Cannabis for pain, or Opioids …

Trial evidence comparing cannabinoids and opioids is limited.37 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;39 cannabinoids can cause psychiatric disturbances (e.g. anxiety, agitation, amotivation, psychosis).37 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%.25 With non-medical cannabis, estimated to be 9%.26 (The risk with medical cannabis 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 a 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.58 **Phytocannabinoid**: 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. Topical cannabis 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, budder, wax: contains THC as high as 90%. **Dabbing**: vaporising 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.58,66


... 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

<table>
<thead>
<tr>
<th>Generics/Trades</th>
<th>Indications &amp; Comments</th>
<th>DOSING</th>
<th>$/30d</th>
<th>Adverse Events AE</th>
<th>Contraindications CI</th>
<th>Drug Interactions DI</th>
<th>Monitor M</th>
</tr>
</thead>
</table>
| **Nabilone** CESAMET, g synthetic THC analogue 0.5, 1mg cap X △ 0.25mg cap □ | Preferred over cannabis, 2,18 > severe nausea/vomiting from cancer chemotherapy ▲ off-label: AIDS-related anorexia ▲ Palliative pain ▲ Neuropsychiatric pain | Initial: 0.25-0.5mg po HS
Usual: 1-2mg po daily-BID for CINV
1mg BID for neuropathic pain
Usual max: 6mg/day | $22-18 g | | | | |
| **Nabiximols** SATIVEX x extracted THC/CBD 2.7mg THC & 2.5mg CBD per spray (peppermint flavour; poor taste) (contains alcohol) ▲ refrigerate prior to dispensing Not available in USA. | Preferred over cannabis, 2,18 > advanced cancer pain (adjunctive) ▲ multiple sclerosis neuropsychiatric pain or spasticity (adjunctive) ▲ Spasticity may require lower doses than pain (e.g. 4-5 sprays vs >8 sprays per day). ▲ Detected in SK urine drug screen | • Spray under the tongue or into side cheek (may alternate sides).
• Shake vial gently. Device requires priming (3 sprays). | Initial: 1 spray sublingually HS
Usual: 1 spray sublingually q4h
Usual max: 12 sprays per day | 3 vial pack = $700 ($2.60/spray/vial)
$84 | | | |
| **Cannabinoid** EPIDIOLEX extracted CBD 100mg/mL solution | (.0.14 X) | Treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients ≥2 years of age | Not available in Canada | | | | |
| **Dronabinol** MARINOL synthetic THC USA only: 2.5, 5mg, 10 cap (in sesame oil) 5mg/mL solution SYNDROS (contains alcohol) | > severe nausea/vomiting from cancer chemotherapy ▲ AIDS-related anorexia | Initial: 2.5mg po HS
2.5mg po TID-QID for chemo nausea/vomiting (<5mg/m²)
2.5mg po BID ac lunch and supper for anorexia | D/C from Canadian market | | | | |
| **Oral Cannabis Oils** THC/CBD in various ratios, e.g.: 25mg THC / 0mg CBD per mL 1mg THC / 20mg CBD per mL 3mg THC / 3mg CBD capsule many other formulations & potencies available. | No official indication. May be medically authorized in Canada to any patient for any indication (i.e., “off-label use”). ▲ THC detected in urine drug screen up to 4 weeks after last dose (e.g., chronic/heavy users) ▲ Oral vs inhaled: Oral has lower bioavailability (∼10% vs ∼25%), slower onset (30-60min vs 5-10min), longer duration (4-8 hrs vs 2-4 hrs), & does not have respiratory risk. ▲ Smoked vs vaped: smoking speculated to have more respiratory risk (but data limited), but vaping has risk too. ▲ Vaping (<2,602 reports of vaping lung injury in US).70,71 Vaping <2x more potent (smoking destroys drug via combustion). ▲ Vaping devices: Consider a Health Canada approved vaporizer. | 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 & nabiximols labelling suggest max doses of 25-30mg THC per day.) • Food increases absorption. • Consider 1st dose at 7p.m. to leave time for testing effect. • Consider weekend trial start (or when impairment less disastrous). Guidelines recommend avoiding smoked cannabis.2,7 | $7
 e.g. 60mL bottle of oil containing 1200mg CBD = $130 | | | | |
| **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 | No official indication. May be medically authorized in Canada to any patient for any indication (i.e., “off-label use”). ▲ THC detected in urine drug screen up to 4 weeks after last dose (e.g., chronic/heavy users) ▲ Oral vs inhaled: Oral has lower bioavailability (∼10% vs ∼25%), slower onset (30-60min vs 5-10min), longer duration (4-8 hrs vs 2-4 hrs), & does not have respiratory risk. ▲ Smoked vs vaped: smoking speculated to have more respiratory risk (but data limited), but vaping has risk too. ▲ Vaping (<2,602 reports of vaping lung injury in US).70,71 Vaping <2x more potent (smoking destroys drug via combustion). ▲ Vaping devices: Consider a Health Canada approved vaporizer. | Initial: 1-2 puffs inhaled HS (1 puff of joint = 1-10mg THC) Variation is due to inhalation depth, puff size, THC potency, smoked vs vaped, joint size, etc.) ▲ Usual: Uncertain due to poor quality evidence. Titrate slowly. Based on market data for 2017 in Canada, medical cannabis patients titrated themselves to an average dose of 750mg dried cannabis per day.16 | In 2019 in Canada, the average retail price was $10/g and the average street price was $6/g. | $12-24 for 1-2 puff HS $180 for 750mg/day $720 for 3g/day | | | |

**Notes:**
- **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).64 CBD possibly safer than THC, but some of its psychotropic effects are underappreciated (e.g. vs placebo in predominately pediatric trials: aggression/anger 3-5% vs <1%; irritability/agitation 5-9% vs 2%; somnolence 25% vs 8%).31
dizziness up to 50% across cannabinoids.2
psychiatric disturbances up to 17% across cannabinoids; and up to 27% with inhaled cannabis.66 including depression, anxiety, panic, paranoia, hallucination. In Canada, accounts for 25% of cannabis related hospital visits. More than acute psychosis or dissociation up to 5% across cannabinoids.2
1st episode psychosis daily cannabis ↑3x & THC ↑10x ↑5x vs never users.11,39 schizophrenia unmasking: cannabis may hasten first psychotic episode by 2-6 yrs.8 speech disorders up to 32%, and ataxia up to 30% across cannabinoids.1 impaired memory up to 11% across cannabinoids.36 cannabis hyperemesis syndrome: severe abdominal pain/vomiting; requires drug discontinuation; relieved by hot shower; applying capsaicin to abdomen useful.32 pneumonia up to 8% with oral CBD.31
↑ LFTs up to 16% of pts on CBD;31 Treated to concomitant valproate/clobazam. driving impairment: risk of fatal car crash approximately doubles with THC.28,29 withdrawal with abrupt discontinuation (see withdrawal symptoms on next page) red eyes reported with non-medical use of oral and smoked THC.

- **LFTs:**
- **Drug Interactions:**
- **Caution:**

- **A note on drug interactions:** Interactions are not fully understood; many are theoretical. Cannabis has many compounds besides THC & CBD, which may have unknown drug interactions. Watch closely for pharmacodynamic (additive) interactions. All cannabinoids: additive CNS effects (e.g. sedation, confusion) with ETOH, BZDs, opioids, anticholinergics, anti-epileptics, etc. Avoid ≥ 3 CNS drugs. BEERS19 [beers18.maxifet.org if ETOH in product] THC-containing products 2C9 & 3A4 substrate: ↑ levels by CBZ, SIW, phenytoin, etc. ↑ levels by clarithromycin, fluvoxamine, fluoxetine, lamotrigine, fluconazole, gemfibrozil, etc. CBD-containing products 2C19 & 3A4 substrate: ↓ levels by CBZ, SIW, phenytoin, etc. ↑ levels by clarithromycin, fluvoxamine, fluconazole, gemfibrozil, etc. 2C19 inhibitor: ↑ levels of citalopram, clobazam; ↓ levels of clobazolopropionate hepatic toxicity risk with valproic acid or Clobazam.19,20

- **NB:**
- **HR:**
- **BP:**
- **CN:**
- **TS:**
- **AG:**
- **CM:**
- **PN:**
- **LFTs**
Cannabinoids: 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.  
  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 page 130). A summary of these principles is as follows:

- Optimize suitable non-cannabis therapies first (drug and non-drug)
- Check Prescription Drug Monitoring Programs (e.g. PIP in SK) at baseline & at each visit
  These programs do not record medical cannabis. 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
  Reasonable trial duration may be ~12 weeks
- Obtain Treatment Agreement and Informed Consent
  Search “agreement” at www.rxfiles.ca for a sample cannabinoid tx agreement.
  Agreement includes safe storage – especially important if kids nearby!
  Possible taper to prevent withdrawal: ↓ by 25% q1week.

Monitoring for Cannabis Use Disorder (CUD)

9% of adults who use cannabis non-medically may develop addiction (& up to 17% if started in adolescence). 51

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

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

<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 Saskatchewan, 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 vigorous production standards than Rx drugs.</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 prescriber for further authorization."  
  • Overall, less control than prescription products (e.g. "dosing interval" does not exist). | 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.  
  • SK EDS and prior approval criteria for specific indications. | No coverage by any drug plans or private insurance; can’t be claimed on income tax. |
| EDS in SK ※prior approval NIH E ≠not covered SK ◗not covered NIH H ◗=palliative care 2 AG=2 Arachidonoylgllycerol AEA=Anandamide 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=pharmaceutical information program TCA=tricyclic antidepressant SCI=spinal cord injury SIN=S. John’s Wort THC=delta-9-tetrahydrocannabinol

Paperwork Required for Medical Cannabis

1. Complete medical document form (link ❶):
   In SK, complete treatment agreement form (link ❶, or visit RxFiles.ca and search "agreement"). 56
2. Submit medical document to Licensed Producer (link ❶) 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 ❶).
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 less of 150g or 30 times daily amount.

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

A Crawley BSP, M LeBras Pharm D, L Regier BSP © www.RxFiles.ca Feb 2020

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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,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:


https://doi.org/10.1016/j.jcjd.2019.05.010.
Pharmacotherapies for cannabis dependence. Cochrane Database Syst Rev. 2019 Jan 28;1:C008940. There is incomplete evidence for all of the pharmacotherapies investigated, and for many outcomes the quality of the evidence was low or very low. Findings indicate that SRRI antidepressants, mixed action antidepressants, bupropion, buspirone and atomoxetine are probably of little value in the treatment of cannabis dependence. Given the limited evidence of efficacy, THCs preparations should be considered still experimental, with some positive effects on withdrawal symptoms and craving. The evidence base for the anticonvulsant gabapentin, oxycotin, and N-acetylcycteine is weak, but these medications are also worth further investigation.

Nutt D. Why medical cannabis is still out of patients' reach—an essay by David Nutt. BMJ. 2019 May 1;365:l1903.


