**Clinical Pearls**

- Routinely ask about cannabis use in primary care (just like tobacco and alcohol), & monitor for cannabis use disorder.
- After failure of ≥2 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.2,25 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 underestimated by patients. Informed consent and patient education are advisable. The RxFiles Cannabis Patient Booklet may be a useful tool (available online).”

**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 includeAEA & 2-AG. Two studied, although 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 & 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 (2019) 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. Some cannabis edibles/topicals are legal (2019).

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Do Cannabinoids Work (Medically)?

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

**Compared to placebo, cannabinoids may** (limited, low quality evidence):

- ↓ 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.3
- ↓ 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=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” NHH=4; sedation NHH=5; speech disorders NHH=5; dizziness NHH=5; and ataxia/muscle twitching NHH=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?

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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.
- **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%.29 With non-medical cannabis, estimated to be 9%.29 (The risk with medical cannabinoids is unstudied.)
- **Fatal overdose risk:** With prescription opioids, 0.23% with >100mg morphine per day (↑risk with ↑dose).23 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.

**... Or Something Better?**

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

### Prescription Cannabinoids (pharmaceutical grade)

**Cannabinoids**

<table>
<thead>
<tr>
<th><strong>Prescription Cannabinoids</strong></th>
<th><strong>Indications &amp; Comments</strong></th>
<th><strong>Dosage</strong></th>
<th><strong>Adverse Events/Contraindications</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>THC/CBD ratios</strong></td>
<td><strong>THC/CBD in Veteran’s Affairs</strong></td>
<td><strong>Usual</strong></td>
<td>$22-18.2 g $112-215 g $112 g $310 g $1200 g</td>
</tr>
<tr>
<td><strong>Dronabinol CESAMET, g</strong></td>
<td>synthetic THC analogue 0.5, 1mg cap ▼ □ 0.25mg cap ▼ □</td>
<td>Initial: 0.25-0.5mg po HS 1-2mg po daily-BID for CINV 1mg BID for neuropathic pain Usual max: 6mg/day</td>
<td></td>
</tr>
<tr>
<td><strong>Nabiximols SATIVEX X</strong></td>
<td>extracted THC/CBD 2.7mg THC &amp; 2.5mg CBD per spray (peppermint flavour; poor taste) (contains alcohol)</td>
<td>Spray under the tongue or into side cheek (may alternate sides).</td>
<td></td>
</tr>
<tr>
<td><strong>Nabiximols SATIVEX</strong></td>
<td>synthetic THC</td>
<td>Initial: 1 spray sublingually HS Usual: 1 spray sublingually q4h Usual max: 12 sprays per day</td>
<td></td>
</tr>
<tr>
<td><strong>Cannabis Oils</strong></td>
<td>Cannabis use USA</td>
<td>Seizures (Lennox-Gastaut or Dravet): ≥2yr: 2.5-10mg/kg-dose po BID usually give before a meal Food ↑3% (increases absorption).</td>
<td></td>
</tr>
<tr>
<td><strong>Cannabinoids</strong></td>
<td>not available in USA.</td>
<td>Not available in Canada</td>
<td></td>
</tr>
<tr>
<td><strong>Cannabis Oils</strong></td>
<td>Treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients ≥2 years of age</td>
<td>3 vial pack = $700 (52.60/spray) (30 spray/vial)</td>
<td></td>
</tr>
<tr>
<td><strong>Dronabinol MARINOL</strong></td>
<td>synthetic THC</td>
<td>Initial: 2.5mg po HS 2.5mg po TID-QID for chemo nausea/vomiting (“5mg/m”) 5mg po BID ac lunch and supper for anorexia AIDS</td>
<td>D/C from Canadian market</td>
</tr>
<tr>
<td><strong>Cannabis Oils</strong></td>
<td>USA only: 2.5, 5mg, 10 cap (in sesame oil) 5mg/mL solution SYNDROS</td>
<td>Max: 20mg/day</td>
<td></td>
</tr>
<tr>
<td><strong>Cannabis Oils</strong></td>
<td>Not available in Canada</td>
<td>$7 e.g. 60mL bottle of oil containing 1200mg CBD = $130</td>
<td></td>
</tr>
<tr>
<td><strong>Cannabinoids</strong></td>
<td>No official indication. May be medically authorized in Canada to any patient for any indication (i.e., “off-label use”).</td>
<td>Initial: 2-3mg of CBD +/- THC po HS (e.g. 0.1mL of 20mg/mL CBD) Usual: Uncertain due to lack of randomized trials. Titrate slowly. (Consider: dronabinol &amp; nabiximols labelling suggest max doses of 25-30mg THC per day.) Food increases absorption. Consider 1st dose at 7 p.m. to leave time for assessing effect. Consider weekend trial start (or when impairment less disastrous). Guidelines recommend avoiding smoked cannabis.</td>
<td></td>
</tr>
<tr>
<td><strong>Cannabinoids</strong></td>
<td>Smoked vs vaporized: smoking speculated to have more respiratory risk (but data limited), but vaping has risk too.</td>
<td>Initial: 1-2 puffs inhaled HS (1 puff of joint = 1-10mg THC. Variation is due to inhalation depth, puff size, THC potency, etc.) Usual: Uncertain due to poor quality evidence. Titrate slowly.</td>
<td></td>
</tr>
<tr>
<td><strong>Cannabinoids</strong></td>
<td>Vaping: slower onset (30 mins), more potent (smoking destroys some drug via combustion).</td>
<td>In 2017 in Canada, the average medical price was $58/g and the average street price was $7.5/g.</td>
<td></td>
</tr>
<tr>
<td><strong>Cannabinoids</strong></td>
<td>Vaping devices: Consider a Health Canada approved vaporizer.</td>
<td>$12-24 for 1-2 puff HS $180 for 750mg/day $720 for 3g/day</td>
<td></td>
</tr>
</tbody>
</table>

**Adverse Events/Contraindications**

- **AE:** Some notes on adverse effects:
  - percentages below are often “worst case scenarios” from systematic reviews, yet due to trial-design issues could also be underestimates.
  - adverse effects appear dose-related (↑dose = ↑AE)
  - it is difficult to compare AE rates between agents, due to few head-to-head trials.
  - THC appears to be the main component responsible for causing a “high” (low-quality evidence).<sup>11</sup> CBD possibly safer than THC, but some of its psychotropic effects are underappreciated (e.g. vs placebo in predominately pediatric trials: aggression/agner 3-5% vs <1%; irritability/agitation 5-9% vs 2%; somnolence 25% vs 6%).

- **CNS:** Drowsiness or sedation up to 50% across cannabinoids.<sup>2</sup>
- **Dizziness** up to 32% across cannabinoids.<sup>2</sup>
- **Psychiatric disturbances** up to 17% across cannabinoids.<sup>4</sup>
- **Acute psychosis or dissociation** up to 5% across cannabinoids.<sup>2</sup>
- **CNS:** Euphoria up to 15%, and feeling “high” up to 35% across cannabinoids.<sup>2</sup>

**Notes on adverse effects:**

- **Common adverse events:**
  - Drowsiness or sedation up to 50% across cannabinoids.<sup>2</sup>
  - Dizziness up to 32% across cannabinoids.<sup>2</sup>
  - Psychiatric disturbances up to 17% across cannabinoids.<sup>4</sup>
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**Notes on adverse effects:**

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  - Psychiatric disturbances up to 17% across cannabinoids.<sup>4</sup>
  - Acute psychosis or dissociation up to 5% across cannabinoids.<sup>2</sup>
Cannabidiols: Prescribing Considerations

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.\(^2\) 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 psychosis/schizophrenia, 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-cannabinoid 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\(^67\)
- Monitor for benefits & harms. Exit Strategy: stop (often taper) if trial unsuccessful. Possible taper to prevent withdrawal: ↓ by 25% q1week.

Monitoring for Cannabis Use Disorder (CUD)

Prior to Tx: Screen for CUD

1) Options for screening:
- CUDIT-R specific to cannabis.\(^45\)
- CAGE-AID Questionnaire short & practical.\(^46\)
2) Diagnosing:
- use DSM-5 criteria.\(^53\)

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

Safely

general, follow

In primary care,\(^7\) watch for:
- respiratory problems
- depression/amotivation
- issues functioning/concentrating (e.g. in studies, work, relationships)

Treating CUD: 58-50

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

[Note: Pharmacologic tx, e.g. naltrexone, appears ineffective at this time] Cochran’19

Symptoms of Cannabis Withdrawal (onset 1-2 days, peak 2-6 days)

- Anger, aggression, appetite change, weight loss, anxiety, irritability, restlessness, sleep disturbance, cannabis craving, physical discomfort.

Choosing Between Products

| Prescription Cannabinoids e.g. nabihone, nabiximols | Cannabis |
| --- | --- | --- |
| via medical authorization | via retail sale |
| Quality Control | Quality Control |
| Regulated. Health Canada pharmaceutical production standards in place (has Drug Identification Number). | In Saskatchewan, sellers from both medical & retail streams use the same cannabis sources (a Health Canada licensed producer). Production standards exist, including testing for pesticides & THC/CBD concentrations.\(^43\) However, similar to non-Rx herbal supplements, cannabis may have less rigorous production standards than Rx drugs. |
| Dosing & Guidance | Dosing & Guidance |
| • Standardized. Some indications and dosing are Health Canada approved. | • Challenging. e.g. THC in 1 puff of cannabis joint can range from 1 to >10mg. No “studied usual dose”. |
| • Will show up on the electronic medical record (e.g. PIP in Saskatchewan). | • 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." |
| Note: despite prescriber attempts to guide product and dosing, patients may supplement with retail cannabis against medical advice. | • Overall, less control than prescription products (e.g. "dosing interval" does not exist). |
| Access | Access |
| Dispensed by community pharmacy. | Exclusively by mail/courier. |
| Paperwork | Paperwork |
| Written or electronic prescription. | See Paperwork Required for Medical Cannabis box, right. |
| Coverage | Coverage |
| • Occasional private insurance coverage. | • Occasional private insurance coverage (e.g. Manulife and Sunlife on a case-by-case basis as of 2018). |
| • SK EDS and prior approval criteria for specific indications. | • Veteran’s affairs coverage (max $3g/day dried cannabis) |
| | • [Calculator for home production limit amount - link below] |
| | Average price still uncertain (Ranges from $8.20-gram) |

Paperwork Required for Medical Cannabis

1. Complete medical document form (link ❶). In SK, complete treatment agreement form (link ❷, or visit RxFiles.ca and search “agreement”).\(^8\)
2. Submit medical document to Licensed Producer (link ❸) 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 ❹).
4. Medical document must be re-authenticated at least once per year.
5. In SK, prescribers required to keep list of pts.
6. No set daily limit; maximum possession is lesser of 150g or 30 times daily amount.

Note:

- ❶ www.hc-sc.gc.ca/phmp/eng/forms/npfs/ndwco的第一link.html
- ❷ http://www.ipps.ca/PPD/Documents/Programs/Ethnic/IPPS-Patient/Programs/HealthCare/Wellness/ sidewalk%20Medical%20Cannabis.pdf
- ❸ www.hc-sc.gc.ca/phmp/eng/forms/ndwco/need-for-authorization.pdf
- ❹ www.hc-sc.gc.ca/phmp/eng/forms/ndwco/need-for-authorization.pdf
- ❺ http://www.rxfiles.ca/%20Medical%20Cannabis.pdf

Cannabis and health can be a two-stream system: medically authorized cannabis, and cannabis through retail sale.

Cochran’19

www.RxFiles.ca

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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, McNaughton A, McNaughton A, McNaughton A. THE EFFECTS OF CANNABIS ON RESPIRATORY FUNCTION, RELATED SYMPTOMS AND PHYSICAL PERFORMANCE. 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:


