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A user's guide to cannabinoid therapies in oncology

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ABSTRACT

"Cannabinoid" is the collective term for a group of chemical compounds that either are derived from the *Cannabis* plant, are synthetic analogues, or occur endogenously. Although cannabinoids interact mostly at the level of the currently recognized cannabinoid receptors, they might have cross reactivity, such as at opioid receptors.

Patients with malignant disease represent a cohort within health care that have some of the greatest unmet needs despite the availability of a plethora of guideline-driven disease-modulating treatments and pain and symptom management options. Cannabinoid therapies are varied and versatile, and can be offered as pharmaceuticals (nabilone, dronabinol, and nabiximols), dried botanical material, and edible organic oils infused with cannabis extracts. Cannabinoid therapy regimens can be creative, involving combinations of all of the aforementioned modalities. Patients with malignant disease, at all points of their disease trajectory, could be candidates for cannabinoid therapies whether as monotherapies or as adjuvants.

The most studied and established roles for cannabinoid therapies include pain, chemotherapy-induced nausea and vomiting, and anorexia. Moreover, given their breadth of activity, cannabinoids could be used to concurrently optimize the management of multiple symptoms, thereby reducing overall polypharmacy. The use of cannabinoid therapies could be effective in improving quality of life and possibly modifying malignancy by virtue of direct effects and in improving compliance or adherence with disease-modulating treatments such as chemotherapy and radiation therapy.

Key Words Cannabinoids, Δ-9-tetrahydrocannabinol, THC, cannabidiol, CBD, medical cannabis, pharmaceutical cannabinoids, marijuana

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INTRODUCTION

The *Cannabis* plant has a long and colourful history that spans more than 5000 years of world history and human usage[1–4]. In contemporary times, the term "cannabis" has commonly been supplanted by the more colloquial term "marijuana" (also spelled "marihuana"). An extremely versatile and easily cultivatable plant, *Cannabis* was used by ancient cultures for food, fibre, and medicinal purposes[1–4]. In the 20th century, it was a topic of much folklore, pop culture, controversy, and loathing.

The chemical characterization of the main active elements from the *Cannabis* plant and the identification of human cannabinoid receptors have together served as validation and a scientific platform to launch further research into the utility of cannabinoids in the health care arena. Thus, cannabis and its derivatives hold much promise and potential as *bona fide* therapeutic agents. Moreover, a paradigm shift, fueled by an almost exponential expansion of basic scientific and clinical research since the end of the 20th century, is showing that cannabinoids have beneficial effects beyond pain and symptom management and could be entering into the domain of disease modulation[1].

DOCUMENTING THE SHIFT

Differentiating Medical Cannabis from Recreational Cannabis

Starting in the early 2000s, Canada was one of the first of a growing number of countries to legalize botanical *Cannabis* for medical purposes[5]. Medical cannabis, also known as medical marijuana, which intends to relieve symptoms and potentially to modulate disease, must be distinguished from recreational cannabis, which intends to deliver a psychotomimetic state of "high." Cannabis strains used for recreational purposes tend to contain higher levels of Δ-9-tetrahydrocannabinol (THC) and a lower ratio of cannabidiol (CBD) to THC.

Medical cannabis in Canada is cultivated under quality-controlled conditions and contains reproducible

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levels of the main cannabinoid and non-cannabinoid substances. Moreover, the composition of medical cannabis can be tailored to meet the particular needs of the patient. The *Cannabis* genus has two main species —namely, *Cannabis sativa* and *Cannabis indica*[1–4]. The *Cannabis* plant generates more than 400 chemical compounds, of which approximately 80 are cannabinoid compounds and more than 200 are non-cannabinoid compounds[1–4]. From a health care perspective, the most clinically relevant compounds include the cannabinoid agents THC and CBD, and the non-cannabinoid terpenoids and flavonoids[1–4].

It has been postulated that the main cannabinoid and non-cannabinoid components of medical cannabis show synergistic clinical effects (dubbed the "entourage effect")[6]. Medical cannabis can be dispensed in a dried botanical format that might be smoked, vaporized, brewed as tea, or cooked as edible food products[1–4]. More recently in Canada, medical cannabis extracts compounded in organic edible oils can be orally ingested, administered through vaporization, or applied topically[7]. Anecdotally, experienced users say that, compared with *C. indica, C. sativa* is likely to produce more of a "high" and a euphoria that tends to produce a more relaxed feeling. That difference might be attributable to different THC:CBD ratios in the two plant species. Usually, *C. sativa* has a higher concentration of THC; CBD predominates in *C. indica*[1–4]. However, the purported differences between the two plants might also be a result of different levels of other components such as terpenes and flavonoids[1–4].

The Endocannabinoid System

The endogenous opioid and cannabinoid systems are the only chemical systems in the human body that have survived more than 500 million years of human evolution[1–4]. Interestingly, the endogenous cannabinoid system might have evolved millions of years before the evolution of the *Cannabis* plant itself[1]. The endogenous cannabinoid system is composed of all cannabinoid receptors, endogenous ligands (endocannabinoids), second messengers, and endocannabinoid degradation pathways, most notably the fatty acid amide hydrolase system[1–4,7–11]. Although an understanding of the endogenous cannabinoid system is far from complete, two human receptors, CB1 and CB2, have currently been defined and cloned[1–4,8–11]. A third putative human cannabinoid receptor, GPR55, is currently in the process of being characterized[8–10].

Cannabinoid receptors are ubiquitous and have an estimated 10-to-1 preponderance over opioid receptors in humans[1–4]. Furthermore, unlike opioid receptors, which are located only extracellularly, cannabinoid receptors are also expressed on intracellular organelles such as mitochondria, the Golgi apparatus, and nuclei[12]. The cannabinoid receptors that are located on cell membranes are functionally coupled with G proteins[1–4,8–10]. The CB1 receptors are located mostly on neural tissue within the central nervous system and afferent nociceptors. The CB2 receptors, although located mostly in immune system tissues such as spleen, tonsils, lymph nodes, mast cells, macrophages, and lymphocytes, are also expressed within the central nervous system through their presence on microglia.

Generally speaking, CB1 signalling mediates neuromodulatory activities, and CB2 signalling mostly mediates immunomodulatory activities. Thus, cannabinoid signalling is intrinsically involved in multiple physiologic and homeostatic systems as well as in pathophysiologic mechanisms[1–4,8–10]. The main human endocannabinoids are *N*-arachidonylethanolamide and 2-arachidonlyglycerol. Those two molecules activate CB1, CB2, GPR55, and transient receptor potential ion channels such as TRPV1[1–4,8–10]. Endocannabinoids, acting as retrograde synaptic messengers at neural synapses, are short-lived because they are degraded by fatty acid amide hydrolase.

Exogenous cannabinoids, whether pharmaceutical or botanically sourced, mimic and potentiate signalling by the endocannabinoids[1–4,8–10]. Exogenous cannabinoids such as botanically derived THC and pharmaceuticals such as nabilone and dronabinol are agonists of both CB1 and CB2[1–4,8–10]. Cannabidiol functions as an activator of TRPV1, an inhibitor of both cyclooxygenase and lipoxygenases, and reduces *N*-methyl-D-aspartate toxicity. The activity of CBD as a negative allosteric inhibitor of CB1 helps to reduce the CB1-mediated psychotomimetic effects of THC, thereby increasing its therapeutic potential[11,13,14].

Cannabinoid Pharmacology

In Canada, more than 200 strains of medical cannabis are available from licensed producers[5]. Given the heterogeneity of both the cannabinoid and non-cannabinoid components of those multiple strains, it is not surprising that their complete pharmacologic profiles have not been fully elucidated. Although much is known about botanically sourced THC and CBD, and the pharmaceutical cannabinoid agents, little clinical data on the pharmacology of terpenoids and flavonoids have been published. Adverse outcomes such as psychotomimetic reactions and hypotension are more likely to occur with recreational cannabis because it tends to be preponderant in THC. The *Cannabis* plant yields inactive acidic forms of THC and CBD, namely THC-A and CBD-A. The process of decarboxylation, which occurs through thermal treatment (heating or combustion), generates the pharmacologically active formats[15,16]. Although dried botanical cannabis from licensed producers for medical use is not thermally treated, medical cannabis oils contain cannabinoids that have undergone decarboxylation (Tweed Inc. Personal communication, 18 September 2016).

Generally speaking, higher bioavailability levels are achieved with smoking and vaporization than with oral ingestion. The bioavailability of smoked or vaporized THC is 10%–25% and depends on the duration of breath hold and depth of inhalation[5,17–22]. Peak serum concentrations occur within 2–10 minutes. Absorption of both THC and CBD from the gastrointestinal tract is good, but both molecules undergo extensive first-pass metabolism. The bioavailability of orally administered THC and CBD is in the range of only 2%–20%[5,17–22]. Table I summarizes the pharmacokinetic profiles of the various forms of cannabinoid therapies[5,17–22].

As summarized in Table II, THC and CBD are both processed through the cytochrome P450 (CYP) system in the liver[5,17–22]. The effect of CYP 2C9 on THC metabolism is significantly affected by genetic polymorphisms; compared with individuals carrying high-functioning variants, those

TABLE I Pharmacokinetic profile of various cannabinoid therapies

Route of administration	Action		Amenable to self-titration
	Onset (min)	Duration (h)	
Smoked	5	2–4	++++
Vaporized	5	2–4	++++
Oral			
Botanical			
Cooked	30–60	8–12	+
Oil	30–60	8–12	+
Tea	30–60	8–12	+
Nabilone	60–90	8–12	+
Dronabinol	30–60	4–6	+
Oromucosal (nabiximols)	15–40	2–4	++

TABLE II Cannabinoid cytochrome P450 metabolism

	Metabolizing enzyme	Enzyme inhibition	Enzyme induction
Smoked cannabis	2C9, 2C19, 3A4	3A4, 2B6, 2C9, 2D6	1A2
Tetrahydrocannabinol	2C9, 3A4	3A4	—
Cannabidiol	2C19, 3A4	2B6, 2C9, 2D6, 3A4	—
Nabilone	2C9	—	—
Dronabinol	2C9, 3A4	3A4	—

who carried genetic variants with diminished function experienced a doubling or tripling in THC exposure[23]. Furthermore, higher levels of THC and CBD can be observed with concomitant use of strong CYP 3A4 inhibitors. Although neither THC nor CBD are inducers of CYP enzymes, both are inhibitors of a number of those enzymes, most notably 3A4, the enzyme that has the largest number of commonly used medical drugs as substrates[22]. Smoked cannabis has been noted to induce CYP 1A2[24].

Being highly lipophilic, THC and CBD both have a large volume of distribution. They are also highly bound by serum proteins. Although, theoretically, a high incidence of drug–drug interaction by displacement from protein binding sites might be expected, only one case report to date has described the occurrence of an increased normalized ratio and bleeding complications in a patient who smoked recreational cannabis[25].

Cannabinoids for Medical Use

Although the assessment and treatment of pain and other symptoms in patients with advanced cancers has become a standard of care, many patients still have incomplete symptom control[26]. That situation persists despite a plethora of pharmaceutical therapies, including opioid analgesics and adjuvant or targeted therapies (for example, antiepileptic and antidepressant therapies). Traditionally, patients with cancer-related symptoms have constituted only 6%–8% of those requesting medical cannabis[5,27], but the proportion has rapidly increased in Canada with the institution of the Marihuana for Medical Purposes Regulations, enacted in April 2014, and the current program, Access to Cannabis for Medical Purposes Regulations, enacted in August 2016. Many oncology physicians are unaware of the potential medical benefits of cannabis[28] and are unwilling or unable to authorize their use. As a result, patients and caregivers might seek out illegal sources ("street marijuana"), which can be fraught, having implications such as dangerously tainted products and potential social and emotional harms[29–33]. A selective review of the best-supported treatments follows.

Pain

Cannabinoids, including herbal cannabis and extracts, have been used for the treatment of pain for centuries. There is evidence in historical texts and ancient pharmacopeia of treatment for various pain syndromes—from menstrual cramps to childbirth to headaches[1–3]. In terms of cannabinoid use in the modern era, an emerging literature includes systematic reviews that are showing benefit in several areas, including non-cancer pain[34,35]. Early studies using dronabinol, nabilone, and levonantradol demonstrated benefit, but their methodologies were not as rigorous as in more recent trials, and so the benefits might have been overestimated[36]. The few trials using cannabinoids in acute pain have shown essentially no benefit, and present recommendations are against cannabinoid use in the postoperative setting[37–39].

Cannabinoid treatments for cancer pain have been studied in a few randomized trials, but the evidence has been less than convincing. Earlier studies (published before 2001, as reviewed by Campbell *et al.*[36]) demonstrated mild benefits, with adverse effects limiting the dose used. Comparators such as codeine and secobarbital are not commonly used in patients with severe cancer pain, and so it is difficult to extrapolate the results. More recently, two placebo-controlled trials using a cannabis extract (nabiximols) did show modest benefit when used in addition to opioids and other adjuvant pain medications in patients with chronic cancer pain[40,41].

Chronic neuropathic pain has received the most focus, with studies looking at the use of pharmaceutical cannabinoids and cannabis and its extracts in a variety of settings (posttraumatic neuropathies, diabetic neuropathy, AIDS-related neuropathic pain, and so on). Two recent publications confirmed the benefit of cannabinoid use, with twenty-nine randomized studies having been examined and included in separate systematic analyses[34,35]. Cannabinoids were found to be safe, modestly effective, and a reasonable option for treating chronic neuropathic pain. Those data have contributed to the revision, by the Canadian Pain Society, of their consensus statement on the treatment of chronic neuropathic pain to include cannabinoids as third-level therapy[42]. Inhaled or vaporized cannabis has also been studied, but, again, few randomized trials have been conducted. A recently published meta-analysis demonstrated that 1 in 5–6 patients would benefit from the use of inhaled cannabis treatments for neuropathic pain[43].

Nausea and Vomiting

Controlling nausea and vomiting was one of the initial uses of cannabinoids documented in the modern scientific literature. In 1975, Sallan *et al.*[44] showed that use of THC could control the nausea associated with chemotherapy and almost eliminate emesis. Since then, several larger-scale studies—including placebo-controlled randomized studies using dronabinol, nabilone, and cannabis extracts—have been completed. At least two systematic reviews on the topic have shown benefit with the use of cannabinoids, especially pharmaceutical cannabinoids, in patients undergoing chemotherapy[45,46].

When looking at the use of cannabis or extracts to control nausea and emesis, the picture is not quite as clear. Many of the published studies were observational or uncontrolled, and certainly randomized controlled trial data for cannabis use are in short supply[47,48]. Preclinical research has established animal models for nausea (mouse, shrew), which have shown benefit with the use of CBD[49]. That benefit has been especially evident in a model of anticipatory nausea, a condition that has been difficult to treat for patients undergoing longer-term chemotherapy[49]. Anecdotal reports to us from patients who routinely smoke or vaporize cannabis (containing varying amounts of THC and CBD) before chemotherapy confirm improvement in their quality of life (as measured by the Edmonton Symptom Assessment System) and subsequent appetite and food intake.

Although treatment of some specific body areas (abdomen, chest, whole brain) with radiotherapy can induce nausea, very few reports of cannabinoid use in those situations have been published, and the reports that exist have used mainly pharmaceutical cannabinoids[50]. A recently published placebo-controlled study demonstrated that quality of life for patients with head-and-neck cancers undergoing radiotherapy is not improved with the use of nabilone[51]. The authors postulated that nabilone on its own is not potent enough to affect symptoms. However, they did find taking the medication did not worsen the patient's measured quality of life. Another recently published study surveyed 15 patients with previously treated head-and-neck cancer about their use of medical cannabis, and all respondents endorsed the benefits of cannabis in the treatment of the long-term residual effects of radiation[52].

Appetite Stimulation

The data supporting cannabis and cannabinoid use in appetite stimulation is less conclusive than it is in pain or nausea. When used in cancer patients with cachexia, cannabinoids appear to be only modestly effective. A study from the North Central Cancer Trial Group compared the use of an oral cannabinoid (dronabinol) with oral megestrol acetate and with the two drugs together. Final results did not show any statistical improvement in weight with dronabinol, either alone or in combination[53]. A Swiss-led study using cannabis extract in cancer patients also did not show benefit in terms of appetite or weight gain, and the trial was closed early after a mandated review[54]. A small Canadian study using oral dronabinol in advanced cancer patients demonstrated improved sense of taste and subsequent increased protein consumption. That change did not translate to weight gain, but patients did express improvement in quality of life measurements[55].

More promising results were seen in studies of the non-cancer population. A study of response to smoked cannabis, dronabinol, or placebo in patients with AIDS demonstrated that the patients using smoked cannabis experienced the greatest weight gain (3.51 kg vs. 3.18 kg vs. 1.5 kg respectively)[56]. An earlier study in patients with dementia treated with either dronabinol or placebo documented an increase in appetite, increased weight gain, and modulated aggressive behaviour[57].

CAN CANNABINOIDS CURE CANCER?

Although the main use of cannabinoids in patients with cancer and palliative patients has been symptom management, there could be other roles for these molecules in the treatment of malignancies. In one of the first reports of cannabinoids having antitumour effects, extracts of cannabis were shown to inhibit the growth of lung adenocarcinoma cells *in vitro*[58]. An *in vivo* mouse model produced similar results. Preclinical studies have investigated cannabinoid activity in several malignancies (lung, glioma, thyroid, lymphoma, skin, pancreas, endometrium, breast, prostate)[59–61], demonstrating antiproliferative, anti-metastatic, antiangiogenic, and proapoptotic effects (reviewed by Velasco *et al.*[62]).

Cannabis has not been studied clinically as a treatment for malignancy. Unfortunately, many claims of "curative" benefits of cannabis (fresh buds, dried cannabis, or "oil" products) can be found on the Internet, extrapolating the results of preclinical work to humans without any basis in fact. The only clinical study published to date that used cannabinoids enrolled patients with glioblastoma multiforme and was based on extensive preclinical work by the same investigators[63]. Their small study (9 patients) showed the safety of intracranial administration of THC and demonstrated antiproliferative effects in some of the patients. All patients eventually progressed and died, but not because of any effects of the extract. The investigators are actively continuing their clinical and research work, focusing on tumours of the central nervous system[62].

Oncologists might be concerned that cannabinoids could reduce the effectiveness of established chemotherapy agents. Several authors have investigated cannabis extracts used in tandem with a variety of chemotherapy agents *in vitro* and in animal models, showing synergism in reducing cell numbers, and no negative effect on anticancer function. Cell cultures from pancreatic[64], glioma[65], gastric[66], lung[67], and colon[68] cancers have been investigated using a range of antineoplastic agents, including gemcitabine, temozolomide, paclitaxel, and 5-fluorouracil. Synergism in inducing cancer cell death is a common finding, which bodes well for the possibility of human clinical trials in future[62].

Despite the emerging evidence of antineoplastic activity, some older *in vitro* studies demonstrated cancer cell proliferation and loss of immune-mediated cancer suppressor activity after treatment with cannabinoid preparations[58,69]. Some studies have even shown discordant results depending on the concentration of cannabinoids: low doses stimulated cancer proliferation, and higher doses demonstrated

antineoplastic activity[62]. Thus, conflicting evidence points to the need for sober second thought before outright recommendations of cannabinoids for cancer patients can be made. To quote Dr. Donald Abrams[28]:

> But again, mice and rats are not people, and what is observed *in vitro* does not necessarily translate into clinical medicine. The preclinical evidence that cannabinoids might have direct anticancer activity is provocative as well, but more research is warranted.

Currently, several clinical studies using cannabinoids in cancer therapy are registered at http://ClinicalTrials.gov (accessed 4 September 2016). An Israeli group is studying the use of cannabis extracts (cannabidiol) in patients whose cancers are resistant to the usual chemotherapy protocols (NCT02255292). Another phase I/II study is using nabiximols combined with temozolomide in patients with recurrent glioblastoma multiforme (NCT01812603, NCT01812616). Two more studies in the preliminary stages include the safety of dexanabinol in patients with advanced cancers (NCT01489826, NCT02423239) and cannabis (high CBD concentration) for pain and inflammation in lung carcinomas (NCT02675842).

ASSESSMENT OF PATIENTS REQUESTING MEDICAL CANNABIS

When a patient is referred to our outpatient clinic with a request for medical cannabis, several questions come to mind:

- Is this for a legitimate medical symptom?
- Is the patient being led to ask by another person? [Could be for good intentions (family offering treatment options) or for diversion (sharing of cannabis for recreational purposes).]
- Does the patient really know anything about medical cannabis?

Most of our patients have either tried medical cannabis or read about its role in symptom control. Those who have tried it (recreationally or for medical purposes) can accurately reflect on the benefits or the adverse effects experienced, which makes the discussion somewhat easier. Those who have little knowledge and less experience require a complete discussion with respect to the benefits, the possible adverse effects, the process of application and authorization, and the cost (which is borne by the patient, because it is not covered by provincial or private medical insurance). Table III lists our contraindications to authorization, which are similar to those published by Health Canada[70], the College of Family Physicians of Canada[71], and the Canadian Medical Protective Association[72]. It should be noted that no special license or additional certification is necessary to authorize the use of medical cannabis, but a working knowledge of cannabis (as already presented) is helpful for oncology professionals who are considering a patient request. Alternatively, consultation with a local expert (colloquially known as a "pot doc") might be necessary.

Once the decision is made to support authorization, the choice of which licensed producer and product to use can be somewhat difficult for some patients. The more than 30 licensed producers list more than 300 products for sale, which can be a problem for those who do not have experience with cannabis or patients who might be elderly or excessively fatigued. We do not advise that patients smoke the dried product; rather, they should vaporize, which is likely safer in the long run[73]. We also advise neophytes to choose a product that has a balanced THC:CBD ratio (for example, 5%:6% or 9%:9%). Cannabinoid proportions can be guided by available efficacy data (summarized in Table IV). Once patients have started to use the product and document the effects, the THC:CBD ratio for subsequent dosing can then be adjusted to meet symptom needs.

Given the lack of published guidelines or dose studies for the use of medical cannabis, the dictum "start low and go slow" should be used. Titration of dose should follow the effect on the symptom in question (for example, pain

TABLE III Contraindications and precautions associated with high use of tetrahydrocannabinol

Contraindications	Precautions
Age under 25	Driving motor vehicles
Pregnancy and lactation	Operating industrial equipment
Schizophrenia	Current use of sedatives and hypnotics
Psychosis with recreational cannabis	Hypotension
Compromised cardiac status	Heavy tobacco smoking[a]
History of alcohol or substance abuse	Use of strong CYP 3A4 inhibitors[b]*

[a] Risk of cannabis-induced arteritis.
[b] Clarithromycin, ketoconazole, indinavir, lopinavir, ritonavir.

TABLE IV Conditions potentially responding to cannabinoid therapies[74–78]

Target symptom	Tetrahydrocannabinol	Cannabidiol
Neuropathic pain	+++	+
Chemotherapy-induced		
Peripheral neuropathy	++	?
Nausea or vomiting	+++	Preclinical animal models
Anticipatory nausea	+	Preclinical animal models
Appetite stimulation	++	?
Spasticity or spasms	+++	+
Inflammation	+	++
Seizures	+	+++
Anxiety	+ or –	Simulated situations
Depression	+ (adjuvant)	Preclinical animal models
Malignancy		
Preclinical	++	++
Clinical	+	?

reduction, nausea control). Follow-up with patients is essential to determine benefits and any adverse effects, questions about use or strain selection, and outcomes. Certainly, if the adverse effects are not tolerable, then an alternative therapy should be considered. If the patient is not getting the desired symptom control, then some dose modification might be necessary. Discontinuation of cannabis should be considered if an adequate trial does not result in the desired outcome as determined by the treating team or the patient.

The Importance of Inter-professional Collaboration

Inter-professional collaboration is the new paradigm under which modern health care operates[79]. Research has demonstrated that inter-professional collaboration is enabled and promoted by inter-professional education, especially at the undergraduate level[79,80]. Although physicians ultimately authorize and prescribe cannabinoid therapies, valuable insights and inputs about achieving optimal patient outcomes can be derived from other members of the health care team, including nurses, social workers, rehabilitation therapists, and pharmacists.

Pharmacists are particularly central to the process because they have the training to assess and corroborate the appropriateness and safety of the use of cannabinoids through their access not only to the patient's electronic medical record, but also to advanced database tools capable of assessing potential drug–drug interactions and cytochrome P450 interactions[81,82]. Furthermore, pharmacies are designed to ensure proper storage and security of medical products. Pharmacists are also well positioned to comprehensively counsel patients and caregivers on the optimal methods of opioid (and by extension, cannabis) storage and disposal so as to limit diversion and unintentional exposure[83]. Thus, pharmacists are the ideal "gate-keepers" for medical cannabis once a patient has been identified by the physician and the inter-professional team. Moreover, given the emergence of cannabinoids as a novel therapeutic class, cannabinoid education for medical professionals as well as for patients and caregivers should be conducted per the principles of inter-professional education[80].

Cannabinoid Therapies As a Harm Reduction Strategy

Industrialized countries are experiencing exponential increases in the utilization of opioids[84,85]. Major public health issues are emerging as a result, not the least of which relate to drug diversion, opioid addiction, and death from opioid overdose[84,85]. Currently, opioids remain the mainstay of cancer pain management, and increased cancer survival translates into patients using opioids for longer periods of time[86]. Yet despite the widespread use of opioids, 50%–80% of advanced cancer patients die with unmet pain-relief needs[87].

High-dose and long-term opioid therapy in cancer patients is becoming a concern, given observed risks such as poly-endocrinopathy, osteoporosis, and immunosuppression[88]. Preclinical studies have demonstrated that certain opioids—such as codeine, morphine, methadone, and remifentanil—are associated with increased morbidity and mortality attributable to worsening of cancer and infections[88]. Opioid-induced hyperalgesia syndrome is also being reported with increased incidence, especially in patients with advanced cancer and escalating pain[85]. Thus, it behooves physicians to explore options that will allow for improved overall pain relief while curbing the overuse of opioids. Observational studies in advanced cancer cohorts have demonstrated that cannabinoid therapies are associated with opioid-sparing and improved analgesia[89].

A recent U.S. study demonstrated that the death rate from accidental opioid overdose has been reduced in the states in which medical cannabis is legal[90]. Published data on the addiction potential for recreational cannabis reflects a risk of 9.1%, which is lower than the risk for anxiolytics (9.2%), alcohol (15.4%), cocaine (16.7%), heroin (23.1%), and tobacco (31.9%)[91]. Finally, a British study showed that the overall harm score for user and society for recreational cannabis (score: 20) is less than that for amphetamines (score: 23), tobacco (score: 26), cocaine (score: 27), methamphetamines (score: 33), crack cocaine (score: 54), heroin (score: 55), and alcohol (score: 72)[92]. Because medical cannabis generally tends to have a higher ratio of CBD to THC, it would be expected to be associated with a lower predilection to diversion, less addiction potential, and lower overall harm scores than those for recreational cannabis[93].

SUMMARY AND FUTURE DIRECTIONS

The integration and broader utilization of cannabinoid therapies within the domain of oncology (including palliation) carries the potential not only for improved health care outcomes for patients but also for economic savings and greater safety for society[90,94]. Patient reports of improvement in quality of life, especially for those undergoing intensive treatment regimens, could be key to patients continuing with lifesaving or life-prolonging therapies. Cannabinoids might be able to help patients throughout their disease trajectory, but evidence about the ideal timing for cannabinoid initiation is lacking. Enrolment in clinical trials will help to answer many of those questions, and it can be hoped that support (financial and otherwise) from the medical community will increase as the public's acceptance of medical cannabis use broadens. More research will guide oncology and palliative care teams in their pursuit of excellence in cancer and symptomatic care.

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CONFLICT OF INTEREST DISCLOSURES

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