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INTRODUCTION

Cannabis has been in the news in Canada regularly, but the medical use of cannabis is not yet widely understood or accepted. Addressing questions and concerns about the subject was one focus of the recent International Annual Congress on Controversies on Cannabis-Based Medicines, held in Vienna, Austria in June. More than 200 attendees from 31 countries presented, debated, and discussed issues related to cannabis-based medicines and their currently accepted role in clinical practice. This document includes highlights from that conference in addition to an overview of cannabis use in Canada.

Cannabis differs from other medications in a number of ways. It is not a single chemical—more than 500 natural compounds, including over 120 cannabinoids, have been isolated from *Cannabis* species, including the medically relevant and well researched cannabinoids THC (delta-9-tetrahydrocannabinol) and CBD (cannabidiol). Cannabis is available in a number of formulations—it is being sold as dried cannabis, oils, capsules, and softgels (encapsulated oils) containing different amounts of THC and CBD. In addition, cannabis products vary in their cannabinoid contents due to normal botanical variability in strains and plants (think wine or coffee: soil, weather, and plant varieties all affect the final product). Cannabis represents a new therapeutic class with a multiplicity of effects acting through a number of mechanisms.

However, it's not that different. Like other medications, cannabis is frequently one tool in a toolbox of therapies that the clinician may use to treat an individual patient's condition. Its effects will vary between individuals and titration may be necessary. Its results can be measured on patient-related outcome (PRO) scales, and patients can take a drug holiday and re-evaluate its continuing efficacy. With time, cannabis and its derivatives will find their way into even more clinicians' treatment patterns.

Introduction to Cannabinoids

Despite the frequent discussions of cannabis in the news, it's easy to confuse the various terms getting thrown around. Here's a basic glossary:

- **Cannabis:** The plant from which cannabinoids are extracted. Also used to refer to the dried form of this plant, which can be smoked, vaporized, or eaten. Two of the most commonly cultivated species are *Cannabis sativa* and *Cannabis indica*, although centuries of crossbreeding means that most current cannabis varieties are hybrids.
- **Cannabinoids:** Molecules that interact with the endocannabinoid system. **Endocannabinoids** are naturally produced in the body, while **phytocannabinoids** are found in several plants but in highest concentrations in cannabis.
- **THC:** An abbreviation for delta-9-tetrahydrocannabinol, the cannabinoid responsible for many of the pharmacological and psychoactive effects of cannabis.
- **CBD:** An abbreviation for cannabidiol, a cannabinoid without euphoric effects that appears to have pharmacological benefits.
- **Terpenes:** Aromatic compounds found in essential oils, including cannabis oil, that may interact with cannabinoids to cause specific effects.
- **Dronabinol:** A synthetic cannabinoid with the same chemical structure as THC. Once marketed in Canada as Marinol® and sold as capsules but is not currently available in Canada.
- **Nabilone:** A synthetic cannabinoid that is an analogue of THC. Marketed in Canada as Cesamet® and sold as capsules.
- **Nabiximols:** A cannabis extract (a mixture of plant-extracted THC and CBD in a 1:1 ratio, also containing other cannabinoids and terpenes) that is sold as an oral-mucosal spray. Marketed in Canada as Sativex®.

The endocannabinoid system

The body's endocannabinoid system is composed of three parts: receptors, ligands, and metabolic enzymes. The two most common endocannabinoid receptors are CB1 and CB2. They are both located throughout the body, but CB1 receptors are more common in the central and peripheral nervous systems and the gastrointestinal system, while CB2 receptors cluster in the immune system, including the spleen and lymph nodes. Two main endocannabinoids have been identified to date: anandamide (AEA) and 2-arachidonoylglycerol (2-AG). These endogenous cannabinoids are agonists, or ligands, acting on endocannabinoid receptors. Metabolic enzymes synthesize and degrade the endocannabinoids, regulating their levels.

CB1 receptors are primarily located on presynaptic neurons. When a CB1 receptor is activated (by THC, endocannabinoids, or nabilone), it activates a signalling cascade that prevents the release of neurotransmitters into the synaptic cleft (for both excitatory and inhibitory neurons). Endocannabinoids are produced by postsynaptic neurons and work on the presynaptic terminal in a retrograde signalling process. CB2 receptors, on the other hand, are primarily found on immune cells and affect the release of cytokines and other molecules.

How cannabinoids work

Via the CB1 and CB2 receptors, cannabinoids act on a number of pathways in the body, which allow them to affect systems as diverse as feeding behaviours, insulin sensitivity, stress responses, gut permeability, inflammation, and emotional states. THC exerts its effects primarily through the activation of CB1, while CBD doesn't bind to either CB1 or CB2, but inhibits or activates other receptors, enzymes, and molecules.

The pathways underlying cannabis analgesia are only beginning to be understood, partly because there is no single site activated in the brain when pain is felt, and partly because cannabis may act on more than 20 pain pathways, including those not mediated by endocannabinoids. However, CB1 receptors are distributed more densely in the frontolimbic part of the brain, and this suggests that cannabis may preferentially target the affective qualities of pain. Studies using functional neuroimaging support this, showing that cannabis affects the activity of the anterior midcingulate cortex and the amygdala, both of which play a role in the emotional interpretation of pain.¹

Using Cannabinoids in Practice

In Canada, cannabis is available as dried flowers, as cannabis oil, and as softgels or capsules containing the oil. It can be administered by ingestion of the oil or by smoking or vaporizing the dried flowers.

Ingestion of oil, capsules, or softgels provides the most accurate dosing (Table 1).

Vaporizing (heating the cannabis to a temperature that volatilizes the cannabinoids and other compounds without combusting them) is preferred over smoking because it is associated with fewer toxic by-products and adverse health effects.

Information within the coloured boxes was not presented at the conference but was included to address significant topics not covered.

Table 1. Modes of administration of cannabis and their effects.

	INHALED	INGESTED
Onset	5–10 minutes	1–3 hours
Duration of effect	2–4 hours	6–10 hours
Starting dose	1 inhalation (using 1/2 teaspoon [0.1 g] of dried flower)	2.5 mg THC ± CBD
Absorption	Through the lungs directly into the bloodstream	From the gastrointestinal tract, metabolized by the liver before entering the bloodstream

Dosing and titrating

Vaporizing is measured in inhalations of cannabis. One common dosing method is as follows:

1. Start with ½ teaspoon (0.1 g) of dried flower.
2. Start with 1 inhalation; wait 15 minutes before consuming more.
3. Increase by 1 inhalation every 15–30 minutes until an optimal dose is achieved. (Add up the total number of inhalations to get the total optimal dose.)
4. If unwanted side effects occur, try a lower dose or a product with a different CBD to THC ratio.

5. Once the optimal dose has been determined, including the duration of effect, dose regularly or as needed.

When dosing with oil, softgels, or capsules, use the starting doses and titration schedule recommended by the authorizing health care practitioner. Use a starting dose on Days 1 and 2; if this dose is tolerated, increase the dose every two days. Continue until the patient reaches a dose that provides optimal benefit. Once-daily dosing is recommended during the dose escalation phase, but once you have identified your patient's optimal dose, you can adjust dose frequency based on symptom severity throughout the day.

The “start low, go slow, stay low” dictum applies to cannabis initiation: slow upward dose titration promotes tolerance to the psychoactive effects of THC.² According to experts, initiation and titration of cannabis eventually becomes similar to the titration of insulin. The optimal dose should improve symptoms and functioning while causing minimal euphoria or cognitive impairment.³

Cannabis-based oral products (oils, capsules, and softgels) are similar to long-acting formulations, since they have a longer duration of action and are generally used for chronic conditions. Vaporization of dried plant provides a rapid onset of action and is a shorter-acting route of administration frequently helpful for acute conditions. Patients on long-acting products can use supplemental doses of inhaled cannabis on a prn basis to maintain symptom control. However, the pharmacokinetics of oral and inhaled administration are different: do not use equivalency factors to convert from one form to the other.

Authorizing medical cannabis use in Canada

Under the Access to Cannabis for Medical Purposes Regulations, health care professionals (HCPs) may authorize and support their patients' use of cannabis for any condition at their medical discretion. Patients may access cannabis legally only through licensed producers, which are regulated by Health Canada, and must provide two documents to their licensed producer: an original medical document signed by their HCP and a signed registration form issued by the producer.

The medical document provides information about the HCP (including license number), the patient, and the dosage prescribed and must be sent by digital portal, secure fax, or original paper copy to the licensed producer

chosen by the patient. Health Canada requires that HCPs specify the number of grams of dried cannabis the patient is authorized to purchase on a daily basis (the average for medical purposes is 0.5–1.5 grams/day) and the duration of patient access (up to 12 months). Licensed producers have equivalency factors to determine the equivalent volume of oil or other product formulations based on the patient's maximum daily authorization.

Health care professionals must remind patients to obtain their cannabis through government-regulated retail outlets and not through unlicensed (illegal) dispensaries or other sources. Licensed producers offer pharmaceutical-grade products, made using Good Manufacturing Practices under the oversight of Health Canada and containing consistent percentages of THC and CBD, something that cannot be guaranteed with other products. In addition, patients who try to self-medicate using recreational cannabis will lack the critical guidance and management of all the HCPs normally involved in their care.

Clinical Evidence and Cannabis

Randomized controlled trials (RCTs) have long been considered the pinnacle of evidence in the medical arena (with the possible exception of meta-analyses, which analyze the same kind of trials). Unfortunately, publication in a peer-reviewed journal does not guarantee that a trial is providing unequivocal evidence for its conclusions: choices around trial size, randomization, blinding, and analysis can turn negative results into positive ones or vice versa.

Conducting RCTs with cannabis is challenging for a number of reasons:

- Depending on the country, government regulations may limit patient participation.
- Placebos for plant cannabis can be difficult to obtain.
- Difficulties can occur with blinding.
- Research Ethics Board constraints affect which patients are permitted to use the drugs.
- Effects of cannabis (such as pain intensity versus unpleasantness around pain) are not easily measured.

Past cannabis studies have been limited. In particular, most studies have focused on the potential harms rather than the benefits of cannabis. As well, most have been done on recreational, rather than medical, users.

In addition, many cases of small patient populations, lack of randomization, lack of blinding, and a short duration of interventions have limited the conclusions that can be drawn.

Rather than demanding larger and more rigorous RCTs (using which products? at what doses?) in order to learn more about medical cannabis use, it has been suggested that researchers look for surrogates, such as open-label, longitudinal, or case control studies. With enough data, statistical significance would be reached.

Another approach is the use of registries. Unlike RCTs, which tend to exclude patients with comorbid conditions, registries can include a wide range of patients and thus get data on the effects of cannabis use on concurrent conditions such as depression, anxiety, and insomnia. The Quebec Cannabis Registry is an example of one such patient registry in Canada. Designed in response to the need for a pharmacovigilance framework for cannabis in Quebec, it was launched in May 2015, first in 25 pilot clinics, then across the province. Its goal is to recruit 3,000 users of medical cannabis and follow them for four years in order to identify patient responses.

Another example is DATACANN (DATAbase for CANNabinoid Consumption and Study), a provincial pain registry that will serve as a longitudinal study of patients' use of medical cannabis. Set up by researchers at Hamilton Health Sciences and McMaster University in Ontario, the database will collect real-world data on large numbers of patients with chronic noncancer pain who are using cannabis medically.

Experts have also suggested that clinicians personalize their cannabis patient management through the use of n-of-1 trials: individual patient case studies in which experimental and control interventions are tried sequentially with their order randomized (to achieve patient and sometimes physician blinding). This approach is the epitome of individualized medicine and can be used in cannabis patients to determine the most effective combination of plant varieties and dosage forms.

Table 2. Pros and cons of RCTs, registries, and n-of-1 studies.

RCTs	REGISTRIES	N-OF-1 STUDIES
<p>PROS:</p> <ul style="list-style-type: none"> • Randomization removes the effects of confounding variables • Blinding eliminates observation bias • Control group allows a true with/without comparison • Close monitoring of patients • Ability to show causal relationships 	<p>PROS:</p> <ul style="list-style-type: none"> • Patients match those seen in clinical practice (generalizable) • Generally larger than RCTs • Able to detect rare events • Suitable for much longer follow-up than RCTs • Possible to study multiple outcomes 	<p>PROS:</p> <ul style="list-style-type: none"> • Can be done in any patient • Results take into account all patient variables • Crossover design allows for control period • Inexpensive
<p>CONS:</p> <ul style="list-style-type: none"> • Not always generalizable to population seen in clinical practice • Short follow-up period • Can't detect rare events • Usually only ask one question • Often small N • Expensive 	<p>CONS:</p> <ul style="list-style-type: none"> • Cannot judge efficacy without a control group • May be confounded by multiple variables and biases • Can't establish causal relationships • Expensive (less than RCTs) 	<p>CONS:</p> <ul style="list-style-type: none"> • Not generalizable to other patients • May require multiple treatment periods to find an ideal solution

Table 3. Conditions in which there is trial evidence for THC, THC/CBD, and CBD efficacy.

THC/Dronabinol/Nabilone	Cannabis/Nabilimols (THC/CBD)	CBD
Neuropathic pain ^{7,9}	Rheumatoid arthritis ⁴	Social anxiety disorder ^{23,24}
Fibromyalgia ^{10–12}	Cancer pain ^{5,6,20}	Schizophrenia ^{27,28}
Anxiety ²¹	Neuropathic pain ⁸	Parkinson's disease psychosis ²⁹
Chemotherapy-induced nausea and vomiting ¹⁹	Palliative care quality of life ¹⁵	Epilepsy ³⁸
Anorexia nervosa ²⁵	Dementia ³¹	
PTSD ²⁶	Cannabis use disorder ^{34,35}	
Alzheimer's disease dementia ³⁰	Multiple sclerosis spasticity ^{39–43}	
Cannabis use disorder ³⁶		

Cannabis in Chronic Pain

Every chronic pain patient is different, and many chronic pain conditions are resistant to currently available treatment options. This is a ripe area for cannabis-based medicines, especially if they can reduce opioid use and the possibility of overmedication among pain patients.

Few human trials have been performed using cannabis-based medicines, especially in inflammatory pain conditions. For example, the only trial done in rheumatoid arthritis pain was a randomized, double-blind, parallel-group trial comparing Sativex® with placebo in 58 patients.⁴ Sativex produced statistically significant improvements in pain on movement, pain at rest, sleep quality, 28-joint Disease Activity Score (DAS28), and the short-form McGill Pain Questionnaire “pain at present” component. There were no adverse event–related withdrawals or serious adverse events in the Sativex-treated group.

No clinical trials have been done in osteoarthritis pain, but two have examined intractable cancer pain.

One randomized 360 patients with opioid-refractory cancer pain to receive placebo or a low (1–4 sprays/day), medium (6–10 sprays/day), or high (11–16 sprays/day) dose of Sativex.⁵ Over five weeks, the low- and medium-dose groups reported reduced pain and reduced sleep disruption. Adverse effects were dose-related.

Another cancer pain trial compared Sativex with a THC extract and placebo in 177 patients with advanced cancer and opioid-resistant pain.⁶ The change from baseline in the mean pain numerical rating scale (NRS) score was significantly in favour of Sativex compared with placebo, while THC alone produced a nonsignificant change. Forty-three percent of the Sativex group showed a reduction of more than 30% from their baseline pain NRS score.

Neuropathic pain appears to respond particularly well to cannabinoids. A meta-analysis of individual patient data from five RCTs compared inhaled cannabis with placebo in 178 patients with diabetic, traumatic, or HIV-related neuropathic pain lasting for at least 3 months.⁷ Cannabis resulted in short-term reduction of at least 30% in pain outcomes in 1 in 6 patients (number needed to treat 5.6), with an odds ratio of 3.2.

Other cannabis-based medicines have had similarly positive results in neuropathic pain:

- Sativex significantly reduced pain over 5 weeks in patients on stable analgesia.⁸

- Dronabinol significantly reduced central neuropathic pain intensity in multiple sclerosis patients.⁹

Fibromyalgia patients have been shown to benefit from both nabilone and medical cannabis. A trial of 40 patients who received nabilone or placebo found significant decreases in both pain and anxiety in the nabilone-treated group but not the placebo group.¹⁰ Another RCT compared nabilone to amitriptyline in fibromyalgia patients with chronic insomnia and found nabilone to be superior in improving sleep.¹¹ A retrospective review of hospital registries found that all 26 patients with fibromyalgia who were treated with medical cannabis had improved significantly in every aspect of the Revised Fibromyalgia Impact Questionnaire.¹²

In their 2017 report, the National Academies of Sciences, Engineering, and Medicine in the United States concluded that there is moderate-grade evidence supporting the effectiveness of cannabinoids for the treatment of fibromyalgia.¹³

Other Indications

PALLIATIVE CARE

Public support has grown for the availability of medical cannabis for palliative care patients, and reported benefits include improvements in pain, nausea, weight loss, appetite loss, insomnia, spasticity, stress management, and mood. However, evidence has been relatively disappointing to date.

A 2017 systematic review and meta-analysis of the efficacy, safety, and tolerability of cannabinoids (dronabinol, nabiximols, and herbal cannabis) in palliative medicine found only nine randomized controlled and/or crossover studies with a total of 1,561 participants, with quality of evidence rated low to very low.¹⁴ In cancer patients, the analysis found no differences between cannabinoids and placebo in caloric intake, appetite, nausea/vomiting, pain reduction, or sleep. In HIV patients, cannabinoids were superior to placebo for weight gain and appetite but not for nausea/vomiting. Safety and tolerability were similar to placebo in both groups.

However, a recent trial, not included in that meta-analysis, produced somewhat more promising results.¹⁵ Nearly 400 advanced cancer patients with chronic pain (≥ 4 and ≤ 8 on a 0–10 rating scale) unalleviated by optimized opioid therapy were randomized to Sativex ($n = 199$) or

placebo (n = 198) and allowed to self-titrate for two weeks before remaining on the same dose for three weeks. Results showed improvement in the primary end point (median percent improvements in average pain score from baseline to five weeks) in the per-protocol population but not the intent-to-treat population. Quality of life scores, however, showed significant improvements in the Sativex group, especially at Week 5 and especially in American patients, possibly due to patients in other parts of the world having more advanced disease.

CANCER

Although there is a great deal of public interest in the cancer-fighting abilities of cannabis products, clinical trial evidence is lagging behind. However, there is a great deal of suggestive preclinical evidence. Since 1975, when Munson reported that THC reduced the growth of implanted Lewis lung carcinomas in mice,¹⁶ there have been dozens of investigations of THC and CBD *in vitro* and in mice and rats, many of which have produced positive results.¹⁷

In one encouraging human safety study, THC was injected directly into glioblastoma multiforme tumours in nine patients who had failed standard therapy (surgery, radiation, and chemotherapy) and had evidence of tumour progression.¹⁸ The primary end point was the safety of intracranial THC administration, which was successfully demonstrated. In addition, tumour growth was curbed for about nine weeks in one patient, along with clear improvement in clinical symptoms, and another patient's clinical symptoms were largely improved.

Cannabis may have a greater role to play in the management of cancer symptoms and chemotherapy side effects. For example, dronabinol is effective in the management of breakthrough chemotherapy-induced nausea and vomiting (CINV) and is included among recommended CINV treatments by major oncology guidelines.¹⁹ One survey found that cancer patients themselves perceived improvements in pain, general well-being, appetite, and nausea with the use of cannabis.²⁰

PSYCHIATRY

The evidence for the use of cannabinoids in psychiatric disorders is limited, comprising small studies and few RCTs. However, this use has a comparatively long history: studies of nabilone in the treatment of anxiety were being published in 1981—although they came to opposite conclusions. One of these early trials involved 25 outpatients suffering from anxiety and found that nabilone

dramatically improved anxiety when compared with placebo.²¹ However, another found little anti-anxiety effect from nabilone in eight anxious volunteers.²²

Cannabidiol has demonstrated promising results in social anxiety disorder (SAD). A double-blind trial randomized 24 patients with SAD to treatment with either CBD 600 mg or placebo 90 minutes before a simulation public speaking test.²³ Subjects who received CBD experienced significantly reduced anxiety, cognitive impairment, and discomfort in their speech performance.

Another small trial in 10 generalized SAD patients found that oral CBD (400 mg) was associated with significantly reduced subjective anxiety without effects on sedation or "other feelings/attitudes."²⁴

In anorexia nervosa, dronabinol has been found to increase weight gain. Twenty-five adult women with anorexia nervosa for at least five years were randomized to receive dronabinol (2.5 mg bid) or placebo, each for four weeks, in a double-blind, crossover trial.²⁵ Dronabinol induced a small but significant weight gain without causing severe adverse events.

Nabilone capsules appear to be helpful in the treatment of post-traumatic stress disorder (PTSD)-associated nightmares. A double-blind, crossover trial studied 10 Canadian military personnel who continued to experience trauma-related nightmares despite standard treatment.²⁶ Subjects were randomized to receive nabilone (0.5 mg titrated up to an effective dose or to 3.0 mg) or placebo. After seven weeks and a two-week washout period, they were titrated with the other treatment and followed for another seven weeks. Nabilone therapy was associated with significant decreases in nightmares (as measured by CAPS Recurring and Distressing Dream scores) and significant increases in Mean Global Improvement and general well-being.

Cannabidiol has shown encouraging results in schizophrenia. In one double-blind randomized controlled trial in 42 adults with acutely exacerbated schizophrenia, CBD (titrated up to 800 mg/day and maintained for three weeks) produced clinical improvement in psychotic symptoms to the same degree as the antipsychotic amisulpride, and with many fewer side effects.²⁷

In another double-blind trial, 88 patients with schizophrenia were randomized to receive CBD (1,000 mg/day) or placebo in addition to their existing antipsychotic medication.²⁸ After six weeks of treatment, the CBD group had lower levels of positive psychotic symptoms and improved ratings according to treating clinicians. Adverse

events were similar to placebo.

Psychosis in Parkinson's disease was examined in a small open-label pilot study of six outpatients with Parkinson's disease and psychosis for at least three months.²⁹ The patients received a flexible dose of CBD, starting at 150 mg/day, for four weeks in addition to usual therapy. Psychotic symptoms, as measured by the Brief Psychiatric Rating Scale and the Parkinson Psychosis Questionnaire, significantly decreased, as did total scores on the Unified Parkinson's Disease Rating Scale. No adverse effects were observed.

Cannabinoids have also been examined in dementia. In a small placebo-controlled study, dronabinol decreased the severity of disturbed behaviour in 15 patients with a probable diagnosis of Alzheimer's disease.³⁰

Open-label trials and case reports have reported decreased agitation, delusions, and nighttime behaviour and increased neuropsychiatric inventory scores with the use of THC in dementia.³¹

However, two randomized controlled trials (n = 22 and 24) did not find THC to have any benefit in reducing behavioral disturbance or neuropsychiatric inventory scores in dementia patients.^{32,33}

Cannabinoids may also have a role in the management of cannabis use disorder (dependence). A 2016 case series assessed the use of self-titrated dosages of Sativex (along with motivational enhancement therapy and cognitive behavioral therapy) in five treatment-seeking cannabis-dependent subjects and found that it reduced withdrawal symptoms while cannabis use decreased.³⁴

A follow-up double-blind pilot study involving 40 subjects also found reduction of cannabis use with reduced cannabis craving.³⁵ In a placebo-controlled pilot study of 11 cannabis users examining withdrawal effects, the combination of nabilone and zolpidem was more effective than zolpidem alone.³⁶ The addition of nabilone to zolpidem treatment decreased withdrawal-related disruptions in mood and food intake and decreased self-administration of active cannabis.

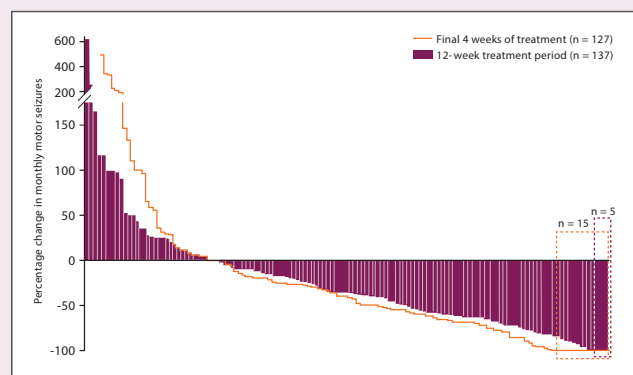
However, in a larger RCT, dronabinol and lofexidine did not improve abstinence rates among 156 cannabis-dependent adults.³⁷

SEIZURES AND SPASTICITY

An open-label trial gave patients with severe, intractable, childhood-onset, treatment-resistant epilepsy (who were receiving stable doses of antiepileptic drugs) oral CBD at

2–5 mg/kg/day, uptitrated until intolerance or to a maximum dose of 25 or 50 mg/kg/day.³⁸ Of the 162 patients in the safety and tolerability analysis, 128 (79%) reported adverse events, particularly somnolence, decreased appetite, diarrhea, fatigue, and convulsions. In the 137 patients in the efficacy analysis, monthly motor seizures were reduced by a median of 36.5% and completely resolved in some patients (Figure 1).

Figure 1. Percentage change in monthly frequency of motor seizures. Percentage changes for each patient are ordered from greatest increase to greatest decrease. The dashed boxes indicate patients who became free of that seizure type during the 12-week treatment period (dark magenta) or the last 4 weeks of treatment (orange).



Several phase III randomized clinical trials have demonstrated the efficacy of Sativex in spasticity due to multiple sclerosis (MS).^{39–43} One of the largest used an enriched study design: subjects with MS spasticity not fully relieved with current therapy were treated with Sativex (as add-on therapy) in a single-blind manner for four weeks, after which those achieving at least a 20% improvement in spasticity progressed to a 12-week randomized, double-blind, placebo-controlled phase.³⁹ In this population (n = 241), Sativex was associated with significant improvement in mean spasticity numeric rating scale, spasm frequency, sleep disturbance, and patient, carer, and clinician Global Impressions of Change.

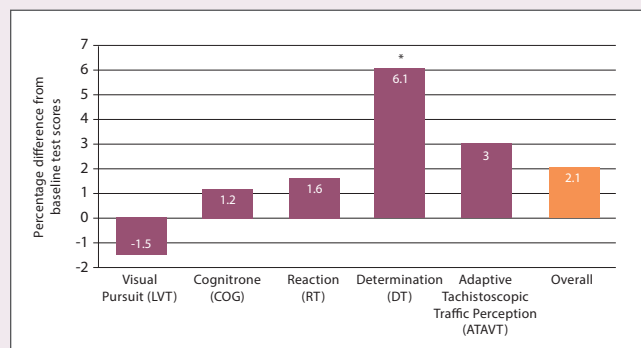
SOCIAL AND OCCUPATIONAL ISSUES

The social and occupational safety concerns associated with cannabis use in the home or the workplace tend to echo those associated with the use of opioids: driving, working with heavy machinery, tending small children, and so on. Unfortunately, most studies focusing on these issues have involved recreational, rather than medical, cannabis users.

For example, a meta-analysis of 21 observational studies found that acute cannabis intoxication was related to a 22% increase in the risk of road traffic accidents.⁴⁴ A study by the US National Highway Traffic Safety Administration in Virginia found that THC was associated with a 25% increase in the risk of crashing.⁴⁵ A study presented in a poster at the Vienna conference found that vaporized cannabis (whether high-THC or high-CBD/THC) impaired most driving and cognition measures in healthy volunteers.⁴⁶

However, this risk may or may not be present for medical cannabis users. A study in multiple sclerosis patients with spasticity found that after four to six weeks of Sativex treatment, driving ability according to validated tests was unchanged or improved versus baseline (Figure 2).⁴⁷

Figure 2. Effect of Sativex on driving-related ability dimensions (Visual Pursuit Test, Concentration Cognitron Test, Stress Tolerance Determination Test, Motor Speed Reaction, and Adaptive Tachistoscopic Traffic Perception Test) in MS patients with moderate-to-severe resistant spasticity.⁴⁷ The asterisk denotes $p = 0.0255$ versus baseline.



As with opioids, common sense is vital: patients need to be reminded to be particularly cautious during the first days of cannabis use or after increasing the dosage. The College of Family Physicians of Canada recommends that medical users of dried cannabis be advised not to drive for at least four hours after inhalation, at least six hours after oral ingestion, and at least eight hours after either of those if the patient experiences euphoria.³

DRUG INTERACTIONS AND ADVERSE EVENTS

The metabolism of cannabinoids involves cytochrome P450 (CYP450) enzymes, which brings up the possibility of drug interactions with other agents. However, very few clinical studies have shown relevant drug interactions with cannabinoids:

- Rifampin (a CYP inducer) decreases the maximum concentration (C_{max}) and area under the concentration-time curve (AUC) of both THC and CBD.⁴⁸
- Ketoconazole (a CYP inhibitor) increases the C_{max} and AUC of THC and CBD.⁴⁸
- Theophylline clearance is higher in frequent marijuana smokers.⁴⁹
- Clobazam metabolism is inhibited by CBD (thus increasing clobazam concentrations).⁵⁰
- Abnormalities of liver transaminases and platelets were seen with concomitant THC/CBD therapy and valproic acid.⁵¹

The April 2018 Canadian Pharmacists Association (CPhA) monograph for cannabis lists a number of additional potential drug interactions (anticholinergics, CNS depressants, CYP1A2 substrates, other CYP inducers and inhibitors, disulfiram, transdermal nicotine, and stimulants) but notes that many of these are theoretical or based on anecdotal reports from recreational cannabis consumers using high doses.⁵²

One study investigated the interactions between cannabinoids and opioids.⁵³ Although it was a small trial of short duration, the results showed that cannabinoids had no significant effect on opiate metabolism and did not change opioid serum levels—and that cannabis appeared to augment the analgesic effects of opioids.

In general, additive adverse events are a greater consideration than drug interactions when prescribing cannabis in patients taking other medications.

Adverse events associated with cannabis-based medicines (Table 4) are primarily mediated by THC and tend to be dose-dependent.²

Table 4. Adverse effects associated with cannabis-based medicines.²

MOST COMMON	COMMON	RARE
Drowsiness/fatigue	Euphoria	Orthostatic hypotension
Dizziness	Blurred vision	Toxic psychosis/paranoia
Dry mouth	Headache	Depression
Cough, phlegm, bronchitis (smoking only)		Ataxia/dyscoordination
Anxiety		Tachycardia (after titration)
Nausea		Cannabis hyperemesis
		Diarrhea

The COMPASS study was the first prospective cohort study of the long-term safety of medical cannabis use.⁵⁴ Subjects were adult Canadians with chronic noncancer pain lasting at least six months. Over a one-year period, the cannabis group received a standardized herbal cannabis product containing 12.5% THC; the control group were individuals from the same pain clinics who were not cannabis users. The cannabis group used the delivery system with which they were most comfortable; their mean use was 2.5 g/day.

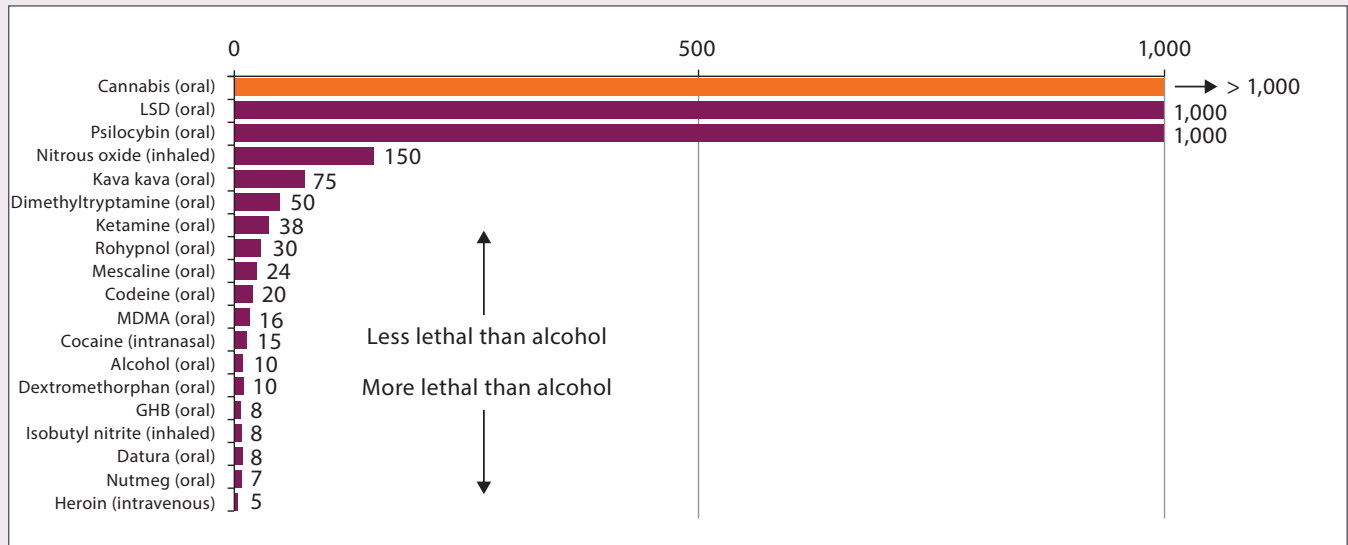
There was no significant difference in the risk of serious adverse events between the two groups (adjusted incidence rate ratio 1.08, 95% CI 0.57–2.04) and no differences between groups in pulmonary function tests, neurocognitive

tests, hematological profile, or liver, renal, or endocrine function. However, cannabis users were at increased risk of nonserious adverse events (adjusted incidence rate ratio 1.73, 95% CI 1.41–2.13). The most common adverse events reported were headache, nasopharyngitis, nausea, somnolence, and dizziness.

The therapeutic index (TI), or the comparison between the minimum effective dose and the minimum toxic dose, for medical cannabis is very wide, unlike the narrow TI for opioids. Therefore, it is extremely difficult to experience a fatal overdose with medical cannabis alone: it has been suggested that it would require smoking 1,500 pounds (680 kg) of dried cannabis within 15 minutes to induce a lethal response.

Figure 3 shows the relative risks associated with various recreational drugs.⁵⁵


Figure 3. Ratio of fatal dose to effective dose for recreational drugs.⁵⁵



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