Cannabinoids in Diabetes: Taking a Look at the Evidence

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Faculty/Presenter Disclosure

- **Faculty/Presenter:** Angela Puim

- **Relationships with commercial interests:** *(grants/research support, consulting fees, etc.)* None

Disclosure of Financial Support

- **<u>Potential for conflict(s) of interest</u>:**

I am receiving an honorarium from Langs for my time. I have no conflicts of interest.

Mitigating Potential Bias

My presentation includes evidence based information and is not influenced by the sponsoring organizations.

Faculty/Presenter Disclosure

- **Faculty/Presenter:** Joey Champigny

- **Relationships with commercial interests:** *(grants/research support, consulting fees, etc.)* None

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Background Information [1,2,3]

- **CB1 receptors:** Primarily CNS & PNS
- **CB2 receptors:** Mainly immune system
- Two major endogenous cannabinoids:
  - Anandamide
  - 2-AG (2-arachidonoyl glycerol)
- Cannabis *sativa*, *indica, ruderalis**
  - **Common myth:** *sativa* = energizing & *indica* = sedating
- >400 distinct compounds, varies
- Temperatures >120 °C promote decarboxylation (eg. TCHA --> THC)

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THC [2]

- THC is a partial activator at both CB1 & CB2.
- Modulates the effects of other neurotransmitters at the synaptic level
  - Causes release of dopamine in the brain → pleasurable effects with recreational use

CBD [2]

- Interacts with CB receptors to block or modulate them, questionable whether in physiologically meaningful concentrations
- Does not cause “high”, but does enter CNS
  - Analgesic, anti-inflammatory, anxiolytic, etc.

Pharmacokinetics [1]

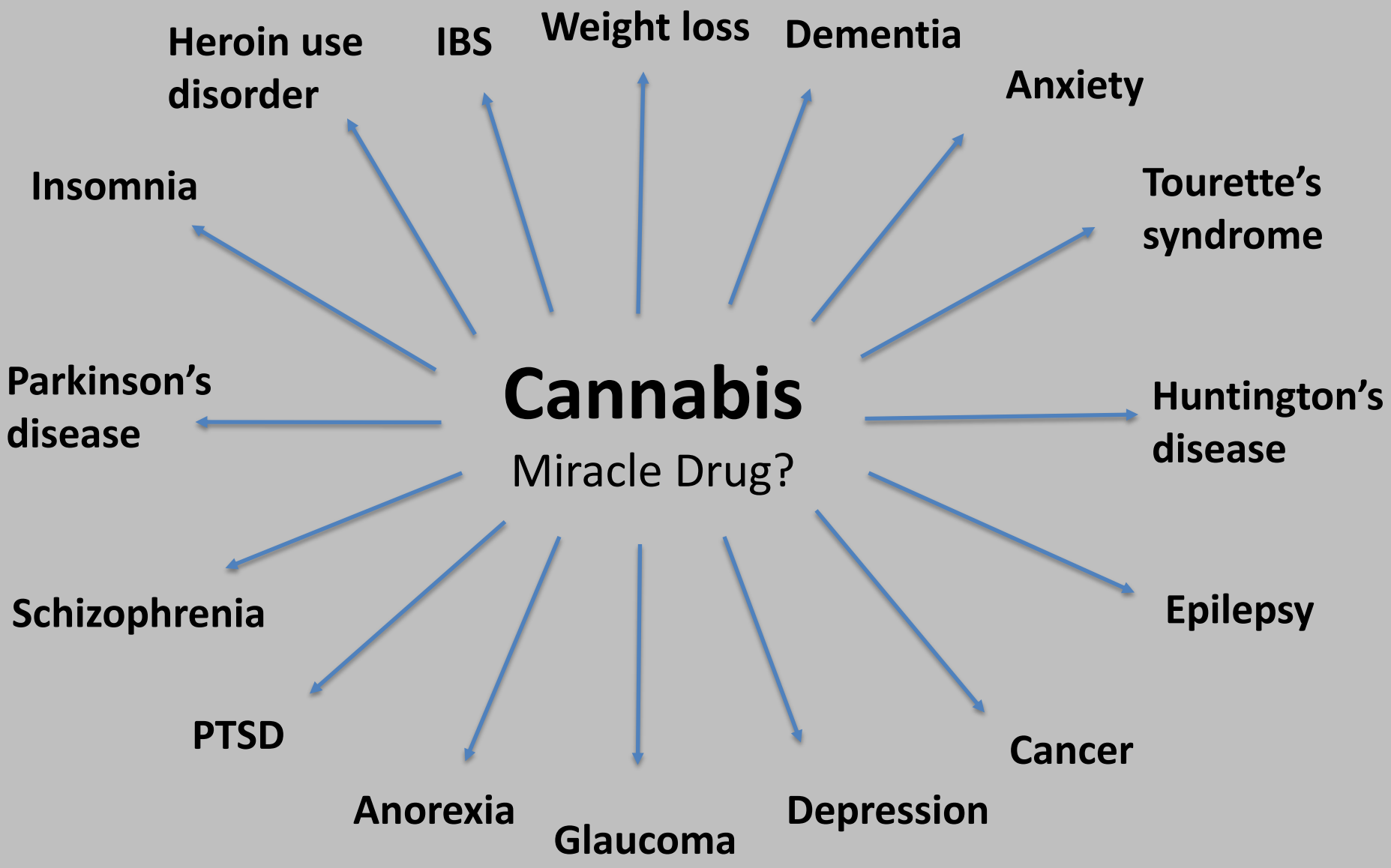
Oral-mucosal:
Most commonly a tincture (oil applied under the tongue, spray in mouth) for quick onset.

Inhalation:
Vaping ~2x more potent (smoking destroys some drug via combustion)

Topical:
May have local effects, systemic absorption unclear. CBD may be better absorbed than THC.

Ingestion:
Lower bioavailability, slower onset, longer duration vs. inhalation

Rx Cannabinoid	Generic	Brand name	Indications	Onset & Duration	Dosing	Price/30 days
	Nabilone (synthetic THC analogue)	Cesamet	Severe CINV **Off-label:** AIDS related anorexia Palliative pain Neuropathic pain	O: 60-90 min D: 8-12 h	**Initial:** 0.25-0.5mg HS **Usual:** 1-2mg QD-BID for CINV 1mg BID for NP **Usual max:** 6mg/d	$22 $112-215 $112 $310
	Nabiximols (27mg/ml THC + 25mg/ml CBD)	Sativex	- Advanced cancer pain (ajd) - MS neuropathic pain or spasticity (adj)	O: 15-40 min D: 2-4 h	**Initial:** 1 spray SL HS **Usual:** 1 spray SL Q4h **Usual max:** 12 sprays/d	$84 $504 $1008
Plant Product	Cannabis (smoked)	N/A	N/A	O: 5 min D: 2-4 h	**Initial:** 1-2 puffs HS (1 puff of joint = 1-10mg THC) **Usual:** Uncertain, titrate slow *Minimum effective dose/starting dose of THC ~2.5mg orally*	$12-24 for 1-2 puffs HS $180 for 750mg/d $720 for 3g/d
	Cannabis (vaped)	N/A	N/A	O: 5 min D: 2-4 h		
	Cannabis (oral oils)	N/A	N/A	O: 30-60 min D: 8-12 h	**Initial:** 2-3mg CBD +/- THC HS (eg. 0.1ml of 20mg/ml CBD) **Usual:** Uncertain, titrate slow	$7 (60ml bottle of oil with 1200mg CBD = $130)



Indications with Supporting Evidence[1]

- Chronic neuropathic pain
  - **NNT = 11** for ≥ 30% reduction over ~4 weeks
- Chemotherapy-induced nausea/vomiting (CINV)
  - **NNT = 3** for control of N/V over ~1 day
- Spasticity of MS or SCI
  - **NNT = 10** for ≥ 30% reduction over ~6 weeks
- Drug-resistant seizure disorders in children
  - **NNT = 4-7** for ≥ 50% reduction over ~14 weeks (CBD)
- Cachexia in HIV/AIDS, cancer & palliative care: **weak evidence**

Neuropathic pain – Cochrane Review [5]

Study Duration:

- RCTs < 1 week = RR of 1.58 (95% CI 1.13 to 2.20), **NNT = 5**
- RCTs 2-5 weeks = RR of 1.79 (95% CI 1.31 to 2.43), **NNT = 7**
- RCTs 9-15 weeks = **NS** RR of 1.07 (95% CI 0.87 to 1.32)

Type of Administration:

- Inhaled cannabinoids RR = 1.52 (95% CI 1.17 to 1.99), **NNT = 6**
- Buccal-spray RR = 1.28 (95% CI 1.02 to 1.61), **NNT = 16**

Safety Profile

THC/CBD Combination:[1]

- **~8-9/10** patients will develop an adverse effect and **~1/10** will stop therapy as a result
- Adverse effects include:
  - Feeling “high” **NNH = 4**
  - Sedation **NNH = 5**
  - Speech disorders **NNH = 5**
  - Dizziness **NNH = 5**
  - Ataxia/muscle twitching **NNH = 6**

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Pharmacodynamic Effects[1,6,7,8,9]

Cardiovascular & Cerebrovascular System	Effect observed
HR/rhythm	**Tachycardia** with acute dosage, premature ventricular contractions, Afib, ventricular arrhythmia. **Effect attributed to THC in addition to increased carboxyhemoglobin**
CO	Increased CO and myocardial oxygen demand.
MI	Increased risk of acute MI within 1h after smoking cannabis, especially in individuals with existing CV disease.
Stroke	Increased risk of stroke after an acute episode of smoking cannabis
Angina	Reduces angina threshold
Reproductive System	
Males	Chronic administration: Anti-androgenic, decreased sperm count & sperm motility, altered sperm morphology in animals.
Females	May affect fertilization, ovum transport, implantation & fetal development. More likely to have low birth weight baby.

Gastrointestinal System	Effect observed
Diarrhea	Increased in up to 20% of pts with **CBD**
Vomiting	Increased in up to 15% of pts with **CBD**
Hyperemesis	Rare, but patients should seek emergency care
Miscellaneous	
Anxiety	Mixed reviews. No association between cannabis use, development of anxiety disorders, except social anxiety disorder with regular cannabis use **THC/CBD**
Depression	Small increase in risk for developing depression (pOR 1.17), dose-response relationship **THC/CBD**
LFTs	Increased in up to 16% of pts on **CBD**
Pneumonia	Incidence up to 8% with oral **CBD**
Schizophrenia	Pooled OR 5.07 of diagnosis, may hasten first psychotic episode by 2-6 yrs with **THC/CBD**
Driving impairment	Risk of fatal car crash ~2x with **THC**

Drug Interactions & Long-term Effects[1,10]

- Affects short term memory, learning & attention, however long-term effects on cognitive decline have yet to be proven.
- Smoking affects CYP 1A2
- **Any patient using cannabis should be referred to a pharmacist for a medication review**

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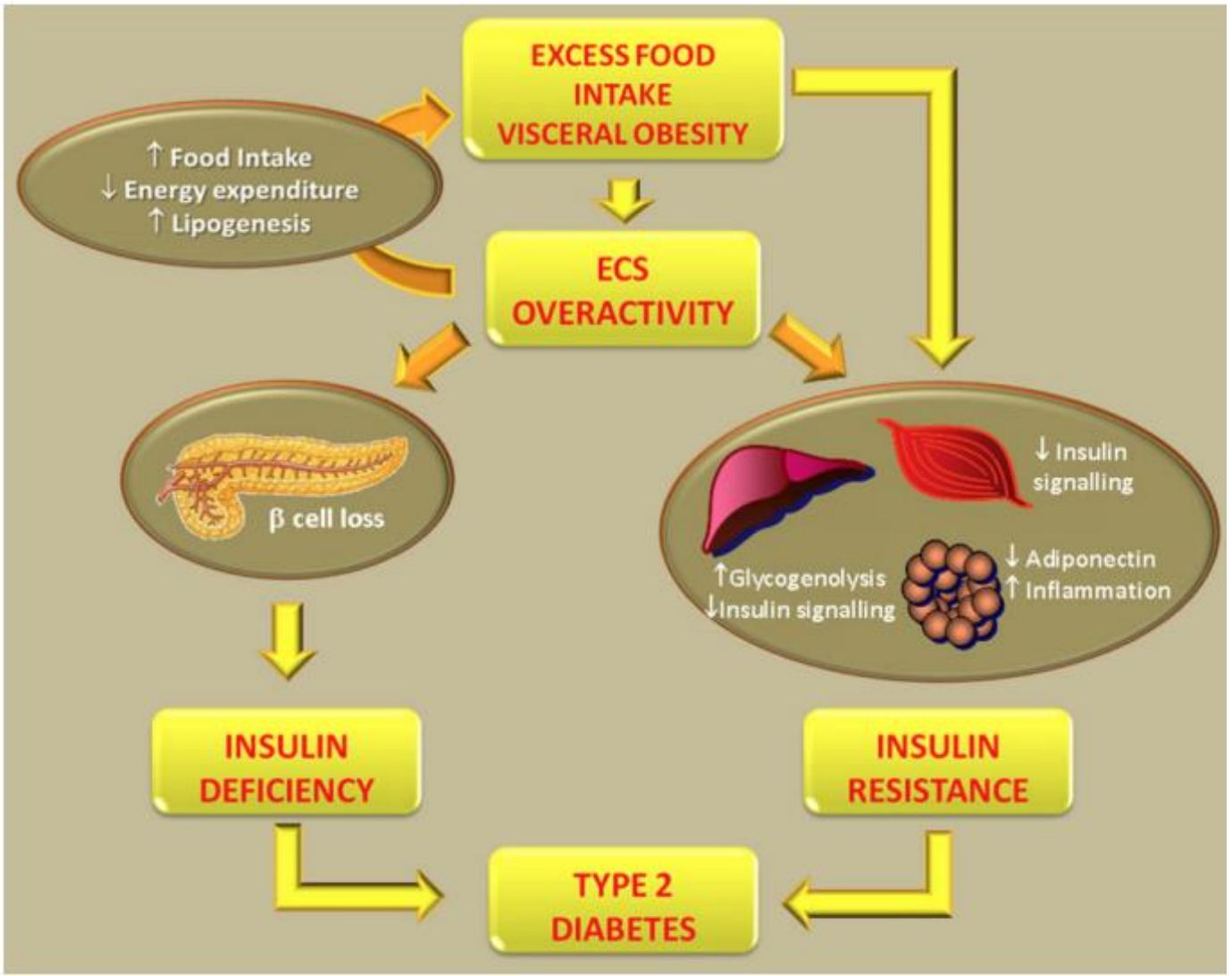
Contraindications [1,2]

- Pregnancy
- Breastfeeding
- Age <25
- Psychosis or schizophrenia history

Caution: elderly, substance abuse history, driving, other sedating meds, CV disease respirato as

Offence	Ticket	Maximum Jail
Using drugs within 2 hours of driving	Up to $1000	Up to life

Role of ECS in Diabetes [11]

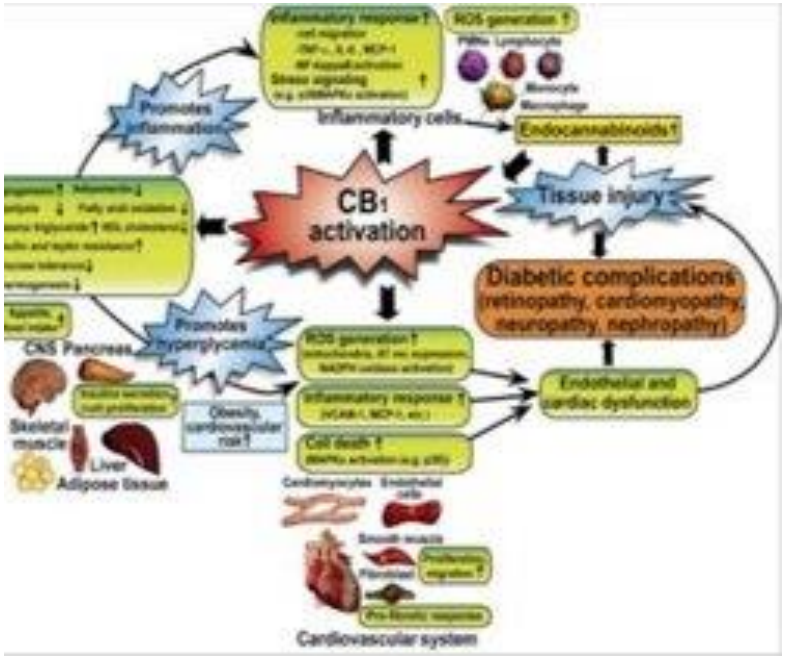


Canadian Diabetes Association Position[12]

- Cannabis use may negatively affect A1c & DKA
- Scope of review:
  - Metabolic factors & diabetes complications
  - Diabetes self-management behaviors in pts >13 y/o
- Gaps in knowledge linking cessation of cannabis use & improved outcomes
- Sufficient data to begin developing recommendations for type 1 & 2 diabetes about education, counseling & management

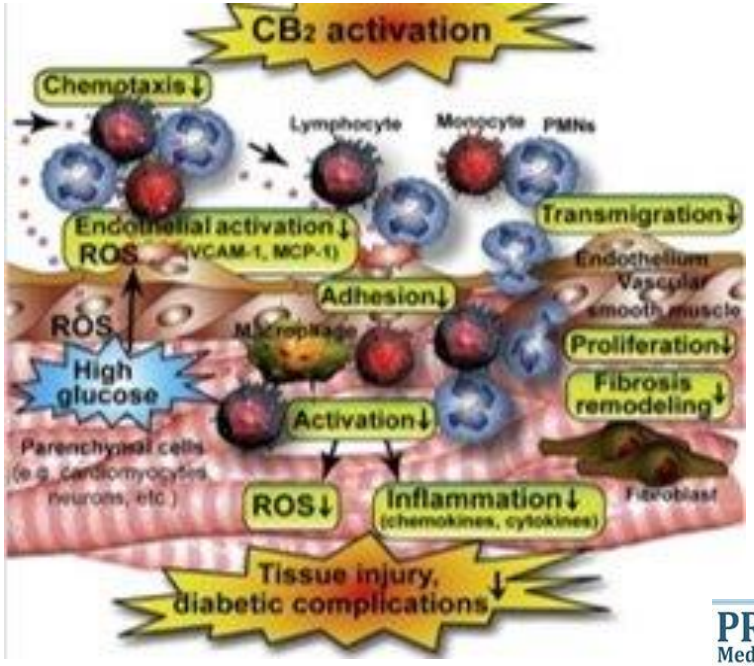
CB1 Activator[13]

- Increases insulin secretion*
- Promotes vasoconstriction, inflammatory responses & immune responses
- **Inhibition:** increases β-cell production



CB2 Blocker[13]

- Unclear role in insulin secretion
- Decreases immune responses & has been shown to reduce oxidative stress, inflammation and apoptosis after cisplatin administration.



National Cannabis Survey [14]

Highest prevalence of recreational consumption = 15-24 y/o (18%)

Cannabis use may be associated with alterations in caloric intake & BMI

Effects of recreational cannabis use on glycemic control parameters[15-19]

5 studies; 1004 participants with T1D who consumed cannabis

Statistically significant worse glycemic control

Frequency of use indicated in only 1 study

Quantification of the effect size not determined (A1c categorization vs. Mean A1c)

Effect on diabetes self-care behaviors[20]

Cross-sectional study, 138 college students with T1D aged 17-25 in the US & Canada

Self-reported substance use, diabetes self-management, most recent A1c

Students who smoked cannabis more frequently experienced higher A1c & were less likely to achieve glycemic targets

Further Evidence

Akturk & colleagues [15]

- T1D user vs. non-users
- Higher A1c (0.41%) following adjustment of insulin delivery, method, income & age

Winhusen & colleagues [21]

- Case control study >1.2 million people, 1184 T2DM pts who used cannabis
- Higher risk of diabetes complications including peripheral arterial occlusion, MI & renal disease

Akturk & colleagues [15]

- 1° outcome = DKA hospitalization in last 12 months
- T1D pts: ~2x risk of DKA (OR 1.98; 1.01-3.91)
- Possible mechanistic link that cannabinoids alter gut motility & may cause hyperemesis, leading to increased risk for DKA in T1D

Future Directions - CB1 Antagonists & CB2 Agonists[21]

- CB1 antagonist (rimonabant) has been associated with:
  - improved A1c levels
  - reduced insulin doses
  - weight loss
  - reduced TGs
  - improved HDL levels
- CB2 agonists involved in preventing inflammation & immune reactions
- Agents have yet to transition out of developmental stages

Cannabis Use Disorder (CUD)[22]

DSM V Sample Criteria

Chronic use >12 months, including*:

- Taking larger amounts for longer period than intended
- Cannot cut down
- Cravings
- Strong desire to use
- Interferes with fulfilling major obligations
- Persistent use despite side effects

Mild: 2-3 symptoms

Moderate: 4-5 symptoms

Severe: ≥6 symptoms

*List not exhaustive

Prescribing/Authorizing Cannabinoids Safely [1]

- Baseline urine drug screen
- Assess risk of addiction
- Agree on trial period (~12 wks)
  - Start with lower THC, limit to <9%
  - Avg use ~1.5-3g of herbal cannabis/day
- Use HC licensed producer
- Monitor benefits & harms
- Exit strategy
  - Taper to prevent withdrawal: ↓ 25% every week
  - After d/c, symptoms start in 1-2 days, peak 2-6 days, and disappear within 2 weeks.

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SUMMARY

- Use of cannabinoids associated with worse A1c and increases the risk of DKA[14]
- Supporting evidence only available for few indications with significant safety profile to consider
- Patients using cannabis should be referred to a pharmacist for a medication review

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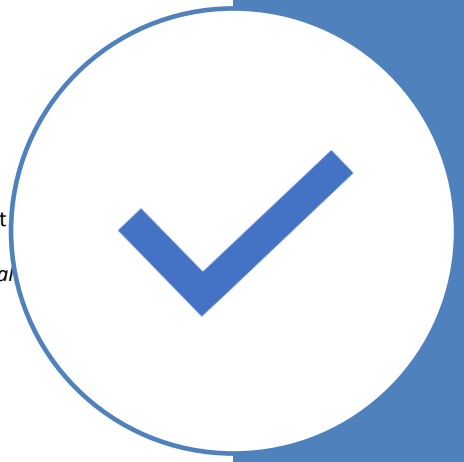


Cannabis Regulations (19+ ON)[4]

Recreational use

- **Can purchase ≤30g of dried/equivalent at a time**
- Share ≤30 g with other **adults** at a time
- Can buy (dried/fresh/oil) from provincially licensed retailer

Product	Weight (grams)	Adult limit (grams)
Dried	1	30
Fresh	5	150
Edible product*	15	450
Liquid product	70	2100
Concentrates (solid or liquid)*	0.25	7.5
Seeds	1 seed	30 seeds

*not yet available as of early 2019

Medical Use

- Patient must have a license or be registered
- Medical documentation
- Prescribed by MD or NP
- **Max single authorization = 1 yr**
- **Max quantity for possession = 30 day supply or 150g (whichever is less)**

Cannabis Plant [1,2,3]

- Cannabis *sativa*, *indica, ruderalis**
  - **Common myth:** *sativa* = energizing & *indica* = sedating
- >400 distinct compounds with >70 different phytocannabinoids
- Heating at temperatures >120 °C promotes decarboxylation (eg. TCHA → THC)
- Cannabinoid concentrations vary across:
  - Species, strains, different parts of the plant, plant's lifecycle & growing conditions

Drug Interactions to Note[1]

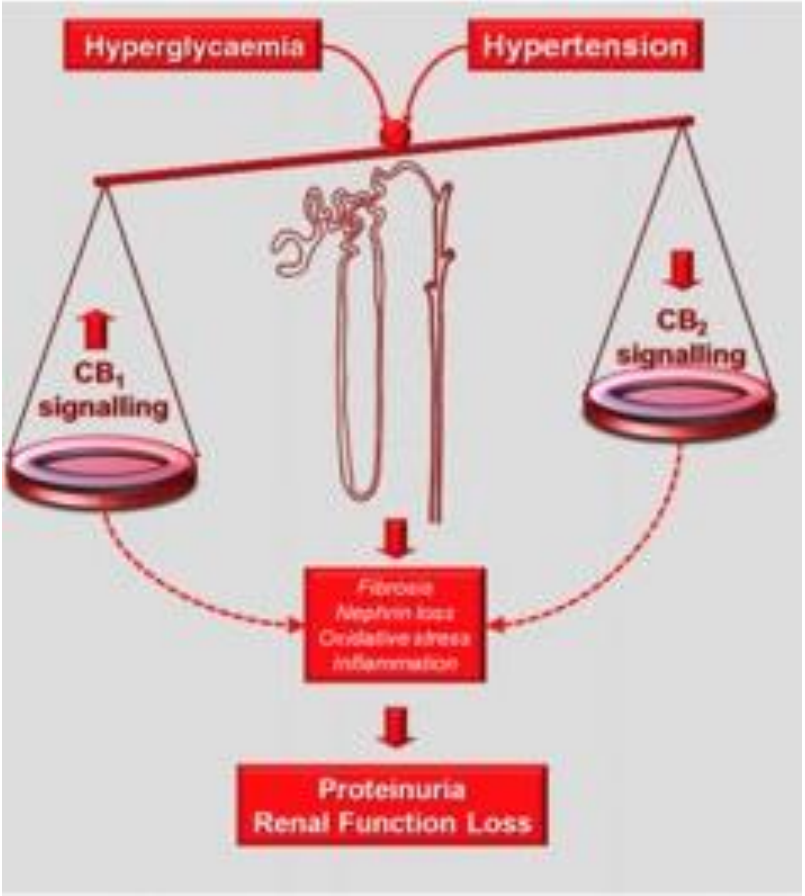
- Extensively metabolized in the liver
- CBD & THC are 2C9, 2C19 & 3A4 substrates:
  - **Inducers:** ↓ [ ] with CBZ, rifampin, SJW, phenytoin, clopidogrel
  - **Inhibitors:** ↑ [ ] with citalopram, ketoconazole, clobazam clarithromycin, fluoxetine, fluvoxamine, gemfibrozil
- Smoking cannabis induces CYP 1A2 (eg. may ↓ effect of olanzapine, chloropromazine)
- THC can inhibit 3A4, CBD can inhibit 1A2 & 2D6
- Potential additive hepatotoxicity risk with valproic acid or clobazam

ECS Role in Diabetes

- CB1 inhibition may directly attenuate inflammatory responses and ROS generation in endothelial, immune, and other cell types, as well as in target tissues of diabetic complications, far beyond its known beneficial metabolic consequences.
- CB2 agonists may exert beneficial effects on diabetes and diabetic complications by attenuating inflammatory response and ensuing oxidative stress

Effect of CB receptors on renal function

- The CB1 receptor promotes inflammation, oxidative/nitrative stress, and cell death through the activation of the p38-MAPK pathway.
- CB2 receptor agonists limit damage after cisplatin administration by reducing oxidative stress, inflammation, and apoptosis.



CASE
Kevin

- 34 y/o male with type 2 diabetes
- Last A1c 7.9%
- Poor diet, BMI = 28

Past Medication History:
- Metformin 1000mg BID
- Ozempic 1mg SC weekly

Current medication regimen:
- Jardiance 25mg QD
- Januvia 100mg QD

- **Difficulty getting his A1c <7.0%, wants to know more about medical cannabis?**

CB1 Antagonist - SERENADE Trial

- 278 drug-naive type 2 diabetic patients
- Baseline A1C (7.9%) −0.8% with rimonabant vs. −0.3% with placebo (P = 0.0002)
  - Larger effect in patients with baseline A1C ≥8.5% (P = 0.0009)
- Weight loss −6.7 kg with rimonabant vs. −2.8 kg with placebo (P < 0.0001).
- Reduction in waist circumference (−6 vs. −2 cm; P < 0.0001)
- Reduction in FBS (−0.9 vs. −0.1 mmol/l; P = 0.0012)
- Reduction in TGs & increase in HDL cholesterol
- AEs included: dizziness (10.9 vs. 2.1%), nausea (8.7 vs. 3.6%), anxiety (5.8 vs. 3.6%), depressed mood (5.8 vs. 0.7%), and paresthesia (2.9 vs. 1.4%).

How to get cannabis? [2]

Figure 1. Sample label 1
(Source: Ontario Cannabis Store)

Figure 2. Sample label 2
(Source: Ontario Cannabis Store)

In Cambridge:

- Shoppers Drug Mart
- Bodystream Medical Cannabis Clinic
- Total Medical Marijuana Clinics
- Go Greens Consulting
- Panday Group Medical Clinic

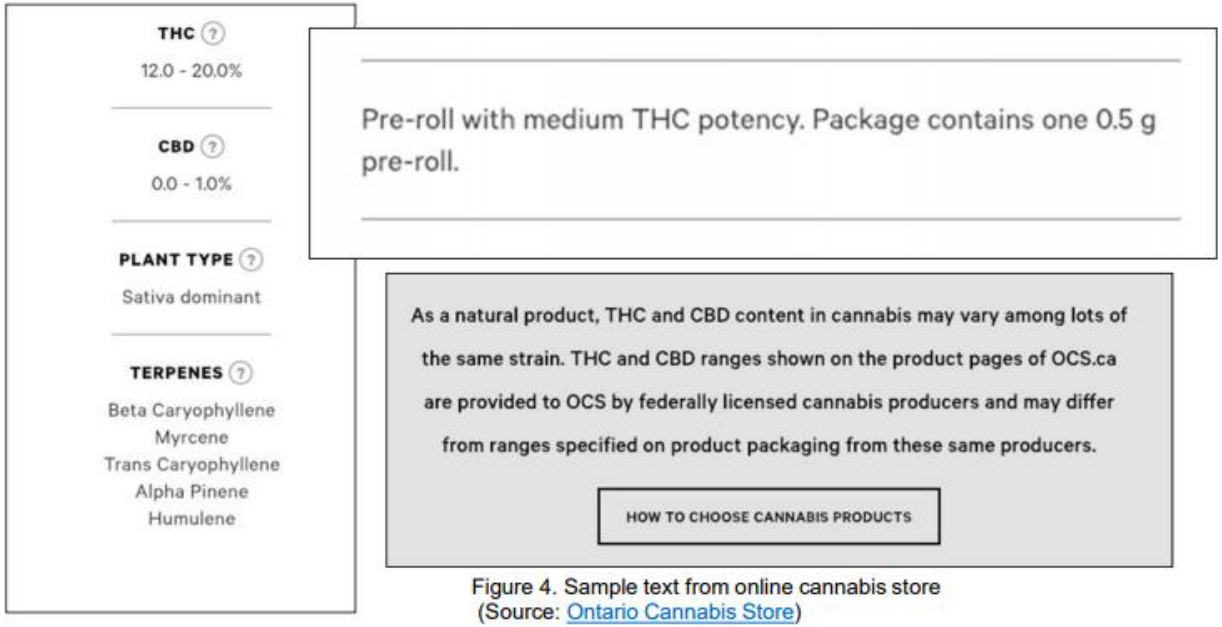


Figure 4. Sample text from online cannabis store
(Source: Ontario Cannabis Store)

Converting Between Smoked & Oral Doses[11]

"Smoked Dose"† % THC in a 750 mg cannabis cigarette (Total available mg Δ^9-THC)	Estimated Oral Dose (mg Δ^9-THC)‡
1 % THC (7.5 mg)	18.8 mg
2 % THC (15 mg)	37.5 mg
2.5 % THC (18.8 mg)	46.8 mg

	To Smoked Dose†	To Oral Dose‡
From Smoked Dose†	**Bioavailability = 25%**	**Multiply** the dose of Δ^9-THC (in mg) in the dried plant material to be smoked by a factor of 2.5 to obtain the estimated dose of Δ^9-THC (in mg) to be ingested orally. (Smoked dose in mg X 2.5 = Oral dose in mg)
From Oral Dose‡	**Divide** the dose of Δ^9-THC (in mg) to be ingested orally by a factor of 2.5 to obtain the estimated dose of Δ^9-THC (in mg) to be smoked. (Oral dose in mg ÷ 2.5 = Smoked dose in mg)	**Bioavailability = 10%**

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Past Medication History:
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- Gliclazide 60mg daily

Current medication regimen:
- Jardiance 25mg QD
- Januvia 100mg QD

- **Difficulty getting his A1c <7.0%, wants to know more about medical cannabis?**

Cohort study [17]

132 participants

Smoking cannabis weekly

Higher A1c (r=0.30, p<0.01)

Higher ACR (r=0.22 , p<0.05)

RIO Diabetes Clinical Trial

- Purpose: clarify the efficacy and safety of the CB1 antagonist RIO in obese or overweight patients with type 2 diabetes inadequately controlled by either metformin or sulfonylureas
- Intervention: CB1 antagonist RIO vs. placebo
- Results:
  - RIO treatment showed greater weight loss, reduction in waist circumference, hemoglobin A1c levels, and fasting glucose concentrations vs. placebo.
  - Significant improvement in HDL cholesterol, triglyceride, and non-HDL cholesterol levels, as well as in systolic blood pressure.

Comparing Resources

Anxiety

National Academies	Health Canada	Medical Cannabis Monograph
"There is limited evidence that cannabidiol is an effective treatment for the improvement of anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders."	Anxiety and depression are discussed in the same section: - dose-dependent effects (low = anxiolytic, high = anxiogenic - efficacy for anxiety/depression secondary to HIV/MS/neuropathic pain	Inconclusive or insufficient "Some trials have found some benefit when using CBD for the treatment of generalized anxiety disorder or social phobia" . . . "may trigger episodes of anxiety and panic"

Cannabis-based medicines compared with placebo for chronic neuropathic pain

Patient or population: adults with chronic neuropathic pain
Settings: outpatient study centres and hospitals in Europe and North America
Intervention: cannabis-based medicines (smoked cannabis; oral plant-based (dronabinol) or synthetic tetrahydrocannabinol (THC) (nabilone); oromucosal spray of THC and cannabidiol (CBD))
Comparison: placebo

Outcomes	Probable outcome with intervention 95% CI	Probable outcome with placebo	Relative effect Risk difference (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
Participant-reported pain relief of 50% or greater	209 per 1000 (196 to 222)	173 per 1000	0.05 (0.00 to 0.09)	1001 (8 studies)	⊕⊕◯◯ **low**[1,2]	NNTB 20 (11 to 100)
Patient Global Impression of Change much or very much improved	261 per 1000 (246 to 276)	211 per 1000	0.09 (0.01 to 0.17)	1092 (6 studies)	⊕◯◯◯ **very low**[1,3,4]	NNTB 11 (6 to 100)
Withdrawals due to adverse events	104 per 1000 (99 to 107)	47 per 1000	0.04 (0.02 to 0.07)	1848 (13 studies)	⊕⊕⊕◯ **moderate**[1]	NNTH 25 (16 to 50)
Serious adverse events	66 per 1000 (63 to 69)	52 per 1000	0.01 (-0.01 to 0.03)	1876 (13 studies)	⊕⊕◯◯ **low**[1,2]	NNTH not calculated
Participant-reported pain relief of 30% or greater	377 per 1000 (358 to 396)	304 per 1000	0.09 (0.03 to 0.15)	1586 (10 studies)	⊕⊕⊕◯ **moderate**[1]	NNTB 11 (7 to 33)
Specific adverse events: nervous system disorder	611 per 1000 (576 to 644)	287 per 1000	0.38 (0.18 to 0.58)	1304 (9 studies)	⊕⊕◯◯ **low**[1,3]	NNTH 3 (2 to 6)
Specific adverse events: psychiatric disorders	165 per 1000 (156 to 174)	49 per 1000	0.10 (0.06 to 0.15)	1314 (9 studies)	⊕⊕◯◯ **low**[1,3]	NNTH 10 (7 to 16)

Issues with the evidence include:

- Sample size
- Study duration
- Lack of long-term data
- Blinding
- Detection Bias
- Different strains/extracts

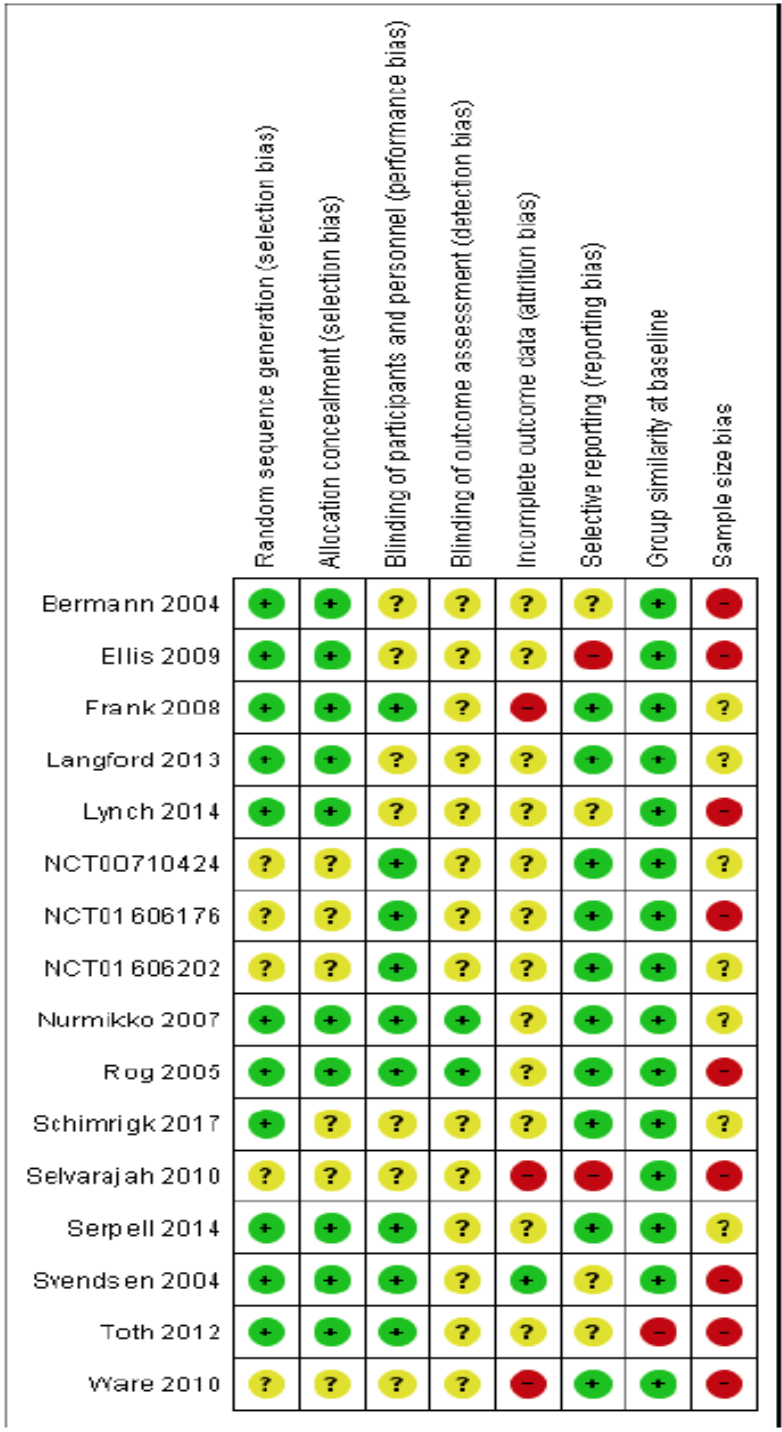
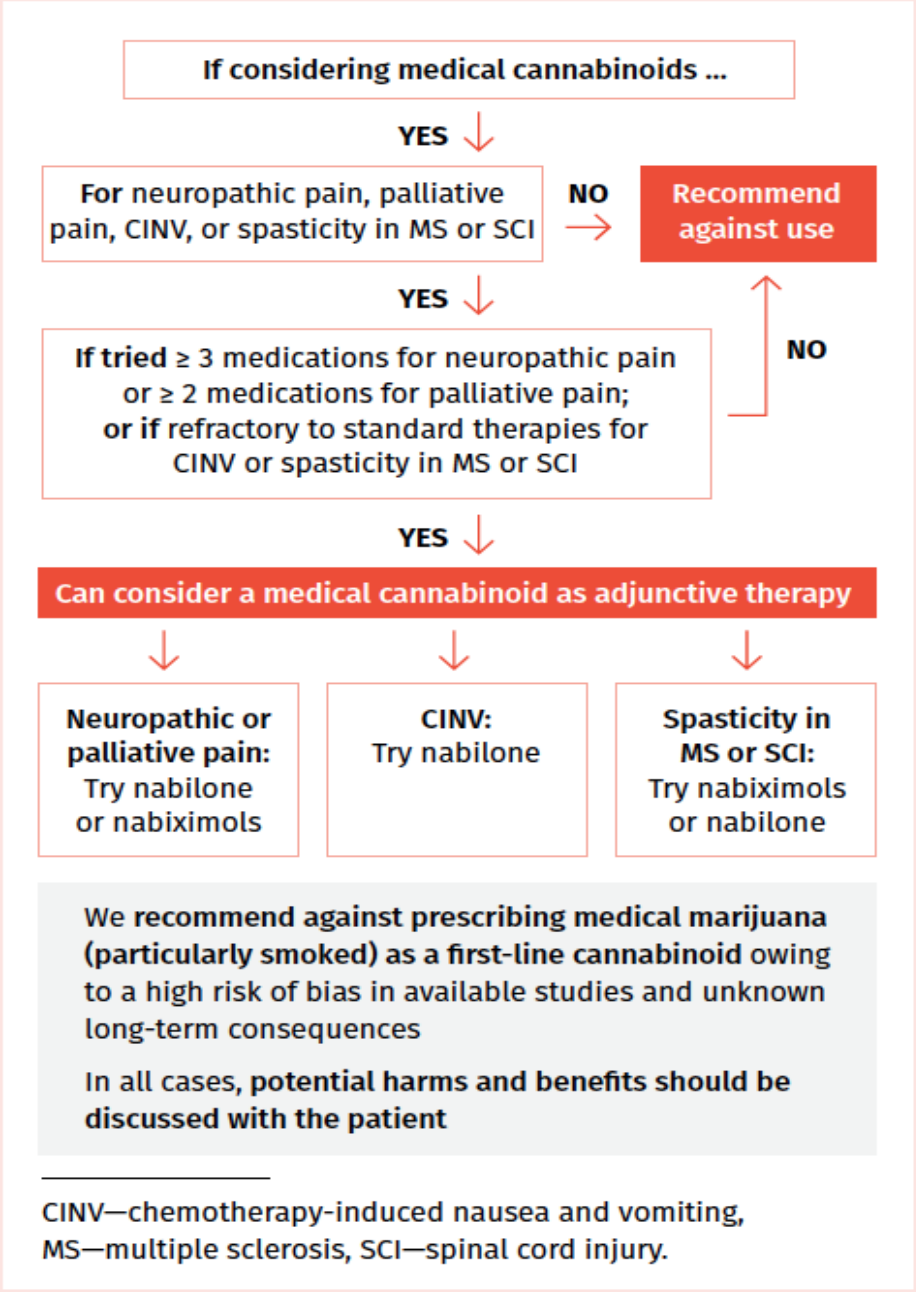


Figure 1. Medical cannabinoid prescribing algorithm



CINV—chemotherapy-induced nausea and vomiting, MS—multiple sclerosis, SCI—spinal cord injury.

KEY POINTS [13]

- Cannabinoids should not be used as 1st line options
- Cannabinoids should be used as adjunct treatment
- Cannabinoids should be trialed with appropriate monitoring & discontinuation if lack of benefit or intolerability
- Oral > vaped > smoked

Medical Document Authorizing the use of Cannabis for Medical Purposes under the Access to Cannabis for Medical Purposes Regulations

Help on accessing alternative formats, such as Portable Document Format (PDF), Microsoft Word and PowerPoint (PPT) files, can be obtained in the alternate format help section.

For related information, please see Health Canada's Information for Health Care Practitioners.

This document may be completed by the applicant's health care practitioner as defined in the Access to Cannabis for Medical Purposes Regulations (ACMPR). A health care practitioner includes medical practitioners and nurse practitioners. In order to be eligible to provide a medical document, the health care practitioner must have the applicant for the medical document under their professional treatment. Regardless of whether or not this form is used, the medical document must contain all of the required information, (see in particular s. 8 of the ACMPR).

Your health care practitioner may use this form to provide you authorization to use cannabis for medical purposes. Your health care practitioner may use a different form, but the required information as per section 8 of the ACMPR (outlined below) must be included.

Access via Health Canada licensed producers: Should you choose to access cannabis from a licensed producer, this form must be sent directly to the licensed producer of your choice. You may choose any licensed producer who is authorized to sell to registered clients. Please see the Health Canada website for a list of licensed producers. Should you wish to switch from one Health Canada licensed producer to another a new medical document will be required as licensed producers are required to keep the original medical document on file.

Access via production for own medical purposes: Should you choose to produce your own cannabis, or designate someone to produce it for you, the original of this document must be sent to Health Canada with your Registration Application Form.

Patient's Given Name and Surname:

Patient's Date of Birth (DD/MM/YYYY):

Daily quantity of dried marihuana to be used by the patient: grams / day

The period of use is day(s) or week(s) or month(s).

Note: The period of use cannot exceed one year

Health care practitioner's given name and surname:

Profession:

Health care practitioner's business address:

Canada

Full business address of the location at which the patient consulted the health care practitioner (if different than above):

Phone Number:

Fax Number (if applicable):

Email Address (if applicable):

Province(s) Authorized to Practice in:

Health Care Practitioner's Licence number:

By signing this document, the health care practitioner is attesting that the information contained in this document is correct and complete.

Health Care Practitioner's Signature: _____

Date Signed (DD/MM/YYYY):

Important Note for Authorizing Health Care Practitioner

If the patient chooses to produce cannabis for their own medical purposes or you are not submitting this document via secure fax do not initial the box below.

If your patient chooses to access cannabis for medical purposes via a licensed producer, this medical document can be submitted from the health care practitioner's office to the licensed producer by secure fax. If you choose to submit the medical document by secure fax, initial the statement below to acknowledge agreement.

I, the health care practitioner, acknowledge that the faxed medical document is now the original medical document and that I have retained a copy of this document for my records only.

Initial here:

Cannabis Use Disorder: Treatment [12]

- CBT, motivational enhancement therapy, group counselling
- Limited evidence for gabapentin & N-acetylcysteine to reduce cravings
  - Small studies & short-term
  - Little to no evidence: Bupropion, citalopram, buspirone, valproic acid
- No evidence to suggest pharmaceutical cannabis as substitution for CUD or withdrawal