Colloquium

The Role for Medical Cannabis in Chronic Pain Management

Medical cannabis has been a reality in Canada since 2001 when Health Canada's Marihuana Medical Access Regulations (MMAR) allowed patients with certain conditions whose conventional treatments had failed to possess limited amounts of dried marijuana. The law has evolved slowly over the ensuing years and today the use of medical cannabis is governed by the Access to Cannabis for Medical Purposes Regulations (ACMPR). The latest data suggest that by the end of March 2018, more than 296,700 clients had registered with Health Canada through ACMPR, up from fewer than 100 in 2001.

Health practitioners, however, remain widely reluctant to prescribe medical cannabis for their patients, owing largely to a dearth of education and training opportunities, pervasive social and professional stigma surrounding cannabis, and limited research in many therapeutic areas. The net result is that many patients who may benefit from medical cannabis for a variety of indications are not being given the choice.

This discussion will examine the complexity and utility of prescribing cannabinoids to manage pain in a primary care setting, how to interpret the evidence supporting their use, the importance of maintaining a medical channel for clinical use of cannabis and other key considerations.

CHAIR:

Alan Bell, MD, FCFP
Department of Family and Community Medicine,
University of Toronto,
Humber River Hospital
Toronto, ON

THE PANEL

Hance Clarke, MD, FRCPC, PhD
Director, Pain Services
Medical Director,
Pain Research Unit
Toronto General Hospital
Toronto, ON

Matthew Hill, PhD
Hotchkiss Brain Institute,
University of Calgary
Executive Director,
Canadian Consortium for the Investigation of Cannabinoids
Calgary, AB

Caroline MacCallum, BScPharm, MD, FRCPC
Department of Medicine,
University of British Columbia
Medical Director,
Greenleaf Medical Clinic,
Vancouver, BC

Blake Pearson, MD
Founder & Chief
Medical Officer,
Greenly Medical Consulting and Greenly Health,
Sarnia, ON

Shelita Dattani, BScPharm, PharmD
Director, Practice Development and Knowledge Translation,
Canadian Pharmacists Association
Pharmacist,
West Carleton Pharmasave,
Ottawa, ON

MADE POSSIBLE THROUGH THE FINANCIAL SUPPORT OF SPECTRUM CANNABIS

The current opioid crisis suggests there are unmet needs in the management of chronic pain. What are those unmet needs?

Dr. Hance Clarke, Toronto General Hospital: Our entire chronic pain approach has traditionally been centred upon treating numbers, not patients. Lowering pain scores has become the focal point, and there's a pervasive belief among physicians that opioids are going to magically fix that number.

It is critical to remember that not all pain is created equal — neuropathic pain is completely different from inflammatory pain, which is different from visceral pain and ischemic pain. Opioids are the best medications available for acute pain, but when it comes to chronic non-cancer pain they are not the ideal choice because of the risk for physical dependence, toxicity and bothersome side-effects over the long term.

The real unmet need, then, is to move beyond pain scores to treat patients holistically and focus on what's truly important, which is their functioning, how well they are coping with their condition, and their quality of life.

What does the collective clinical experience tell us about medical cannabis as a tool to treat pain?

Dr. Clarke: For chronic neuropathic pain, the Canadian Pain Society (CPS) guidelines [1] recommend gabapentinoids, tricyclic antidepressants and SNRIs as first-line therapies, with tramadol and controlled-release opioids as second line ahead of third-line cannabinoids. When we wrote those guidelines, we based our guidance solely on available evidence, and at the time there just wasn't anything that supported putting cannabinoids ahead of opioids, even from a harm reduction perspective. As evidence unfolds over time and better science is brought to the table over the next few years, that discussion will be revisited and there may be sufficient reason to move cannabinoids above opioids.

Clinicians who are comfortable prescribing cannabis are certainly identifying windows where it is readily utilized, and I think appropriately so. Opioids, for example, can be difficult for patients to self-manage in conditions that feature waxing and waning symptoms or peaks and valleys of pain. These patients can use cannabis for as long as they need — it helps them to function and they can put it aside when they feel they no longer need it. That can be a challenge with opioids because it takes time to stabilize the opioid dose and then appropriately wean patients off them. In the palliative care setting I have been able to utilize cannabis for select patients who needed some pain relief for two to four hours and also wanted to remain lucid with their family.

Overall, we need to identify — through better research and the development of academic centres of excellence — where medical cannabis fits clinically and whom it helps and where it doesn't. We do have positive data about cannabis and pain; it can be another tool in the armamentarium. Is it the only drug we should be using? No. But all pain medications reduce central nervous system excitability and that is exactly what cannabis does and it does it well.

What do primary care physicians need to understand about how the endocannabinoid system influences pain? Why is modulating it an attractive target for pain management?

Matthew Hill, PhD, Hotchkiss Brain Institute: The endocannabinoid system provides a multi-pronged approach to influencing pain pathways in the body. Endocannabinoids behave like endorphins: when a noxious stimulus occurs, there is a release of endocannabinoids that suppress the perception of pain. There is also evidence that a component of stress-induced analgesia, which is not regulated by several neuropeptides and neurotransmitters such as endogenous opioid, monoamine, y-aminobutyric acid and others, is endocannabinoid dependent.[2] Endocannabinoids can work at the spinal level to affect nerve transmissions related to pain [3] while other evidence suggests they can reduce peripheral pain, even at pain initiation.[4]

Interestingly, they also seem to modulate the way the frontal limbic part of the brain manages the emotional component of pain. There's clearly a very significant overlap between emotion and pain sensitivity —people who have chronic pain often have psychiatric comorbidities, while those who experience high emotionality tend to be more prone to developing chronic pain.[5] There is evidence to show that when you elevate endocannabinoid signalling, you can reduce the emotional component of pain, such as anxiety and depressive symptoms, in animal models. Conversely, if you inhibit endocannabinoid functioning, it can make these symptoms worse.

Limited clinical data coupled with a growing number of anecdotal reports also suggest that medical cannabis may improve quality of sleep. This could be a useful function because sleep disturbance is a common thread across almost every single disease state in which cannabis treatment is used. One thing we've learned in the neuroscience and psychiatric communities is that poor sleep can create a vicious cycle for

THE ROLE FOR MEDICAL CANNABIS IN CHRONIC PAIN MANAGEMENT

TABLE 1. THC vs CBD

THC (tetrahydrocannabinol)	CBD (cannabidiol)
Partial agonist of CB1 and CB2 receptors	Antagonist with low affinity for CB1 and CB2 receptors; affects activity of other enzymes and receptors
Euphoric	Non-euphoric, opposes action of THC (makes the "high" more tolerable)
Mixture of stimulant and depressant effects: • Elevated mood, relaxation, increased appetite • Paranoia, depression, anxiety • Hypertension, tachycardia • Analgesic, antiemetic, appetite stimulant and anti-spasticity properties	• Anxiolytic, neuroprotective • Anticonvulsant, analgesic, antiemetic, anti-inflammatory properties

psychiatric conditions which can, in turn, increase pain sensitivity. Endocannabinoid signalling, because it can regulate these processes, may offer a different modality that could influence outcomes in chronic pain beyond analgesia.

Are there meaningful differences in the effects of cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC) on pain?

Dr. Hill: Everything that we study in the endocannabinoid system typically focuses on endocannabinoid signalling at CB1 receptors, which mediates the ability of endocannabinoids to reduce pain sensitivity and modulate the emotional component of pain. THC has a very clear target: it acts on those CB1 receptors. We still don't really know how CBD works, however. It's an interesting molecule that seems to influence a host of different systems. Certainly, cannabis formulations that evenly balance THC and CBD have been found to have some benefit. There is some evidence to suggest that CBD may also mitigate some of the adverse central side-effects of THC, such as anxiety or the "high" that recreational users want (see Table 1).

We need more research to better understand how all of the components of cannabis work and in the next few years I think we will see genuine evidence emerge to answer some of these questions in a more accurate manner.

Some of the revenue from the sales of legalized recreational marijuana is earmarked to support research, which will go a long way in clinical circles to raise the level of comfort for adding medical cannabis to the treatment arsenal.

What does the evidence tell us about the efficacy and safety of medical cannabis in chronic pain and other conditions?

Dr. Caroline MacCallum, University of British Columbia: There is good evidence for cannabis use, as reported in hundreds of peer-reviewed studies. In 2017, the National Academies of Sciences, Engineering and Medicine published an extensive review of 10,000 cannabis publications titled *The Health Effects of Cannabis and Cannabinoids*. It concluded that there is "conclusive or substantial" evidence for the application of medical cannabis in chronic pain in adults, patient-reported multiple sclerosis spasticity symptoms and as an antiemetic in the treatment of chemotherapy-induced nausea and vomiting.[6] Health Canada also summarized current research in its 2014 publication *Information for health care professionals: cannabis (marihuana marijuana) and the cannabinoids*.[7]

The Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS) is the largest analysis of the long-term safety of cannabis for the treatment of chronic pain. Patients in the cannabis group saw improvements in pain, symptom distress, mood and quality of life with no increased risk of serious adverse drug events or harms on cognitive, pulmonary, liver and renal function, or hematological profile.[8]

Cannabis may have application in treating several other conditions, but more studies are needed.

In terms of safety, there have been no recorded deaths due to overdose attributable to medical or recreational cannabis use; this is due to lack of CB1 receptors in the brainstem cardiorespiratory centres.[9] The lethal dose is approximately 1,500 pounds inhaled over 15 minutes. The therapeutic index for cannabis, or the ratio of effective dose to fatal dose, is >1:1,000, compared with opiates (1:5) and alcohol (1:10).[10] In terms of cannabis dependency,

the risk based on a recreational cannabis population is approximately 9%, in comparison with heroin (23%), alcohol (15%) and tobacco (32%).[11]

The side-effects of THC are dose-dependent. The more common acute symptoms include dizziness, drowsiness/fatigue, anxiety and euphoria (see Table 2).[7, 12] Rarer side-effects are tachycardia, psychosis/paranoia, hypotension and cannabis hyperemesis. Interestingly, CBD has demonstrated benefit in psychosis when used as an adjuvant in psychosis clinical trials.[13] Many patients also report fewer THC-associated side-effects when used in combination with CBD.[14] Naive cannabis users without tolerance to THC may be more prone to experience side-effects. Medical cannabis users develop tolerance over time and frequently experience fewer and milder side-effects.

CBD has minimal side-effects. In some psychosis and seizures trials using large doses of CBD (1000 to 2000 mg/day) fatigue (12% vs. 2% in placebo) and GI symptoms such as nausea and diarrhea (19% vs 6% in placebo) were noted.[15] These side-effects may be dose dependent; we need further research to determine the adverse events of CBD.

The systematic review by the National Academies found an increase in respiratory symptoms, including bronchitis, cough and phlegm with smoking but not with vaporizing cannabis. Studies show that vaporization produces little if any carbon monoxide.[15] Health Canada has approved two vaporizers as medical devices for this reason.

There is moderate evidence to show that there is no statistically significant association between cannabis and lung or head and neck cancers, and limited evidence of a statistical association between cannabis use and ischemic stroke/subarachnoid hemorrhage and acute myocardial infarction.[6]

TABLE 2. Adverse events associated with cannabis-based medicines

Side-effect	Most common	Common	Rare
Drowsiness/Fatigue	✓		
Dizziness	✓		
Dry mouth	✓		
Cough, phlegm, bronchitis (smoking only)	✓		
Anxiety	✓		
Nausea	✓		
Cognitive effects	✓		
Euphoria		✓	
Blurred vision		✓	
Headache		✓	
Orthostatic hypotension			✓
Toxic psychosis/paranoia			✓
Depression			✓
Ataxia/dyscoordination			✓
Tachycardia (after titration)			✓
Cannabis hyperemesis			✓
Diarrhea		✓	

Adapted from MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. ***Eur J Intern Med*** 2018;49:12-19.

What do we know about the relative differences in dosing, frequency, delivery routes, etc.?

Dr. MacCallum: Cannabis comes in several administration and dosage forms (see Table 3).[12] Oral oil (or oil-filled capsules for ingestion) is long-acting, with an onset of one to two hours and effects lasting six to eight hours on average, which makes it applicable to chronic or persisting symptoms. Vaporization of dried plant can be considered a short-acting dosage form for acute or intermittent symptoms with an onset of five to 10 minutes and effects lasting one to four hours on average. Oils for ingestion are easier to reliably dose in comparison to inhaled dried product. There are other dosage forms including sublingual tinctures, topical (which likely feature fewer systemic side effects versus oral or inhaled forms, but the evidence here is limited) and suppositories, which may be ideal for GI symptoms and in palliative or geriatric care.[12]

Both CBD and THC cross the blood brain barrier and affect the brain. However, CBD is non-intoxicating and does not cause euphoria while THC can cause intoxication, depending on the dose.

Cannabis and opioids are synergistic. Preclinical studies have demonstrated that mean effective dose of morphine with THC was

THE ROLE FOR MEDICAL CANNABIS IN CHRONIC PAIN MANAGEMENT

TABLE 3. Administration factors in cannabis delivery

	Vaporization/Smoking	Oral	Oral mucosal	Topical
Onset (minutes)	5 to 10	60 to 180	15 to 45	Variable
Duration (hours)	1 to 4	6 to 8	6 to 8	Variable
Pro	Rapid onset for acute or episodic symptoms	Less odour, discreet and convenient — an advantage for chronic disease/ symptoms	Pharmaceutical form (nabiximols) available with documented efficacy and safety	Less systematic effect; good for localized symptoms
Con	Dexterity required; some vaporizers are expensive, not all are portable Smoking is associated with inhalation of known harmful products of combustion. Long-term effects of vaporization are unknown.	Titration challenge due to delayed onset	Expensive, spotty availability	Only local effects

Adapted from MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. ***Eur J Intern Med*** 2018;49:12-19.

3.6 times lower than morphine alone and mean effective dose of codeine with THC was 9.5 times lower.[17] Medical cannabis users have reduced their consumption of opioids, benzodiazepines, antidepressants, alcohol, tobacco and illicit drugs.[18] Furthermore, there are data showing that medical cannabis legalization in the United States has significantly reduced opioid prescriptions[19] and overdose mortality rates.[20]

What knowledge gaps remain about medical cannabis?

Dr. MacCallum: One of the more pressing knowledge gaps is how to evaluate cannabis effects in the workplace and driving impairment. This is especially important for medical cannabis patients who develop tolerance when using reasonable daily doses of THC and who may experience minimal, if any, impairment compared with naive, intermittent or heavy recreational users. There are no serum assays that can accurately measure impairment due to THC. Similarly, we need to understand the relationship between serum/buccal THC concentration and impairment, and whether CBD minimizes THC impairment. Development of THC-specific functional impairment testing vs. body fluid quantification is essential.

We need more clinical trials to examine the pharmacokinetics and dynamics of delivery routes and formulations, as well as the utility of cannabis for other medical conditions, especially mental health. More evidence is also needed on individual cannabis plant varieties, which contain unique combinations of CBD, THC and other cannabinoids and terpenes, to determine which is best for specific conditions in order to personalize cannabis therapy.

Finally, we need growing and testing standards to ensure quality control of cannabis products. Cannabis plants should be standardized as much as possible. This will create a consistent product with reproducible effects from batch to batch. Standardized laboratory testing is much in need. Currently there can be great variation between labs due to methods used. Cannabis should be free of contaminants such as pesticides, bacteria, fungus, heavy metals and solvents such as butane.

Where does medical cannabis fit in current Canadian treatment guidelines?

Dr. Alan Bell, University of Toronto: Medical cannabis has yet to make significant inroads with treatment guidelines in Canada. This is largely due to a lack of the large randomized controlled trials that guidelines rely so heavily upon. However, it's also clear that the deeply ingrained bias against cannabis among the public and within research, policy and clinical circles

has obscured its potential utility in clinical practice.

Earlier this year, the College of Family Physicians of Canada published guidelines[21] for prescribing medical cannabinoids to treat pain, chemotherapy induced nausea and vomiting, spasticity and other conditions in primary care.

Unfortunately, these recommendations take a decidedly cynical approach to encapsulating and interpreting the accumulated evidence. The authors broadly advise physicians to limit medical cannabinoid use in general and, in bold type, specifically recommend against their use in each of these clinical areas. However, read past the topline recommendations and you will find that they acknowledge the potential of cannabinoids to treat refractory neuropathic and cancer pain, chemotherapy-induced nausea and vomiting and spasticity in multiple sclerosis and spinal cord injury. Unfortunately, they do so in a way that emphasizes potential harms and de-emphasizes potential benefits. Regarding harms, it is important to remember that recorded experience concerning cannabis use disorder, psychosis, cannabis-induced vomiting and others are based on recreational, not medical, use.

Current CPS guidelines[1] for the management of chronic neuropathic pain recommend cannabinoids as a third-line analgesic, up from fourth line in their previous recommendations. While that move is commendable, cannabinoids are preceded in the CPS algorithm by tramadol and controlled-release opioids. I would argue that high potency, high toxicity agents (opioids) may be better placed after lower potency, lower toxicity agents (cannabinoids). This is particularly true in a society facing an opioid crisis, for which the medical profession must take some responsibility.

Once recreational marijuana is legal, should patients using medical cannabis remain within the medical system for treatment and monitoring?

Dr. Bell: It is critically important to maintain a two-stream system for recreational and medical use of cannabinoids. When prescribing cannabis, the goal is to find the optimal dose and combination of THC and CBD. A careful titration process, which requires cooperation between patient and health care professional, is needed to find the "sweet spot" that maximizes relief of the target symptoms and minimizes euphoria and other side-effects.

In addition to affecting direct patient care, a single stream would have a significantly negative system impact. Obvious examples of this include medical users paying sales and "sin" taxes aimed at recreational users and major barriers to insured reimbursement of product costs. We could also expect to see a reduction in medical chemotype availability because commercial producers would have greater financial incentive to focus on producing recreational marijuana strains. Overall, we'd also see a reduction in funding for medical cannabis research, something all stakeholders agree is critical to advancing the science.

In the absence of a medical stream, undergraduate programs and CME providers would be less inclined to offer education on cannabinoid use. Physicians would continue to be stigmatized for authorizing what would be considered a recreational substance. They would be forced to recommend potentially inappropriate cannabis chemotypes and dosing forms or forego authorizing it altogether.

For patients, a single stream would further expose them to the stigma around cannabis use. It would also put them at risk for developing serious side-effects such as psychosis, dependence and toxicity if their use of commercial cannabis is not medically supervised, or through increased use of illegal products.

Are primary care physicians comfortable with prescribing medical cannabis to treat pain?

Dr. Bell: Most clinicians have not been educated about the use of medical cannabis and the evidence behind it, and as such they are uncomfortable authorizing it. As with any treatment, incorporating cannabinoids into practice requires training. The good news is that there are many more education programs available today for clinicians to improve their knowledge and skills in this area. That said, accrediting bodies still seem to be more apprehensive about approving CME on cannabinoids versus other agents, again due to the pervasive stigma around it.

There is a significant opportunity in Canada for physicians to acquire the knowledge to manage medical cannabis in appropriate patients. Cannabis is not a first-line treatment for any condition, but it is a valuable second- and third-line agent we can and should add to our clinical toolkit for pain and other conditions.

Where does medical cannabis fit into the larger toolbox on a practical level?

Dr. Blake Pearson, Greenly Medical: Cannabis is a reasonable alternative for chronic pain patients who have not had relief with their initial pain medications, as well as for those who are unable to tolerate certain medications due to side-effects, allergies or comorbid conditions. For me, it is a logical next step in some chronic pain diagnoses before trying opioids.

THE ROLE FOR MEDICAL CANNABIS IN CHRONIC PAIN MANAGEMENT

Physicians considering cannabis as a pain management strategy may find reassurance in knowing that we often see good results using the non-impairing cannabinoid CBD in many chronic pain diagnoses, such as osteoarthritis. Prescribing a high CBD agent, containing only minimal amounts of THC, avoids the euphoric effects for which THC is responsible.

Some diagnoses, such as neuropathic pain, tend to benefit more from THC. In these cases, clinicians could consider combining THC with CBD to mitigate some of THC's euphoric effects.

What considerations should be top of mind when assessing patients with chronic pain and selecting treatments? What are the considerations for selecting agents from the cannabinoid class?

Dr. Pearson: When assessing patients with pain and selecting treatments, physicians should consider the diagnosis responsible for the pain, duration, therapies tried to date, medical history and current medications to determine if cannabinoid therapy is an appropriate option.

If cannabinoid therapy is warranted, physicians must consider whether the patient needs treatment to be fast-acting or long-lasting. As Dr. MacCallum points out, inhaled cannabinoids have a rapid onset of action and may be more desirable in the management of acute symptoms such as chemotherapy-induced nausea or breakthrough pain. Inhaled cannabinoids should be vaporized rather than smoked to avoid the harmful by-products of combustion. Ingested cannabinoids are longer-lasting and more appropriate for the management of persistent symptoms such as chronic pain, insomnia or spasticity where longer duration is the priority.

What does follow-up, titration and treatment plan adjustment look like in the age of medical cannabis?

Dr. Pearson: If I determine that cannabinoid therapy is a suitable treatment, I create the patient's Medical Document Authorizing the use of Cannabis for Medical Purposes. A follow-up appointment is booked one month after starting treatment because there is a self-titration process — which generally starts at 2.5 mg of either THC or CBD or both, depending on condition (1.25 mg if young, elderly or there are other concerns) — that must be closely monitored in the beginning. The next appointment will take place at three months, at which point most patients will have reached their target therapeutic dose. Barring any changes in condition, I generally see them twice a year for follow-up.

Since cannabis is a multi-modal therapy, around the three-month mark some patients may experience improvement in other symptoms unrelated to the original condition for which cannabinoid therapy was started. Some patients may want to wean other medications on their own once they have started cannabinoid therapy. It is imperative that physicians advise their patients not to begin the weaning process on their own. Once patients have reached their therapeutic goals, physicians can review medications and develop a polypharmacy reduction plan, as appropriate. This may require further titration of the cannabis.

How does medical cannabis impact practice in issuing prescriptions, updating EMR and other considerations?

Dr. Pearson: Initially, practicing cannabinoid medicine can be slightly intimidating because it involves a new and different process compared to our standard treatment and prescription model. However, it really is quite straightforward and, once you handle a few cases, it will become second nature.

Physicians can use any EMR and document cannabinoid therapy like any other treatment. Unlike traditional prescription medications that are dispensed directly from the pharmacy, medical cannabis must be ordered online from one of Health Canada's approved licenced producers.

Some producers have made the process easier for physicians by creating an online portal where you can quickly create the Medical Document. Once the Medical Document is created for a given patient, the renewal process is quick and simple.

Doctors writing a Medical Document for cannabis must authorize a maximum number of grams per day. For a new patient, a reasonable amount would be 0.5 to 1.0 grams per day. The duration of therapy must also be specified; I always recommend a short period of two to three months for new patients to ensure adequate follow-up and to assess the efficacy of treatment. Once patients have reached their therapeutic goals, I recommend follow-up every six months. The maximum duration of a Medical Document is currently 12 months.

Is pharmacy prepared for an increase in the use of medical cannabis? What is the pharmacist's role in advising and supporting patients and consumers who use cannabis?

Dr. Shelita Dattani, Canadian Pharmacists Association: Pharmacists continue to be approached by patients and prescribers with questions about the use of cannabis for various medical conditions. Public opinion polls confirm that patients want to talk to their

pharmacist about this therapeutic entity, just like any other drug that they use as part of a treatment regimen. Patients who use medical cannabis often want —and they should have —the opportunity to consult with their pharmacist.

Pharmacists are regulated healthcare professionals and trained medication experts who are the most accessible health care professionals across the country in all urban, rural and remote communities. Pharmacists are accustomed to advising and guiding patients and prescribers through complex drug regimens. Cannabis is often third- or fourth-line adjunctive therapy for many patients, and this compounds the potential for drug interactions and adverse effects with cannabis and other concurrent medication. Cannabis must be contextualized within the patient's overall medication regimen.

What role does pharmacy play in the larger medical cannabis system?

Currently pharmacists do not have an opportunity at the point of dispensing to provide formal clinical oversight to patients as part of the circle of care. Dispensing a medication is a regulated act that must involve counselling about side-effects, interactions and appropriate use.

We feel it is essential that patients have as much support from healthcare professionals as possible, especially with respect to medication safety. For all other prescription drug products there is a well-defined and highly accessible framework in which the circle of care includes the safety net of a pharmacist to provide support, support, insight, recommendations and authorization for controlled dispensing of a prescription order. All of this is predicated on patient safety.

Many pharmacists already play a role in providing counselling and support to patients who use cannabis for medical purposes. We feel that the medical stream should be maintained and further strengthened by including us in the dispensing of medical cannabis so that we can review potential benefits and harms of medical cannabis on its own and within a patient's broader therapeutic regimen. In the spirit of harm reduction, and knowing the expertise that pharmacists provide, we feel that the oversight of and collaboration with pharmacists is absent the way things stand now.

The Canadian Pharmacists Association has taken a leadership role to develop evidence-based education and resources, such as an evidence guide and a product monograph on cannabinoids, to ensure that pharmacists can provide effective medication education to their patients—with respect to all medications, including cannabis.

References

1. Moulin DE et al. Pharmacological management of chronic neuropathic pain: Revised consensus statement from the Canadian Pain Society. *Pain Res Manag* 2014;19(6):328–335.
2. Hohmann AG et al. An endocannabinoid mechanism for stress-induced analgesia. *Nature* 2005;435(7045):1108-12.
3. Starowicz K, Finn DP. Cannabinoids and pain: Sites and Mechanisms of Action. *Adv Pharmacol* 2017;80:437-475.
4. Clapper JR et al. Anandamide suppresses pain initiation through a peripheral endocannabinoid mechanism. *Nat Neurosci* 2010 Oct;13(10):1265-70. Epub 2010 Sep 19.
5. Asmundson GJ et al. Understanding the co-occurrence of anxiety disorders and chronic pain: state-of-the-art. *Depress Anxiety* 2009;26(10):888-901.
6. National Academies of Sciences, Engineering, and Medicine. The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research. Washington, DC: The National Academies Press, 2017. Online https://doi.org/10.17226/24625
7. Health Canada. Information for health care professionals: cannabis (marihuana, marijuana) and the cannabinoids. Ottawa: 2013. https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/marihuana/med/infoprof-eng.pdf
8. Ware MA et al. Cannabis for the management of pain: assessment of safety study (COMPASS). *The Journal of Pain* 2015;16(12):1233–42.
9. Herkenham M et al. Cannabinoid receptor localization in brain. *Proc Natl Acad* Sci 1990;87:1932–6.
10. Gable R. The toxicity of recreational drugs. *American Scientist* 2006;94(3):206–208.
11. Anthony JC et al. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: basic findings from the National Comorbidity Survey. *Experimental and Clinical Psychopharmacology* 1994;2(3):244–268.
12. MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. *Eur J Intern Med* 2018;49:12-19.
13. Mcguire P et al. Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: a multicenter randomized controlled trial. *Am J Psychiatry* 2018;175(3):225–231.
14. Sellers EM et al. A multiple dose, randomized, double-blind, placebo-controlled, parallel-group QT/QTc study to evaluate the electrophysiologic effects of THC/CBD spray. *Clin Pharmacol Drug Dev* 2013;2:285–94.
15. Devinsky O et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. *N Engl J Med* 2017;376(21):2011–2020.
16. Abrams D et al. Vaporization as a smokeless cannabis delivery system: a pilot study. *Clin Pharmacol Ther.* 2007;82(5):572-8.
17. Nielsen S et al. Opioid-sparing effect of cannabinoids: a systematic review and meta-analysis. *Neuropsychopharmacology.* 2017;42(9):1752-1765.
18. Lucas P et al. Medical cannabis access, use, and substitution for prescription opioids and other substances: A survey of authorized medical cannabis patients. *Int J Drug Policy.* 2017;42:30-35.
19. Ashley C et al. Association between US state medical cannabis laws and opioid prescribing in the Medicare Part D population. *JAMA Intern Med.* 2018;178(5):667-672.
20. Bachhuber MA et al. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. *JAMA Intern Med.* 2014;174(10):1668-1673.
21. Allan GM et al. Simplified guideline for prescribing medical cannabinoids in primary care. *Can Fam Physician.* 2018 Feb;64(2):111-120.

Colloquium

Colloquium™ is a regular sponsored feature designed to provide Canadian physicians with the latest in clinical thinking and therapeutic practice. Before prescribing any mentioned medication, please refer to "Information for Health Care Professionals: Cannabis (marihuana, marijuana) and the cannabinoids" Health Canada, 2013. The information and opinions contained herein reflect the views and experience of the authors and not necessarily those of the sponsor.

Group Brand Director/Healthcare: DONNA KERRY
Senior Account Manager: NORMAN COOK
Editor: DEIRDRE MACLEAN
Project Editor: BRAD HUSSEY
Art Direction: LINDA RAPINI
This supplement is published by EnsembleIQ, 20 Eglinton Ave. W., Suite 1800 Toronto, ON M4R 1K8. Colloquium is a trademark of EnsembleIQ.

MADE POSSIBLE THROUGH THE FINANCIAL SUPPORT OF SPECTRUM CANNABIS