

Medical marijuana and community oncology practice: the good, the bad, and the potentially ugly

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ABSTRACT

Apart from immuno-oncology agents, few topics in the past two years have generated more questions for medical oncologists, and attention from the popular press, than medical marijuana.¹⁻⁶ While a great deal is known about the various medicinal cannabinoids, in oncology large gaps persist relating to basic pharmacology and potential drug interactions.^{1,7,8} The situation is further complicated by the lack of randomized controlled clinical trials and the huge variety of cannabinoid preparations and formulations currently available, each presenting biochemical complexity and quality control issues.^{1,2,9} This lack of high-level scientific evidence, coupled with deficiencies in pertinent physician education, ethical

issues, and complex federal and provincial college regulations, leave many clinicians in the dark on how to advise individual patients.^{10,11} This review provides a practical update in relation to many of these concerns, as well as summarizing the current state of regulation and prescribing of medical marijuana in Canada

Keywords: medical marijuana, medical cannabis, medical cannabinoids, delta-9-tetrahydrocannabinol, cannabidiol, THC, CBD, ethical issues and cannabis, cannabis for medical purposes, cannabinoid therapies, medical cannabinoid guidelines, anticancer mechanisms of cannabinoids, cancer symptom management, Canadian medical marijuana

INTRODUCTION

Cannabis is one of humanity's oldest cultivated crops, with millennia of use as a source of food, fibre, oil and medicine, as well as deliberate inebriation. More than 4,000 years ago, Chinese emperors were suggesting that marijuana be used for medicinal purposes, and the esteemed Roman historian Pliny the Younger mentions the use of cannabis as an intoxicant.^{1,2,4} Modern interest germinated in 1842, when William O'Shaughnessy, an Irish physician, encountered Indian hemp in Calcutta and emphasized its efficacy as a muscle relaxant, painkiller and anticonvulsant of great value.² Marijuana was actually listed in the US Pharmacopeia, which traditionally means that a drug is regarded as safe for use, from 1851 on (see **Figure 1**). Thus, the criminalization of marijuana by medicolegal and mainstream culture, with the associated rejection of its possible medicinal benefits, is a relatively recent development, emerging early in the 20th century, when irrational fears escalated that recreational cannabis use might lead to crime and socially deviant behaviours.^{2,4,9}

Currently, cannabis is the most widely consumed drug in the world, with an annual prevalence between 2.8 and 4.5%.¹ In Canada an estimated 43 % of adults report prior lifetime usage, 12% within the past year.² The average Canadian user consumes cannabis 2 to 3 times a week, with 40% actually consuming >14 grams per week.^{2,11} On average, the number of registered medical marijuana users in Canada has virtually tripled annually since 2014, with a total of over 200,000 registered in 2017.¹¹

FIGURE 1: An antique bottle of cannabis extract



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MEDICAL CANNABIS, CANNABINOIDS AND THE ENDOCANNABINOID SYSTEM

In Canada more than 200 types of medical cannabis are available from licensed producers.^{2,11} Individual cannabis types have been erroneously referred to as strains, though the preferred term is chemical variety or “chemovar.” Marijuana plants contains more than 421 different chemical compounds, including more than 115 known cannabinoids; when smoked, more than 2,000 compounds are produced by pyrolysis.¹⁻⁴ From an oncology perspective, the most

clinically relevant compounds include the cannabinoid agents, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), and the non-cannabinoid terpenes and flavonoids.^{2,3,4} There is evidence of synergistic relationships between cannabinoids and terpenes, the so-called “entourage effect” of cannabis, but little clinical data on the pharmacology of terpenes and flavonoids is available.¹⁻⁴

Medical cannabis can be dispensed in a dried botanical form that can be smoked, vaporized or used as edible food products.^{2,3,4} More recently, medically compounded cannabis extracts and organic edible oils have been produced that can be ingested orally, vaporized, or applied topically.⁵ There is no guaranteed consistency between individual cannabis plants or strains, and impurities such as pesticide residue or fungal contaminants may also be present.^{2,5}

The endocannabinoid system consists of natural cannabinoid neurotransmitters and target receptors in multiple organs such as the brain.^{1,2,4,9} These receptors are ubiquitous and have an estimated 10 to 1 preponderance over opioid receptors.⁴ The endocannabinoid system appears to help regulate numerous aspects of normal physiologic function, including cognition, coordination, memory, appetite, pain perception, heart rate, gastrointestinal mobility, intraocular pressure and immune function.^{1,4,9,12} Cannabinoid receptors that are located on cell membranes are functionally coupled with G proteins, and hence may play an important role in intracellular transport of various molecules.¹² Of the 2 principal receptors, CB1 receptors are the most widely expressed, located mainly in the central and peripheral nervous systems, plus a few other locations including cardiovascular, visual and gastrointestinal systems. CB2 receptors have a more limited distribution, being located primarily in the immune system, including lymphatic tissue, spleen, macrophages and the immune cells of the central nervous system.^{1,4,12} CB2 receptors have significantly lower affinity for THC than CB1 receptors.^{1,12} Psychotropic effects are largely due to activation of the CB1 receptors, while the CB2 receptors in the periphery affect immune cells and play a role in inflammation and immune response.^{4,12} Interestingly, endocannabinoid signalling works in a retrograde fashion, with messengers synthesized

postsynaptically that then travel backwards across the synapse to inhibit presynaptic neurotransmission and modulate the release of other presynaptic neurotransmitters.²

PHARMACODYNAMICS OF CANNABINOIDS

THC is the primary psychoactive component of cannabis. It works primarily as a weak partial agonist on CB1 and CB2 receptors, with well-known effects on pain, appetite, digestion, emotions and thought processes.^{4,8,12} It may cause adverse events depending on dose and tolerance.¹³ THC acts via the dopaminergic system to increase dopamine production. Chronically THC-stimulated dopamine elevations may cause a down-regulation of innate dopamine production as well as up-regulation of existing CB1 receptors, such that additional amounts may be needed to maintain the same effect, or existing doses may produce less effect, over time. While no studies dealing specifically with addiction in users of medical cannabis have yet been published, among chronic

TABLE 1. Medical cannabinoids in community oncology practice: the good and the bad^{1-6,11-16}

THC/CBD Benefits	THC/CBD Adverse effects
<p>Documented beneficial effects — general</p> <p>Inflammation reduction Anorexia and cachexia reduction Wasting attenuation Pain relief—especially chronic or neuropathic Anxiety reduction Insomnia reduction Nausea reduction Emesis reduction Seizure reduction</p> <p>Documented beneficial effects — specific conditions</p> <p>Seizure disorders Glaucoma HIV/AIDS Posttraumatic stress disorder Spastic muscle disorders Arthritic pain, including fibromyalgia Neuropathic syndromes, including peripheral neuropathy Neurodegenerative disorders, including Alzheimer’s Inflammatory bowel disease</p> <p>Documented beneficial effects — cancer-related</p> <p>Cancer cachexia reduction Chemotherapy-induced emesis reduction Chemotherapy-induced nausea reduction Chronic cancer pain reduction</p> <p>Possible beneficial effects — cancer-related</p> <p>Inhibition of angiogenesis Facilitation of apoptosis Stimulation of autophagy Antiproliferative growth inhibition (animal models) Possible immunoregulatory role</p>	<p>Documented adverse effects — general</p> <p>Addictive potential Possible motor vehicle problems Psychosocial/neuropsychiatric Impaired short-term memory Impaired motor coordination Possible altered judgement Possible impaired social interactions Possible paranoia and psychosis Vascular instability, including stroke, arrhythmia Cannabinoid hyperemesis syndrome Associated with smoking/inhalation: <ul style="list-style-type: none"> • Chronic bronchitis • Possible lung cancer risk • Bladder head and neck cancer risk uncertain </p> <p>Possible adverse effects — cancer-related</p> <p>Possible proliferation of cancer cells at lower doses Suppression of the antitumour immune response</p>

CBD: cannabidiol; THC: tetrahydrocannabinol.

recreational users, an “addictive” potential of around 10% has been noted.^{2,4,13}

In contrast to THC, CBD has little affinity for the endocannabinoid receptors directly, but rather is a negative modulator of CB1.^{1,2,4} CBD is non-intoxicating and without psychotropic properties, but represents a pharmacologic analgesic with neuroprotective, sedative, antipsychotic, antiemetic, antispasmodic and anti-inflammatory and immunoregulatory properties.^{2,4,12} CBD seems to attenuate several adverse THC effects, including tachycardia, psychotic symptoms, and strong psychological reactions, including anxiety.^{2,4}

The potential benefits and harms of medical cannabinoids are described in **Table 1**. In terms of positive effects in cancer patients, relief of refractory chemotherapy emesis or pain, stimulation of appetite, and help with sleep and relaxation are most commonly described.^{4,5,14} When used with the proper preparation and in the right dosing, there seems to be a consensus that medical cannabinoids have a tolerable side effect profile, possibly more tolerable than conventional therapies.^{3,14} Particularly appealing is the concept of being able to use a single medication for a variety of problems, such as pain, anxiety, sleep disorders and anorexia.^{2,3,14} There are few absolute contraindications to cannabinoid therapy, but these include psychosis, bipolar disorder, significant cardiac disorder, lactation and pregnancy, prior history of significant substance abuse, and documented cannabis allergies.^{13,14} Driving is generally not recommended for 4 hours after inhaled medical marijuana, 6 hours after oral, or 8 hours if any “high” or euphoria was experienced.¹⁴

While to date only described in recreational cannabis users, a rare but noteworthy complication is the cannabinoid hyperemesis syndrome, characterized by abdominal pain and a cyclical vomiting syndrome in a context of chronic usage, typically over many years.¹⁵ Vomiting may occur >20 times per day and episodes can last from 24 to 48 hours. A history of repetitive daily multiple hot showering or bathing, providing symptomatic relief, is a clinical pearl supposedly pathognomonic for this diagnosis.¹⁵

TYPICAL CANCER CANNABINOID USE AMONG PATIENTS WITH CANCER

A 2004 Spanish study of over 2,000 patients, over 50% of whom had cancer, makes it possible to profile cannabinoid use in the context of malignancy for symptom relief, and estimate typical anticipated benefits and side effects.¹ The typical patient was age 45, using cannabinoids for <1 year. Consumption was mainly smoked (70%), but also ingested (23%) or infused (16%). Therapy had been self-initiated in 60%, while in 10% of cases a medical professional was involved. Beneficial effects were noted in over 50%, included hypnotic effect (56%), nausea improvement (47%), and improved pain relief and appetite (both 46%). Commonest reported adverse effects included dry mouth, emotional lability, memory impairment, and ocular irritation.¹

In another study in Israel involving almost 1,700 cancer patients treated with medical cannabis between 2015 and 2017 for pain, insomnia, nausea, vomiting and anorexia,

approximately 60% achieved treatment success at 6 months, while 4% reported no change.¹⁶ Improvements were also reported in insomnia, restlessness, anxiety, depression, pruritus and headache. Study patients were frequently able to decrease their dose of conventional medications; in the case of opioids, approximately 50% continued to take the same dose, 10% decreased the dose, and 36% ceased taking them completely. At least 30% of patients experienced one side effect, the most common being, in decreasing order of frequency, dizziness, dry mouth, hyperphagia, sleepiness and psychoactive effect. This study concluded that cannabis represented a safe and well-tolerated palliative treatment for a majority of cancer patients.¹⁶

PHARMACOKINETICS OF CANNABINOIDS

Precise dosing and balance of THC and CBD are difficult to achieve with medical cannabis and make it somewhat problematic to generalize from the studies that have been accomplished. The highest percentage of THC that has been studied is 9.4%, while many products are more potent, with THC levels around 15%.¹¹ Route of administration also makes a difference.⁵ The various effects of cannabis-based products will depend not only on the relative content of the active molecules and proportion of CBD and THC, but also on the method of consumption.^{1,11,14} Absorption is affected by bioavailability and lipophilicity.^{1,5} Cannabinoids are lipophilic with low water solubility, so absorption is improved in the presence of fat or oils. Bioavailability following smoking is in the range of 10% to 25%, while use of a pipe increases this to 45%.¹ The bioavailability of ingested cannabinoids is only in the range of 2% to 10%. Peak effects with smoking occur within 15 minutes versus 2 to 3 hours for oral therapy. Total duration of effect is typically 4 hours for smoking and 6 to 8 hours for oral therapy.^{1,2,4,5}

CYTOCHROME METABOLISM OF CANNABINOIDS

The cytochrome P450 (CYP450) enzymatic system is utilized for the biotransformation of most medications during activation and metabolism.^{7,8,12} Drugs may be substrates, inhibitors or inducers of these enzyme systems. Humans have approximately 60 CYP genes, and the enzymes are found primarily in liver cells, where most drug metabolism occurs.^{1,12} The CYP3A4 enzyme is responsible for the metabolism of more than 50% of all medications.^{7,8} CYP2D6 is the most efficient of the hepatic cytochromes and is responsible for the metabolism of 25% to 30% of all medications. Cytochrome CYP2C9 represents about 18% of total liver cytochromes and is involved in the metabolism of a number of anticancer agents.⁸

Most of the potential cannabinoid cytochrome interactions concern inhibition, rather than stimulation of transport or metabolism.^{1,8} THC and CBD are both substrates for CYP3A4, while THC is also metabolized by CYP2D9 and CBD by CYP2C19.^{1,7,8} Both THC and CBD competitively inhibit CYP3A4, with CBD being far more potent in this regard.^{7,8} A variety of documented and potential interactions with medical cannabinoids and the cytochrome system have been both postulated and described (see **Table 2**).

Of considerable concern is the fact that some anticancer medications are also metabolized by cytochromes CYP3A4 and CYP2D6.^{7,8} Fewer anticancer drugs are metabolized by cytochrome CYP2D6, but interactions may have major consequences. For instance, CYP2D6 interactions are responsible for the >50% lowering in efficacy of tamoxifen seen with certain antidepressant therapy.¹ To date, theoretically postulated interactions between medical cannabinoids, the cytochrome system and antineoplastic agents lack scientific evidence, although there is no reason to expect that they are any less significant than interactions that have already been identified.

Concern has also been raised that cannabinoids may interfere with the glucuronidation and urinary elimination of antineoplastic agents, or with the activity of cellular membrane transporters, possibly including P-glycoprotein, and breast-cancer resistance proteins BCRP and MRP.^{1,12}

The possibility of significant interactions with the immunobiology of tumours has also been raised.¹⁷

ETHICAL RESPONSIBILITIES RELATING TO THE PRESCRIPTION OF MEDICAL CANNABINOIDS

The 4 principles of the ethical practice of medicine are respect for autonomy, beneficence, non-maleficence and justice.^{18,19} Beneficence and non-maleficence require a discussion regarding the potential risks and benefits before prescribing any treatment or medication.¹⁸ In the case of medical cannabinoids, this often places physicians in an ethical quandary, since relevant clinical data, including long-term side effects, are not available for use in many of the medical conditions for which they are prescribed. This is compounded by the large variety of THC/CBD preparations available, each with varying therapeutic ratios.

The price of medical cannabis is currently not regulated

TABLE 2. Potential concerns around drug-drug interactions^{1,7,8,12,17,20}

<p>Some known knowns</p> <p>THC is metabolized by CYP3A4 and CYP2C9. CBD is metabolized by CYP3A4 and CYP2C19. Cannabinoid levels may therefore be increased or decreased through interactions.</p> <p>Concerns are based on:</p> <ul style="list-style-type: none"> • Study with ketoconazole, a strong CYP3A4 inhibitor, produced a 20% increase in THC levels and a two-fold increase in CBD levels. • Study with rifampin, a strong 3A4 inducer, decreased THC levels by 20% to 40%, and decreased CBD levels by 50% to 60%. • Study showed poor CYP2C9 metabolizers have THC concentration 3x higher than extensive metabolizers. <p>Both THC and CBD competitively inhibit CYP3A4, with CBD being far more potent in this regard. CBD also inhibits CYP2C19.</p> <ul style="list-style-type: none"> • Study with clobazam combined with CBD resulted in a 500% increase in noreclobazam levels (principal active metabolite).
<p>Some known unknowns</p> <p>Concerns are based on:</p> <p>Evidence that CYP3A4 inhibitors increase serum concentration of THC and CBD; therefore:</p> <ul style="list-style-type: none"> • Use alongside strong inhibitors (ketoconazole, clarithromycin, antiretrovirals, idelalisib) may increase levels of THC/CBD • Use alongside moderate inhibitors (aprepitant, diltiazem, imatinib, nilotinib, fluconazole, grapefruit juice) may increase levels of THC/CBD <p>Evidence that CYP3A4 inducers reduce serum levels of THC and CBD</p> <ul style="list-style-type: none"> • Use alongside strong inducers (carbamazepine, phenytoin, enzalutamide, St John's wort) may decrease levels of THC/CBD <p>Theoretical possibility that CYP2C9 inhibitors may increase serum concentration of THC</p> <ul style="list-style-type: none"> • Use alongside strong inhibitors (capecitabine, 5-fluorouracil) could theoretically increase levels of THC. • Use alongside moderate inhibitors (abiraterone, sorafenib, omeprazole, sulfa compounds) could theoretically increase levels of THC. <p>Another concern: CBD, and to a lesser extent, THC, may inhibit CYP3A4, but to date possible interactions have not been investigated with cancer medications that have CYP3A4 interactions. These include: axitinib, bosutinib, crizotinib, dabrafenib, erlotinib, gefitinib, ibrutinib, imatinib, lapatanib, nilotinib, olaparib, pazopanib, ruxolitinib, sunitinib, bortezomib (CYP3A4 and CYP2C19), cabazitaxel, docetaxel, vinca alkaloids.</p>
<p>Some unknown unknowns</p> <p>Possible deleterious interactions in tumours between cannabinoids and drug transporters: P-glycoprotein and other membrane transporter enzymes.</p> <p>Possible deleterious interactions in tumours between cannabinoids and glucuronyl transferases.</p> <p>Possible proliferation of cancer cells with varying THC/CBD dosing.</p> <p>Need for additional research into:</p> <ul style="list-style-type: none"> • Potential for cannabinoids to adversely interact with the benefits of the new immune therapies. A retrospective study found that response rates to nivolumab were 37.5% in patients not using cannabinoid therapies, and 15.9% in patients who were. • Potential for cannabinoids to suppress the immune system by stimulating the release of myeloid-derived suppressor cells. • Potential for cannabinoids to suppress T-cell function, decrease IL-2 and interferon, and decrease T-cell proliferation.

CBD: cannabidiol; THC: tetrahydrocannabinol.

TABLE 3. Current individual provincial requirements for authorizing medical cannabis

Province	Medical form required details	Registration with provincial college required	Keeping & sending of information	Specified prescription length	Other qualifiers
British Columbia	Medical form/record required in all jurisdictions: Must include patient information, prescriber information, and prescribed dried cannabis quantity in grams per day, including assigned period of use.	No	Retain copy as per normal document keeping	Documentation and prescription for medical cannabis must be filled out on an annual basis	Must document the failure of conventional therapies, use of addiction risk tool, and a patient medication PharmaNet review.
Alberta		Yes	Retain copy and send copy to college within one week of document completion		Must follow every 3 months once stabilized.
Saskatchewan		No	Retain copy as per normal document keeping; some provinces also require a separate log of all authorizations to be available for subsequent College review if requested	Prescription length follows provincial legislations for prescription of controlled substances	Patient must sign treatment agreement.
Manitoba		No			
Ontario		No			Must have THC % documented. No prescriptions for age <25. Must document conventional treatment failure.
Quebec		No			Currently only to be prescribed in context of a recognized research project.
New Brunswick		No			Must specify maximum daily amount; patient must store in a safe location.
Nova Scotia		No			Must have direct contact with patient. No direct billing of patients allowed for cannabis services.
Prince Edward Island		No			Written consent must detail risks and side effects and mention lack of scientific verification. No telehealth prescriptions allowed.
Newfoundland		No			Must document use of addiction risk tool. Periodic reassessment required.

in Canada. The price is set by producers licensed by Health Canada, and averages around \$7 per gram. Given that most patient smoke 1 to 3 g per day, the typical cost can approach \$600 per month.¹¹ Other than Veteran’s Affairs, there is presently little public funding for medical cannabinoids, and very few private insurers offer coverage. Special funding exemptions may be obtained through the Canada Pension Plan Disability Program and the Ontario Disability Support Program, however the financial burden would appear to be in direct conflict with the ethical principle of justice, which implies equal access to therapy regardless of financial means.²

Medical marijuana in Canada has become a huge industry, capitalized at billions of dollars and involving millions of dollars in sales. Industry strength is illustrated by the federal government’s recent decision to reduce Veterans Affairs marijuana benefits from 10 g a day to 3 g a day after the budget for veterans ballooned from around \$4 million in 2014 to over \$60 million in 2016.²¹ This intersection of medicine and commercial interests, coupled with somewhat vague therapeutic indications and high availability, may see commercial interests push utilization, and expose both cli-

nicians and patients to ethical dilemmas similar to those seen with the pharmaceutical industry.^{18,19} When recreational marijuana is not legal, there are concerns that prescription marijuana is used by people other than the patients authorized to receive it. In the US, 40% of adolescents report obtaining marijuana from someone with a medical marijuana prescription.¹⁸

MEDICAL, LEGAL AND PROFESSIONAL REGULATORY CONCERNS

Community oncologists face a number of medical-legal and provincial medical College obstacles in prescribing cannabinoids.^{2,10,11} With the rapidly approaching legalization of recreational marijuana in Canada, one faction of the Canadian Medical Association wants to wash their hands completely of the medical cannabis program, arguing that there is no longer any need for a medical/physician gatekeeper role.²² The abolition faction also believes that a lack of scientific evidence puts the prescribing physician in a tenuous position. The opposing faction argues that medical cannabinoids represent potent pharmaceutical substances that merit

professional medical input and regulation like any other prescription medication.²²

The Canadian Medical Protective Association (CMPA), which provides medical legal protection for the vast majority of Canadian physicians, produced a duties and responsibilities document regarding medical cannabis in August 2016.¹⁰ This stressed the absence of scientific evidence on the benefits of cannabinoids, as well as the challenge of dealing with patient requests for access to medical marijuana. This document essentially reinforced the Canadian federal marijuana regulations (Access to Cannabis for Medical Purposes Regulations [ACMPR]), which require that every licensed healthcare practitioner provide a medical document that specifies the daily quantity, expressed in grams of dried marijuana, authorized for the patient.¹⁰ In Canada, commercial producers of medical marijuana are licensed and must meet strict quality control, safety and security requirements. The licensed producer will be the one to determine the equivalent quantity of alternate products (e.g. cannabis oil) in relation to the dried marijuana prescribed.^{2,10} With the medical document in place, patients may also register with Health Canada to self-produce a limited amount of marijuana for medicinal purposes, or designate someone as producer for them.

The CMPA bulletin emphasizes the need for individual physician prescribers to be knowledgeable and abide by their individual provincial colleges' regulations relating to cannabinoids.¹⁰ It also references the College of Family Physicians of Canada guidelines.¹¹ The CMPA emphasizes that prescribing physicians must have the necessary clinical knowledge to engage in meaningful discussions with the patients about medical marijuana and that consent must be documented in the patient's medical records. As a corollary, physicians who are unfamiliar or uncomfortable with medical cannabis should not in any way feel obligated to prescribe.^{10,11}

The Canadian Family Physicians 2018 simplified guideline for prescribing medical cannabis does not endorse generalized use, but suggests restricted use in subsets of medical conditions, specifically neuropathic pain, refractory palliative and end-of-life pain, refractory chemotherapy-induced nausea and vomiting and spasticity due to multiple sclerosis or spinal cord injury.¹¹ In most of these instances, cannabinoids are not recommended as the first line of therapy, and a pharmacologically developed product is endorsed over smoked or ingested cannabis formulations.

The various provincial medical college requirements are summarized in **Table 3**. These specify that the "medical document" must state a daily allotment in grams and the length of time for which the patient might access medical cannabis. It should be noted that Health Canada neither approves nor regulates medical cannabis in the way it does for pharmaceuticals, hence the "medical document" issued by physicians is distinct from and only partially analogous to a prescription. Instead, it might be viewed as a recommendation to the medical cannabis program.²

COMMUNITY ONCOLOGIST CONCERNS REGARDING MEDICAL CANNABIS AUTHORIZATION

A summary of concerns for community oncologists is pro-

TABLE 4 . Issues for community oncology practitioners

- Provincial and federal government regulatory processes
- Provincial medical college regulatory processes
- CMPA and potential medical litigation concerns
- Professional relationship to industry and industry-sponsored marijuana clinics
- Informed patient consent in relation to THC/CBD products
- Ethical issues relating to patient autonomy, beneficence, non-maleficence and justice
- Patient education and knowledge in relation to cannabis products
- Patient interactions with the THC/CBD black market
- Medical cannabis sources and quality issues
- Prescription amount, dosing and assignment of administration responsibilities
- Followup responsibilities for medical cannabis patients, including dealing with complications
- Cost to patients and coverage issues
- Possible patient and physician social stigma

CMPA: Canadian Medical Protection Association; CBD: cannabidiol; THC: tetrahydrocannabinol.

vided in **Table 4**. A 2018 American Society of Clinical Oncology (ASCO) survey revealed that 80% of oncologists in the US had discussed medical marijuana use with their patients.²³ Eighty percent reported that these conversations were most frequently initiated by the patient or their family. On the other hand, less than 30% of oncologists felt knowledgeable enough about medical marijuana to make concrete recommendations, even though 70% believed medical marijuana to be helpful to cancer patients.²³

Patients must be informed about potential adverse effects such as acute impairment of memory, coordination, and judgement, as well as possible chronic effects such as cannabis abuse disorder, cognitive impairment, and chronic bronchitis, as well as the possibility of increased risk for motor vehicle accidents.^{10,11,14} Prescribing physicians should be knowledgeable about individual cannabinoids and carefully consider the risk benefit ratio for the individual patient.^{2,14} This includes selection criteria such as age, severity and nature of the medical disorder, prior or current serious psychiatric or substance abuse disorder, prior trial of standard medical therapy, lack of serious underlying cardiopulmonary disease or mental illness, and agreement to followup visits.^{2,11,14}

In this era of team-based multidisciplinary interprofessional collaborative care, it might seem that clinical pharmacists, with their access to the electronic drug history and documented skills in assessing potential drug interactions, would be the ideal "gatekeepers" for medicinal cannabis.⁵ However, at this point in time, nowhere in Canada are they able to play this role. Similarly, Canadian nurse practitioners are currently restricted from authorizing medical cannabis.¹⁰

CONCLUSIONS

Even as medical oncologists see increased interest in and requests for medical cannabis, knowledge about the multiplicity of preparations, forms and dosing is lacking and there remain many unknowns regarding possible interactions between cannabinoids and other therapeutic agents. The only

published study to date investigating medicinal cannabis with chemotherapeutic agents found no effect on plasma pharmacokinetics, however theoretical concerns persist based on how similar drugs are known to interact with the cytochrome system. Of all the cannabinoids, CBD appears to be the most promising molecule, but it is also the natural cannabinoid with the greatest risk for drug interactions. In addition to needing better education and more evidence about cannabinoid pharmacokinetics, community oncologists face a number of medical legal, ethical and professional issues in authorizing cannabis use.

Currently we can be confident that medical cannabinoids have some utility in symptom management for patients living with and beyond cancer. Compared with most therapeutic agents that oncologists use, the side effect profile of medical cannabinoids appears acceptable, and most adverse effects are well identified and manageable. For a single agent to manage a multiplicity of symptoms simultaneously including nausea, anorexia, pain, insomnia as well as anxiety would seem to be advantageous. Hopefully this review will help to provide some insights for those who continue to struggle with this challenging issue. 

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