Use of Cannabinoids in Medical Practice

Annual Scientific Assembly

Family Medicine Review 2016

Murray Opdahl
BSPE, MD, CCFP
Objectives

- Briefly present:
  - An overview of available cannabinoids
  - Concerns voiced to physicians from various associations
  - Some supportive research, treatment guidelines and educational materials related to cannabinoids
  - The steps involved with authorizing a patient to purchase cannabis from a licensed producer
Concentrations of CB₁ receptors

- Basal Ganglia¹
  Movement

- Cerebral Cortex¹
  Higher cognitive function

- Cerebellum¹
  Movement

- Hypothalamus²
  Appetite

- Hippocampus¹
  Learning, memory, stress

- Medulla³,⁴
  Nausea/vomiting, chemoreceptor trigger zone (CTZ)

- Spinal Cord¹
  Peripheral sensation including pain

References:
THC vs CBD

- THC (Delta-9-tetrahydrocannabinol) is thought to be responsible for the psychoactive effects ("high"), immunosuppressiv, anti-inflammatory and analgesic properties of cannabis.

- CBD (Cannabidiol), which lacks any psychoactive effect, gives cannabis it’s anti-inflammatory, analgesic, anti-nausea, anti-psychotic, anxiolytic and anti-epileptic effects.
Nabilone (Cesamet)

- Indicated for chemotherapy induced nausea and vomiting and HIV related cachexia
- 0.5 and 1 mg capsules
- Unlikely to interfere with P-450 enzymes and cause drug interactions in clinical use
- Common side effects are dizziness, drowsiness and dry mouth

Product monograph
Nabiximols (Sativex)

- THC/CBD Mouth Spray
- Indicated for Multiple Sclerosis related spasticity and neuropathic pain
- Indicated for advanced cancer related pain
- Common side effects are nausea, fatigue, dizziness
- No clinically apparent drug-drug interactions have been seen in trials at clinical doses.
- May cause inhibition of CYP450 3A4 so caution with fentanyl suggested
- Self titration starting with one spray per day and increasing as needed (usual dose is 4-8 sprays/day

Product monograph 2015
Dried Medical Cannabis

- For smoking or vaporizing
- Patients with a “medical document” can legally purchase from 34 Licenced Producers in Canada
- Variable concentrations of THC and CBD available
- Currently >70,000 patients are registered in Canada
  - About 1300 new patients per month
Licenced Producers have multiple products with variable strengths of THC/CBD

- For example:

<table>
<thead>
<tr>
<th>Ratio</th>
<th>THC</th>
<th>CBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>22.1</td>
<td>22.0%</td>
<td>less than 1.0%</td>
</tr>
<tr>
<td>17.1</td>
<td>17.0%</td>
<td>less than 1.0%</td>
</tr>
<tr>
<td>15.5</td>
<td>15.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>12.0</td>
<td>12.5%</td>
<td>less than 0.5%</td>
</tr>
<tr>
<td>9.9</td>
<td>9.0%</td>
<td>9.5%</td>
</tr>
<tr>
<td>4.1</td>
<td>4.0%</td>
<td>10.0%</td>
</tr>
<tr>
<td>1.13</td>
<td>0.7%</td>
<td>13.0%</td>
</tr>
</tbody>
</table>
Edible Oils

- Available from some LPs
- Products contain variable combinations of THC/CBD
  - 18:0, 10:10, 1:20
- Taken orally, slower onset of action
Health Canada: Marijuana for Medical Purposes Regulations (MMPR)

- Effective April 1, 2014 only regulated licensed producers can sell to patients with a physician provided “medical document”

- Physicians can authorize patients to purchase up to 5 grams of dried cannabis per day for a maximum of 12 months

- No longer any specific medical conditions that qualify
ACMPR updated regulations

- The federal marijuana regulations were recently updated with the introduction of the *Access to Cannabis for Medical Purposes Regulations (ACMPR)* on August 24, 2016.

- Patients with a medical document can register with Health Canada to produce a limited amount of marijuana for their own medical purposes or designate someone else to produce it for them.

- Health Canada will determine the maximum number of marijuana plants the patient is allowed to have for each production period.
Physician reluctance to authorize cannabis

- Based on advice from multiple medical associations and current available published evidence for cannabis as a medical therapy
Dried marijuana is not an approved drug or medicine in Canada. The Government of Canada does not endorse the use of marijuana, but the courts have required reasonable access to a legal source of marijuana when authorized by a physician.
“Health Canada places family physicians in an unfair, untenable and to a certain extent, unethical position by requiring them to prescribe cannabis in order for patients to obtain it legally. Health Canada should explicitly state the indications, precautions and contraindications for medical marijuana, as it does with all other medications.”

“The CFPC recommends the 'declaration' approach in lieu of 'prescribing'. 'A 'declaration' by a health professional states only that the patient meets Health Canada criteria allowing access to marijuana for medical use. Unlike a prescription, a declaration does not give doses or directions, and does not imply that the physician recommends or advises the patient to smoke or ingest marijuana.’
While acknowledging the unique requirements of patients suffering from a terminal illness or chronic disease for which conventional therapies have not been effective and for whom marijuana may provide relief, physicians remain concerned about the serious lack of clinical research, guidance and regulatory oversight for marijuana as a treatment.

Marijuana is a complex substance, and there is not sufficient clinical information on clinical safety and efficacy. Notably, there is little information around indications for its use, therapeutic and toxic dosages and knowledge on interactions with medications.

There is a need for unbiased, accredited educational modules and decision support tools based on the best available evidence.
The Canadian Medical Association has consistently opposed Health Canada’s approach which places physicians in the role of gatekeeper in authorizing access to marijuana.

Physicians should not feel obligated to authorize marijuana for medical purposes.

Physicians who choose to authorize marijuana for their patients must comply with their provincial or territorial regulatory College’s relevant guideline or policy.
Brief summary of published information on medical use of Cannabis
Medical cannabis has been shown through scientific study to alleviate symptoms of the following conditions:

- Chronic pain
- Insomnia
- Fibromyalgia
- Arthritis
- Neuropathic pain
- Glaucoma
- Depression and anxiety
- Nausea and vomiting
- Cancer
- HIV and AIDS
- Multiple Sclerosis
- Crohn’s disease and Ulcerative colitis
- Epilepsy
- PTSD
- Parkinson’s disease

Medical Cannabis Resource Guide
Cannimed April 2015
Medical Cannabis and Pain

Table I
Randomized controlled trials of cannabinoids in pain-related disorders 2004-14

<table>
<thead>
<tr>
<th>Nabilone</th>
<th>Nabiximols (oromucosal spray; 2.5mg THC + 2.5mg CBD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathic pain (Frank et al.\textsuperscript{19})</td>
<td>Brachial plexus avulsion (Berman et al.\textsuperscript{30})</td>
</tr>
<tr>
<td>Fibromyalgia pain (Skrabek et al.\textsuperscript{20}) and sleep (Ware et al.\textsuperscript{21})</td>
<td>Rheumatoid arthritis (Blake et al.\textsuperscript{31})</td>
</tr>
<tr>
<td>Spinal cord injury (Pooyania et al.\textsuperscript{22})</td>
<td>MS neuropathic pain (Rog et al.\textsuperscript{32})</td>
</tr>
<tr>
<td>Diabetic neuropathy (Toth et al.\textsuperscript{23})</td>
<td>MS Spasticity (Novotna et al.\textsuperscript{33})</td>
</tr>
<tr>
<td><strong>Dronabinol (oral capsule)</strong></td>
<td><strong>Cancer pain (Portnoy et al.\textsuperscript{34})</strong></td>
</tr>
<tr>
<td>MS spasticity (Svensen et al.\textsuperscript{24})</td>
<td><strong>Herbal cannabis (1.8-9.4%THC)</strong></td>
</tr>
<tr>
<td>Chronic pain + opioids (Narang et al.\textsuperscript{25})</td>
<td>HIV neuropathy (Abrams et al.\textsuperscript{35}, Ellis et al.\textsuperscript{36})</td>
</tr>
<tr>
<td>Spinal cord injury (Rinatala et al.\textsuperscript{26})</td>
<td>Neuropathic pain (Wilsey et al.\textsuperscript{37,38})</td>
</tr>
<tr>
<td>Chronic pain + opioids (Issa et al.\textsuperscript{27})</td>
<td>Post traumatic neuropathy (Ware et al.\textsuperscript{39})</td>
</tr>
<tr>
<td><strong>Cannador (oral capsule; 2.5mg THC + 1.2mg CBD)</strong></td>
<td>MS spasticity (Corey-Bloom et al.\textsuperscript{40})</td>
</tr>
<tr>
<td>Spasticity in MS (Zajicek et al.\textsuperscript{14,28,29})</td>
<td>Crohn’s disease (Naftali et al.\textsuperscript{41})</td>
</tr>
</tbody>
</table>
Findings: inhaled cannabis reduced pain scores in people with pain originating from damage or dysfunction of their nervous system
Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials

Mary E. Lynch¹ & Fiona Campbell²

¹Department Anesthesia, Psychiatry, Dalhousie University, Halifax, Canada, and ²Department of Anaesthesia and Pain Medicine, Hospital for Sick Children, University of Toronto, Toronto, Canada

“…it is reasonable to consider cannabinoids as a treatment option in the management of chronic neuropathic pain with evidence of efficacy in other types of chronic pain such as fibromyalgia and rheumatoid arthritis as well”

Based on review of 18 good quality RCTs

Lynch & Campbell BJCP 2011
In summary the current systematic review provides further support that cannabinoids are safe, demonstrate a modest analgesic effect and provide a reasonable treatment option for treatment chronic non-cancer pain.
CONSENSUS STATEMENT

Pharmacological management of chronic neuropathic pain: Revised consensus statement from the Canadian Pain Society

DE Moulin MD, A Boulanger MD, AJ Clark MD, H Clarke MD PhD, T Dao DMD PhD, GA Finley MD, A Furlan MD PhD, I Gilron MD MSc, A Gordon MD, PK Morley-Forster MD, BJ Sessle MDS PhD, P Squire MD, J Stinson RN PhD, P Taenzer PhD, A Velly DDS PhD, MA Ware MD, EL Weinberg MD, OD Williamson MBBS

---

Moulin DE, et al
PR&M 2014
Authorizing Dried Cannabis for Chronic Pain or Anxiety

PRELIMINARY GUIDANCE

September 2014
“Quality-controlled herbal cannabis, when used by patients with experience of cannabis use as part of a monitored treatment program over 1 year, appears to have a reasonable safety profile. Longer-term monitoring for functional outcomes is needed.”
Cannabis for the management of pain: assessment of safety study (COMPASS)

- One year study of chronic pain patients:
  - 174 cannabis users vs 204 controls
  - 12.5% THC, Median dose 2.5 g/day
  - Mostly smokers but some oral ingestion
  - Pain scores improved in the Cannabis group but not control group

Mark Ware, et al
Journal of Pain 2015
Non serious adverse effects
“certainly/very likely” related to cannabis

Somnolence-5
Amnesia-4
Cough-4
Nausea-4
Dizziness-3
Secondary Outcomes

78 Subjects in Cannabis group underwent blood testing at baseline and one year.

No differences were noted for any biomechanical, liver, renal and endocrine function testing parameters between baseline and one year.
Table 1. Provincial regulatory authorities’ policies on authorizing dried cannabis

<table>
<thead>
<tr>
<th>Requirements Applying to Physicians</th>
<th>BC</th>
<th>AB</th>
<th>SK</th>
<th>MB</th>
<th>QC</th>
<th>NB</th>
<th>NL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conflict of interest</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Must not apply to become a licensed producer</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Must not store, provide, or dispense marijuana</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Must not have any financial or management interest in a licensed distributor or producer</td>
<td></td>
<td></td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Must not have any personal gain from providing a non-medical service</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>●</td>
</tr>
<tr>
<td><strong>Authorizations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>State patient’s medical condition on medical document</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Register with regulator as a dried cannabis authorizer</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Provide a copy of the medical document to the regulator</td>
<td>●</td>
<td></td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Send original medical document to licensed producer, give copy to patient, and enter another copy in chart</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Review available prescription databases to determine patient’s medication usage</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Welcome to the CCIC!

The CCIC is a federally registered Canadian nonprofit organization of basic and clinical researchers and health care professionals established to promote evidence-based research and education concerning the endocannabinoid system and therapeutic applications of endocannabinoid and cannabinoid agents. We will do this by:

**EDUCATING** Researchers, health care practitioners and the public about the endocannabinoid system and possible roles of cannabinoids in clinical practice

**FACILITATING** Research regarding the endocannabinoid system, mechanisms of action and clinical safety and efficacy of cannabinoids

**CREATING** A networking forum for researchers investigating endocannabinoids and cannabinoids

**ADVANCING** Our understanding of the role of endocannabinoids and cannabinoids in health and disease
Steps involved with a medical cannabis authorization

- thorough evaluation of the patient including past medical history, past treatments provided and an addiction risk evaluation
- a discuss possible risks of cannabis (on lungs, brain, etc) and recommendation for use by vaporization or oral ingestion rather than smoking;
- provide regular follow-up to ensure appropriate use and evidence of benefit such as reduced pain and improved function.
- documentation of the initial assessment and ongoing follow-up visits is critical.
- a written treatment agreement should be signed by the patient to indicate the cannabis will be used appropriately. Do urine drug tests as you would with patients on opioids.
Table 2. Sample treatment agreement

Because we take our responsibilities to authorize and supervise the medical use of marijuana (dried cannabis) very seriously, we ask you to read, understand, and sign this form.

1. I request Dr ___________, MD, to sign a medical document for me under the Health Canada MMPR legislation, so that I may legally use marijuana to treat my medical condition.

2. I agree to receive a medical document for marijuana only from one physician, Dr ___________, MD.

3. I agree to consume no more marijuana than the doses authorized for me by Dr ___________, MD. I will not request a refill before the agreed-upon refill date.

4. I agree to not distribute my marijuana to any other person, for personal use or for sale. I am aware that redistribution of any marijuana for sale is an illegal activity.

5. I am aware that using marijuana is associated with psychosis in persons who are still undergoing neurodevelopment (brain growth). Therefore, I will ensure that no person under the age of 25 years has access to my marijuana.

6. I agree to the safe storage of my marijuana.

7. I am aware that taking marijuana with other substances, especially sedating substances, may cause harm and possibly even death. I will not use illegal drugs (eg, cocaine, heroin) or controlled substances (eg, narcotics, stimulants, anxiety pills) that were not prescribed for me.

8. I will not use controlled substances that were prescribed by another doctor unless Dr ___________, MD, is aware of this.

9. I agree to testing (eg, urine drug screening) when and as requested by my physician.

10. I agree to have an office visit and medical assessment at least every _____ (months or weeks).

11. I understand that Health Canada has provided access to marijuana by signed medical document from a physician for the treatment of certain medical conditions, but despite this, Health Canada has not approved marijuana as a registered medication in Canada.
Sample Medical Document for the Marihuana for Medical Purposes Regulations

Patient's Given Name and Surname:
Patient's Date of Birth (DD/MM/YYYY):
Daily quantity of dried marihuana to be used by the patient: _ g/day

The period of use is ____day(s) _____week(s) _____month(s).

NOTE: The period of use cannot exceed one year

Health care practitioner's given name and surname:
Profession:
Health care practitioner's business address:
Full business address of the location at which the patient consulted the health care practitioner (if different than above):

Phone Number:
Fax Number (if applicable):
Email Address (if applicable):

Province(s) Authorized to Practice in:
Health Care Practitioner's Licence number:

By signing this document, the health care practitioner is attesting that the information contained in this document is correct and complete.

Health Care Practitioner's Signature:
Date Signed (DD/MM/YYYY):

Summary

• Currently in Canada, physicians have been placed as the sole gatekeepers in authorizing legal access to cannabis for medical reasons.

• Physicians can authorize patients to purchase cannabis for medical reasons by providing a “medical document” after a number of requirements are completed.

• Clearly, more research in the clinical use of cannabinoids is required to address the fact that society’s demand for this remedy is ahead of the evidence that is available for safe and effective use of cannabis as a medical treatment.
Let's discuss this controversial topic
The need for research

Safety and improved care for people living with arthritis are The Arthritis Society’s top priorities. Given the significant gaps in information about medical cannabis and its use in treating arthritis symptoms, The Society is actively supporting additional research, the goal of which is to provide patients and physicians with greater access to credible and complete information upon which to base treatment decisions.

Some of the questions about medical cannabis and arthritis that research will help us answer include:

- How does medical cannabis work?
- How effective is medical cannabis for managing pain and fatigue caused by arthritis? How does medical cannabis affect inflammation?
- If effective, what is the best delivery method?
- What factors affect dosage, delivery mode and efficacy? Do they vary depending on the patient, disease type or amount of pain being experienced?
- Does medical cannabis have any adverse interactions with other medications or conditions?
- Is it possible to separate the cannabinoid molecules that contribute to pain relief from those that have unwanted side effects?
- Which patients will benefit the most from medical cannabis?
- What are the risks associated with using medical cannabis?
Vaporizing
Distribution of CB1 receptors (www.ccic.net)