### Cannabinoids: Overview

**Clinical Pearls**

- Routinely ask about cannabis use in primary care (just like tobacco/alcohol), & monitor for cannabis use disorder (up to 1 in 5 may develop with ongoing use).76,77
- After failure of ≥3 other drugs, a trial of prescription cannabinoids (rather than cannabis) may be reasonable for treating neuropathic pain.2
- Approach cannabinoids with similar caution as opioids – see box below.
- Start cannabinoids at a low dose, and gradually titrate. A few clinical trials suggest some efficacy even at very low doses.23,25 Adverse effects are common; monitor & document; stop or taper if not tolerated.
- Inhaled cannabis is not a preferred route of administration due to difficulty dosing, risk of respiratory damage, and multi-component composition.
- Medical cannabis is not recorded on PIP in Saskatchewan (Rx-cannabinoids are).
- The potential harms of cannabinoids are often underappreciated by patients. Informed consent and patient education are advisable. See the RxFiles Cannabis Patient Booklet (available online; colour, or B/W, or print copy).

**Definitions and Background Information**

**Cannabinoid receptors:** CB1 receptors (primarily in the central and peripheral nervous systems) and CB2 receptors (primarily in the immune system) are part of an endocannabinoid system in humans.1

**Cannabinoids:** compounds that activate cannabinoid receptors. Endogenous cannabinoids in humans include AEA & 2-AG.

Two studied, although still poorly understood, cannabinoids are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD).

Cannabis: aka marijuana. Contains 400+ compounds, including 140+ cannabinoids. Marketing based on concentration of THC & CBD, although it is uncertain if these are the only important compounds in cannabis. (e.g. Potential for “entourage effect” of many components.)

**Prevalence (2019):** 18% of Canadian adults used cannabis in last 3mos, 6% used daily, & 2% were registered for medical use.16,30

**Challenges with the evidence:** limited & small RCTs, of short duration, studying differing routes, forms & types of cannabinoids results in low confidence in assessing benefits & harms. Trials with longer duration tend to show less benefit,11 implying that if an effect exists, it may wear off over time. Further, few cannabinoid trials are adequately blinded due to the psychotropic effects of cannabinoids (~90% of patients can guess their allocation),11 which is thought to bias results toward benefit.17

**Current (2020) legal status in Canada:** Rx cannabinoids are Schedule II (controlled substances). Dried cannabis & oils are legal from licensed producers with Rx authorization (“medical cannabis”), or from a cannabis retail store. Some edibles/topicals are legal (2019).

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### Do Cannabinoids Work (Medically)?

**Cannabis** may (limited, low quality evidence for benefit, compared to placebo):

- ↓ chronic neuropathic pain NNT=11 for ≥30% reduction over ~4 wks.2,15
  (Balance of evidence for ↑ pain, but some ↑ harms shared decision making) 78,79
- ↓ chemotherapy-induced nausea & vomiting NNT=3 for control of nausea/vomiting over ~1 day.2
- ↓ spasticity of multiple sclerosis or spinal cord injury NNT=10 for ≥30% ↓ spasticity over “6 wks.”2
- ↓ seizures in Lennox-Gastaut & Dravet syndrome with CBD NNT=4-7 for ≥50% reduction in seizure frequency over “~4 wks.”15

**Are Cannabinoids Safe?**

Adverse effects (AE) are very common with cannabinoids. Approximately 8-9 patients out of 10 will develop an adverse effect to cannabinoid therapy and ~1 patient in 10 will stop therapy because of an adverse effect.2 Notable AEs include feeling “high” NNH=4; sedation NNH=5; speech disorders NNH=5; dizziness NNH=5; and ataxia/muscle twitching NNH=6.2 Additional concerns include driving impairment, addiction risk, euphoria, and psychosis. Some cannabinoids may be safer than others, but this is not well studied (including specific THC/CBD ratios). See next page. Option, but caution in older adults.74

Cannabis use disorder is associated with self-harm & overdose death in youth.74

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### Perspectives on Cannabis Usefulness and Medical Cannabis

**Cannabis is useful?**

- Some patients have tried a dozen or so standard medications without success, and now are trying, or want to try cannabis. If these patients find success with cannabis, and we help them do so safely, we will have done a great service for them.
- When patients say a medication helps, we should listen to them, just as we listen when patients tell us the antidepressant or anti-emetic we prescribed is helping.
- By developing products with a higher CBD-to-THC ratio, many tolerability concerns will be overcome.
- If cannabis helps our patients use less opioids, that’s an attractive tradeoff.
- I plan to discuss what would constitute success, set realistic expectations, and conduct a trial over 4-12 weeks, after which any benefits vs harms will be assessed along with the decision on whether to continue or discontinue.

**Medical Cannabis**

- Every other medication we prescribe has standard dosing and potency; no other medication is smoked. Inhaled cannabis contains 400+ compounds, and it’s unclear which are important and how they interact. On top of that, each inhaled puff can be different from the last.
- There is no evidence that cannabis is superior to prescription cannabinoids; therefore regulated & approved prescription cannabinoids should always be preferred.
- In clinical trials, benefits are typically small and may just be a placebo effect. Meanwhile, adverse events are common. We have a professional duty to only prescribe medications when it can be done safely, and with cannabis the harms almost always outweigh the benefits. These harms may not be fully appreciated by patients.
- If we routinely authorize cannabis today, will it mirror the opioid crisis tomorrow?

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### Cannabinoids for pain, or Opioids …

Trial evidence comparing cannabinoids and opioids is limited.57 But they do have some similarities and differences to consider:

- **Efficacy:** For both drug classes, RCT evidence is of low quality and short duration, and tends to show only a modest reduction in pain. Longer trials tend to show less benefit.

  However, despite the relative lack of quality evidence, patients often have strong beliefs about the value of each drug class. [Ask “Who is using? How are they using?, & Why…?”]

- **Adverse effects:** Nausea, sedation, and euphoria are adverse effects of both drug classes. Opioids can cause constipation;1 cannabinoids can cause psychiatric disturbances (e.g. anxiety, agitation, amotivation, psychosis).27 Adverse effects appear dose-related (↑dose = ↑AE). Both drug classes may be used by patients as an “escape.”

- **Addiction risk:** With prescription opioids, estimated to be 5.5%.76 With non-medical cannabis, estimated to be ~9%.26 (The risk with medical cannabinoids is unstudied.)

- **Fatal overdose risk:** With prescription opioids, 0.23% with >100mg morphine per day (↑risk with ↑dose).26 With cannabis, fatal overdose risk appears to be negligible.1

For both drug classes, the concept of an n=1 trial with an exit strategy is important. Not all patients will respond to, or function well on, these medications.

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### Or Something Better?

If patients are wanting an escape from pain – physical or emotional – there are often better choices! Non-pharmacological approaches to coping and living well with pain will be essential for success!
### Cannabinoids: Comparison Chart

#### Prescription Cannabinoids (pharmaceutical grade)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Side Effects</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dronabinol (Marinol)</strong></td>
<td>Oral solution (100mg/mL)</td>
<td><strong>Seizures:</strong> Lennox-Gastaut syndrome or Dravet syndrome in patients with Tuberous sclerosis complex</td>
<td>Treatment for the symptoms of anorexia and nausea in patients with AIDS, and to prevent chemotherapy-induced nausea and vomiting.</td>
</tr>
<tr>
<td><strong>Cannabinol Oils</strong></td>
<td>THC/CBD in various ratios</td>
<td><strong>Severe nausea/vomiting from chemotherapy</strong></td>
<td>Manage the symptoms of chemotherapy-induced nausea and vomiting.</td>
</tr>
<tr>
<td><strong>Nabilone (Cesamet)</strong></td>
<td>Synthetic THC analogue</td>
<td><strong>Severe nausea/vomiting from cancer chemotherapy</strong></td>
<td>Provides relief from nausea and vomiting.</td>
</tr>
<tr>
<td><strong>Nabiximols (Sativex)</strong></td>
<td>Extracted THC/CBD (2.7mg THC &amp; 2.5mg CBD per spray)</td>
<td><strong>Seizures:</strong> Lennox-Gastaut syndrome or Dravet syndrome in patients with Tuberous sclerosis complex</td>
<td>Treatment for the symptoms of anorexia and nausea.</td>
</tr>
</tbody>
</table>

#### Generic/Trade

<table>
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<th>Drug</th>
<th>Formulation</th>
<th>Side Effects</th>
<th>Indications</th>
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<tr>
<td><strong>Dronabinol (Marinol)</strong></td>
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</tr>
</tbody>
</table>

### Medical Cannabis (Plant)

<table>
<thead>
<tr>
<th>Plant</th>
<th>Cultivars</th>
<th>Effects</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cannabis sativa</strong></td>
<td><strong>Hybrid</strong></td>
<td><strong>Euphoria</strong></td>
<td><strong>Dizziness, dry mouth, drowsiness</strong></td>
</tr>
<tr>
<td><strong>Cannabis indica</strong></td>
<td><strong>Indica</strong></td>
<td><strong>Relaxation</strong></td>
<td><strong>Sleepiness</strong></td>
</tr>
</tbody>
</table>

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**Dosing:**
- **Initial:** 0.25-0.5mg THC per os, increasing as needed.
- **Usual:** 1-2mg THC daily-BID for CINV.
- **Max:** 5mg THC daily-BID for neuropathic pain.

**Adverse Events:**
- **Psychiatric disturbances** up to 17% across cannabinoids, and up to 27% with inhaled cannabinoids, including depression, anxiety, panic, paranoia, hallucinations.
- **Sleep disorders** up to 32%, and **ataxia** up to 30% across cannabinoids.
- **Impaired memory** up to 11%.
- **Psychosis** in up to 5% of patients on cannabinoids.
- **Acute psychosis or dissociation** up to 5% across cannabinoids.

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**Legal Status:**
- **US:** Marijuana is illegal at the federal level.
- **Canada:** Recreational use is legal for adults over 18 years old.

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**References:**
- A Crawley BSp, M LeBras Pharm D, L Regier BSp, B Jensen BSp © www.RxFiles.ca Nov 2021
Who could be a candidate for cannabinoid therapy?

- Cannabinoids are generally not considered first- or second-line therapy for any indication. Reserve use for patients who have failed other therapies. Conduct a trial over 4-12 wks; review benefits vs harm.
- Check Prescription Drug Monitoring Programs (e.g. PIP in SK) at baseline & at each visit. These programs do not record medical cannabis. Opt to check order hx with Licensed Producer. Document cannabis use on local EMR (just like tobacco, alcohol, etc.).
- Baseline urine drug screen, and randomly thereafter. THC metabolite detected = THC-COOH. Note: urine drug screens in SK do not test for CBD.
- Assess risk of addiction, and monitor for cannabis use disorder.
- Ensure the patient understands cannabinoids are prescribed as a trial. Reasonable trial duration may be ~12 weeks.
- Obtain Treatment Agreement and Informed Consent. Search “agreement” at www.rxfiles.ca for a sample cannabis tx agreement. Agreement includes safe storage – especially important if kids nearby.
- Monitor for benefits & harms. Exit Strategy: stop (often taper) if trial unsuccessful. Possible taper to prevent withdrawal: ↓ by 25% q1week. Monitor more vigilantly in those at higher risk, esp where quality evidence/guidelines lacking.

Cannabis are potential drugs of abuse; caution is needed when prescribing. In general, follow similar principles to prescribing opioids (see page 131-132). A summary of these principles is as follows:

1. **Options for Screening:**
   - **CUDIT-R** specific to cannabis. 45
   - **CAGE-AID Questionnaire** short & practical. 46
2. **Diagnosing:**
   - Use DSM-5 criteria. 51
   - 11 components, 2 or more +=

**4Cs of Addiction:** Craving, loss of Control, Compulsive use, Continued use despite harm

**Symptoms of Cannabis Withdrawal**

- Onset: 1-2 days, peak 2-6 days
- Anger, aggression, appetite change, weight loss, anxiety, irritability, restless, sleep disturbance, cannabis craving, physical discomfort.

**CUD increased 3-4 fold over 20 years following legalization in Denmark.** 52

Choosing Between Products

<table>
<thead>
<tr>
<th>Prescription Cannabinoids (e.g. nabilone, nabiximols)</th>
<th>Cannabis via medical authorization</th>
<th>Cannabis via retail sale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality Control</td>
<td>Regulated. Health Canada pharmaceutical production standards in place (has Drug Identification Number).</td>
<td>In SK, sellers from both medical &amp; retail streams use the same cannabis sources (a Health Canada licensed producer). Production standards exist, including testing for pesticides &amp; THC/CBD concentrations. 43 However, similar to non-Rx herbal supplements, cannabis may have less rigorous production standards than Rx drugs. Products require standardized symbols: red stop-sign shape with cannabis leaf &amp; “THC.” Edibles must have child-resistant packaging.</td>
</tr>
</tbody>
</table>

**Dosing & Guidance**

- **Standardized.**
- **Some indications and dosing are Health Canada approved.**
- **Will show up on the electronic medical record (e.g. PIP in Saskatchewan).**
- **Challenging.** e.g. THC in 1 puff of cannabis joint can range from 1 to >10mg. No “studied usual dose”.
- **Prescriber may pick strain/ratio and max quantity allowed for patient. May limit duration, e.g. “one 60mL bottle of CBD oil, then see prescriber for further authorization.”**
- **Overall, less control than prescription products (e.g. “dosing interval” does not exist).**

**Note:** despite prescriber attempts to guide product and dosing, patients may supplement with retail cannabis against medical advice.

<table>
<thead>
<tr>
<th>Access</th>
<th>Dispensed by community pharmacy.</th>
<th>Exclusively by mail/courier.</th>
<th>At cannabis retail store; online ordering possible too.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paperwork</td>
<td>Written or electronic prescription.</td>
<td>See Paperwork Required for Medical Cannabis box, right.</td>
<td>None.</td>
</tr>
<tr>
<td>Coverage</td>
<td>Occasional private insurance coverage.</td>
<td>Occasional private insurance coverage (e.g. Manulife and Sunlife on a case-by-case basis as of 2018).</td>
<td>No coverage by any drug plans or private insurance; can’t be claimed on income tax.</td>
</tr>
<tr>
<td>5K EDS and prior approval criteria for specific indications.</td>
<td>Veteran’s affairs coverage (max 3g/day dried cannabis)</td>
<td>“$8/gram; May grow at home to -1costs. (Calculator for home production limit amount - link below)</td>
<td>Average price still uncertain (Ranges from $8-20/gram).</td>
</tr>
</tbody>
</table>

**Paperwork Required for Medical Cannabis**

1. Complete medical document form (link ❶). In SK, complete treatment agreement form (link ❷). See “agreement”). 50
2. Submit medical document to Licensed Producer (link ❺) who mails cannabis (dried, oil, buds, or leaves) to patient.
3. Or, patients may apply to grow their own product at home (e.g. 15 plants for 3g/day, see link ❻). 47
4. Medical document must be re-authorized at least once per year.
5. In SK, prescribers required to keep list of pts. 6

9. No set daily limit; max possession is lesser of 150g or 30 times daily amount.

**Notes: (e.g. motivational enhancement, CBT)**

- Respiratory problems
- Depression/Anxiety/Amotivation
- Issues functioning/concentrating (e.g. in studies, work, relationships)
- Those at ↑ risk of self-injury/harm (e.g. veterans - suicidality, seniors - AEs, DIs)

**Medications for cannabis withdrawal**

- Anticonvulsants
- Mood stabilizers
- Benzodiazepines

**Medical usage (vs recreational):**

- Use more frequently
- Use products other than dried flower & trend towards low THC/high CBD
The College’s bylaw which regulates physician authorization of medical marihuana is now in effect. The bylaw is numbered Bylaw 19.2 of the regulatory bylaws of the College and is available at the College’s website. Visit: http://www.cps.sk.ca/imis/CPSS/CPSS/Programs_and_Services/Medical_Marijuana/Medical_Cannabis.aspx. A summary of the bylaw follows:

1. The bylaw begins with a statement that there has not been sufficient scientific or clinical assessment to provide evidence about the safety and efficacy of marihuana for medical purposes. The bylaw begins with an acknowledgement that federal government regulations have authorized the use of marihuana for medical purposes.

2. A physician cannot authorize the use of marihuana for a patient unless the physician is also the treating physician for the condition for which the patient is authorized to use marihuana. For example, if a patient is to be authorized to use medical marihuana to deal with symptoms of MS, the physician must also be the treating physician for the patient’s MS.

3. A physician must review the patient’s medical history, review relevant records pertaining to the condition for which the use of marihuana is authorized and conduct an appropriate physical examination before authorizing the patient’s use of marihuana.

4. The patient must sign a written treatment agreement which contains the following:
   A) A statement from the patient that the patient will not seek a prescription for marihuana from any other physician during the period for which the marihuana is prescribed;
   B) A statement by the patient that the patient will utilize the marihuana as prescribed, and will not use the marihuana in larger amounts or more frequently than is prescribed;
   C) A statement by the patient that the patient will not give or sell the prescribed marihuana to anyone else, including family members;
   D) A statement by the patient that the patient will store the marihuana in a safe place.

Sample treatment agreement: http://www.cps.sk.ca/iMIS/Documents/Programs%20and%20Services/Patient%20Agreement%20Template%20-%20Medical%20Cannabis.pdf

Or visit www.RxFiles.ca and search “agreement”.

5. The physician’s record for the patient must include the requirements for all medical records and, in addition, contain the following:
   A) The treatment agreement signed by the patient;
   B) The diagnosis for which the patient was authorized to purchase marihuana;
   C) A statement of what other treatments have been attempted for the condition for which the use of marihuana was prescribed and the effect of such treatments;
   D) A statement of what, if anything, the patient has been advised about the risks of the use of marihuana;
   E) A statement that in the physician’s medical opinion the patient is likely to receive therapeutic or palliative benefit from the use of marihuana to treat the patient’s condition.

6. The physician must retain a single record, separate from other patient records, which can be inspected by the College, and which contains:
   A) The patient’s name, health services number and date of birth;
   B) The quantity and duration for which marihuana was prescribed;
   C) The medical condition for which marihuana was prescribed;
   D) The name of the licensed producer from which the marihuana will be obtained, if known to the physician.

7. Physicians who prescribe marihuana will be required to provide the College with the information referenced in paragraph 6:
   A) Every twelve months if the physician has prescribed marihuana to fewer than 20 patients in the preceding 12 months;
   B) Every six months if the physician has prescribed marihuana to 20 or more patients in the preceding 12 months.

8. The bylaw prohibits physicians from diagnosing or treating patients at the premises of a licensed producer;

9. The bylaw prohibits physicians who prescribe marihuana from having an economic or management interest in a licensed producer;

10. The bylaw prohibits physicians from storing or dispensing marihuana from any location where the physician practices medicine.
Submitting Adverse Effect information to Health Canada:

Tips on filling out Part D (for cannabis products i.e. dried cannabis or cannabis oils)
- DIN or NPN is not required
- Include: brand name, strain name, lot #, licensed holder name, intended use (medical or non-medical)
- If the product was not purchased from a legal retailer it can still be reported but it would be useful to indicate if it was purchased from a non legal source so it can be processed properly in our database.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Page</th>
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</thead>
<tbody>
<tr>
<td>Cannabinoid</td>
<td>139</td>
</tr>
<tr>
<td>Cannabinoid Use Disorder</td>
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<td>Cannabis</td>
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<tr>
<td>CBD</td>
<td>139</td>
</tr>
<tr>
<td>Marijuana</td>
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<td>Medical Cannabis</td>
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<tr>
<td>Anorexia</td>
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<tr>
<td>Cannabidiol</td>
<td>140</td>
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<tr>
<td>Cannabinoid</td>
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<td>Nabiximols</td>
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<tr>
<td>Tetranabinex/nabidiolex</td>
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</tr>
<tr>
<td>THC</td>
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</table>
References: Cannabinoid Chart – www.RxFiles.ca


35. Aldington S, Williams M, Nowitz M, Weatherall M, Pritchard A, McNaughton A, Robinson G, Beasley R. The EFFECTS OF CANNABIS ON PULMONARY STRUCTURE, FUNCTION AND SYMPTOMS. Thorax. 2007 Jul 31; [Epub ahead of print] Smoking cannabis was associated with a dose-related impairment of large airways function resulting in airflow obstruction and hyperinflation. In contrast, cannabis smoking was seldom associated with macroscopic emphysema. The 1:2.5 to 5 dose equivalence between cannabis joints and tobacco cigarettes for adverse effects on lung function is of major public health significance.


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