo | Neuropathic pain ($n$ = 39) | Visual analog scale pain intensity. (Cross-over) | Three 6-h study sessions separated by 3-14 days | Analgesic response to vaporized cannabis. No difference between the 2 active dose groups; NNT (30% pain reduction) was 3.2 for placebo *vs* low-dose, 2.9 for placebo versus medium-dose | Psychoactive effects were minimal and well tolerated. Neuropsychological effects were of limited duration and reversible within 1 to 2 h | + |
| Lynch *et al.* (2014)[39] | Nabiximols (maximum of 12 sprays per day) *vs* placebo | Chemo-therapy-induced neuropathic pain ($n$ = 16) | Change in NRS for pain intensity from baseline to final week of stable dose. (Pilot trial- crossover) | First study period of 4 weeks. 2 weeks washout. Extension trial of 6 months | No difference between the treatment and the placebo groups. Five participants reported a two-point or greater reduction in pain. NNT = 5 | Fatigue, dizziness, dry mouth, and nausea were mild and transient. No serious medication-related AEs. | +/− |

**Table 3** continued

| Main author (date) | Cannabinoid and dosage (control group) | Type of pain (number of patients who completed) | Primary outcome(s) (method) | Duration of the trial | Results | Adverse events | Outcome |
|---|---|---|---|---|---|---|---|
| Serpell *et al.* (2014)[40] | Nabiximols (maximum of 8 sprays in a 3-h period up to a maximum of 24 sprays per 24-h period) *vs* placebo | Peripheral neuropathic pain associated with allodynia (post-herpetic neuralgia, peripheral neuropathy, focal nerve lesion, complex regional pain syndrome-II) ($n$ = 173) | Co-primary endpoints : 30% responder rate in peripheral NP (NRS) and mean change from baseline (Parallel group) | 15 weeks (1-week baseline and 14-week treatment period) | Statistically significant treatment differences in favor of THC/CBD spray in the full analysis. | Mild to moderate AEs in both treatment groups : dizziness, nausea, fatigue and dysgeusia, etc. Serious AEs in 10 patients (8%) receiving THC/CBD spray, none of which was considered to be treatment-related *vs* 6 patients (5%) receiving placebo. | + |
| Turcotte *et al.* (2015)[41] | Nabilone (1 mg twice daily) combined with gabapentin at stable dose *vs* placebo and gabapentin | Multiple sclerosis-induced neuropathic pain ($n$ = 14) | VAS of pain intensity and VAS of impact of pain on daily activities. (Parallel group) | Titration over 4 weeks (0.5mg/week increase) followed by 5-week maintenance | The adjusted rate of decrease for both outcomes (pain intensity and pain impact) was statistically greater in nabilone *vs* placebo study group | Nabilone was well tolerated, with dizziness / drowsiness most frequently reported. No serious AEs were reported in either study group. | + |
| Wallace *et al.* (2015)[42] | Vaporized cannabis: low (1% THC), medium (4% THC), or high (7% THC) or placebo | Painful diabetic peripheral neuropathy ($n$ = 16) | Differences in spontaneous pain over time between doses (Crossover) | Four dosing sessions separated by 2 weeks | Dose-dependent reduction in pain intensity in response to inhaled cannabis<br>There was a significant negative effect (impaired performance) of the high dose on 2 of the 3 neuropsychological tests. | Euphoria ranged from 100% for high-dose cannabis to 60% for placebo. Only high-dose cannabis had a larger proportion of participants reporting somnolence *vs* placebo | + |

AEs = adverse events; CBD = cannabidiol; NNT = number needed to treat; NP = neuropathic pain; NRS = numerical rating scale; THC = tetrahydrocannabinol; VAS = visual analogue scale

- Nova Scotia – "The College considers the authorization of marijuana for medical purposes to be comparable to prescribing medication" and "… authorization of marijuana for medical purposes to be a clinical act and insured service"[20]
- Ontario – "… medical document required under the MMPR is equivalent to a prescription" and "… must comply with … the expectations and guidelines that are set out in the College's Prescribing Drugs policy"[17]
- British Columbia – "The College considers the medical document authorizing patient access to marijuana to be equivalent to a prescription"[13]

Many of the licensing authorities advise consideration of a treatment agreement and/or completion of a consent form (i.e., Saskatchewan,[15] British Columbia,[13] Quebec.[18] In addition, it would also be prudent to follow recommendations and/or guide lines of relevant professional societies - i.e., College of Family Physicians of Canada (CFPC),[53] Canadian Pain Society.[55]

As a general rule, practitioners are advised through these directives and other published documents (mentioned above) first to consider adequate trials of other pharmacologic and non-pharmacologic therapies appropriate to the medical condition being treated. It would also include adequate trials of prescription pharmaceutical cannabinoids. The practitioner authorizing medical cannabis should be primarily responsible for managing specific medical condition(s) for which cannabis is being used.[53] As in other areas of medicine, it can be appropriate for specialist practitioners to provide recommendations to the primary care provider if asked for advice.

## Contraindications and cautions

There are several recommended contraindications to, and cautions about, the use of medical cannabis.[53,54,57-63]

Contraindications include the following.

- Age under 25
- Personal or family history of psychosis and schizophrenia
- Current or past history of cannabis use disorder
- Active substance use disorder
- Significant cardiovascular or respiratory disease
- Pregnancy or breast-feeding

Cautions include the following.

- Concurrent active mood or anxiety disorder
- Use of tobacco
- Risk factors for cardiac disease
- Heavy user of alcohol, opioids, and/or benzodiazepines

## Harm reduction

Harm reduction[53-55,64-66] should always be considered when authorizing medical cannabis and should include advice about: (1) route/delivery mode: oral/vaporization/smoking; (2) side effects; (3) driving and operating heavy machinery.

## Dosing

The basic dosing principle is to "start low and go slow."[53,56] Ware and Desroches noted that "with herbal cannabis, prudence suggests a "start low, go slow" strategy using non-smoking delivery mechanisms, quality-controlled products, and the lowest level of THC required to achieve therapeutic aims and minimize side effects."[56]

Reasonable doses are considered to be up to 1-3 $g \cdot day^{-1}$.[37,44,67] Doses $> 5$ $g \cdot day^{-1}$ warrant careful review.[56] When the inhaled route is used,the practitioner should give the following advice (adapted from CFPC preliminary guidance).[53]

1. Consider vaporized over smoked cannabis.
2. Use inhaled cannabis in a well-ventilated, private, calm environment.
3. Use the lowest effective level of THC available.
4. Start any new cannabis product with a slow, single inhalation. Then, wait four hours to appreciate the effects fully.
5. Allow several single inhalation trials of a product to observe and then discuss their responses with the physician, before increasing the number of inhalations or changing the product.
6. Inform and alert the patient about cannabis's potential mood altering, euphoric, and/or sedative effects.
7. Encourage patients to keep notes on effects and experiences with the therapy to facilitate discussion with the authorizing physician/health professional.

## Documentation

Documentation is essential to show that the patient has been evaluated. It also displays the rationale for the use of medical cannabis in the context of the overall management plan and the periodic review of the patient's status.

An algorithm for the treatment of chronic pain with medical cannabis is provided in the Figure. Common side effects associated with the use of medical cannabis are detailed in Table 4.

## Discussion

Although the pharmacological effects of cannabis have been exploited for nearly 5,000 years for medicinal purposes, it is only during the last decades that crucial scientific discoveries have been made about cannabinoids.[68] THC is an agonist to two major cannabinoid receptors ($CB_1$ and $CB_2$), which have their own endogenous agonists (endocannabinoids). These agonists are of central physiological importance, with direct biological effects modulating an array of neurotransmitter systems.[69] The cannabinoids available to treat certain disorders include mainly phytocannabinoids (with varying THC and/or CBD contents) and synthetic cannabinoids, such as nabilone, dronabinol (withdrawn from the market), and nabiximols (THC-CBD extracts).

One in five Canadians lives with chronic pain. The costs associated with chronic pain are higher than those for cancer, heart disease, and HIV combined. Estimates place direct health care costs in Canada at more than $6 billion per year, and productivity costs related to job loss and sick days are at $37 billion per year.[70] For many patients, current pain management interventions, including drug treatment, are insufficient to provide adequate pain relief and are associated with adverse health and societal effects. In this context, many with chronic pain are turning to other therapies including cannabinoids.[71]

The legal status of cannabis worldwide varies among countries. One country (Uruguay) and several US states have made herbal cannabis fully legal. More importantly, four countries, including Canada (together with Israel, Czech Republic, and The Netherlands) have or had formal research programmes.[72] The *Health Canada's Medical Marihuana Research Program* was in place in 2001 but was abolished in 2006 because of budget restrictions, having funded only two clinical studies.[44,73] Unfortunately,

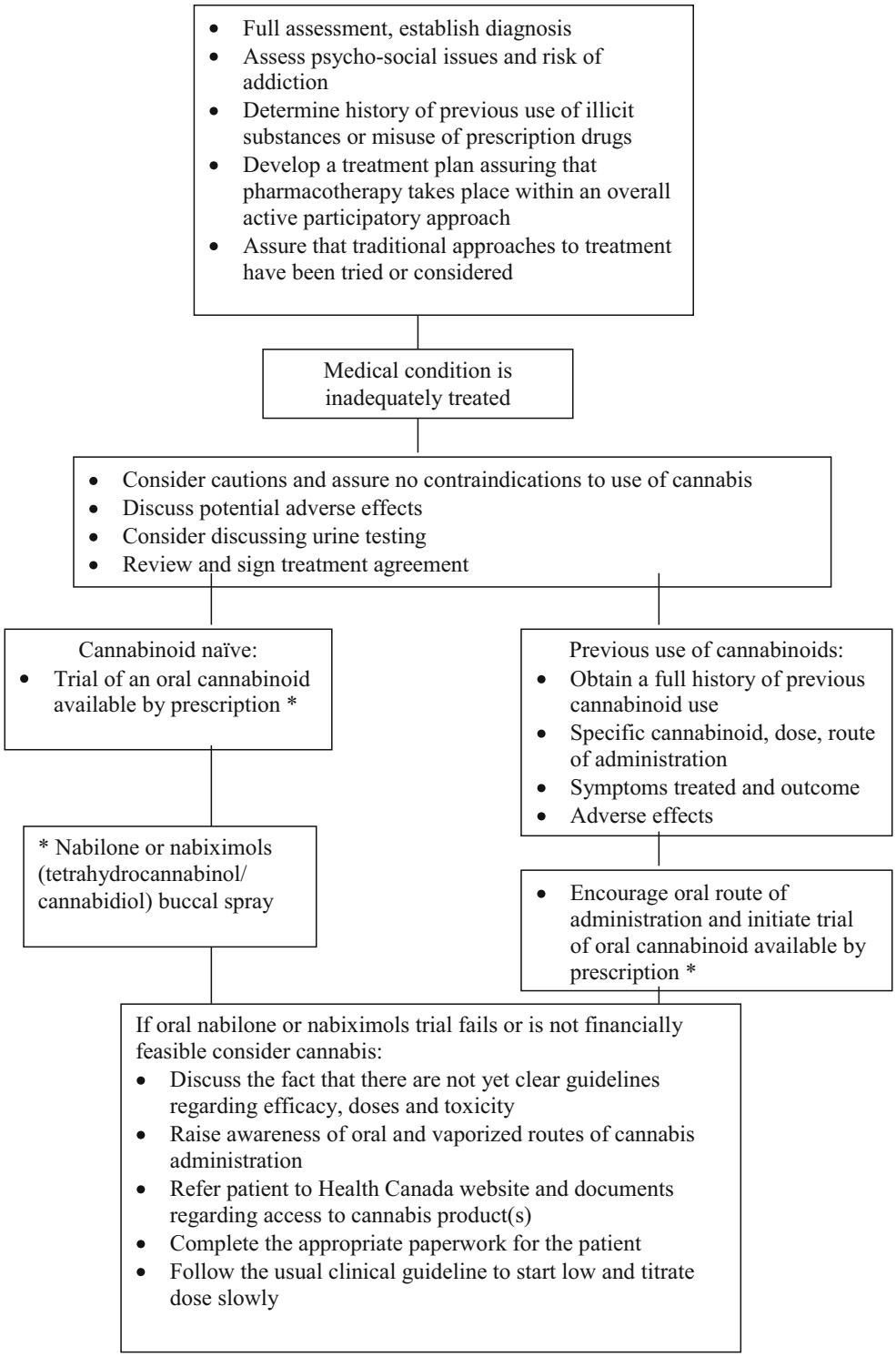


**Figure** Algorithm for treatment with medical cannabis (adapted with permission from the Canadian Pain Society's guidelines for the use of cannabinoid compounds in chronic pain).[55]

as the number of patients accessing cannabis-based therapies has increased, research has not expanded.[74] Many countries (Austria, Belgium, Germany, Italy, Spain and more that 20 US states) have explicit exemptions for prescribed medical cannabis.

Canada is ahead of many other countries, having had federal regulations that allow patients to access herbal cannabis with a doctor's authorization since 2001.[74] In Canada, however, "cannabis (marijuana, marihuana) is not an approved therapeutic substance and has not been issued

**Table 4** Common important side effects of cannabinoids (adapted with permission from the Canadian Pain Society's guidelines for the use of cannabinoid compounds in chronic pain)[55,76]

| |
|---|
| Central nervous system |
| Euphoria |
| Anxiety |
| Panic |
| Paranoia |
| Psychosis |
| Sedation |
| Dizziness |
| Somnolence |
| Depression |
| Ataxia |
| Visual/hearing disturbances? |
| Asthenia |
| Possible cognitive effects |
| Cardiovascular system |
| Tachycardia |
| Postural hypotension |
| Palpitations |
| Vasodilation (flushing, red eyes) |
| Increased risk of myocardial infarction within one hour of use |
| Respiratory (if smoked) |
| Bronchitis/chronic obstructive pulmonary disease/lung infection |
| Other |
| Dry mouth |
| Headache |
| Abdominal pain/bloating |
| Cannabinoid hyperemesis syndrome[76] |

a notice of compliance by Health Canada authorizing sale in Canada."[28] Many changes have occurred in recent months in Canada regarding the way medical cannabis is being reorganized. Health Canada has licensed authorized producers across the country but, more importantly, it has decided to be less involved in how medical cannabis is used. The licensing authorities in each province/territory have put in place regulations concerning the use of medical cannabis (see New Canadian regulation on medical cannabis). Under this new system, where producers are licensed to grow and distribute various strains of cannabis, the patient population has reached almost 24,000 in mid-2015, and approximately 4,000 physicians have completed the medical documentation concerning cannabis.[74] This leads to a need for educational programs for practitioners and for companies to share the information they receive from patients about benefits and side effects in regard to various medical conditions. The rapid changes surrounding the medical use of cannabis has had a considerable impact on healthcare practitioners, who currently receive little or no education on issues regarding medical cannabis.[75] Some authors[74] proposed a "cannabis curriculum" that covers botanical, physiological, clinical, and legal issues to allow healthcare practitioners to engage in discussions with their patients and colleagues. As a result of this lack of education nationwide, patients are at the moment nearly left alone to decide which product to use, how often, and at what dose. It is crucial that health practitioners obtain adequate training and that each province monitor the patient's health when cannabis is prescribed. Such a system is already in place in Quebec, with the building of a database (Quebec Cannabis Registry) that can be used as a research tool.[18]

Many of the clinical trials investigating the efficacy of cannabinoids for pain relief have been reported during the past decade. Based on a 2015 systematic review and meta-analysis, Whiting *et al.*[5] reported that there was moderate-quality evidence to support the use of cannabinoids to treat chronic pain and that most trials suggested that symptom alleviation was associated with cannabinoids. These associations, however, did not reach statistical significance in all studies. It is interesting to note that several trials also showed improvement in secondary outcomes such as sleep, muscle stiffness, and spasticity. We did not include clinical trials performed in patients with multiple sclerosis when the primary outcome was not pain, but this subject also was recently reviewed.[5]

Adverse effects most frequently reported are fatigue, dry mouth, somnolence, and dizziness, but they are of mild to moderate severity and are generally well tolerated. Administration of cannabis and cannabinoids do put the patient at an increased risk of short-term adverse events. These findings are detailed in a recent prospective cohort study of one year that described safety issues among subjects with chronic non-cancer-related pain.[44] In the cannabis group, the most common serious adverse events were abdominal pain (12%), intestinal obstruction (12%), and nephrolithiasis (12%). The most common non-serious adverse events were nervous system (20%), gastrointestinal (13.4%), and respiratory (12.6%) disorders. Furthermore, the authors showed that herbal cannabis, when used by cannabis-experienced patients as part of a monitored treatment program, seems to have a reasonable safety profile. The authors suggest that longer-term monitoring for functional outcomes is needed.

## Conclusion

We present the new Canadian regulations concerning the use of cannabis for medical purposes. We also report provincial licensing authorities' regulations on medical cannabis and the various dried marijuana products available for purchase from the Canadian Licensed Producers approved by Health

Canada as well as the upcoming alternative products. We also provide guidance for the safe use of medical cannabis and outline how to evaluate a patient for a trial using medical cannabis. Overall, the recent literature supports the idea that currently available cannabinoids are modestly effective analgesics that provide a safe, reasonable therapeutic option for managing chronic non-cancer-related pain and possibly cancer-related pain. Despite significant progress in understanding how cannabis and cannabinoids work to decrease pain, there is still a need to confirm these beneficial effects clinically and to establish acceptable benefit-to-risk ratios.

The science of medical cannabis and the education of healthcare practitioners and patients desperately need to be seen as of greater importance than the development of policy regarding medical cannabis.

**Authors' contributions:** *Pierre Beaulieu* wrote the abstract, introduction, clinical trial section, discussion, conclusion, and reference section. *Aline Boulanger* wrote the sections on new Canadian regulations on medical cannabis and provincial licensing authorities guidelines and policies. *Julie Desroches* wrote the section on available cannabis in Canadian market (companies, plants, mode of delivery). *Alexander J. Clark* wrote the section on guidance for use of medical cannabis and participated in the discussion section and revision of the entire manuscript.

**Conflicts of interest** None declared.

**Disclosures** Dr. Aline Boulanger has received an honorarium for a presentation for CanniMed and to be on an advisory board for Bedrocan. Dr. Julie Desroches us a scientific consultant for the Canadian Consortium for the Investigation of Cannabinoids (CCIC) and involvement in the Québec Cannabis Registry team as a Data Manager. Dr. Alexander J. Clark is President, Board of Directors, Canadian Consortium for the Investigation of Cannabinoids (CCIC).

## References


1. *ElSohly MA*, *Gul W*. Constituents of cannabis sativa. In: Pertwee RG, editor. Handbook of Cannabis. Oxford: Oxford University Press; 2014 .
2. *Guindon J*, *Beaulieu P*, *Hohmann AG*. Pharmacology of the cannabinoid system. In: Beaulieu P, Lussier D, Porreca F, Dickenson AH, editors. Pharmacology of Pain. Seattle: IASP Press; 2010 .
3. *Lynch ME*, *Campbell F*. Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. Br J Clin Pharmacol 2011; 72: 735-44.
4. *Hill K*. Medical marijuana for treatment of chronic pain and other medical and psychiatric problems: a clinical review. JAMA 2015; 313: 2474-83.
5. *Whiting PF*, *Wolff RF*, *Deshpande S*, *et al*. Cannabinoids for Medical use: a systematic review and meta-analysis. JAMA 2015; 313: 2456-73.
6. *Minister of Justice*. Marihuana Medical Access Regulations, SOR/2001-227 (2001). Available from URL: http://laws-lois.justice.gc.ca/PDF/SOR-2001-227.pdf (accessed December 2015).
7. *Court of Appeal for Ontario*. R. v. Parker, Canadian Legal Information Institute 5762 (On CA 2000). Available from URL: http://www.ontariocourts.on.ca/decisions/2000//july/parker.pdf (accessed December 2015).
8. *Canadian Centre on Substance Abuse*. Marijuana for Medical Purposes. July 2015. Available from URL: http://www.ccsa.ca/Resource%20Library/CCSA-Medical-Purposes-Marijuana-Policy-Brief-2015-en.pdf (accessed December 2015).
9. *Government of Canada*. Canada Gazette, Vol 146, no 50, December 15, 2012. Available from URL: http://www.gazette.gc.ca/rp-pr/p1/2012/2012-12-15/html/reg4-eng.html#archived (accessed December 2015).
10. *Government of Canada*. Marihuana for Medical Purposes Regulations, SOR/2013-119 (2013). Available from URL: http://www.laws-lois.justice.gc.ca/PDF/SOR-2013-119.pdf (accessed December 2015).
11. *Judgments of the Supreme Court of Canada*. R. v. Smith, 2015 34. Available from URL: http://scc-csc.lexum.com/scc-csc/scc-csc/en/item/15403/index.do (accessed December 2015).
12. *Kalan H, Porath-Waller AJ*. Clearing the Smoke on Cannabis. Medical use of Cannabis and Cannabinoids. 2014. Available from URL: http://www.ccsa.ca/Resource%20Library/CCSA-Medical-Use-of-Cannabis-2012-en.pdf (accessed December 2015).
13. *College of Physicians and Surgeons of British Columbia*. Professional Standards and Guidelines: Marijuana for Medical Purposes. May 5 2015, revised July 30 2015. Available from URL: https://www.cpsbc.ca/files/pdf/PSG-Marijuana-for-Medical-Purposes.pdf (accessed December 2015).
14. *College of Physicians and Surgeons of Alberta*. Medical Practice: Marihuana for Medical Purposes. April 3, 2014. Available from URL: http://www.cpsa.ca/standardspractice/marihuana-medical-purposes/ (accessed December 2015).
15. *College of Physician and Surgeons of Saskatchewan*. Prescription Review Program: Medical Marihuana. 2013. Available from URL: https://www.cps.sk.ca/CPSS/Programs_and_Services/Prescription_Review_Program.aspx?PrescriptionCCO=4 (accessed December 2015).
16. *College of Physicians & Surgeons*. Statement no 187: Marijuana (cannabis) for medical purposes. March 2014. Available from URL: http://cpsm.mb.ca/cjj39alckF30a/wp-content/uploads/st187.pdf (accessed December 2015).
17. *College of Physicians and Surgeons of Ontario*. Policy statement #1-15, Marijuana for Medical Purposes. 2015. Available from URL: http://www.cpso.on.ca/CPSO/media/documents/Policies/Policy-Items/Marijuana-for-Medical-Purposes.pdf?ext=.pdf (accessed December 2015).
18. *Collège des Médecins du Québec*. Guidelines concerning the prescription of dried cannabis for medical purposes. April 2014, updated May 2015. Available from UR: http://www.cmq.org/publications-pdf/p-1-2014-04-01-en-directives-concernant-ordonnance-cannabis-seche-fins-medicales.pdf?t=1445313262790 (accessed December 2015).
19. *College of Physicians and Surgeons of New Brunswick*. Guidelines, Medical Marijuana. April 2014. Available from URL: https://www.cpsnb.org/english/Guidelines/MedicalMarijuana.htm (accessed December 2015).
20. *College of Physicians and Surgeons of Nova Scotia*. Policy Regarding the Authorization of Marijuana for Medical Purposes. June 26, 2016. Available from URL: https://www.cpsns.ns.ca/DesktopModules/Bring2mind/DMX/Download.aspx?PortalId=0&TabId=129&EntryId=52 (accessed December 2015).
21. *College of Physicians and Surgeons of Prince Edward Island*. Policy: Prescribing of Medical Marijuana. May 26, 2014, amended September 2014. Available form URL: http://cpspei.ca/wp-content/uploads/2014/12/Marijuana-Prescribing-revised-

May-1313-April-314May-2614-amended-Sept-2014.pdf (accessed December 2015).
22. *College of Physicians and Surgeons of Newfoundland and Labrador.* Advisory to the Profession and Interim Guidelines: Marijuana for Medical Purposes. March 2014. Available from URL: http://www.cpsnl.ca/userfiles/file/CPSNL%20%20Medical%20Marihuana%20%20March%202014%20rev%201_0.pdf (accessed December 2015).
23. *Yukon Medical Council.* Medical Practice: Marijuana for Medical Purposes. Available from URL: http://www.yukonmedicalcouncil.ca/pdfs/Marijuana_for_Medical_Purposes.pdf (accessed December 2015).
24. *The Canadian Medical Protective Association.* Medical marijuana: New regulation, new College guidance for Canadian doctors. May 2014, revised October 2015. Available from URL: https://www.cmpa-acpm.ca/en/legal-and-regulatory-proceedings/-/asset_publisher/a9unChEc2NP9/content/medical-marijuana-new-regulations-new-college-guidance-for-canadian-doctors (accessed December 2015).
25. *Health Canada:* Authorized Licensed Producers under the Marihuana for Medical Purposes Regulations, 2015. Available from URL: http://www.hc-sc.gc.ca/dhp-mps/marihuana/info/list-eng.php (accessed December 2015).
26. *Health Canada.* Daily Amount and Dosing Information Sheet, 2014. Available from: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/marihuana/med/daily-quotidienne-eng.pdf (accessed December 2015).
27. *McClure EA*, *Stitzer ML*, *Vandrey R*. Characterizing smoking topography of cannabis in heavy users. Psychopharmacology (Berl) 2012; 220: 309-18.
28. *Health Canada*. Information for Health Care Professionals, Cannabis (marihuana, marijuana) and the cannabinoids (2013) - Abramovici H. Available from URL: http://www.hc-sc.gc.ca/dhp-mps/marihuana/med/infoprof-eng.php#fnb273 (accessed December 2015).
29. *Beaulieu P*, *Ware M*. Reassessment of the role of cannabinoids in the management of pain. Curr Opin Anaesthesiol 2007; 20: 473-7.
30. *Raft D*, *Gregg J*, *Ghia J*, *Harris L.* Effects of intravenous tetrahydrocannabinol on experimental and surgical pain. Psychological correlates of the analgesic response. Clin Pharmacol Ther 1977; 21: 26-33.
31. *Beaulieu P*. Effects of nabilone, a synthetic cannabinoid, on postoperative pain. Can J Anesth 2006; 53: 769-75.
32. *Wallace M*, *Schulteis G*, *Atkinson JH*, *et al*. Dose-dependent effects of smoked cannabis on capsaicin-induced pain and hyperalgesia in healthy volunteers. Anesthesiology 2007; 107: 785-96.
33. *Kraft B*, *Frickey NA*, *Kaufmann RM*, *et al*. Lack of analgesia by oral standardized cannabis extract on acute inflammatory pain and hyperalgesia in volunteers. Anesthesiology 2008; 109: 101-10.
34. *Jefferson DA*, *Harding HE*, *Cawich SO*, *Jackson-Gibson A*. Postoperative analgesia in the Jamaican cannabis user. J Psychoactive Drugs 2013; 45: 227-32.
35. *Selvarajah D*, *Gandhi R*, *Emery CJ*, *Tesfaye S*. Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. Diabetes Care 2010; 33: 128-30.
36. *Langford RM*, *Mares J*, *Novotna A*, *et al*. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. J Neurol 2013; 260: 984-97.
37. *Wilsey B*, *Marcotte T*, *Deutsch R*, *Gouaux B*, *Sakai S*, *Donaghe H*. Low-dose vaporized cannabis significantly improves neuropathic pain. J Pain 2013; 14: 136-48.
38. *Pini LA*, *Guerzoni S*, *Cainazzo MM*, *et al*. Nabilone for the treatment of medication overuse headache: results of a preliminary double-blind, active-controlled, randomized trial. J Headache Pain 2012; 13: 677-84.
39. *Lynch ME*, *Cesar-Rittenberg P*, *Hohmann AG*. A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. J Pain Symptom Manage 2014; 47: 166-73.
40. *Serpell M*, *Ratcliffe S*, *Hovorka J*, *et al*. A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. Eur J Pain 2014; 18: 999-1012.
41. *Turcotte D*, *Doupe M*, *Torabi M*, *et al*. Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: a randomized controlled trial. Pain Med 2015; 16: 149-59.
42. *Wallace MS*, *Marcotte TD*, *Umlauf A*, *Gouaux B*, *Atkinson JH*. Efficacy of inhaled cannabis on painful diabetic neuropathy. J Pain 2015; 16: 616-27.
43. *Abrams DI*, *Couey P*, *Shade SB*, *Kelly ME*, *Benowitz NL*. Cannabinoid-opioid interaction in chronic pain. Clin Pharmacol Ther 2011; 90: 844-51.
44. *Ware MA, Wang T, Shapiro S, Collet JP; COMPASS study team.* Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS). J Pain 2015; 16: 1233-42.
45. *Portenoy R*. Treatment of cancer pain. Lancet 2011; 377: 2236-47.
46. *Noyes R Jr*, *Brunk SF*, *Baram DA*, *Canter A*. Analgesic effect of delta-9-tetrahydrocannabinol. J Clin Pharmacol 1975; 15: 139-43.
47. *Noyes R Jr*, *Brunk SF*, *Avery DA*, *Canter AC*. The analgesic properties of delta-9-tetrahydrocannabinol and codeine. Clin Pharmacol Ther 1975; 18: 84-9.
48. *Staquet M*, *Gantt C*, *Machin D*. Effect of a nitrogen analog of tetrahydrocannabinol on cancer pain. Clin Pharmacol Ther 1978; 23: 397-401.
49. *Jochimsen PR*, *Lawton RL*, *VerSteeg K*, *Noyes R Jr*. Effect of benzopyranoperidine, a delta-9-THC congener, on pain. Clin Pharmacol Ther 1978; 24: 223-7.
50. *Johnson JR*, *Burnell-Nugent M*, *Lossignol D*, *Ganae-Motan ED*, *Potts R*, *Fallon MT*. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. J Pain Symptom Manage 2010; 39: 167-79.
51. *Portenoy RK*, *Ganae-Motan ED*, *Allende S*, *et al*. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. J Pain 2012; 13: 438-49.
52. *Johnson JR*, *Lossignol D*, *Burnell-Nugent M*, *Fallon MT*. An open-label extension study to investigate the long-term safety and tolerability of THC/CBD oromucosal spray and oromucosal THC spray in patients with terminal cancer-related pain refractory to strong opioid analgesics. J Pain Symptom Manage 2013; 46: 207-18.
53. *College of Family Physicians of Canada.* Authorizing Dried Cannabis (Medical Marijuana) for Chronic Pain and Anxiety. Preliminary Guidance, 2014. Available from URL: http://www.cfpc.ca/ProjectAssets/Templates/Resource.aspx?id=7056&terms=marijuana (accessed December 2015).
54. *National Opioid Use Guideline Group (NOUGG).* Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain. Canada, 2010. Available from URL: http://

nationalpaincentre.mcmaster.ca/opioid/documents.html (accessed December 2015).
55. *Clark AJ, Lynch ME, Ware M, Beaulieu P, McGilveray IJ, Gourlay D*. Guidelines for the use of cannabinoid compounds in chronic pain. Pain Res Manag 2005; 10 Suppl A: 44A-6A.
56. *Ware MA, Desroches J*. Medical Cannabis and Pain. Pain Clinical Updates, International Association for the Study of Pain, 2014. Available from URL: http://www.iasp-pain.org/PublicationsNews/NewsletterIssue.aspx?ItemNumber=3878 (accessed December 2015).
57. *van der Pol P*, *Liebregts N*, *de Graaf R*, *et al*. Mental health differences between frequent cannabis users with and without dependence and the general population. Addiction 2013; 108: 1459-69.
58. *Manrique-Garcia E*, *Zammit S*, *Dalman C*, *Hemmingsson T*, *Andreasson S*, *Allebeck P*. Cannabis, schizophrenia and other non-affective psychoses: 35 years of follow-up of a population-based cohort. Psychol Med 2012; 42: 1321-8.
59. *Kuepper R*, *van Os J*, *Lieb R*, *Wittchen HU*, *Hofler M*, *Henquet C*. Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study. BMJ 2011; 342: d738.
60. *van der Pol P*, *Liebregts N*, *de Graaf R*, *Korf DJ*, *van den Brink W*, *van Laar M*. Predicting the transition from frequent cannabis use to cannabis dependence: a three-year prospective study. Drug Alcohol Depend 2013; 133: 352-9.
61. *Thomas G*, *Kloner RA*, *Rezkalla S*. Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana inhalation: what cardiologists need to know. Am J Cardiol 2014; 113: 187-90.
62. *Casier I*, *Vanduynhoven P*, *Haine S*, *Vrints C*, *Jorens PG*. Is recent cannabis use associated with acute coronary syndromes? An illustrative case series. Acta Cardiol 2014; 69: 131-6.
63. *Reid PT, Macleod J, Robertson JR*. Cannabis and the lung. J R Coll Physicians Edinb 2010; 40: 328-3; quiz 33-4.
64. *Reisfield GM*. Medical cannabis and chronic opioid therapy. J Pain Palliat Care Pharmacother 2010; 24: 356-61.
65. *Hartman RL*, *Huestis MA*. Cannabis effects on driving skills. Clin Chem 2013; 59: 478-92.
66. *Neavyn MJ*, *Blohm E*, *Babu KM*, *Bird SB*. Medical marijuana and driving: a review. J Med Toxicol 2014; 10: 269-79.
67. *Hazekamp A*, *Heerdink ER*. The prevalence and incidence of medicinal cannabis on prescription in The Netherlands. Eur J Clin Pharmacol 2013; 69: 1575-80.
68. *Pertwee R*. Handbook of Cannabis. Oxford: Oxford University Press; 2014 .
69. *Woodhams SG*, *Sagar DR*, *Burston JJ*, *Chapman V*. The role of the endocannabinoid system in pain. Handb Exp Pharmacol 2015; 227: 119-43.
70. *Lynch ME*. The need for a Canadian pain strategy. Pain Res Manag 2011; 16: 77-80.
71. *Lynch ME*, *Ware MA*. Cannabinoids for the treatment of chronic non-cancer pain: an updated systematic review of randomized controlled trials. J Neuroimmune Pharmacol 2015; 10: 293-301.
72. *Gould J*. The cannabis crop. Nature 2015; 525: S2-3.
73. *Ware MA*, *Wang T*, *Shapiro S*, *et al*. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ 2010; 182: E694-701.
74. *Page J*, *Ware M*. Perspective: close the knowledge gap. Nature 2015; 525: S9.
75. *Ware MA*, *Ziemianski D*. Medical education on cannabis and cannabinoids: perspectives, challenges, and opportunities. Clin Pharmacol Ther 2015; 97: 548-50.
76. *Galli JA*, *Sawaya RA*, *Friedenberg FK*. Cannabinoid hyperemesis syndrome. Curr Drug Abuse Rev 2011; 4: 241-9.