

# Cannabinoids / Medical Cannabis

A deep dive into shallow evidence, in the hunt for pearls

**FALL/WINTER 2018**

## DID YOU KNOW?

- 1) Approximate monthly costs:  
dried cannabis (750 mg/d) = \$180  
oil (varies) = \$130/60 mL bottle
- 2) In 2018, at least 14% of  
Canadians reported using cannabis  
recreationally
- 3) evidence for cannabinoid benefit  
in neuropathic pain shows a possible  
NNT=11 over placebo; most will also  
experience an adverse event, but not  
necessarily stop using
- 4) cannabis addiction risk with  
recreational use in adults ~9%
- 5) urine drug screens in SK do not  
routinely test for CBD
- 6) risk of car crash with THC  
roughly doubles

## CANNABIS

Questions  
about cannabis,  
and the  
Answers  
that may  
SURPRISE YOU

A booklet for people thinking  
about starting medical cannabis



## PATIENT INFORMATION BOOKLET

Simplified guideline for prescribing medical  
cannabinoids in primary care

<http://www.cfp.ca/content/64/2/111>

CUDIT-R Screening Tool (for Cannabis Use Disorder)  
[https://bpac.org.nz/BPJ/2010/June/docs/addiction\\_CUDIT-R.pdf](https://bpac.org.nz/BPJ/2010/June/docs/addiction_CUDIT-R.pdf)

Canada's Lower Risk Cannabis Use Guidelines: Patient Pamphlet  
<https://www.camh.ca/-/media/files/pdfs--reports-and-books--research/canadas-lower-risk-guidelines-cannabis-pdf.pdf>

Professional Summary  
[https://www.camh.ca/-/media/files/lrcug\\_professional-pdf.pdf](https://www.camh.ca/-/media/files/lrcug_professional-pdf.pdf)

Cannabinoids! What can we say, except that we had to land on this topic at this time. We have attempted to pursue a balanced discussion for a complicated and controversial topic. Diving in has been interesting, as has the review process. Some have suggested a need for more caution in the discussion. Others, have suggested less. The next 20 years will tell.

The challenge with cannabinoids is that there is enough reason to consider a medical role, but this is against little evidence, regrets around our past enthusiasm with opioids, and the societal backdrop of recreational cannabis and substance use disorders.

There remains many uncertainties with cannabinoids. Can safety concerns be addressed by modifying the THC-to-CBD ratio? What will happen after a year, or a decade of continuous cannabinoid use? Claims and anecdote abound, but evidence has a long way to catch up. Thus – if proceeding down the road of cannabinoid therapy, a heads-up approach with proactive safeguards is warranted.

### IF CONSIDERING PRESCRIBING/AUTHORIZING CANNABINOID FOR MEDICAL PURPOSES:

- ♦ Remember there is the potential for both benefit and harm.
- ♦ Cannabinoids are not recommended for those at high risk of major harms including those who:
  - a) have a history or high risk of psychosis
  - b) have a history or high risk of substance use disorder
  - c) are pregnant or breastfeeding
  - d) are under the age of 21-25 years.
- ♦ An appropriate cannabinoid trial will include:
  - a) careful patient selection, follow-up and preferably a treatment agreement
  - b) attention to suitable dosing and/or potency issues (Start low, go slow!)
  - c) an emphasis on function and a multimodal therapeutic approach, especially when trialing for chronic pain
  - d) a preference for non-smoked formulations
  - e) attention to issues around impairment and misuse, especially with formulations high in THC content.

### WHEN FOLLOWING PATIENTS WHO MAY BE USING CANNABIS RECREATIONALLY:

- ♦ Incorporate screening for Cannabis Use Disorder into daily practice. This may present as subtly as a lack of motivation, declining function in studies or work, problematic relationships and respiratory problems.
- ♦ Discuss and caution regarding driving while impaired, as a matter of life & death.

The cannabinoid/cannabis landscape is changing. Your attention to this area, both medically and recreationally, will be important in pursuing patient & societal safety.

## 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.<sup>2</sup>
- 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.<sup>21,22</sup> 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 [RxFiles.ca](#)).

## 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.<sup>1</sup>

**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 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.<sup>16,30</sup>

**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,<sup>11</sup> 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),<sup>11</sup> which is thought to bias results towards benefit.<sup>17</sup>

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

## Do Cannabinoids Work (Medicinally)?

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.<sup>2,15</sup>
- ↓ chemotherapy-induced nausea & vomiting **NNT=3** for control of nausea/vomiting over ~1 day.<sup>2</sup>
- ↓ spasticity of multiple sclerosis or spinal cord injury **NNT=10** for ≥30% ↓ spasticity over ~6wks.<sup>68</sup>
- ↓ seizures in Lennox-Gastaut & Dravet syndrome with CBD **NNT=4-7** for ≥50% reduction in seizure frequency over ~14 wks.<sup>2</sup>
- ↓ cachexia in HIV/AIDS, cancer, palliative care: weak evidence.

## 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.<sup>2</sup> Notable adverse effects include feeling "high" **NNH=4**; sedation **NNH=5**; speech disorders **NNH=5**; dizziness **NNH=5**; and ataxia/muscle twitching **NNH=6**.<sup>2</sup>

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 are 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?

**A final thought:** If a patient told you they were getting benefit from ibuprofen over-the-counter, you might recommend they continue taking it. You might even prescribe it. But would you feel the same way if the patient was using 6 grams of ibuprofen per day? Or if the patient insisted that the ibuprofen was improving their blood sugar control? Or if the patient had a history of GI bleeds?

## Cannabinoids for pain, or Opioids ...

Trial evidence comparing cannabinoids and opioids is limited.<sup>57</sup> 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;<sup>25</sup> cannabinoids can cause psychiatric disturbances (e.g. anxiety, agitation, amotivation, psychosis).<sup>27</sup> Adverse effects appear dose-related ( $\uparrow$ dose =  $\uparrow$ AE). Both drug classes may be used by patients as an "escape".
- Addiction risk:** With prescription opioids, estimated to be 5.5%.<sup>25</sup> With *non-medical* cannabis, estimated to be 9%.<sup>26</sup> (The risk with medical cannabinoids is unstudied.)
- Fatal overdose risk:** With prescription opioids, 0.23% with >100mg morphine per day ( $\uparrow$ risk with  $\uparrow$ dose).<sup>25</sup> With cannabis, fatal overdose risk appears to be negligible.<sup>1</sup>
- 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!

Generic/TRADE	Indications & Comments	DOSING	\$/30d	Adverse Events AE / Contraindications CI / Drug Interactions DI / Monitor M	
Prescription Cannabinoids (pharmaceutical grade)	<b>Nabilone CESAMET</b> , g THC analogue 0.5, 1mg cap   0.25mg cap  	Preferred over cannabis. <sup>CFP'18</sup> ✓ severe nausea/vomiting from cancer chemotherapy  off-label: AIDS-related anorexia  Palliative pain  Neuropathic pain  • Not detected in SK urine drug screen	Initial: 0.25-0.5mg po HS <b>Usual:</b> 1-2mg po daily-BID for CINV 1mg BID for neuropathic pain <b>Usual max:</b> 6mg/day	\$22-18 g  \$112-215 g \$112 g <b>\$310 g</b> <small>\$1200</small>	<b>AE:</b> 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 ( $\uparrow$ dose = $\uparrow$ 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>44</sup> 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%). <sup>31</sup>
	<b>Nabiximols SATIVEX</b> 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. <sup>CFP'18</sup> ✓ 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).	• Spray under the tongue or into side cheek (may alternate sides). • Shake vial gently. Device requires priming (3 sprays).	3 vial pack = \$700 (\$2.60/spray) (90 spray/vial)  \$84 <b>\$504</b> <b>\$1008</b>	<b>drowsiness or sedation</b> up to 50% across cannabinoids. <sup>2</sup> <b>dizziness</b> up to 32% across cannabinoids. <sup>2</sup> <b>psychiatric disturbances</b> up to 17% across cannabinoids, <sup>2</sup> and up to 27% with inhaled cannabis, <small>COMPASS</small> including depression, anxiety, panic, paranoia, hallucination. <b>euphoria</b> up to 15%, and <b>feeling "high"</b> up to 35% across cannabinoids. <sup>2</sup> <b>acute psychosis or dissociation</b> up to 5% across cannabinoids. <sup>2</sup> <b>speech disorders</b> up to 32%, and <b>ataxia</b> up to 30% across cannabinoids. <sup>2</sup> <b>impaired memory</b> up to 11% across cannabinoids. <sup>2</sup> <b>irritability or agitation</b> up to 9%, and <b>anger or aggression</b> up to 5% with CBD. <sup>31</sup> <b>appetite changes:</b> decreased appetite in up to 22% of patients on CBD, <sup>31</sup> but conversely increased appetite in up to 38% of patients on dronabinol. <sup>18</sup> <b>GI issues:</b> dry mouth; diarrhea up to 20%, vomiting up to 15% with CBD. <sup>19,31</sup> <u>Conversely</u> ↓ nausea in up to 20% of pts with dronabinol. <sup>18</sup> <b>SATIVEX:</b> mouth irritation. <b>pneumonia</b> up to 8% with oral CBD. <sup>31</sup> ↑ LFTs up to 16% of pts on CBD, <sup>31</sup> related to concomitant valproate/clobazam. <b>driving impairment:</b> risk of fatal car crash approximately doubles with THC. <sup>28,55</sup> <b>schizophrenia unmasking:</b> cannabis may hasten first psychotic episode by 2-6yrs. <sup>8</sup> <b>withdrawal</b> with abrupt discontinuation (see withdrawal symptoms on next page) <b>cannabis hyperemesis syndrome:</b> severe abdominal pain/vomiting; requires drug discontinuation; relieved by hot shower; applying capsaicin to abdomen useful. <sup>32</sup> <b>red eyes</b> reported with non-medical use of oral and smoked THC. <b>rare or uncertain:</b> sexual problems, ?cancer testicular, ? $\downarrow$ BMD, ?pancreatitis.
	<b>Cannabidiol EPIDIOLEX</b>   extracted CBD 100mg/mL solution <small>FDA'18</small> (contains alcohol & sesame oil)	✓ Treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients $\geq 2$ years of age	<b>Seizures</b> (Lennox-Gastaut or Dravet): <b><math>\geq 2</math> yrs:</b> 2.5-10mg/kg/dose po BID usually give before a meal • Food increases absorption.	<b>Not available in Canada</b>	<b>GI issues:</b> dry mouth; diarrhea up to 20%, vomiting up to 15% with CBD. <sup>19,31</sup> <u>Conversely</u> ↓ nausea in up to 20% of pts with dronabinol. <sup>18</sup> <b>SATIVEX:</b> mouth irritation. <b>pneumonia</b> up to 8% with oral CBD. <sup>31</sup> ↑ LFTs up to 16% of pts on CBD, <sup>31</sup> related to concomitant valproate/clobazam. <b>driving impairment:</b> risk of fatal car crash approximately doubles with THC. <sup>28,55</sup> <b>schizophrenia unmasking:</b> cannabis may hasten first psychotic episode by 2-6yrs. <sup>8</sup> <b>withdrawal</b> with abrupt discontinuation (see withdrawal symptoms on next page) <b>cannabis hyperemesis syndrome:</b> severe abdominal pain/vomiting; requires drug discontinuation; relieved by hot shower; applying capsaicin to abdomen useful. <sup>32</sup> <b>red eyes</b> reported with non-medical use of oral and smoked THC. <b>rare or uncertain:</b> sexual problems, ?cancer testicular, ? $\downarrow$ BMD, ?pancreatitis.
	<b>Dronabinol MARINOL</b>  synthetic THC  USA: 2.5, 5mg, 10 cap (in sesame oil) 5mg/mL solution <b>SYNDROS</b> (contains alcohol)	✓ severe nausea/vomiting from cancer chemotherapy ✓ AIDS-related anorexia	<b>Initial:</b> 2.5mg po HS <b>Usual:</b> 2.5-5mg po TID-QID for chemo nausea/vomiting (~5mg/m <sup>2</sup> ) 2.5mg po BID ac lunch and supper for anorexia <small>AIDS 3</small> <b>Max:</b> 20mg/day	<b>D/C from Canadian market</b>	<b>GI issues:</b> dry mouth; diarrhea up to 20%, vomiting up to 15% with CBD. <sup>19,31</sup> <u>Conversely</u> ↓ nausea in up to 20% of pts with dronabinol. <sup>18</sup> <b>SATIVEX:</b> mouth irritation. <b>pneumonia</b> up to 8% with oral CBD. <sup>31</sup> ↑ LFTs up to 16% of pts on CBD, <sup>31</sup> related to concomitant valproate/clobazam. <b>driving impairment:</b> risk of fatal car crash approximately doubles with THC. <sup>28,55</sup> <b>schizophrenia unmasking:</b> cannabis may hasten first psychotic episode by 2-6yrs. <sup>8</sup> <b>withdrawal</b> with abrupt discontinuation (see withdrawal symptoms on next page) <b>cannabis hyperemesis syndrome:</b> severe abdominal pain/vomiting; requires drug discontinuation; relieved by hot shower; applying capsaicin to abdomen useful. <sup>32</sup> <b>red eyes</b> reported with non-medical use of oral and smoked THC. <b>rare or uncertain:</b> sexual problems, ?cancer testicular, ? $\downarrow$ BMD, ?pancreatitis.
	<b>Oral Cannabis Oils</b> x   THC/CBD in various ratios, e.g.: 25mg THC / 0mg CBD per mL 0mg THC / 20mg CBD per mL 3mg THC / 3mg CBD capsule many other formulations & potencies available.  <b>Veteran's Affairs:</b> coverage available for some patients	No official indications. May be medically authorized in Canada to any patient for any indication.  • THC detected in urine drug screen up to 4 weeks after last dose (esp. chronic/heavy users) • <b>Oral vs inhaled:</b> Oral has lower bioavailability (~10% vs ~25%), <sup>1</sup> slower onset (30-60min vs 5-10min), <sup>4</sup> longer duration (4-8 hrs vs 2-4 hrs), <sup>1</sup> & does not have respiratory risk. • <b>Smoked vs vaped:</b> smoking speculated to have more respiratory risk (but data limited). Vaping ~2x more potent (smoking destroys some drug via combustion). • <b>Vaping devices:</b> Consider a Health Canada approved vaporizer.  <b>"Marijuana Math"</b> <small>note: estimate only – some uncertainty!</small> What is the estimated THC dose if 1 joint, containing 0.5 grams of 10% THC dried cannabis, is smoked? <b>Answer:</b> 500mg cannabis x 10% THC x 50% loss to combustion $\approx$ 25mg THC	<b>Initial:</b> 2-3mg of CBD +/- THC po HS (e.g. 0.1mL of 20mg/mL CBD) <b>Usual:</b> 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 1 <sup>st</sup> dose at 7p.m. to leave time for assessing effect. • Consider weekend trial start (or when impairment less disastrous).	\$7  e.g. 60mL bottle of oil containing 1200mg CBD $\approx$ \$130	<b>Harms specific to smoked cannabis:</b> cough 7%, respiratory issues (e.g. development of COPD, pulmonary aspergillosis, ?lung cancer), <sup>35</sup> cardiovascular issues (e.g. $\uparrow$ HR, <sup>1</sup> postural hypotension, <sup>1</sup> ? $\uparrow$ MI 1 hour after smoking, <sup>39</sup> ?steatosis with hepatitis C, ?gynecomastia, ?thrombophlebitis, contaminants in unregulated cannabis (e.g. lead, fentanyl, pesticides)
Medical Cannabis	<b>Dried Cannabis</b> x  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 <b>Veteran's Affairs:</b> coverage available for some patients  Trend: towards $\uparrow$ potency products. <sup>54</sup> (e.g. 4% THC in 1995 $\rightarrow$ 12% in 2014) <b>Average joint:</b> $\approx$ 0.5g dried cannabis. <sup>WHO</sup> <b>Medical use in USA:</b> 31 States & D.C.	• THC detected in urine drug screen up to 4 weeks after last dose (esp. chronic/heavy users) • <b>Oral vs inhaled:</b> Oral has lower bioavailability (~10% vs ~25%), <sup>1</sup> slower onset (30-60min vs 5-10min), <sup>4</sup> longer duration (4-8 hrs vs 2-4 hrs), <sup>1</sup> & does not have respiratory risk. • <b>Smoked vs vaped:</b> smoking speculated to have more respiratory risk (but data limited). Vaping ~2x more potent (smoking destroys some drug via combustion). • <b>Vaping devices:</b> Consider a Health Canada approved vaporizer.  <b>"Marijuana Math"</b> <small>note: estimate only – some uncertainty!</small> What is the estimated THC dose if 1 joint, containing 0.5 grams of 10% THC dried cannabis, is smoked? <b>Answer:</b> 500mg cannabis x 10% THC x 50% loss to combustion $\approx$ 25mg THC	<b>Guidelines recommend avoiding smoked cannabis.</b> <sup>2,7</sup>  <b>Initial:</b> 1-2 puffs inhaled HS. (1 puff of joint $\approx$ 1-10mg THC). Variation is due to inhalation depth, puff size, THC potency, smoked vs vaped, joint size, etc.  <b>Usual:</b> 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. <sup>16</sup>	In 2017 in Canada, the average medical price was \$8/g and the average street price was \$7.5/g  \$12-24 for 1-2 puff HS <b>\$180</b> for 750mg/day <b>\$720</b> for 3g/day	<b>DI: A note on drug interactions:</b> Interactions are not fully understood; many are theoretical. Cannabis has many compounds besides THC & CBD; these may have unknown drug interactions. Watch closely for <b>pharmacodynamic</b> (additive) interactions. <b>All cannabinoids:</b> additive CNS effects (e.g. sedation, confusion, impairment) with alcohol, anticholinergics, anti-epileptics, benzos, opioids, etc. <b>THC-containing products</b> 2C9 & 3A4 substrate: $\downarrow$ levels by CBZ, SJW, phenytoin, etc. ↑ levels by clarithromycin, fluconazole, fluvoxamine, gemfibrozil, etc. <b>CBD-containing products</b> 2C19 & 3A4 substrate: $\downarrow$ levels by CBZ, SJW, phenytoin, etc. ↑ levels by clarithromycin, fluconazole, fluvoxamine, gemfibrozil, etc. 2C19 inhibitor: ↑ levels of citalopram, <b>clobazam</b> ; $\downarrow$ levels of clopidogrel ?additive hepatotoxicity risk with valproic acid or clobazam <sup>19,20</sup> <b>Smoked cannabis:</b> smoking may result in 1A2 induction; e.g. $\downarrow$ levels of antipsychotics, caffeine, TCAs, theophylline, warfarin <b>Nabilone:</b> while a THC-mimic, does not have THC drug interactions.
				<b>M:</b> HR, BP, CNS adverse effects, psych symptoms, tx agreement, CUD, LFTs (with <b>EPIDIOLEX</b> )	

## 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.<sup>2</sup>  
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-cannabis 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](http://www.rxfiles.ca) for a sample cannabinoid tx agreement.  
Agreement includes safe storage – especially important if kids nearby!<sup>17</sup>
- 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)

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

Prior to Tx: Screen for CUD	During Tx: Monitor for CUD	In primary care, <sup>47</sup> watch for:
<p><b>1) Options for screening:</b> CUDIT-R specific to cannabis.<sup>45</sup> CAGE Questionnaire short &amp; practical.<sup>46</sup></p> <p><b>2) Diagnosing:</b> use DSM-5 criteria.<sup>53</sup></p>	<ul style="list-style-type: none"> <li>rapid or unsanctioned dose ↑</li> <li>frequent changes needed</li> <li>wants dried cannabis only</li> <li>wants high potency THC only</li> <li>misuse of other substances</li> <li>urine drug screen: aberrant</li> <li>concerns from friends/family</li> <li>poor functioning (school/work/social)</li> <li>missed follow-up; reports of lost or stolen cannabis</li> </ul>	<p>♦ respiratory problems ♦ depression/anxiety/amotivation ♦ issues functioning/concentrating (e.g. in studies, work, relationships)</p> <p><b>Treating CUD:</b><sup>48-50</sup></p> <ol style="list-style-type: none"> <li>Brief interventions</li> <li>Withdrawal management (e.g. sleep hygiene, brief symptomatic relief, ?nicotine replacement)</li> <li>Psychosocial interventions (e.g. motivational enhancement, CBT)</li> </ol> <p>[Note: Pharmacologic tx, e.g. with naltrexone, appears ineffective]</p>
<p><b>Symptoms of Cannabis Withdrawal</b> (onset 1-2 days, peak 2-6 days) Anger, aggression, appetite change, weight loss, <b>anxiety</b>, irritability, restlessness, sleep disturbance, cannabis craving, physical discomfort.</p>		

### Choosing Between Products

note: currently Canada has a "two-stream" cannabis system: medically authorized cannabis, and cannabis through retail sale.

	Prescription Cannabinoids e.g. nabilone, nabiximols	Cannabis		Paperwork Required for Medical Cannabis
		via medical authorization	via retail sale	
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. <sup>43</sup> However, similar to non-Rx herbal supplements, cannabis may have less vigorous production standards than Rx drugs.		<ol style="list-style-type: none"> <li>Complete medical document form (link ①). In SK, complete treatment agreement form (link ②, or visit <a href="http://www.RxFiles.ca">RxFiles.ca</a> and search "agreement").<sup>56</sup></li> <li>Submit medical document to Licensed Producer (link ③) who mails cannabis (dried, oil, buds, or leaves) to patient.</li> <li>Or, patients may apply to grow their own product at home (link ④).</li> <li>Medical document must be re-authorized at least once per year.</li> <li>In SK, prescribers required to keep list of pts.</li> <li>No set daily limit; max possession is lesser of 150g or 30 times daily amount.</li> </ol>
Dosing & Guidance	<ul style="list-style-type: none"> <li>Standardized.</li> <li>Some indications and dosing are Health Canada approved.</li> <li>Will show up on the electronic medical record (e.g. PIP in Saskatchewan).</li> </ul> <p><b>Note:</b> despite physician attempts to guide product and dosing, patients may supplement with retail cannabis against medical advice.</p>	<ul style="list-style-type: none"> <li>Challenging. e.g. THC in 1 puff of cannabis joint can range from 1 to &gt;10mg. No "studied usual dose".</li> <li>Physician may pick strain/ratio and max quantity allowed for patient. May limit duration, e.g. "one 60mL bottle of CBD oil, then see physician for further authorization."</li> <li>Overall, less control than prescription products (e.g. "dosing interval" does not exist).</li> </ul>	Patient selects the product, dose, dosing interval, and route of administration.  <p>Difficult to provide monitoring, boundaries, or education.</p>	
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	<ul style="list-style-type: none"> <li>Occasional private insurance coverage.</li> <li>SK EDS and prior approval criteria for specific indications.</li> </ul>	<ul style="list-style-type: none"> <li>Occasional private insurance coverage (e.g. Manulife and Sunlife on a case-by-case basis as of 2018).</li> <li>Veteran's affairs coverage (max 3g/day dried cannabis)</li> </ul> <p>~\$8/gram May grow at home to ↓ costs.</p>	No coverage by any drug plans or private insurance; can't be claimed on income tax.  Average price still uncertain (Ranges from \$8-20/gram)	<ol style="list-style-type: none"> <li><a href="http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/marijuana/info-med-eng.pdf">www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/marijuana/info-med-eng.pdf</a></li> <li><a href="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</a></li> <li><a href="http://www.hc-sc.gc.ca/dhp-mps/marijuana/info/list-eng.php">www.hc-sc.gc.ca/dhp-mps/marijuana/info/list-eng.php</a></li> <li><a href="http://www.canada.ca/en/health-canada/topics/production-cannabis-for-your-own-medical-purposes.html">www.canada.ca/en/health-canada/topics/production-cannabis-for-your-own-medical-purposes.html</a></li> </ol>

▲=EDS in SK ▲=prior approval NIH ▲=not covered SK ▲=not covered NIH ▲=NIHB palliative care 2-AG=2-Arachidonoylglycerol AEA=Anandamide CBD=cannabinol 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 SJW=St. John's Wort THC=delta-9-tetrahydrocannabinol

- 1. Why are there so many uncertainties with cannabinoids and cannabis use?**
- 2. Who should avoid using cannabinoids and cannabis?**
- 3. Who could be a candidate for cannabinoid or cannabis therapy?**
- 4. What should patients expect?**
- 5. How should a trial of cannabis be stopped?**
- 6. Are cannabinoids opioid sparing?**
- 7. What about cannabinoids for anxiety, sleep or PTSD?**

## **1. Why are there so many uncertainties with cannabinoids and cannabis use?**<sup>i,ii</sup>

Confident estimation of the benefits or harms is challenging due to the quality of available literature and varying clinical and patient experiences.

A large portion of the cannabinoid/cannabis evidence base is observational which has inherent limitations, such as:

- recall bias (e.g. most studies rely on patient self-report of cannabis use)
- misclassification bias (e.g. assessment of outcomes or risk factors/exposure; for example, definition of cannabis user vs non-user varied amongst studies)
- poor reporting (e.g. THC or CBD concentrations, administration/route; for example, ~67% [N=16/24] of studies did not report the chemical constituents of the cannabis e.g. THC vs CBD)<sup>iii</sup>
- potential for confounding (e.g. cannabis and lung cancer association may partly be confounded by cigarette smoking as many users from studies smoked joints containing both cannabis and nicotine)<sup>iv</sup>

The majority of the RCT data also has important limitations, such as:

- short duration of follow up (e.g. systematic review - chronic neuropathic pain: studies of less than 1 week up to 15 weeks <sup>Allan 2018</sup>)
- small number of participants (e.g. systematic review - chronic neuropathic pain: sample size ranged from 20-330 participants with the majority of trials [N=9/16 RCTs] enrolling <100 participants <sup>Cochrane 2018</sup>)
- selection bias (e.g. most studies enrolled previous cannabis users who already tolerated the drug; this likely underestimates the incidence of adverse effects)
- exclusion of certain populations (e.g. most studies excluded those with comorbidities, psychiatric disorders, or a history of substance use disorder)
- non-standardized intervention (e.g. exposure to cannabis varied across studies due to different amounts or concentrations of THC or CBD, administration/route, & non-THC or CBD constituents studied; also, inability to determine dose in some studies as amount or grams of cannabis used was not reported)<sup>v</sup>
- unblinding of participants (e.g. ~90% can guess whether they received cannabinoids or placebo)
- non-standardized reporting of outcomes (e.g. specifically for harms, some studies would report "CNS" adverse effects while others would report "sedation", "high", or "euphoria" making meta-analysis or comparisons challenging)
- generalizability (e.g. highest inhaled THC % in chronic pain RCTs was 9.4% but much higher potencies are available via licensed producers e.g. CanniMed© 22·1 dried cannabis product contains THC 22% or through the black market.<sup>vi</sup> Also, the majority of cannabis studies for chemotherapy-induced nausea/vomiting were completed during the 1970-80s and comparators did not include contemporary, gold standard therapies such as ondansetron, dexamethasone, and aprepitant)

Most professional associations and colleges caution against the use of cannabis due to, "little evidence to support its use in the absence of regulatory oversight and approval."<sup>1</sup> Clinical and patient experience may lean strongly towards differences with the evidence in regards to benefits and harms due to many factors such as variations in product/formulation, THC/CBD ratio, etc. And some patients, regardless of available science, will consume (or continue to consume cannabis) due to perceived medical benefit or desire for other effects (e.g. euphoria).<sup>1</sup>

## 2. Who should avoid using cannabinoids and cannabis?

### Patients <21-25 years of age<sup>vii</sup>

- The brain does not complete development until ~ 25 years.<sup>viii</sup> Substance exposure prior to this may have a more lasting impact. For example, the prefrontal cortex is one of the last regions of the brain to mature and it contains one of the densest areas of CB1 receptors in the body resulting in high vulnerability to cannabis exposure.<sup>ix,x,xi,xii</sup>
- These patients are at increased risk of impaired cognition, psychosis, and cannabis use disorder:
  - Impaired Cognition: cannabis use initiated prior to 18 years of age was associated with greater neurocognitive impairment and imaging differences compared to those with onset after 18 years.<sup>xiii</sup>
  - Psychosis: cannabis use initiated in adolescence or early adulthood was associated with psychosis (risk increases up to ~4.5 compared to non-users).<sup>xiv,xv,xvi</sup>
  - Cannabis Use Disorder: risk increases to ~1 in 6 people when cannabis use was initiated in adolescence compared to overall lifetime risk of ~1 in 10 people.<sup>xvii,xviii</sup>
- Cannabis use during adolescence is linked to impairments in academic achievement, education, employment, income, social relationships and social roles; however evidence is uncertain (e.g. high risk of confounding).<sup>xix</sup>
- The Canadian Medical Association (CMA) states 25 years as the ideal minimum age for legal cannabis use. However, the CMA recognizes that a blanket prohibition of possession for young adults would not reflect current reality or a harm reduction approach and recommends that the age of legalization should be 21 years (& that the quantities and potency of cannabis be more restricted to those under age).<sup>xx</sup> The College of Family Physicians of Canada also recommend that use under the age of 25 years is not appropriate (Level II recommendation).<sup>xxi</sup>
- The Federal Government has set the minimum age for recreational cannabis consumption at 18 years. All provinces including Saskatchewan have raised this to 19 years of age with the exception of Alberta and Quebec.
- More information on adolescent neurodevelopment and the potential impact of cannabis will be available in the future (e.g. 10-year prospective examination of 10,000 youths enrolled at age 9-10 years across 21 sites in the US funded by the National Institutes of Health; to be completed in 2025 ABCD study).
- Exception for use in younger adults (benefit outweighs harm): life-limiting or severely debilitating conditions for whom current therapies are inadequate (e.g. cannabidiol [CBD] oil for Lennox-Gastaut or Dravet syndrome).

### Patients with an active substance use disorder or history of substance use disorder (including family history)

- Patients with active or a history of, including family history of, substance use disorder are at an increased risk of developing cannabis use disorder (i.e. cannabis abuse or cannabis dependence).
  - Risk of developing cannabis use disorder is increased in individuals with:
    - Personal history of cannabis use disorder (> 1 year ago) adjusted OR 15.73 (95% CI 9.7-25.1)<sup>xxii</sup>
    - Alcohol use disorder in the past year adjusted OR 4.16 (95% CI 2.27-7.6)<sup>xxiii</sup>
- Consider baseline screening in all patients (e.g. CUDIT-R tool, CAGE tool).

### Patients with psychosis or a family history of psychosis (see "Psychosis" section of Question 4 below)

- Patients who use cannabis, especially frequent or high potency use, are at an increased risk of psychosis or worsening of psychotic symptoms. Risk of psychosis is further increased if positive family history is present.<sup>xxiv</sup>
- The Canadian Psychiatric Association of Canada 2018 Position Statement reports, "Early and regular use increases the risk of developing a primary psychotic illness in those individuals who are vulnerable. Vulnerability factors are not currently clear but may include factors such as childhood trauma and genetics. In those young adults who have developed psychosis, continued cannabis use worsens long-term symptom and functional outcomes."

### Patients who are pregnant, contemplating pregnancy, or breastfeeding

SOGG'17 xxv, ACOG'17 xxvi, CFP Guideline'18 xxvii, xxviii, xxix

- Self-reported cannabis use in pregnancy ranges from 2-5%, but up to ~25-35% in lower socioeconomic women (US data). Legalization of cannabis may reinforce the reputation of cannabis being harmless or a "safe" option to treat nausea and vomiting and result in increased use among pregnant women. For example, 69% of Colorado cannabis dispensaries (medical and/or retail) recommended cannabis products to treat morning sickness.<sup>xxx</sup>
- THC crosses the placenta and CBD impacts placenta permeability. Both enter breast milk. Cannabis use in pregnancy is associated with ↓birth weight, ↑NICU admission, potential neurodevelopment impairment (e.g. ↓visual problem solving skills), & ↑stillbirth (OR 1.74, 95% CI 1.03-2.93; but no adjustment for cigarette smoking confounder).<sup>xxxi</sup> There is insufficient data to evaluate effects during breastfeeding; however, caution is recommended.
- Society of Obstetricians and Gynecologists of Canada (SOGC) Patient Resources: "Not Just a Herb" <https://www.youtube.com/watch?v=hxU5fBsmpKo>; "Times Have Changed" [https://www.youtube.com/watch?v=sZ\\_1v1Sa\\_a8](https://www.youtube.com/watch?v=sZ_1v1Sa_a8)

### 3. Who could be a candidate for cannabinoid or cannabis therapy?

- Cannabinoids or medical cannabis are not considered first or second line therapy for any indication. CPF'18, CPS'14  
Reserve use for patients who have failed other therapies.
- Cannabinoids or medical cannabis may be used in various patients and may be a beneficial therapy for carefully selected patients (see above Question 2 for “Who Should Avoid Using Cannabinoids and Cannabis”).
- Indications with the most evidence of benefit are: chronic neuropathic pain, palliative pain, cancer pain, chemotherapy-induced nausea/vomiting, spasticity (in multiple sclerosis or spinal cord injury), and refractory Pediatric Seizures (i.e. Lennox-Gastaut, Dravet Syndrome).
- There is limited evidence to support use in cachexia (e.g. in HIV/AIDS, cancer, palliative care):
  - weak evidence supports medical cannabinoids as an application to treat cachexia Allan 2018
  - limited evidence in HIV/AIDS and insufficient evidence to support or refute effectiveness in cancer-associated anorexia-cachexia syndrome National Academies 2017
- When used, initiate as a therapeutic trial with clear goals and a timeframe for reassessment. (See below Question 4 “What Should Be Expected”). Note: exit strategy more difficult now that cannabis may be accessed through retail sale e.g. recreational / non-medical cannabis.

*Beware of the many unsubstantiated claims for benefit and safety.  
Too often, we do not take the time to separate the truth from the hype.*

### 4. What should patients expect if they start cannabinoids or cannabis?

**Table 1. Potential Goals & Timeline for Cannabinoid† Therapy vs Placebo**

Indication	Outcome Studied / Goal of Therapy	Result	Timeline	
			Onset of Effect	Trial Duration
Chronic Neuropathic Pain <small>Cochrane'18</small>	improved function/QOL, 30% reduction in pain	↓ pain: <b>NNT=11 over ~4 wks</b>	onset of effect within one week	may trial ~4-6 weeks (and up to ~12 weeks)
Palliative Pain	improved function/QOL, 30% reduction in pain	↓ pain: RR 1.34 (95% CI 0.96-1.86) -not statistically significant; estimated <b>NNT=~15 over ~4wks*</b>		
Cancer Pain	improved function/QOL, 30% reduction in pain	↓ pain: RR 1.35 (95% CI 0.63-2.09) -not statistically significant		
Chemotherapy-induced Nausea/Vomiting	control of nausea/vomiting	control of nausea/vomiting: <b>NNT=3 over ~1 day</b>	unclear, onset of effect likely within hours and median use from RCTs ~1 day (however some patients use longer)	
Spasticity (Multiple Sclerosis or Spinal Cord Injury)	improved patient perception of spasticity, 30% reduction in spasticity	improved patient perception of spasticity: <b>NNT=10 over ~6 weeks</b> ↓ spasticity: <b>NNT=7 over ~6 weeks</b>	onset of effect within one week	may trial ~6 weeks (and up to ~12 weeks)
Refractory Pediatric Seizures† (Lennox-Gastaut, <small>GWPCARE-3 xxxii, GWPCARE-4 xxxiii</small> Dravet Syndrome <sup>xxxiv</sup> )	improved caregiver perception of condition, 50% reduction in seizure	↓ seizures: <b>NNT=4-7 over ~14 weeks</b> improved caregiver perception of condition: <b>NNT=4 over ~14 weeks</b>	may trial up to 14 weeks	
Cachexia (HIV/AIDS, Cancer, Palliative)	increased appetite, decreased weight loss	limited evidence to support use	may trial up to 12 weeks	

†CBD intervention arm (for all other indications the intervention arms were combinations of THC and CBD)

\* Confidence intervals suggest that benefit is likely (risk ratio=1.34, 95% CI 0.96 to 1.86), so estimated NNT provided

## Potential Harms

- Approximately 8 or 9 patients out of 10 will develop an adverse effect to cannabinoid therapy and ~1 patient out of 10 will stop therapy because of the adverse effect. <sup>Allan 2018</sup> Tolerability is improved with gradual titration (e.g. ↑ q2-3 days or ↑ weekly if elderly <sup>expert opinion</sup>). *“Start low, Go slow”*.
- It is important to educate and monitor patients about well-known cannabinoid adverse effects (e.g. drowsiness, dizziness) and less well-known ones (e.g. dry mouth, hypotension). If benefit obtained, but intolerable adverse effect, patients may decrease dose by 50% or return to previous titration step.
- Note: minimal studies included elderly or those with comorbidities so a greater degree of caution and increased monitoring is warranted. Watch for additive side effects such as sedation, dizziness, hypotension or even falls when cannabinoids or medical cannabis is used in conjunction with other medications (e.g. anti-hypertensives, anti-histamines, levodopa, tamsulosin, etc.) or substances (e.g. alcohol).<sup>xxxv</sup>

**Table 2. Harms reported by systematic review of systematic reviews including RCTs** <sup>Allan et al. 2018</sup>

Type of Harm	NNH*, (range)	Cannabinoid Event Rate, %	Placebo Event Rate, %	Number of Systematic Reviews
Overall	6 (5-8)	79-92%	56-78%	5
Serious Adverse Events	NS	6.3-26%	17%	4
Withdrawal due to Adverse Events	14 (NS-22)	4.3-15%	1-11%	8
Sedation	5 (NS-5)	50-59%	25-30%	3
Disorientation/Confusion	15	2%	9%	2
Dizziness	5 (NS-5)	14-32%	11%	3
“Feeling high”	4 (2-4)	35-70%	0-3%	2
Dysphoria	8 (NS-8)	4-13%	0-1%	3
Euphoria	9	15%	2%	2
Dissociation/Acute Psychosis	20 (NS-4)	5%	0%	3
Disturbance in Attention or Disconnected Thoughts	7	17%	2%	1
Blurred Vision or Visual Hallucination	17	6-44%	0-8%	3
Speech Disorders	5	32%	7%	1
Hypotension	8	25%	11%	1
Ataxia or Muscle Twitching	6	30%	11%	
Numbness	6	21%	4%	1

NNH=number needed to harm NS= not statistically significant

\*NNH selected from the largest statistically significant meta-analyses providing event rates from systematic review by Allan et al.

Note: some studies reported “euphoria” while others reported “feeling high”; unclear difference between reported adverse effects

**Additional data on harms not captured by RCTs (i.e. bipolar disorder, lung cancer, myocardial infarction/ischemia, cannabis hyperemesis syndrome, driving & motor vehicle accidents) or important harms (i.e. cognition, psychosis) or are outlined below:**

**Bipolar Disorder:**<sup>xxxvi,xxxvii,xxxviii</sup> *Cannabis may be associated with increased symptoms of mania based on limited evidence.*

**Caution warranted.**

Meta-analysis of 2 prospective observational studies including 5,520 participants without bipolar disorder at baseline demonstrated lifetime cannabis use (e.g. 5 times or more) was associated with an increased incidence of manic symptoms (OR 2.97 95% CI 1.8-4.9) compared to no cannabis use. Cannabis (especially regular use) is also associated with increased symptoms of mania and hypomania (e.g. duration of symptoms) in patients with bipolar disorder. <sup>National Sciences</sup>

**Myocardial Infarction (MI) / Ischemia:** *Evidence assessing the risk of cannabis on MI is inconsistent. Caution: smoked cannabis may exacerbate angina.*

One case-crossover study of 3882 participants with recent acute MI of which 124 participants (3.2%) smoked cannabis in the previous year. Marijuana users mean age was  $44 \pm 8$  years, ~95% were male, ~25% prior MI, 68% current smokers, ~18% used marijuana daily, and 9 participants smoked marijuana within 1 hour of MI symptom onset. Compared to periods of nonuse within the same patient, the risk of MI was increased ~5-fold within 1 hour after smoking marijuana (RR 4.8 95% CI 2.9-9.5;  $p<0.001$ ). However, 3 of the 9 patients who reported smoking marijuana within 1 hour of symptom onset used cocaine or had sexual intercourse which may also trigger an MI and the risk was neutral 2 hours after smoking marijuana (RR 1.7 95% CI 0.6-5.1;  $p=0.34$ ). The study relied on patient self-report and is limited by recall bias. <sup>xxxix</sup>

A retrospective cohort study over a mean period of 10 years included 62,012 participants, of which ~42% were current or former cannabis users. This study found no association between current or former cannabis users and risk of acute MI hospitalization. Authors evaluated cannabis use by self-administered questionnaires and outcomes by linkage to electronic health records in the US. <sup>xli,xlii</sup>

Cannabinoids may contribute to CV ischemia due to resulting tachycardia, hypotension, carboxyhemoglobin (from combustion of cannabis resulting in a decreased oxygen-carrying capacity of blood). Reduced time to onset of angina has been demonstrated with smoked cannabis compared to placebo or nicotine cigarettes. <sup>xlii,xliii</sup>

**Cannabis Hyperemesis Syndrome (CHS):** <sup>:xliiv,xlv,xlvi,xlvii,xlviii,xlix,1,ii</sup> *Under-recognized and under-reported adverse effect involving cyclic vomiting in chronic, high dose cannabis users. First reported in 2004.*

- Prevalence: unclear, emergency department visits in Colorado for cannabis hyperemesis syndrome increased from 41/113,363 visits pre-legalization compared to 87/129,095 visits post-legalization of medical cannabis
- Mechanism (multiple theories): activation of gastrointestinal CB1 receptors resulting in decreased peristalsis; downregulation/desensitization of CB1 receptors in the brain
- Clinical Presentation: cyclic nausea (may be early morning), abdominal pain, anorexia typically precedes frequent emesis in the setting of at least weekly and likely daily cannabis use
  - Hot bathing/showering may relieve symptoms in ~90% of cases (multiple theories for benefit, for example, “cutaneous steal” theory where cutaneous vasodilation from hot water alters splanchnic circulation and core temperature)
- Diagnosis: no gold standard; diagnostic criteria has been proposed based on a case series of 98 patients (see below)
  - Essential/Major features: long-term cannabis use (most  $\geq 1$  year), recurrent nausea and vomiting that resolves after cannabis cessation, relief of symptoms with hot bathing/showering, abdominal pain, at least weekly marijuana use
  - Supportive features: age  $<50$  years, weight loss of  $>5$  kg, morning predominance of symptoms, normal bowel habits, negative laboratory/radiographic/endoscopic test results
  - Caution: mean delay in diagnosis from symptom onset is ~4 years and many patients undergo numerous investigations and tests prior to diagnosis
- Management: cessation of cannabis usually required, and re-occurrence of symptoms is likely if cannabis is restarted
  - May also consider supportive care with IV fluids, electrolyte replacement. Limited evidence to support benefits of antiemetics (e.g. dimenhydrinate, metoclopramide, haloperidol), or topical capsaicin.

**Lung Cancer:**<sup>lvi, lvi, lvi, lvi</sup> *Cannabis smoke contains carcinogens; however, there is inconsistent evidence that lung cancer is associated with inhaled cannabis.*

A systematic review of observational studies found a positive association in 8/12 studies reporting a ~2-4-fold increased risk of lung cancer. The remaining studies were neutral or found a negative association. The control group varied among the studies e.g. nonusers, tobacco only smokers and not all studies adjusted for tobacco smoking (e.g. joints contained both cannabis and nicotine) which is a known risk factor for lung cancer and limits findings. Lastly, while most studies included smoked cannabis, the risk of vaporized cannabis and lung cancer has not been systematically studied.

**Driving and Motor Vehicle Accidents (MVA):** *Cannabis use prior to driving increases the risk of MVA. Caution warranted.*

A systematic review found that self-reported cannabis use or THC metabolite present in blood, saliva or urine was associated with increased odds of a MVA (OR 1.22-1.36 95% CI 1.10-1.61).<sup>lvii</sup>

There has also been an increase in MVAs in US States with legalized recreational marijuana legislation. For example, in Colorado, where recreational marijuana was legalized in 2014, the number of drivers involved in fatal crashes increased from 627 in 2013 to 880 in 2016 and the number of drivers who tested positive for marijuana use increased from 47 in 2013 to 115 in 2016.<sup>NHTSA data</sup> It is uncertain whether cannabis use is solely responsible for the increased number of crashes as a positive blood result does not indicate that the driver was intoxicated or “high” at the time of the crash since use from weeks earlier can also result in a positive test. (Colorado’s legal limit of THC is 5 ng/mL of blood). Additionally, drivers may have also tested positive for alcohol.<sup>lviii</sup> In contrast, MVAs involving drivers who tested positive for cannabis was only increased in 3 of 12 US States where medical marijuana was legalized (studied up to 2009).<sup>lviii</sup>

Implementation of cannabis impaired driving regulations are not clear in Canada (e.g. no available assay that can accurately measure impairment due to cannabis, rather only presence). As per Health Canada Bill C-46, penalties for drug impaired driving are:<sup>lix</sup>

Penalties for drug-impaired driving				
New Summary conviction offence				
<ul style="list-style-type: none"> <li>2 nanograms (ng) but less than 5 ng of THC per millilitre (ml) of blood</li> </ul>		Maximum \$ 1,000 fine		
New Hybrid offences				
<ul style="list-style-type: none"> <li>5 ng or more of THC per ml of blood</li> <li>Any detectable level of LSD, psilocybin, psilocin, ketamine, PCP, cocaine, methamphetamine, 6-mam</li> <li>5 mg/L of GHB</li> </ul>	First offence	Mandatory minimum \$1,000 fine		
	Second offence	Mandatory minimum of 30 days imprisonment		
	Third and subsequent offences	Mandatory minimum 120 days imprisonment		
<ul style="list-style-type: none"> <li>50 milligrams (mg) of alcohol per 100 ml blood + 2.5 ng or more of THC per ml of blood</li> </ul>	First offence	Mandatory minimum \$1,000 fine		
	Second offence	Mandatory minimum of 30 days imprisonment		
	Third offence	Mandatory minimum 120 days imprisonment		
Drug-impaired driving that does not cause bodily harm or death – Maximum penalties				
Summary conviction	18 months imprisonment			
Indictment	5 years imprisonment			
Drug-impaired driving causing bodily harm – Maximum penalty				
Indictment	10 years imprisonment			
Drug-impaired driving causing death – Maximum penalty				
Life imprisonment				
Testing				
Police can demand that a driver comply with either a standardized field sobriety test or provide an oral fluid sample if they reasonably suspect a drug is in the driver’s body. If they have reasonable grounds to believe that an offence has been committed, they can demand a blood sample or a drug recognition evaluation.				

In Canada, a roadside THC saliva screening test (Drager DrugTest 5000©) has been approved for use but it is unclear how this will be implemented.<sup>lx</sup> (Note: this test also screens for the presence of cocaine in oral fluids.)

**Cognition:**<sup>lxii</sup> *Cannabinoid use has resulted in cognitive impairment (e.g. memory) in some RCTs. The risk with long-term use is relatively unknown, and there may be prolonged impairment even after cessations based on limited data.*

RCT data suggests increased memory impairment, disorientation/confusion, disturbance in attention or disconnected thoughts, and “CNS effects” with cannabinoid use compared to placebo (see above table).

A systematic review of 38 observational studies evaluated neurocognitive outcomes in patients abstinent from cannabis for at least 14 days. Prior cannabis use compared to nonuse was statistically associated with impaired attention, motor function, executive functioning, and learning/memory abilities, and structural differences (e.g. limbic system, hippocampus [memory], amygdala [emotion processing]) based on neuro-imaging studies. Cannabis use onset prior to 18 years of age was associated with greater neurocognitive impairment and imaging differences compared to those with onset after 18 years. The findings are limited by high statistical and clinical heterogeneity including variable cannabis exposure (i.e. quantity, frequency, or duration of cannabis use; is there a dose-effect that separates moderate and recreational use from high-risk and heavy use?), abstinence duration, definition and measurement of outcome.<sup>lxiii</sup> A systematic review of 69 observational studies in young adults (mean age 20 years) also found reduced cognitive functioning in heavy cannabis users compared to minimal cannabis users; however, this finding was no longer statistically significant after abstinence for greater than 72 hours.<sup>lxiii</sup>

There is an ongoing prospective, observational study of ~10,000 participants enrolled at ages 9-10 years evaluating cognitive development funded by National Institutes of Health in the USA (Adolescent Brain Cognitive Development Study [ABCD study](#)). The study began in 2015 and will follow participants for 10 years. This study will likely provide further insight on cannabis use and effects on cognitive development during adolescence. Further data available at: <https://abcdstudy.org/index.html>.<sup>lxiv</sup>

**Psychosis:**<sup>lxv, lxvi, lxvii</sup> *Cannabinoids are associated with psychosis and risk is greatest among: frequent users, high potency products (e.g. high THC ± CBD % “skunk” or synthetic cannabinoids “spice”), younger adults/adolescents and those with a genetic predisposition.*

The reviews which informed the Canadian Cannabinoid Guideline included 3 systematic reviews ranging from 2 RCTs (37 participants) to 6 RCTs (571 participants). Incidence of acute psychosis or dissociation was 5% in those receiving cannabinoids compared to 0% in placebo. Although consistently greater numerically, there was not a statistically significantly difference with cannabinoid use compared to placebo.

Cannabis use is consistently associated with greater risk of new-onset psychosis in a dose-related fashion.<sup>lxviii</sup> For example one systematic review of observational studies reported ~2-fold increase in risk with any cannabis use compared to non-use (OR 1.97 95% CI 1.68-2.31) with even greater risk amongst frequent users e.g. daily (OR 3.9 95% CI 2.84-5.35).<sup>lxix</sup> Other studies also report greater risk among individuals using higher potency products.<sup>lx</sup>

Adolescents and younger adults may also be at greater risk for the development of psychosis. A prospective observational study of 2021 participants aged 14-24 years (mean age 18 years at baseline) were followed for 10 years. Cannabis use (5 times or more) at 3.5 years from baseline was associated with ~2-fold (95% CI 1.1-3.1) increased risk of psychotic outcomes at ~8.5 years.<sup>lxxi</sup> In addition, a prospective observational study of 1037 participants with complete data on 759 participants found cannabis users (3 times or more/lifetime) by age 15 years had increased risk of schizophrenia symptoms ( $p=0.001$ ) and schizopreniform disorders (OR 4.5 95% CI 1.11-18.21) compared to no cannabis use by age 15 years (never or 1-2 times/lifetime).<sup>lxixii</sup> Users by age 18 years had increased risk of schizophrenia symptoms ( $p=0.009$ ) but not significant schizopreniform disorders (OR 1.65 95% CI 0.65-4.18).<sup>lxixiii</sup>

The endocannabinoid system appears to be linked to the dopamine reward pathway including areas of the brain such as the ventral tegmental area, nucleus accumbens, prefrontal cortex and anterior cingulate which may in part explain this effect. Interestingly, an exploratory RCT of 83 participants with schizophrenia given CBD 1000mg/d compared to placebo suggests possible benefit (e.g. lower positive psychotics symptoms, and improved clinical global impression).<sup>lxixiv</sup>

While the potential harm is concerning, the evidence is limited by the inclusion of retrospective observational trials in most systematic reviews which cannot reliably assess incidence due to the risk of reverse causation (i.e. cannabis used to self-medicate early psychosis symptoms).<sup>lxv</sup>

## 5. How should a trial of cannabis be stopped?<sup>lxvii, lxxvii</sup>

Tapering is advised for most patients who undergo a therapeutic trial of cannabis. Withdrawal symptoms upon cessation have been reported when cannabis is used daily for a few weeks to months in some individuals (note: severity is proportional to amount and duration of use). Withdrawal symptoms may include: anxiety/nervousness, decreased appetite/weight loss, restlessness, sleep disturbances (e.g. insomnia, strange dreams), chills, shakiness, depressed mood, abdominal pain, sweating. **Generally, symptom onset is 1-2 days, peak 2-6 days, and return to baseline 1-2 weeks after cannabis discontinuation.**

The optimal tapering regimen is unknown; however, may use below.

- General guideline for tapering: decrease dose by 25% every 1-2 weeks as tolerated for most; however, if **frail elderly** go slower e.g. decrease dose by 10% every 1-2 weeks or 25% every 2-4 weeks. expert opinion

Tapering of cannabis is generally not necessary for PRN use (e.g. chemotherapy-induced nausea and vomiting), or if cannabis therapy has not been used for some time (e.g. urine drug screen negative multiple times).

## 6. Are cannabinoids opioid sparing?<sup>lxviii</sup>

The association is unclear between cannabinoids and reduction in opioid use. Available data is encouraging, but majority is based on survey data or epidemiology level data. Further prospective studies at the patient level are required.

Results from prospective observational studies are inconsistent. A survey conducted in Israel of patients at cannabis treatment initiation (2736 participants) and after 6 months (901 participants) reported 143 patients reduced opioid dose or discontinued opioid therapy and 32 patients increased opioid dose or initiated opioid therapy after the initiation of cannabis. In Australia, there was no statistical evidence that cannabis use reduced prescribed opioid dose or increased the rates of opioid discontinuation based on patient interviews/questionnaires at baseline and yearly for 4 years.<sup>lxix</sup>

Multiple retrospective observational trials utilizing patient self-reported surveys show reductions in opioid use or substitution of cannabis for opioids.<sup>lxviii</sup> For example, 32% (n=80) of respondents self-reported substituting cannabis for opioids in an online survey conducted by a Canadian licensed producer in 2015 (note ~50% of respondents reported pain as the primary condition cannabis was prescribed for).<sup>lxix</sup> In Michigan, a survey conducted between 2013-2015 in chronic pain patients using medical cannabis under physician authorization reported a 64% reduction in opioid use.<sup>lxviii</sup>

Evidence is also available at the population level. Based on Veterans Affairs Canada data, the number of veterans with opioid prescriptions has reduced in 2017-2018 (10,130) compared to 2012-2013 (14,732) while the number of veterans with authorization for cannabis has increased in 2017-2018 (7,298) compared to 2012-2013 (68).<sup>lxviii</sup> Reduction in opioid prescribing has also been reported in US States with legalized medical cannabis.<sup>lxviii, lxix</sup> In addition, ~25% reduction in opioid overdose death based on ICD codes was reported in US States with legalization of medical cannabis.<sup>lxviii</sup> These studies are unable to determine causation or assess the impact of other variables e.g. new opioid guidelines and societal pressures which may have also played a role in this reduction.

## 7. What about cannabinoids for anxiety, sleep, or post-traumatic stress disorder (PTSD)?

**Anxiety: role is unclear; potential increased risk of anxiety reported in RCTs.**

- Minimal data in patients with anxiety. One RCT conducted in 24 participants with social anxiety disorder reported benefit based on a simulated public speaking test with CBD 600mg orally x 1 dose compared to placebo. <sup>lxxxvii</sup>
- Some data in patients with chronic pain. Some small studies suggest possible benefit with cannabinoids compared to placebo as measured by various anxiety or subsets of QOL scales/questionnaires. <sup>lxxxviii, lxxxix</sup> Further evaluation is required.
- A systematic review of 15 RCTs (1717 participants) with various medical conditions reported numerically greater risk of anxiety in those treated with cannabinoids vs placebo OR 1.67 (95% CI 0.73-5.35).<sup>xc</sup> Another review found moderate evidence of an association between regular cannabis use and increased risk of social anxiety disorder; however, only limited evidence of an association between near daily cannabis use and increased anxiety symptoms. National Sciences '17 <sup>xcii</sup> A Canadian prospective observational trial over 1 year (431 participants) reported anxiety in 10 patients compared to 2 patients taking cannabis (majority were using combination of smoking, oral, and vaping) or placebo respectively. Of note, these adverse effects were all defined as "non-serious" (e.g. did not require hospitalization) vs "serious" (e.g. required hospitalization) as per definitions from the International Conference on Harmonization Guideline. <sup>COMPASS xcii</sup>
- Cannabis is not recommended due to lack of evidence of benefit and known harms. <sup>CPF'18 (strong recommendation)</sup>

**Sleep: may provide some additional benefit for sleep if used for treatment of a comorbidity.**

- Cannabis has not been studied in primary chronic insomnia. <sup>National Sciences '17 xciii</sup>
- There is moderate evidence that cannabinoids, primarily nabiximols, may be helpful to improve short-term sleep outcomes in those with other comorbidities (e.g. multiple sclerosis). <sup>National Sciences '17 xciv, xcvi</sup>
- Cannabis is not recommended due to lack of evidence of benefit and known harms. <sup>CPF'18 (strong recommendation)</sup>

**PTSD: evolving evidence base; limited RCTs, conflicting observational data but ongoing studies will be important to inform practice.**

- One RCT in Canadian male military personnel with refractory PTSD demonstrated benefit (global clinical state rated as "much or very much improved") in 7 out of 10 participants with nabilone ~2mg HS compared to 2 out of 9 participants with placebo over 16 weeks.<sup>xcvi</sup>
- There are many observational studies reporting mixed results. <sup>xcvii, xcix, xcix</sup> Of note, one retrospective cohort study of 2276 American veterans reported worse PTSD symptoms in cannabis users (continuing users and new users) compared to never users and cannabis discontinuers ( $P<0.0001$ ). Poorer outcomes may be linked to higher doses.
- Ongoing RCTs: NCT02759185 (US Veterans, April 2019), NCT02517424 (Canada, June 2020), Cannabis Use & Veterans<sup>c</sup>
- Cannabis is not recommended due to lack of evidence of benefit and known harms. <sup>CPF'18 (strong recommendation)</sup>

<sup>ci</sup> Veterans Affairs '17 (strong against) [However, evolving evidence e.g. pre-clinical<sup>ci, cii</sup>/clinical trials and patient reports of symptom improvement (nightmares, coping and sleep). <sup>Expert Opinion</sup> Thus, this area may be reviewed in the near future.]

### References for the Cannabinoid Q&A – [www.RxFiles.ca](http://www.RxFiles.ca) (See online for full reference list)

<sup>i</sup> Allan GM, Finley CR, Ton J, Perry D, Ramji J, Crawford K, Lindblad AJ, Korownyk C, Kolber MR. Systematic review of systematic reviews for medical cannabinoids: Pain, nausea and vomiting, spasticity, and harms. *Can Fam Physician*. 2018 Feb;64(2):e78-e94.

<sup>ii</sup> National Academies of Sciences, Engineering, and Medicine. 2017. *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/24625>.

<sup>iii</sup> Ravi D, Ghasemiesfe M, Korenstein D, Cascino T, Keyhani S. Associations Between Marijuana Use and Cardiovascular Risk Factors and Outcomes: A Systematic Review. *Ann Intern Med*. 2018 Feb 6;168(3):187-194.

<sup>iv</sup> Ravi D, Ghasemiesfe M, Korenstein D, Cascino T, Keyhani S. Associations Between Marijuana Use and Cardiovascular Risk Factors and Outcomes: A Systematic Review. *Ann Intern Med*. 2018 Feb 6;168(3):187-194.

<sup>v</sup> Ellis RJ, Toporoff W, Vaida F, van den Brande G, Gonzales J, Gouaux B, Bentley H, Atkinson JH. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. *Neuropsychopharmacology*. 2009 Feb;34(3):672-80.

<sup>vi</sup> Ware MA, Wang T, Shapiro S, Robinson A, Ducruet T, Huynh T, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. *Canadian Medical Association Journal* 2010;184:E694-701.

<sup>vii</sup> Wong SS, Wilens TE. Medical Cannabinoids in Children and Adolescents: A Systematic Review. *Pediatrics*. 2017 Nov;140(5). pii: e20171818. doi:10.1542/peds.2017-1818.

<sup>viii</sup> Giedd, J. N. 2015. The amazing teen brain. *Scientific American* 312(6):32-37.

<sup>ix</sup> Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, Nugent TF 3rd, Herman DH, Clasen LS, Toga AW, Rapoport JL, Thompson PM. Dynamic mapping of human cortical development during childhood through early adulthood. *Proc Natl Acad Sci U S A*. 2004 May 25;101(21):8174-9.

# Medical Cannabinoids - Informed Consent & Agreement

Cannabis (i.e. marijuana) is a plant. The buds (or flowers) of this plant contain over 100 substances called cannabinoids. It is believed that when people use cannabis, it is cannabinoids that cause its effects. You have been prescribed either an extracted or synthetic cannabinoid (such as nabilone or nabiximols, available by prescription), or have been medically authorized to use cannabis itself (often via an oral oil, or sometimes inhaled).

There are both potential benefits and potential harms to using a cannabinoid as a treatment strategy. The purpose of this document is to outline various considerations so that together with your health care practitioner you can determine if they are the right therapy for you to try.

Cannabinoids should always be viewed as a trial. If the goals of using the medication are not realized, the drug will be stopped. Not all people starting cannabinoids will report a benefit from using it. Almost all people starting a cannabinoid will get at least one side effect.

The risks include:

## 1. Psychiatric Disturbance

This has been reported to occur in as many as 1 in 4 people who inhale cannabis (1 in 6 across cannabinoids). This includes conditions such as depression, anxiety, and psychosis.

In some people, taking cannabis may unmask schizophrenia.

Prescription cannabinoids have been shown to cause euphoria, numbness, speech disorders, and muscle disorders.  
[NOTE: psychiatric disturbance may vary with varying dose, potency, product and formulation]

## 2. Drowsiness, Clouded Thinking, Disturbance in Attention

\_\_\_\_\_  
(INITIALS)

I am aware that drowsiness or clouded thinking may make it dangerous for me to drive or operate heavy machinery. Alcohol or other medications that also cause drowsiness may worsen this effect. I agree to wait 4 hours after smoking cannabis, 6 hours after taking a cannabinoid orally, or 8 hours after feeling "high" before driving or operating heavy machinery or signing legal documents.

\_\_\_\_\_  
(INITIALS)

I understand that using alcohol & a cannabinoid together is potentially dangerous. I have been advised not to do this.

## 3. Other Side Effects

include nausea, uncontrollable vomiting, headache, high blood pressure, dizziness, numbness, problems with speech, and appetite changes.

**4. Cannabis Use Disorder (Addiction)** is a disease that occurs in some individuals (it has been reported in about 1 in 11 individuals using cannabis recreationally). Just as becoming overweight does not necessarily mean you will develop diabetes, taking a cannabinoid does not necessarily cause addiction. However, if you have risk factors for addiction (such as a strong family history of drug or alcohol abuse) or have had problems with drugs or alcohol in the past you must notify me since we do not want to cause a relapse. The extent of this risk is not certain. Even people who take a cannabinoid as recommended can become addicted to it.

\_\_\_\_\_  
(INITIALS)

I have notified Dr \_\_\_\_\_ of any personal or family history of drug or alcohol abuse.

There are numerous laws and regulations regarding cannabinoids that your practitioner has to adhere to. The following requests are considered standard best practice and help this healthcare practice and you comply with these laws and regulations.

**The patient agrees:**

- To reliably attend appointments with the practitioner.
- To not use any illegal substances, such as cocaine or heroin.
- To not use unregulated cannabis/marijuana – only to use the supply authorized by the practitioner.
- To not seek out cannabis/marijuana, or any other controlled substance, from any other provider.
- To not give or sell the prescribed/authorized cannabinoid to anyone else, including family members.
- To use cannabinoids as prescribed/authorized and not in larger amounts or more frequently.
- To other pain consultations/management strategies, including non-drug approaches, as advised.
- To safely store the medication. (This is REALLY important as kids can easily accidentally ingest these substances.)
- To not take medical cannabis outside of Canada.
- To periodic urine drug tests as requested by the practitioner or clinic.
- To view cannabinoids as a trial, which will be discontinued if benefits of therapy are not seen, or harms outweigh benefits.
- To understand that if any of these conditions are broken, or if harms begin to outweigh benefits, the practitioner may refuse to provide future medical authorization for a cannabinoid.
- To report any side effects from using cannabinoids to my practitioner as soon as possible.

**The practitioner agrees:**

- To be able to see you within a reasonable time for follow up
- To discuss the results of urine drug testing with you before making any decisions
- If using to treat pain, to offer you treatment for your pain with therapies besides a cannabinoid if these medications are creating more harm than benefit.

**Signatures:**

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Practitioner signature

Date

---

Patient signature

Date

---

Patient name (print)

Form available at:

-Word (Modifiable): <http://www.rxfiles.ca/rxfiles/uploads/documents/Cannabinoids-Informed-Consent-And-Agreement.pdf>  
-Pdf: <http://www.rxfiles.ca/rxfiles/uploads/documents/Cannabinoids-Informed-Consent-And-Agreement.docx>

## Cannabinoids / Medical Cannabis

### Useful Links:

Health Canada Medical Document: [www.hc-sc.gc.ca/dhp-mps/alt\\_formats/pdf/marijuana/info/med-eng.pdf](http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/marijuana/info/med-eng.pdf)  
CPSS Medical Cannabis Treatment Agreement: <http://www.cps.sk.ca/iMIS/Documents/Programs%20and%20Services/Patient%20Agreement%20Template%20-%20Medical%20Cannabis.pdf>

Health Canada Licensed Producers of Cannabis for Medical Purposes List: [www.hc-sc.gc.ca/dhp-mps/marijuana/info/list-eng.php](http://www.hc-sc.gc.ca/dhp-mps/marijuana/info/list-eng.php)  
Cannabis for Medical Purposes: How to Start the Conversation (CPhA): [https://www.pharmacists.ca/cpha-ca/assets/File/cpha-on-the-issues/CannabisTool\\_StartConversation.pdf](https://www.pharmacists.ca/cpha-ca/assets/File/cpha-on-the-issues/CannabisTool_StartConversation.pdf)

CPPSS Prescribing Medical Cannabis- Information for Patients and Physicians:  
<http://www.cps.sk.ca/iMIS/Documents/Programs%20and%20Services/Prescribing%20Medical%20Cannabis.pdf>

Canadian Public Health Association- Pot & Driving Poster:  
[https://www.cpha.ca/sites/default/files/uploads/resources/cannabis/Pot%20+%20Driving%202018/pot+driving\\_poster\\_11x8-5\\_e.pdf](https://www.cpha.ca/sites/default/files/uploads/resources/cannabis/Pot%20+%20Driving%202018/pot+driving_poster_11x8-5_e.pdf)

Non-Medical Cannabis Resource – for primary care provider/patient discussions: <https://thewellhealth.ca/non-medical-cannabis/>

**RxFiles:** Cannabinoid/Medical Cannabis Newsletter, Chart, Q&A: <http://www.rxfiles.ca/rxfiles/uploads/documents/CANNABINOIDS-Newsletter-CHT-QandA-RxFiles.pdf>

**RxFiles:** Medical Cannabinoids – Informed Consent & Agreement:

PDF: <http://www.rxfiles.ca/rxfiles/uploads/documents/Cannabinoids-Informed-Consent-And-Agreement.pdf>

Word (modifiable): <http://www.rxfiles.ca/rxfiles/uploads/documents/Cannabinoids-Informed-Consent-And-Agreement.doc>

**RxFiles:** Cannabis, Medical – Patient Booklet: <http://www.rxfiles.ca/rxfiles/uploads/documents/Cannabis-Medical-Patient-Booklet.pdf>

**RxFiles Cannabinoid Chart - Updates & References:** <http://www.rxfiles.ca/rxfiles/uploads/documents/Pain-QandA-cannabinoids.pdf>

### For patients:

Canada's Lower Risk Use Guideline Public Brochure for people who use cannabis: <https://www.camh.ca/-/media/files/pdfs---reports-and-books---research/canadas-lower-risk-guidelines-cannabis-pdf.pdf>

Cannabis 101: for recreational or medical use (1 pager)

<https://static1.squarespace.com/static/52dc09bee4b00bd4279bf2de/t/5b1a7699758d469d6946160b/1528460966140/Cannabis+Infographic+%282+ sided%29.pdf>

Centre of Excellence for Women's Health- Women & Cannabis

English: <http://bccewh.bc.ca/wp-content/uploads/2018/03/InfoSheet-Women-Cannabis0308.pdf>

French: <http://bccewh.bc.ca/wp-content/uploads/2018/03/Infosheet-Women-CannabisFr0308.pdf>

YouTube Videos:

Cannabis: <https://www.youtube.com/watch?v=waOckLpQHY8>

Youth Specific Effects of Early Cannabis Use: <https://www.youtube.com/watch?v=fqe1h3ErQCA>

Society of Obstetrics & Gynecologists of Canada (SOGC)-Not Just a Herb: <https://www.youtube.com/watch?v=hxU5fBsmpKo>

Society of Obstetrics & Gynecologists of Canada (SOGC)-Times Have Changed: [https://www.youtube.com/watch?v=sZ\\_1vISa\\_a8](https://www.youtube.com/watch?v=sZ_1vISa_a8)

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### Developments - Here are a few changes happening at RxFiles Academic Detailing:

- 1) After 21 years at Saskatoon City Hospital, the RxFiles has moved to the University of Saskatchewan, College of Pharmacy and Nutrition. Some aspects of the transition are still in progress and likely to be completed by July 2019.
- 2) Brenda Schuster, our lead RxFiles Academic Detailer for Regina is passing the baton to Debbie Bunka. (See picture at right.) Welcome Debbie!!!
- 3) Pam Karlson, our RxFiles Academic Detailer in North Battleford, is also stepping away from her long-standing service with RxFiles. This position is not yet filled.
- 4) RxFiles leadership succession plans in progress. After 21 years, Loren Regier is passing the baton to Alex Crawley. Alex is taking on the position of Associate Director, RxFiles Academic Detailing. Loren will continue to provide support to Alex during this transition time for an indefinite period. Welcome Alex!!!



Towards a successful succession!  
Brenda (left) & Debbie (right).

<sup>x</sup> Horti AG, Van Laere K. Development of radioligands for in vivo imaging of type 1 cannabinoid receptors (CB1) in human brain. *Curr Pharm Des.* 2008;14(31):3363-83.

<sup>xi</sup> Lubman DI, Cheetham A, Yücel M. Cannabis and adolescent brain development. *Pharmacol Ther.* 2015 Apr;148:1-16. doi: 10.1016/j.pharmthera.2014.11.009.

<sup>xii</sup> Quickfall J, Crockford D. Brain neuroimaging in cannabis use: a review. *J Neuropsychiatry Clin Neurosci.* 2006 Summer;18(3):318-32.

<sup>xiii</sup> Ganzer F, Bröning S, Kraft S, Sack PM, Thomasius R. Weighing the Evidence: A Systematic Review on Long-Term Neurocognitive Effects of Cannabis Use in Abstinent Adolescents and Adults. *Neuropsychol Rev.* 2016 Jun;26(2):186-222.

<sup>xiv</sup> Kuepper R, van Os J, Lieb R, Wittchen HU, Höfler M, Henquet C. Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study. *BMJ.* 2011 Mar 1;342:d738.

<sup>xv</sup> Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt TE. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *BMJ.* 2002 Nov 23;325(7374):1212-3.

<sup>xvi</sup> Arseneault Louise, Cannon Mary, Poulton Richie, Murray Robin, Caspi Avshalom, Moffitt Terrie E et al. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study *BMJ* 2002; 325 :1212

<sup>xvii</sup> Anthony JC. The epidemiology of cannabis dependence. In: Roffman RA, Stephens RS, eds. *Cannabis dependence: its nature, consequences and treatment.* Cambridge University Press, 2006:58-105.

<sup>xviii</sup> Hall W, Degenhardt L. Adverse health effects of non-medical cannabis use. *Lancet.* 2009 Oct 17;374(9698):1383-91. doi: 10.1016/S0140-6736(09)61037-0.

<sup>xix</sup> National Academies of Sciences, Engineering, and Medicine. 2017. *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research.* Washington, DC: The National Academies Press. <https://doi.org/10.17226/24625>.

<sup>xx</sup> CMA Submission: Bill C-45: The Cannabis Act. Submission to the House of commons Standing Committee on Health. Aug 18<sup>th</sup>, 2017.

<sup>xxi</sup> College of Family Physicians of Canada. Authorizing Dried Cannabis for Chronic Pain or Anxiety: Preliminary Guidance from the College of Family Physicians of Canada. Mississauga, ON: College of Family Physicians of Canada; 2014.

<sup>xxii</sup> Blanco C, Rafful C, Wall MM, Ridenour TA, Wang S, Kendler KS. Towards a comprehensive developmental model of cannabis use disorders. *Addiction.* 2014 Feb;109(2):284-94. doi: 10.1111/add.12382.

<sup>xxiii</sup> Blanco C, Rafful C, Wall MM, Ridenour TA, Wang S, Kendler KS. Towards a comprehensive developmental model of cannabis use disorders. *Addiction.* 2014 Feb;109(2):284-94. doi: 10.1111/add.12382.

<sup>xxiv</sup> Lichtenstein P, Yip BH, Björk C, Pawitan Y, Cannon TD, Sullivan PF, Hultman CM. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *Lancet.* 2009 Jan 17;373(9659):234-9. doi:10.1016/S0140-6736(09)60072-6.

<sup>xxv</sup> <https://sogc.org/files/letSOGCstatementCannabisUse.pdf>

<sup>xxvi</sup> Committee on Obstetric Practice. Committee Opinion No. 722: Marijuana Use During Pregnancy and Lactation. *Obstet Gynecol.* 2017 Oct;130(4):e205-e209. doi:10.1097/AOG.0000000000002354.

<sup>xxvii</sup> Allan GM, Ramji J, Perry D, Ton J, Beahm NP, Crisp N, Dockrill B, Dubin RE, Findlay T, Kirkwood J, Fleming M, Makus K, Zhu X, Korownyk C, Kolber MR, McCormack J, Nickel S, Noël G, Lindblad AJ. Simplified guideline for prescribing medical cannabinoids in primary care. *Can Fam Physician.* 2018 Feb;64(2):111-120. PubMed PMID: 29449241

<sup>xxviii</sup> Ryan SA, Ammerman SD, O'Connor ME; COMMITTEE ON SUBSTANCE USE AND PREVENTION; SECTION ON BREASTFEEDING. Marijuana Use During Pregnancy and Breastfeeding: Implications for Neonatal and Childhood Outcomes. *Pediatrics.* 2018 Sep;142(3). pii: e20181889. doi: 10.1542/peds.2018-1889.

<sup>xxix</sup> Bertrand KA, Hanan NJ, Honerkamp-Smith G, Best BM, Chambers CD. Marijuana Use by Breastfeeding Mothers and Cannabinoid Concentrations in Breast Milk. *Pediatrics.* 2018 Sep;142(3).

<sup>xxx</sup> Dickson B, Mansfield C, Guiahi M, Allshouse AA, Borgelt LM, Sheeder J, Silver RM, Metz TD. Recommendations From Cannabis Dispensaries About First-Trimester Cannabis Use. *Obstet Gynecol.* 2018 Jun;131(6):1031-1038. doi:10.1097/AOG.0000000000002619.

<sup>xxxi</sup> Conner SN, Bedell V, Lipsey K, Macones GA, Cahill AG, Tuuli MG. Maternal Marijuana Use and Adverse Neonatal Outcomes: A Systematic Review and Meta-analysis. *Obstet Gynecol.* 2016 Oct;128(4):713-23. doi:10.1097/AOG.0000000000001649.

<sup>xxxi</sup> Devinsky O, Patel AD, Cross JH, Villanueva V, Wirrell EC, Privitera M, Greenwood SM, Roberts C, Checketts D, VanLandingham KE, Zuberi SM; GWPCARE3 Study Group. Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome. *NEngl J Med.* 2018 May 17;378(20):1888-1897.

<sup>xxxi</sup> Thiele EA, Marsh ED, French JA, Mazurkiewicz-Beldzinska M, Benbadis SR, Joshi C, Lyons PD, Taylor A, Roberts C, Sommerville K; GWPCARE4 Study Group. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet.* 2018 Mar 17;391(10125):1085-1096.

<sup>xxxi</sup> Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nababout R, Scheffer IE, Thiele EA, Wright S; Cannabidiol in Dravet Syndrome Study Group. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. *N Engl J Med.* 2017 May 25;376(21):2011-2020.

<sup>xxxi</sup> Abuhasira R, Schleider LB, Mechoulam R, Novack V. Epidemiological characteristics, safety and efficacy of medical cannabis in the elderly. *Eur J Intern Med* 2018; **49**: 44–50.

<sup>xxxi</sup> Mammen G, Rueda S, Roerecke M, Bonato S, Lev-Ran S, Rehm J. Association of Cannabis With Long-Term Clinical Symptoms in Anxiety and Mood Disorders: A Systematic Review of Prospective Studies. *J Clin Psychiatry.* 2018 Jun 5;79(4).

<sup>xxxi</sup> Marwaha S, Winsper C, Bebbington P, Smith D. Cannabis Use and Hypomania in Young People: A Prospective Analysis. *Schizophr Bull.* 2017 Nov 28. doi:10.1093/schbul/sbx158.

<sup>xxxi</sup> Gibbs M, Winsper C, Marwaha S, Gilbert E, Broome M, Singh SP. Cannabis use and mania symptoms: a systematic review and meta-analysis. *J Affect Disord.* 2015 Jan 15;171:39-47.

<sup>xxxi</sup> Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE. Triggering myocardial infarction by marijuana. *Circulation.* 2001 Jun 12;103(23):2805-9.

<sup>xl</sup> Sidney, S., J. E. Beck, I. S. Tekawa, C. P. Quesenberry, and G. D. Friedman. 1997. Marijuana use and mortality. *American Journal of Public Health* 87(4):585–590.

<sup>xli</sup> Sidney, S. 2002. Cardiovascular consequences of marijuana use. *Journal of Clinical Pharmacology* 42(11 Suppl):64S–70S.

<sup>xlii</sup> Aronow WS, Cassidy J: Effect of marihuana and placebo- marihuana smoking on angina pectoris. *N Engl J Med* 1974; 291(2):65-67.

<sup>xliii</sup> Aronow WS, Cassidy J: Effect of marihuana and placebo- marihuana smoking on angina pectoris. *N Engl J Med* 1974; 291(2):65-67.

<sup>xliv</sup> Cheung E, Ng C, Foote J. A hot mess: a case of hyperemesis. *Can Fam Physician.* 2014 Jul;60(7):633-7.

<sup>xlv</sup> Martinasek MP, McGrogan JB, Maysonet A. A Systematic Review of the Respiratory Effects of Inhalational Marijuana. *Respir Care.* 2016 Nov;61(11):1543-1551. Epub

<sup>xvi</sup> Huang YH, Zhang ZF, Tashkin DP, Feng B, Straif K, Hashibe M. An epidemiologic review of marijuana and cancer: an update. *Cancer Epidemiol Biomarkers Prev.* 2015 Jan;24(1):15-31. doi: 10.1158/1055-9965.

<sup>xvi</sup> Bajgoric S, Samra K, Chandrapalan S, Gautam N. Cannabinoid hyperemesis syndrome: a guide for the practising clinician. *BMJ Case Rep.* 2015 Dec 23;2015. pii: bcr2015210246. doi: 10.1136/bcr-2015-210246.

<sup>xvii</sup> Richards JR. Cannabinoid Hyperemesis Syndrome: Pathophysiology and Treatment in the Emergency Department. *J Emerg Med.* 2018 Mar;54(3):354-363. doi:10.1016/j.jemermed.2017.12.010.

<sup>xix</sup> Richards JR, Gordon BK, Danielson AR, Moulin AK. Pharmacologic Treatment of Cannabinoid Hyperemesis Syndrome: A Systematic Review. *Pharmacotherapy.* 2017 Jun;37(6):725-734. doi: 10.1002/phar.1931.

<sup>xix</sup> Sorensen CJ, DeSanto K, Borgelt L, Phillips KT, Monte AA. Cannabinoid Hyperemesis Syndrome: Diagnosis, Pathophysiology, and Treatment-a Systematic Review. *J Med Toxicol.* 2017 Mar;13(1):71-87. doi: 10.1007/s13181-016-0595-z.

<sup>ii</sup> Simonetto DA, Oxentenko AS, Herman ML, Szostek JH. Cannabinoid hyperemesis: a case series of 98 patients. Mayo Clin Proc. 2012 Feb;87(2):114-9. doi: 10.1016/j.mayocp.2011.10.005.

<sup>iii</sup> Martinasek MP, McGrogan JB, Maysonet A. A Systematic Review of the Respiratory Effects of Inhalational Marijuana. Respir Care. 2016 Nov;61(11):1543-1551.

<sup>iii</sup> Huang, Y. H., Z. F. Zhang, D. P. Tashkin, B. Feng, K. Straif, and M. Hashibe. 2015. An epi- demiologic review of marijuana and cancer: An update. *Cancer Epidemiol, Biomarkers & Prevention* 24(1):15-31.

<sup>iv</sup> Zhang, L. R., H. Morgenstern, S. Greenland, S. C. Chang, P. Lazarus, M. D. Teare, P. J. Woll, I. Orlow, B. Cox, Y. Brhane, G. Liu, and R. J. Hung. 2015. Cannabis smoking and lung cancer risk: Pooled analysis in the International Lung Cancer Consortium. *International Journal of Cancer* 136(4):894-903.

<sup>v</sup> Tashkin, D. P. 2013. Effects of marijuana smoking on the lung. *Annals of the American Thoracic Society* 10(3):239-247

<sup>vi</sup> Rogeberg, O., and R. Elvik. 2016. The effects of cannabis intoxication on motor vehicle collision revisited and revised. *Addiction* 111(8):1348-1359.

<sup>vii</sup> <https://www.denverpost.com/2017/08/25/colorado-marijuana-traffic-fatalities/>

<sup>viii</sup> Masten SV, Guenzburger GV. Changes in driver cannabinoid prevalence in 12 U.S. states after implementing medical marijuana laws. *J Safety Res.* 2014 Sep;50:35-52. doi: 10.1016/j.jsr.2014.03.009.

<sup>ix</sup> Government of Canada. Department of Justice: Impaired Driving Laws. <http://www.justice.gc.ca/eng/cj-jp/sidl-rlcfa/> (access Sept 25<sup>th</sup> 2018)

<sup>ix</sup> <http://www.gazette.gc.ca/rp-pr/p2/2018/2018-09-05/html/sor-dors179-eng.html>

<sup>xi</sup> Broyd, S. J., H. H. Van Hell, C. Beale, M. Yucel, and N. Solowij. 2016. Acute and chronic effects of cannabinoids on human cognition—A systematic review. *Biological Psychiatry* 79(7):557-567.

<sup>lxii</sup> Ganzer F, Bröning S, Kraft S, Sack PM, Thomasius R. Weighing the Evidence: A Systematic Review on Long-Term Neurocognitive Effects of Cannabis Use in Abstinent Adolescents and Adults. *Neuropsychol Rev.* 2016 Jun;26(2):186-222.

<sup>lxiii</sup> Scott JC, Slomjak ST, Jones JD, Rosen AFG, Moore TM, Gur RC. Association of Cannabis With Cognitive Functioning in Adolescents and Young Adults: A Systematic Review and Meta-analysis. *JAMA Psychiatry.* 2018 Jun 1;75(6):585-595. doi:10.1001/jamapsychiatry.2018.0335.

<sup>lxiv</sup> Adolescent Brain Cognitive Development Study. 2016. Adolescent Brain Cognitive Development Study (ABCD). <http://abcdstudy.org>

<sup>lxv</sup> Bagot KS, Chang A. Marijuana and Psychosis: Policy Implications for Treatment Providers. *J Am Acad Child Adolesc Psychiatry.* 2018 Aug;57(8):613-614. doi:10.1016/j.jaac.2018.05.010.

<sup>lxvi</sup> Colizzi M, Murray R. Cannabis and psychosis: what do we know and what should we do? *Br J Psychiatry.* 2018 Apr;212(4):195-196.

<sup>lxvi</sup> Tibbo P, Crocker CE, Lam RW, Meyer J, Sareen J, Aitchison KJ. Implications of Cannabis Legalization on Youth and Young Adults. *Can J Psychiatry.* 2018 Jan;63(1):65-71. doi: 10.1177/0706743718759031.

<sup>lxix</sup> Marconi A, Di Forti M, Lewis CM, Murray RM, Vassos E. Meta-analysis of the Association Between the Level of Cannabis Use and Risk of Psychosis. *Schizophr Bull.* 2016 Sep;42(5):1262-9. doi: 10.1093/schbul/sbw003.

<sup>lxx</sup> Di Forti M, Morgan C, Dazzan P, Pariante C, Mondelli V, Marques TR, Handley R, Luzi S, Russo M, Paparelli A, Butt A, Stilo SA, Wiffen B, Powell J, Murray RM. High-potency cannabis and the risk of psychosis. *Br J Psychiatry.* 2009 Dec;195(6):488-91. doi: 10.1192/bjp.bp.109.064220.

<sup>lxxi</sup> Kuepper R, van Os J, Lieb R, Wittchen HU, Höfler M, Henquet C. Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study. *BMJ.* 2011 Mar 1;342:d738.

<sup>lxxii</sup> Arseneault Louise, Cannon Mary, Poulton Richie, Murray Robin, Caspi Avshalom, Moffitt Terrie E et al. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study *BMJ*2002; 325 :1212

<sup>lxxii</sup> Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt TE. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *BMJ.* 2002 Nov 23;325(7374):1212-3.

<sup>lxxiv</sup> McGuire P, Robson P, Cubala WJ, Vasile D, Morrison PD, Barron R, Taylor A, Wright S. Cannabidiol (CBD) as an Adjunctive Therapy in Schizophrenia: A Multicenter Randomized Controlled Trial. *Am J Psychiatry.* 2018 Mar 1;175(3):225-231 .

<sup>lxxv</sup> Gage SH, Hickman M, Zammit S. Association Between Cannabis and Psychosis: Epidemiologic Evidence. *Biol Psychiatry.* 2016 Apr 1;79(7):549-56. doi:10.1016/j.biopsych.2015.08.001.

<sup>lxxvi</sup> Budney AJ, Hughes JR. The cannabis withdrawal syndrome. *Curr Opin Psychiatry.* 2006 May;19(3):233-8. Review. PubMed PMID: 16612207.

<sup>lxxvii</sup> American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: DSM-5.* 5<sup>th</sup> ed. Washington (DC): American Psychiatric Publishing; 2013.

<sup>lxxviii</sup> Nielsen S, Sabioni P, Trigo JM, Ware MA, Betz-Stablein BD, Murnion B, Lintzeris N, Khor KE, Farrell M, Smith A, Le Foll B. Opioid-Sparing Effect of Cannabinoids: A Systematic Review and Meta-Analysis. *Neuropsychopharmacology.* 2017 Aug;42(9):1752-1765.

<sup>lxxix</sup> Campbell G, Hall WD, Peacock A, Lintzeris N, Bruno R, Larance B, Nielsen S, Cohen M, Chan G, Mattick RP, Blyth F, Shanahan M, Dobbins T, Farrell M, Degenhardt L. Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: findings from a 4-year prospective cohort study. *Lancet Public Health.* 2018 Jul;3(7):e341-e350.

<sup>lxxxi</sup> Corroon JM Jr, Mischley LK, Sexton M. Cannabis as a substitute for prescription drugs - a cross-sectional study. *J Pain Res.* 2017 May 2;10:989-998.

<sup>lxxxi</sup> Lucas P et al. Medical cannabis access, use, and substitution for prescription opioids and other substances: A survey of authorized medical cannabis patients. *Int J Drug Policy.* 2017;42:30-35.

<sup>lxxxii</sup> Boehnke, K. F., E. Litinas, and D. J. Clauw. 2016. Medical cannabis use is associated with decreased opiate medication use in a retrospective cross-sectional survey of patients with chronic pain. *Journal of Pain* 17(6):739-744.

<sup>lxxxiii</sup> <https://www.theglobeandmail.com/canada/british-columbia/article-number-of-veterans-using-opioids-declines-significantly-as-cannabis/>

<sup>lxxxiv</sup> Bradford AC, et al. Medical Marijuana Laws Reduce Prescription Medication Use In Medicare Part D. *Health Aff (Millwood).* 2016 Jul 1;35(7):1230-6. doi: 10.1377/hlthaff.2015.1661

Ashley C et al. Association between US state medical cannabis laws and opioid prescribing in the Medicare Part D population. *JAMA Intern Med.* 2018;178(5):667-672.

<sup>lxxxv</sup> Bachhuber MA, Saloner B, Cunningham CO, Barry CL. Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999–2010. *JAMA internal medicine.* 2014;174(10):1668-1673. doi:10.1001/jamainternmed.2014.4005.

<sup>lxxxvi</sup> Bachhuber MA, Saloner B, Cunningham CO, Barry CL. Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999–2010. *JAMA internal medicine.* 2014;174(10):1668-1673. doi:10.1001/jamainternmed.2014.4005.

<sup>lxxxvii</sup> Bergamaschi MM, Queiroz RH, Chagas MH, de Oliveira DC, De Martinis BS, Kapczinski F, Quevedo J, Roesler R, Schröder N, Nardi AE, Martín-Santos R, Hallak JE, Zuardi AW, Crippa JA. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients. *Neuropsychopharmacology.* 2011 May;36(6):1219-26. doi: 10.1038/npp.2011.6.

<sup>lxxxviii</sup> Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, et al. Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA* 2015;313(24):2456-73. Errata in: *JAMA* 2016;315(14):1522, *JAMA* 2015;314(21):2308, *JAMA* 2015;314(5):520, *JAMA* 2015;314(8):837.

<sup>lxxxix</sup> Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. *J Pain.* 2008;9(2):164-173.

<sup>xc</sup> Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, et al. Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA* 2015;313(24):2456-73. Errata in: *JAMA* 2016;315(14):1522, *JAMA* 2015;314(21):2308, *JAMA* 2015;314(5):520, *JAMA* 2015;314(8):837.

<sup>xcii</sup> National Academies of Sciences, Engineering, and Medicine. 2017. *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/24625>.

<sup>xcii</sup> Ware MA, Wang T, Shapiro S, Collet JP; COMPASS study team. Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS). *J Pain*. 2015 Dec;16(12):1233-1242. doi: 10.1016/j.jpain.2015.07.014.

<sup>xciii</sup> National Academies of Sciences, Engineering, and Medicine. 2017. *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/24625>.

<sup>xciv</sup> National Academies of Sciences, Engineering, and Medicine. 2017. *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/24625>.

<sup>xcv</sup> Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology*. 2005 Sep 27;65(6):812-9.

<sup>xcvi</sup> Jetly, R., A. Heber, G. Fraser, and D. Boisvert. 2015. The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: A preliminary randomized, double-blind, placebo-controlled cross-over design study. *Psychoneuroendocrinology* 51:585-588.

<sup>xcvii</sup> O'Neil ME, Nugent SM, Morasco BJ, Freeman M, Low A, Kondo K, Zakher B, Elven C, Motu'apuaka M, Paynter R, Kansagara D. Benefits and Harms of Plant-Based Cannabis for Posttraumatic Stress Disorder: A Systematic Review. *Ann Intern Med*. 2017 Sep 5;167(5):332-340.

<sup>xcviii</sup> Wilkinson ST, Radhakrishnan R, D'Souza DC. A systematic review of the evidence for medical marijuana in psychiatric indications. *J Clin Psychiatry*. 2016;77:1050-64. [PMID: 27561138] doi:10.4088/JCP.15r10036

<sup>xcix</sup> Walsh Z, Gonzalez R, Crosby K, S Thiessen M, Carroll C, Bonn- Miller MO. Medical cannabis and mental health: a guided systematic review. *Clin Psychol Rev*. 2017;51:15-29. [PMID: 27816801] doi:10.1016/j.cpr.2016.10.002

<sup>c</sup> [https://www.hsrq.research.va.gov/research/abstracts.cfm?Project\\_ID=2141705719](https://www.hsrq.research.va.gov/research/abstracts.cfm?Project_ID=2141705719)

<sup>ci</sup> VA/DOD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder Version 3.0; 2017.

<sup>cii</sup> Hill MN, Campolongo P, Yehuda R, Patel S. Integrating Endocannabinoid Signaling and Cannabinoids into the Biology and Treatment of Posttraumatic Stress Disorder. *Neuropsychopharmacology*. 2018 Jan;43(1):80-102.

<sup>ciii</sup> Boggs DL, Nguyen JD, Morgenson D, Taffe MA, Ranganathan M. Clinical and Preclinical Evidence for Functional Interactions of Cannabidiol and  $\Delta(9)$ -Tetrahydrocannabinol. *Neuropsychopharmacology*. 2018 Jan;43(1):142-154

### **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>

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](http://www.RxFiles.ca)

1. Health Canada. Information for health care professionals: Cannabis (marijuana, marijuana) and the cannabinoids. 2013. Available from <https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/information-medical-practitioners/information-health-care-professionals-cannabis-cannabinoids.html>. Accessed August 17, 2018.
2. Allan GM, Ramji J, Perry D, Ton J, Beahm NP, Crisp N, Dockrill B, Dubin RE, Findlay T, Kirkwood J, Fleming M. Simplified guideline for prescribing medical cannabinoids in primary care. Canadian Family Physician. 2018 Feb 1;64(2):111-20.
3. Fischer B, Russell C, Sabioni P, van den Brink W, Le Foll B, Hall W, Rehm J, Room R. Lower-risk cannabis use guidelines: a comprehensive update of evidence and recommendations. American journal of public health. 2017 Aug;107(8):e1-2.
4. RxTx [Internet]. Ottawa (ON): Canadian Pharmacists Association; c2018. CPS online: Cannabis [cited August 17, 2018]. Available from [www.myrxtx.ca](http://www.myrxtx.ca). Subscription required.
5. Canadian Pharmacists Association. Cannabis for Medical Purposes Guide. 2018. Available from [https://www.pharmacists.ca/cpha-ca/assets/File/education-practice-resources/Cannabis\\_EvidenceGuide\\_2018.pdf](https://www.pharmacists.ca/cpha-ca/assets/File/education-practice-resources/Cannabis_EvidenceGuide_2018.pdf). Accessed August 17, 2018.
6. College of Family Physicians of Canada. Authorizing dried cannabis for chronic pain or anxiety: preliminary guidance. 2014. Available from: [https://www.cfpc.ca/uploadedFiles/Resources/\\_PDFs/Authorizing%20Dried%20Cannabis%20for%20Chronic%20Pain%20or%20Anxiety.pdf](https://www.cfpc.ca/uploadedFiles/Resources/_PDFs/Authorizing%20Dried%20Cannabis%20for%20Chronic%20Pain%20or%20Anxiety.pdf). Accessed August 17, 2018.
7. Kahan M, Srivastava A, Spithoff S, Bromley L. Prescribing smoked cannabis for chronic noncancer pain. Preliminary recommendations. Can Fam Physician 2014;60:1083-90 (Eng), e562-70 (Fr).
8. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. New England Journal of Medicine. 2014 Jun 5;370(23):2219-27.
9. Nugent SM, Morasco BJ, O'neil ME, Freeman M, Low A, Kondo K, Elven C, Zakher B, Motu'apuaka M, Paynter R, Kansagara D. The effects of cannabis among adults with chronic pain and an overview of general harms: A systematic review. Annals of internal medicine. 2017 Sep 5;167(5):319-31.
10. Koppel BS, Brust JC, Fife T, Bronstein J, Youssof S, Gronseth G, Gloss D. Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2014 Apr 29;82(17):1556-63.
11. Allan GM, Finley CR, Ton J, Perry D, Ramji J, Crawford K, Lindblad AJ, Korownyk C, Kolber MR. Systematic review of systematic reviews for medical cannabinoids: Pain, nausea and vomiting, spasticity, and harms. Canadian Family Physician. 2018 Feb 1;64(2):e78-94.
12. Meng H, Johnston B, Englesakis M, Moulin DE, Bhatia A. Selective cannabinoids for chronic neuropathic pain: a systematic review and meta-analysis. Anesthesia & Analgesia. 2017 Nov 1;125(5):1638-52.
13. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, Keurentjes JC, Lang S, Misso K, Ryder S, Schmidtkofer S. Cannabinoids for medical use: a systematic review and meta-analysis. Jama. 2015 Jun 23;313(24):2456-73.
14. Smith LA, Azariah F, Lavender VT, Stoner NS, Bettoli S. Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. Cochrane Database Syst Rev 2015;(11):CD009464.
15. Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W. Cannabis-based medicines for chronic neuropathic pain in adults. The Cochrane Library. 2018 Jan 1.
16. Health Canada. Cannabis Market Data, 2018. Available from <https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/licensed-producers/market-data.html>. Accessed August 17, 2018.
17. Casarett D. The achilles heel of medical cannabis research—inadequate blinding of placebo-controlled trials. JAMA internal medicine. 2018 Jan 1;178(1):9-10.
18. Beal JE, Olson R, Laubenstein L, Morales JO, Bellman P, Yangco B, Lefkowitz L, Plasse TF, Shepard KV. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. Journal of pain and symptom management. 1995 Feb 1;10(2):89-97.
19. Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, Scheffer IE, Thiele EA, Wright S. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. New England Journal of Medicine. 2017 May 25;376(21):2011-20.
20. Devinsky O, Patel AD, Cross JH, Villanueva V, Wirrell EC, Privitera M, Greenwood SM, Roberts C, Checkett D, VanLandingham KE, Zuberi SM. Effect of Cannabidiol on Drop Seizures in the Lennox–Gastaut Syndrome. New England Journal of Medicine. 2018 May 17;378(20):1888-97.
21. Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low-dose vaporized cannabis significantly improves neuropathic pain. J Pain 2013;14(2):136-48.
22. Wilsey B, Marcotte T, Tsodikov A, Millman J, Bentley H, Gouaux B, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. J Pain 2008;9(6):506-21.
23. Elzinga S, Ortiz O, Raber J. The Conversion and Transfer of Cannabinoids from Cannabis to Smoke Stream in Cigarettes. Available from <http://cannabinetics.org/pdfs/thca-a.pdf>
24. Cannimed prices available from <https://www.cannimed.ca/collections/all>. Accessed August 17, 2018.
25. Busse JW, Craigie S, Juurlink DN, Buckley DN, Wang L, Couhan RJ, et al. **Guideline for opioid therapy and chronic noncancer pain. CMAJ.** 2017 May 8;189(18):E659-E666. Also accessible in full online at: <http://nationalpaincentre.mcmaster.ca/guidelines.html>
26. Lopez-Quintero C, Pérez de los Cobos J, Hasin DS, Okuda M, Wang S, Grant BF, Blanco C. Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Drug Alcohol Depend. 2011 May 1;115(1-2):120-30.

27. **COMPASS**. Ware MA, Wang T, Shapiro S, Collet JP; COMPASS study team. Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS). *J Pain*. 2015 Dec;16(12):1233-1242.

28. Laumon, B., Gadegbeku, B., Martin, J. L., and Biecheler, M. B. (2005). Cannabis intoxication and fatal road crashes in France: population based case-control study. *BMJ*. 331: 1371

29. Alberta College of Family Physicians. Tools for Practice #210: **Blazing Through the Evidence on THC Versus CBD Combinations in Medical Cannabinoids**. Danielle Perry, Joey Ton, G. Michael Allan. Available from [https://www.acfp.ca/wp-content/uploads/tools-for-practice/1524259665\\_tfp210thc-cbd.pdf](https://www.acfp.ca/wp-content/uploads/tools-for-practice/1524259665_tfp210thc-cbd.pdf). Accessed August 17, 2018.

30. Health Canada. **National Cannabis Survey, first quarter 2018**. Available from <https://www150.statcan.gc.ca/n1/daily-quotidien/180418/dq180418b-eng.htm>. Accessed August 17, 2018.

31. FDA drug product monograph. Epidiolex (cannabidiol) oral solution. Available from [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/210365lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf). Accessed August 17, 2018.

32. Moon AM, Buckley SA, Mark NM. Successful Treatment of Cannabinoid Hyperemesis Syndrome with Topical Capsaicin. *ACG Case Reports Journal*. 2018;5:e3. doi:10.14309/crj.2018.3.

33. Thiele EA, Marsh ED, French JA, Mazurkiewicz-Beldzinska M, Benbadis SR, Joshi C, et al. Cannabidiol in patients with seizures associated with Lennox–Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2018; 391: 1085–96.

34. Health Canada. Cannabis Stats Hub. Available from <https://www150.statcan.gc.ca/n1/pub/13-610-x/cannabis-eng.htm>. Accessed August 17, 2018.

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.

36. Jouanrus E, Lapeyre-Mestre M, Micallef J; French Association of the Regional Abuse and Dependence Monitoring Centres (CEIP-A) Working Group on Cannabis Complications. Cannabis use: signal of increasing risk of **serious cardiovascular disorders**. *J Am Heart Assoc*. 2014;3:e000638

37. Reis JP, Auer R, Bancks MP, et al. **Cumulative Lifetime Marijuana Use and Incident Cardiovascular Disease** in Middle Age: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Public Health*. 2017 Apr;107(4):601-606.

38. Thomas G, Kloner RA, Rezkalla S. Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of **marijuana** inhalation: what cardiologists need to know. *Am J Cardiol*. 2014 Jan 1;113(1):187-90.

39. Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE. Triggering myocardial infarction by marijuana. *Circulation*. 2001 Jun 12;103(23):2805-9.

40. **WHO** data. World Health Organization (WHO). Cannabis: a health perspective and research agenda. 1997. Available from: <http://apps.who.int/iris/bitstream/handle/10665/63691/WHO?sequence=1>

41. Bonn-Miller MO, Loflin MJE, Thomas BF, Marcu JP, Hyke T, Vandrey R. Labeling Accuracy of Cannabidiol Extracts Sold Online. *JAMA*. 2017 Nov 7;318(17):1708-1709.

42. Vandrey R, Raber JC, Raber ME, Douglass B, Miller C, Bonn-Miller MO. Cannabinoid Dose and Label Accuracy in Edible Medical Cannabis Products. *JAMA*. 2015 Jun 23-30;313(24):2491-3.

43. Health Canada. Additional Information for Licensed Producers under the Access to Cannabis for Medical Purposes Regulations. Available from <https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/licensed-producers/additional-information-licensed-producers-under-access-cannabis-medical-purposes-regulations.html>. Accessed September 7, 2018.

44. Haney M, Malcolm RJ, Babalonis S, Nuzzo PA, Cooper ZD, Bedi G, Gray KM, McRae-Clark A, Lofwall MR, Sparenborg S, Walsh SL. Oral Cannabidiol does not Alter the Subjective, Reinforcing or Cardiovascular Effects of Smoked Cannabis. *Neuropsychopharmacology*. 2016 Jul;41(8):1974-82.

45. bpac.org.nz; The Cannabis Use Disorder Identification Test – Revised. Accessed online 21Sep18 at [https://bpac.org.nz/BPJ/2010/June/docs/addiction\\_CUDIT-R.pdf](https://bpac.org.nz/BPJ/2010/June/docs/addiction_CUDIT-R.pdf)

46. Canadian Guideline for Safe and Effective Use of Opioids for CNCP – Part B. CAGE Questionnaire. Accessed online 21Sep18 at [http://nationalpaincentre.mcmaster.ca/documents/cage\\_questionnaire.pdf](http://nationalpaincentre.mcmaster.ca/documents/cage_questionnaire.pdf)

47. Winstock AR, Ford C, Witton J. Assessment and management of cannabis use disorders in primary care. *BMJ*. 2010 Apr 1;340:c1571.

48. Spithoff S, Kahan M. Cannabis and Canadian youth: evidence, not ideology. *Can Fam Physician*. 2014 Sep;60(9):785-7, 793-5.

49. Sabioni P, Le Foll B. Psychosocial and pharmacological interventions for the treatment of cannabis use disorder. *F1000Res*. 2018 Feb 12;7:173.

50. De Aquino JP, Sherif M, Radhakrishnan R, Cahill JD, Ranganathan M, D'Souza DC. The Psychiatric Consequences of Cannabinoids. *Clin Ther*. 2018 Apr 17. pii: S0149-2918(18)30106-1.

51. Canadian Centre on Substance Use and Addiction. Cannabis – Canadian Drug Summary. 2018 Jun. Accessed online 04 Sept 2018 at <http://www.ccsa.ca/Resource%20Library/CCSA-Canadian-Drug-Summary-Cannabis-2018-en.pdf>

52. Kalk NJ, Boyd A, Strang J, Finch E. Spice and all things nasty: the challenge of synthetic cannabinoids. *BMJ (Clinical research ed.)*. 2016 Oct 24;355:i5639.

53. Miller et al. Marijuana Addictive Disorders and DSM-5 Substance-Related Disorders. *J Addict Res Ther*. January 2017 S11 013. Available from [https://www.researchgate.net/publication/315959756\\_Marijuana\\_Addictive\\_Disorders\\_and\\_DSM-5\\_Substance-Related\\_Disorders](https://www.researchgate.net/publication/315959756_Marijuana_Addictive_Disorders_and_DSM-5_Substance-Related_Disorders)

54. ElSohly MA, Mehmec Z, Foster S, Gon C, Chandra S, Church JC. Changes in cannabis potency over the last 2 decades (1995–2014): analysis of current data in the United States. *Biological psychiatry*. 2016 Apr 1;79(7):613-9.

55. Hels T, Lyckegaard A, Simonsen KW, Steentoft A, Bernhoft IM. Risk of severe driver injury by driving with psychoactive substances. *Accident Analysis & Prevention*. 2013 Oct 1;59:346-56.

56. College of Physician and Surgeons of Saskatchewan. Medical Cannaibs. Accessed from [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) on October 10, 2018.

57. Frank B, Serpell MG, Hughes J, Matthews JN, Kapur D. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. *BMJ*. 2008 Jan 26;336(7637):199-201.

58. Nielsen S, Sabioni P, Trigo JM, Ware MA, Betz-Stablein BD, Murnion B, Lintzeris N, Khor KE, Farrell M, Smith A, Le Foll B. Opioid-Sparing Effect of Cannabinoids: A Systematic Review and Meta-Analysis. *Neuropsychopharmacology*. 2017 Aug;42(9):1752-1765.

59. Campbell G, Hall WD, Peacock A, Lintzeris N, Bruno R, Larance B, Nielsen S, Cohen M, Chan G, Mattick RP, Blyth F, Shanahan M, Dobbins T, Farrell M, Degenhardt L. Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: findings from a 4-year prospective cohort study. *Lancet Public Health*. 2018 Jul;3(7):e341-e350.

60. Corroon JM Jr, Mischley LK, Sexton M. Cannabis as a substitute for prescription drugs - a cross-sectional study. *J Pain Res*. 2017 May 2;10:989-998.

61. Lucas P et al. Medical cannabis access, use, and substitution for prescription opioids and other substances: A survey of authorized medical cannabis patients. *Int J Drug Policy*. 2017;42:30-35.

62. Boehnke, K. F., E. Litinas, and D. J. Clauw. 2016. Medical cannabis use is associated with decreased opiate medication use in a retrospective cross-sectional survey of patients with chronic pain. *Journal of Pain* 17(6):739-744.

63. <https://www.theglobeandmail.com/canada/british-columbia/article-number-of-veterans-using-opioids-declines-significantly-as-cannabis/>

64. Bradford AC. et al. Medical Marijuana Laws Reduce Prescription Medication Use In Medicare Part D. *Health Aff (Millwood)*. 2016 Jul 1;35(7):1230-6. doi: 10.1377/hlthaff.2015.1661

65. Ashley C et al. Association between US state medical cannabis laws and opioid prescribing in the Medicare Part D population. *JAMA Intern Med*. 2018;178(5):667-672.

66. Bachhuber MA, Saloner B, Cunningham CO, Barry CL. Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999–2010. *JAMA internal medicine*. 2014;174(10):1668-1673. doi:10.1001/jamainternmed.2014.4005.

67. Wang GS, Roosevelt G, Heard K. Pediatric marijuana exposures in a medical marijuana state. *JAMA Pediatr*. 2013 Jul;167(7):630-3.

68. Wade DT, Collin C, Stott C, Duncombe P. Meta-analysis of the effcacy and safety of Sativex (nabiximols), on spasticity in people with multiple sclerosis. *Mult Scler* 2010;16(6):707-14.