Cannabinoids: Overview

Clinical Pearls
- Routinely ask about cannabis use in primary care (just like tobacco and alcohol), & monitor for cannabis use disorder.
- 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.²⁵ Adverse effects are common; monitor; 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.
- Cannabis is not recorded on PIP in Saskatchewan (Rx-cannabinoids are).
- The potential harms of cannabis are often underappreciated by patients. Informed consent and patient education are advisable. The RxFiles Cannabis Patient Booklet may be a useful tool (available online).²⁵

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

Cannabis: aka marijuana. Contains 400+ compounds, including 140+ cannabinoids. Often marketed based on THC & CBD concentrations, although it is uncertain if these are the most important compounds in cannabis.

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 (2018) legal status in Canada: Rx cannabinoids are Schedule II (controlled substances). Dried cannabis & oils are legal from a licensed producer with prescriber authorization, or from a cannabis retail store. Cannabis edibles aren’t legal for purchase (yet).

Do Cannabinoids Work (Medically)?

Note: See “Challenges with the evidence” comments, above

Compared to placebo, cannabinoids may (limited, low quality evidence): ¹verter, 2019
- ↓ chronic neuropathic pain NNT=11 for ≥30% reduction over ~4 wks.²,²⁵
- ↓ 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.⁶⁸
- ↓ seizures in Lennox-Gastaut & Dravet syndrome with CBD NNT=4-7 for ≥50% reduction in seizure frequency over ~14 wks.²

Are Cannabinoids Safe?

Adverse effects 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 adverse effects include feeling “high” NNN=4; sedation NNN=5; speech disorders NNN=5; dizziness NNN=5; and ataxia/muscle twitching NNN=6.² Additional concerns include driving impairment, addiction risk, euphoria, and psychosis. Some cannabinoids may be safer than others, but this is generally unstudied (including specific THC/CBD ratios). See next page of this chart.

Differing Health Care Perspectives on Medical Cannabis

Cannabis is useful?
- Some patients have tried a dozen or so standard medications without success, and now 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 different THC-to-CBD ratios, perhaps tolerability concerns can be addressed.
- If cannabis helps our patients use less opioids, that’s an attractive tradeoff.

Cannabis should be avoided?
- 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 we mirror the opioid crisis tomorrow?

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.
- Adverse effects: Nausea, sedation, and euphoria are adverse effects of both drug classes. Opioids can cause constipation;²⁵ 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%.²⁶ 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).²⁵ With cannabis, fatal overdose risk appears to be negligible.¹

For both drug classes, the trial with an exit strategy is important. Not all patients will respond to these medications.

Miscellaneous info: Synthetic illicit cannabinoids: e.g. K2, Spice – highly potent CB1/CB2 receptor agonists; case reports of severe acute toxicity.¹² Phyto-cannabinoids: a cannabinoid derived from cannabis [e.g. THC, CBD, & others]. THC: a partial CB1 & CB2 agonist. CBD: uncertain mechanism of action. Entourage effect: an unproven hypothesis that efficacy of cannabinoids is increased (or adverse effects decreased) when they are used in combination and/or in particular ratios and/or with flavonoids, terpenoids. Terpenoids: e.g. creams: an unproven dosage form, promoted as local analgesia without systemic effect, but currently without trials to support. Concentrated Cannabis: e.g. hash, shatter, badder, wax: contains THC as high as 90%. Dabbing: vaping small amounts of concentrated marijuana. Travelling with cannabis outside of canada: not recommended. Non-medical cannabis: aka “recreational”. Is cannabis opioid-sparing? Evidence is still unclear.¹⁶,⁴⁶ Submitting AE to Health Canada: https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/recalls-adverse-reactions-reporting/report-side-effects-cannabis-products.html (see for tips for cannabis products)
# Cannabinoids: Comparison Chart

## Prescription Cannabinoids

### Nabilone CESAMET, g synthetic THC analogue 0.5, 1mg cap ✔️ 0.25mg cap ✔️
- **Preferred over cannabis**: use often to smoke/vape, Veterans Affairs
- & palpitations
- **Oral**: 5mg/mL solution 2.5, 5mg
- **Synthetic**: Dronabinol
  - 2.7mg
- Refrigerate prior to dispensing
- Not available in USA.

### Nabiximols SATIVEX®, extracted THC/CBD
- 2.7mg THC & 2.5mg CBD per spray (peppermint flavour; poor taste)
- (contains alcohol)
- Refrigerate
- 100mg/mL solution (e.g. 4% THC in 1995)
- 2.5mg po/day
- **Oral**: 1 spray sublingually
- **Usual**: 12 sprays daily

### Cannabidiol EPIDIOLEX
- **Synthetic THC**
- **Seizures** (Lennox-Gastaut or Dravet):
  - 2yr: 2.5-10mg/kg dose per BID usually given before a meal
  - **Food** increases absorption.
- **Max usage**:
  - 2.5mg po pre HS
  - 2.5mg po TID-QID for chemo
  - 2.5mg po BD ac lunch and supper for anorexia
  - **Max**: 20mg/day

### Dronabinol MARINOL®
- **Synthetic THC**
- USA only:
  - 2.5, 5mg, 10 cap (in sesame oil)
  - 5mg/mL solution (contains alcohol)

### Oral Cannabinols Oil(s)
- **THC/CBD in various ratios**:
  - 25mg THC / 0mg CBD per mL
  - 1mg THC / 20mg CBD per mL
  - 3mg THC / 3mg CBD capsule
  - Many other formulations & potencies available.

### Dried Cannabis
- **THC/CBD in various ratios**, often to smoke/vape, e.g.:
  - 12.5% THC
  - 4% THC / 10% CBD
  - 1% THC / 13% CBD
  - Many other potencies available.
- Refrigerate for max stability

### Veteran's Affairs:
- **Coverage available for some patients**

### Trend:
- **Potency products**
- (e.g. 4% THC in 1995 → 12% in 2014)

### Average joint: 0.3g dry cannabis

### Medical Cannabis

### Adverse Events / AE
- **Contraindications** / Drug Interactions
- **CI**
- **Monitoring**

### Medical Cannabis (pharmaceutical grade)

### Cannabinoids: Comparison Chart

### Indications & Comments

#### Preferred over cannabis:

- **Severe nausea/vomiting from cancer chemotherapy**
- **Off-label**: AIDS-related anorexia
- Palliative pain
- Neuropathic pain
- Not detected in SK urine drug screen

#### Preferred over cannabis:

- **Advanced cancer pain (adjunctive)**
- **Multiple sclerosis neuropathic pain or spasticity (adjunctive)**
- Spasticity may require lower doses than pain (e.g. 4-5 sprays vs >8 sprays per day).

#### Seizures (Lennox-Gastaut or Dravet): 2yr:

- 2.5-10mg/kg dose per BD usually given before a meal
- **Food intake** increases absorption.
- **Max usage**:
  - 2.5mg po HD
  - 2.5mg po TID-QID for chemo
  - 2.5mg po BD ac lunch and supper for anorexia
  - **Max**: 20mg/day

#### Guidelines recommend avoiding smoked cannabis.

- **Initial**: 1-2 puffs inhaled HS
- **Usual**: 1 puff of joint = 1-10mg THC
- **Variation** is due to inhalation depth, puff size, THC potency, smoking vs vaporized joint size, etc.

#### In 2017 in Canada, the average medical price was $58/g and the average street price was $75.9/g.

#### Smoking cannabis:

- **Max levels** of antipsychotics, caffeine, TCAs, theophylline, warfarin
- **Nabilone**: while a THC-mimic, does not have THC drug interactions.
Who could be a candidate for cannabinoid therapy?

- 90% of adults who use cannabis non-medically may develop addiction (& up to 17% if started in adolescence).

Monitoring for Cannabis Use Disorder (CUD)

Prior to Tx: Screen for CUD

1) Options for screening:

- CUDIT-R specific to cannabis.
- CAGE-AID Questionnaire short & practical.

2) Diagnosing:

- use DSM-5 criteria.

During Tx: Monitor for CUD

- rapid or unsanctioned dose ↑
- frequent changes needed
- wants dried cannabis only
- wants high potency THC only
- misuse of other substances
- urine drug screen: aberrant
- concerns from friends/family
- poor functioning (school/work/social)
- missed follow-up; reports of lost or stolen cannabis

In primary care,

- respiratory problems
- depression/anxiety/amotivation
- issues functioning/concentrating (e.g. in studies, work, relationships)

Treating CUD: $8-$50

1. Brief interventions
2. Withdrawal management (e.g. sleep hygiene, brief symptomatic relief, ?nicotine replacement)
3. Psychosocial interventions (e.g. motivational enhancement, CBT)

Treatment CUD: www.rxfiles.ca

Paperwork Required for Medical Cannabis

1. Complete medical document form (link). In SK, complete treatment agreement form (link). Visit RxFiles.ca and search ”agreement”.

2. Submit medical document to Licensed Producer (link) 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).

4. Medical document must be re-authorized at least once per year.

5. In SK, prescribers required to keep list of pts.

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

Choosing Between Products

<table>
<thead>
<tr>
<th>Prescription Cannabinoids e.g. nabidolone, nabiximols</th>
<th>Cannabis</th>
</tr>
</thead>
<tbody>
<tr>
<td>via medical authorization</td>
<td>via retail sale</td>
</tr>
</tbody>
</table>

Quality Control

- Regulated. Health Canada pharmaceutical production standards in place (has Drug Identification Number).

Dosing & Guidance

- Standardized.
- Some indications and dosing are Health Canada approved.
- Will show up on the electronic medical record (e.g. PIP in Saskatchewan).

Note: despite prescriber attempts to guide product and dosing, patients may supplement with unsupervised products.

Dosing & Guidance

- 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).

Dosing & Guidance

- Patient selects the product, dose, dosing interval, and route of administration.
- Difficult to provide monitoring, boundaries, or education.

Access

- Dispensed by community pharmacy. Exclusively by mail/courier. At cannabis retail store; online ordering possible too.

Paperwork

- Written or electronic prescription. See Paperwork Required for Medical Cannabis box, right. None.

Coverage

- Occasional private insurance coverage. No coverage by any drug plans or private insurance; can’t be claimed on income tax.

- $8/gm; May grow at home to reduce costs.

[Calculator for home production limit amount - link below]

Average price still uncertain (Ranges from $8-$20/gm)

Cannabinoids: Prescribing Considerations

Cannabinoids are generally not considered first- or second-line therapy for any indication. Reserve use for patients who have failed other therapies. e.g. may consider if tried ≥3 drugs for neuropathic pain or ≥2 drugs for palliative pain or if refractory to standard therapies for CINV, spasticity in MS or SCI, or cachexia [or refractory pediatric seizure]

- Watch for relative contraindications such as pregnancy, breastfeeding, age <21-25, a history of psychoschizophrenia, or substance abuse history. For more details, see RxFiles Cannabis Q and A.

Prescribing/Authorizing Cannabinoids Safely

Cannabinoids are potential drugs of abuse; caution is needed when prescribing. In general, follow similar principles to prescribing opioids (see RxFiles Prescribing Opioids Safely). A summary of these principles is as follows:

- Optimize suitable non-cannabinoids therapies first (drug and non-drug).
- Check electronic health records (e.g. PIP in SK) at baseline and with each visit.
- Note: medical cannabis does not appear on PIP. Option 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 benefits & harms. Exit Strategy: stop (often taper) if trial unsuccessful. Possible taper to prevent withdrawal: ↓ by 25% q1week.

Choosing Between Products

Note: currently Canada has a ”two-stream” cannabinoid system: medically authorized cannabis, and cannabis through retail sale.

Cannabinoids

- #eds SK = prior approval NHIB X = not covered SK = not covered NHIB = NHIB palliative care 2-AG=2-Arachidonoyl glycerol AEA=Aminanide CBD=cannabinoid CB1=cannabinoid receptor type 1 CB2=cannabinoid receptor type 2 COOH=carboxylic acid CUD=cannabis use disorder CVA=cerebrovascular accident CVD=cerebrovascular disease CVA=cerebrovascular accident CVD=cerebrovascular disease CVA=cerebrovascular accident CVD=cerebrovascular disease
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.


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.


Additional references for Cannabinoids:


