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.
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 widely held belief in our profession 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 non-cancer pain, the Canadian Pain Society (CPS) guidelines 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 at the top, so we had to paint the picture of harm reduction as the best we could do.

**What is the current understanding of how cannabinoids work in the treatment of chronic pain?**

**Dr. Hill:** Everything that we study in the endocannabinoid system typically focuses on endocannabinoid signalling at CB1 receptors, which mediate the effects of THC. There is some evidence to suggest that endocannabinoid signalling can reduce pain sensitivity because it can regulate these processes, and it 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 when it helps and where it doesn’t. We do have positive data about cannabis and pain; it can be another tool in the armamentarium, but it can’t be 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, MD, 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 neuroactive transmitter systems such as endogenous opioid, monoamine, y-aminobutyric acid and others, is endocannabinoid dependent.8 Endocannabinoids can work at the spinal level to affect nerve transmissions related to pain9 while other evidence suggests they can reduce peripheral pain, even at pain initiation.9 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.10 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. Clearly, 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 disturbances are a common thread across almost every single disease state in which cannabis treatment is used. One thing we’ve learned in the pediatric pain and psychiatric communities is that poor sleep can create a vicious cycle for psychiatric conditions which can, in turn, increase pain sensitivity. Endocannabinoid signalling, because it can regulate these processes, may offer a different modal- ity that could influence outcomes in chronic pain beyond analgesia.

**Are there meaningful differences in the effects of cannabinoids (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 mediate the effects of THC. There is some evidence to suggest that endocannabinoid signalling at CB1 receptors, which mediate the 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 in the brain and in treating several other conditions, but more studies are needed. In terms of safety, there have been no recorded deaths due to medical cannabis, but more studies are needed. In terms of safety, there have been no recorded deaths due to medical cannabis, but more studies are needed.

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

**Dr. Caroline MacCallum, University of British Columbia:** There is good evidence for cannabis use, as topically applied and by aerosol, from reviewed studies. In 2017, the National Academies of Sciences, Engineering and Medicine published an extensive review of 870+ studies, which is titled *The Health Effects of Cannabis and Cannabinoids. It concluded that there is “conclusive or substantial” evidence of the potential medical 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.10 Health Canada also summarized current research in its 2014 publication *Information for health care professionals: cannabis* (marihuana marijuana) and the cannabinoids.10**

The Cannabis for the Management of Pain: Assessment of Safety (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, cardiovascular, liver and renal function, or hematological profile.11 Cannabinoids can have application in pain management for many conditions, but more studies are needed.

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the risk based on a recreational cannabis population is approximately 9%, in comparison with heroin (23%), alcohol (15%) and tobacco (32%).10,11

The side-effects of THC are dose-dependent. The more common acute symptoms include dizziness, drowsiness/fatigue, anxiety and euphoria (see Table 2).12-13 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.14-18 Many patients also report fewer THC-associated side-effects when used in combination with CBD.19,20 Naïve 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.19-21 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.22-23 Health Canada has approved two vaporizers as medical devices in Canada; however, their efficacy and safety are unknown. There is moderate evidence to demonstrate that mean effective dose of codeine with THC was 9.5 times lower.24,25 Medical cannabis users have reduced their consumption of opioids, benzodiazepines, antidepressants, alcohol, tobacco and illicit drugs.26-28 Furthermore, there are data showing that medical cannabis legalization in the United States has significantly reduced opioid prescriptions29 and overdose mortality rates.30-32

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).29-30 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.31-32 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 3.6 times lower than morphine alone and mean effective dose of codeine with THC was 9.5 times lower.25 Medical cannabis users have reduced their consumption of opioids, benzodiazepines, antidepressants, alcohol, tobacco and illicit drugs.26-28 Furthermore, there are data showing that medical cannabis legalization in the United States has significantly reduced opioid prescriptions29 and overdose mortality rates.30-32

What knowledge gaps remain about medical cannabis? Dr. MacCallum: One of the most pressing knowledge gaps is how to evaluate cannabis efficacy 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 naïve, 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 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 in need of current. 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.
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-step system of 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 systemic 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 cannabis availability because commercial producers would have greater financial incentive to focus on producing recreational marijuana instead. Overall, we'd attract 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 cannabinoid chemotypes and dosing forms or forego authorizing it altogether. For these reasons, and for medical patients, we would further expose them to the stigma around cannabis use. It would also put them at risk for decreased pain treatment and finding effective treatments for pain, such as psychosis, dependence and toxicity if their use of commercial cannabis is not medically supervised, or through increased use of illegal products.

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 appropriate.

If cannabinoid therapy is warranted, physicians must consider whether the patient needs treatment to be fast-acting or long-lasting. 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 break-through 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. 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. Depending on 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 weaning the process on their own. Once patients have reached therapeutic goals, physicians can review medications and develop a polypharmacy reduction plan, as appropriate. This may require further titration of the cannabis.

The role for medical cannabis in chronic pain management has obscured its potential utility in clinical settings. Earlier this year, the College of Family Physicians of Canada published guidelines for prescribing medical cannabinoids to treat pain, chemotherapy-induced nausea and vomiting, and spasticity and other conditions in primary care. Unfortunately, these recommendations recommend a legal approach to encapsulating and interpreting the accumulated evidence. The authors broadly advise physicians to limit medical cannabis use in general and in bold type, specifically recommend against their use in each of these clinical areas. However, read past the top line 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 dis-courages, psychosis, cannabis use in young, elderly or there are other concerns (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. Depending on changes in condition, I generally see them twice a year for follow-up.

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What does follow-up, titration and clinical monitoring 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 Cannabis for Medical Purposes. A renewal process is put in place, 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. Depending on changes in condition, I generally see them twice a year for follow-up.

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How does medical cannabis impact practice in issuing prescriptions, updating EMR and other considerations? Dr. Pearson: Initially, practicing cannabinoid medicine can be slightly intimidating for a number of reasons. Physicians can review medications and develop a polypharmacy reduction plan, as appropriate. This may require further titration of the cannabis.

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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.

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**References**


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