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.\(^2\)
- ↓ 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" **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 generally unstudied *(including specific THC/CBD ratios).* See next page of this chart.

Cannabidiol 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.\(^1\)

Two studies, although still poorly understood, cannabinoids are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD).\(^1\)

**Cannabis:** aka marijuana. Contains 400+ compounds, including 120+ cannabinoids. Often marketed based on THC & CBD concentrations, although it is uncertain if these are the most important compounds in cannabis.

**Prevalence (2018):** 14% of Canadian adults used cannabis in last 3mos, 6% used daily, & 1% 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, 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 towards 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).*

**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 psychiatric disturbances *(e. g. anxiety, agitation, amotivation, psychosis).*\(^27\) Adverse effects appear dose-related *(↑ dose = ↑ AE).* Both drug classes may be patients by an “escape”.
- **Addiction risk:** With prescription opioids, estimated to be 5.5%.\(^19\) With *non-medical* cannabis, estimated to be 9%.\(^28\) (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 concept of a 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 Cannabis

**Cannabis** is often used to treat a variety of conditions, including pain, nausea, and seizures. However, the effects and benefits of cannabis can vary depending on the strain, method of use, and individual response.

#### Indications & Comments

<table>
<thead>
<tr>
<th>Medicinal Cannabis</th>
<th>DOSING</th>
<th>$/30d</th>
<th>&quot;AE: Some notes on adverse effects:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cannabis</strong></td>
<td></td>
<td></td>
<td>• percentages below are often &quot;worst case scenarios&quot; from systematic reviews, yet due to trial-design issues could also be underestimated.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• adverse effects appear dose-related (↑dose = ↑AE)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• it is difficult to compare AE rates between agents, due to few head-to-head trials.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• THC appears to be the main component responsible for causing a high (low-quality evidence).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 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 &lt;1%; irritability/ agitation 5-9% vs 2%; somnolence 25% vs 8%).</td>
</tr>
</tbody>
</table>

**Indications & Comments**

- **Seizures** (Lennox-Gastaut syndrome): CSA, CBP & CBD; these may have adverse effects up to 32%, and specific to smoked cannabis. Cannabis may hasten first psychotic episode by 2-6yrs.
- **Withdrawal** with abrupt discontinuation (see withdrawal symptoms on next page) cannabis hyperemesis syndrome: severe abdominal pain/vomiting; requires drug discontinuation; relieved by hot shower; applying capsaicin to abdomen useful. 2-4 red eyes reported with non-medical use of oral and smoked THC.
- **Rare or uncertain**: Sexual problems, Cannabidiol, 7-HMBD, 7-pancretatitis.

**Cannabis** can be smoked or vaporized, often to smoke/vape, e.g.:
- **12.5% THC**
- **4% THC / 10% CBD**
- **1% THC / 13% CBD**

- **No medical use in Mexico**
- **Recreational use in many states**

**Cannabis** is often used to treat a variety of conditions, including pain, nausea, and seizures. However, the effects and benefits of cannabis can vary depending on the strain, method of use, and individual response.

**Conclusion**: cannabis has significant potential as a medicine, but more research is needed to fully understand its effects and safety profile.

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**Medical Cannabis**

<table>
<thead>
<tr>
<th>Medical Cannabis</th>
<th>DOB/Intake</th>
<th>$/30d</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cannabis</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Prescription Cannabis**

<table>
<thead>
<tr>
<th>Prescription Cannabis</th>
<th>$/week</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cannabis</strong></td>
<td></td>
</tr>
</tbody>
</table>

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**All cannabinoids**: additive CNS effects (e.g. sedation, confusion, impairment) with alcohol, anticholinergics, anti-epileptics, benzos, opioids, etc. Additional effects of THC and CBD.

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**Adverse Events / Contraindications**

- **Psychiatric disturbances** up to 17% across cannabinoids, and up to 27% with inhaled cannabis.
- **Cannabis** may be anxiogenic, inducing depression, anxiety, panic, paranoia, hallucinations.
- **Euphoria** up to 15%, and feeling "high" up to 35% across cannabinoids.
- **Acute psychosis** or dissociation up to 5% across cannabinoids.
- **Speech disorders** up to 32%, and ataxia up to 30% across cannabinoids.
- **Impaired memory** up to 11% across cannabinoids.
- **Irritability or agitation** up to 9%, and anger or aggression** up to 5% with CBD.
- **Appetite changes**: decreased appetite in up to 22% of patients on CBD, and conversely increased appetite in up to 38% of patients on dronabinol.
- **Gastrointestinal issues**: dry mouth; diarrhea up to 20%, vomiting up to 15% with CBD.
- **Contraindications** smoking may result in 1A2 induction; cannabis may heighten first psychotic episode by 2-6yrs. Withdrawal with abrupt discontinuation (see withdrawal symptoms on next page) cannabis hyperemesis syndrome: severe abdominal pain/vomiting; requires drug discontinuation; relieved by hot shower; applying capsaicin to abdomen useful. 2-4 red eyes reported with non-medical use of oral and smoked THC.
- **Rare or uncertain**: Sexual problems, Cannabidiol, 7-HMBD, 7-pancretatitis.
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. 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 Rx Files 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 Rx Files 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 (e.g. just like tobacco, alcohol, etc.).
- Baseline urine drug screen, and randomly thereafter
- Note: 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.
- Possible taper to prevent withdrawal: ↓ by 25% q1week.

Choosing Between Products

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

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. However, similar to non-Rx herbal supplements, cannabis may have less vigorous production standards than Rx drugs.

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 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.

Access

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

Paperwork

- Written or electronic prescription.
- See Worksheet Required for Medical Cannabis box, right.
- No coverage by any drug plans or private insurance; can’t be claimed on income tax.

Coverage

- Written or electronic prescription.
- See Worksheet Required for Medical Cannabis box, right.
- No coverage by any drug plans or private insurance; can’t be claimed on income tax.

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.

Monitoring for Cannabis Use Disorder (CUD)

- 9% of adults who use cannabis non-medically may develop addiction (& up to 17% if started in adolescence).

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, watch for:

- Respiratory problems
- Depression/anxiety/amotivation
- Issues functioning/concentrating
  (e.g. in studies, work, relationships)

Treating CUD: 58-50

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

No coverage by any drug plans or private insurance.

[Note: Pharmacologic tx, e.g. with naltrexone, appears ineffective]

Paperwork Required for Medical Cannabis

1. Complete medical document form (link ❶).
   In SK, complete treatment agreement form (link ❸), or visit Rx Files.ca and search "agreement".

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

(Exclusively by mail/courier)


Cannabis: Prescribing Considerations

A Crawley BSP, M LeBras Pharm D, L Regier BSP © www.RxFiles.ca Oct 2018


EDS=medical cannabis, EP=exclusive producer, NIBH X=not covered SK □=not covered NIBH □=NIBH palliative care 2 AG=2-Arachidonoylglycerol AEA=Anandamide CB= cannabinoid CBD=cannabinoid CB1=cannabinoid receptor type 1 CB2=cannabinoid receptor type 2 CBZ=carbamazepine CINV=chemotherapy-induced nausea and vomiting CUD=cannabis use disorder MS=multiple sclerosis PIP=pharmacetical information program TCA=tricyclic antidepressant; SCI=spinal cord injury SIV=St. John’s Wort THC=tetrahydrocannabinol
College of Physicians & Surgeons of Saskatchewan: The College’s bylaw

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](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](http://www.cps.sk.ca/iMIS/Documents/Programs%20and%20Services/Patient%20Agreement%20Template%20-%20Medical%20Cannabis.pdf)
   Or visit [www.RxFiles.ca](http://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.
References: Cannabinoid Chart – www.RxFiles.ca


69. Additional references for Cannabinoids:


Starzer MSK, Nordentoft M, et al. Rates and Predictors of Conversion to Schizophrenia or Bipolar Disorder Following Substance-Induced Psychosis. Am J Psychiatry. 2017 Nov 28;appiajp201717020223. (Cannabis etc…)
Tan WC, Sin DD. What are the long-term effects of smoked marijuana on lung health? CMAJ. 2018 Oct 22;190(42):E1243-E1244.