Cannabis in CKD: Evidence & Clinical Management

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PRESENTER DISCLOSURE

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Relationships with competing interests: none

OUTLINE



BACKGROUND SUMMARY OF EVIDENCE CLINICAL MANAGEMENT

BACKGROUND (CANNABASICS)

Why did Canada Legalize Cannabis?

On Oct 17th, 2018 Canada became the 2nd country to legalize recreational cannabis.

Objective of legalization and creating a strict legal framework of cannabis under the *Cannabis Act*:

- 1. Displace the illegal market and keep profits out of pockets of criminals.
- 2. Protect public health and safety by allowing adults legal access.
- 3. Keep cannabis out of the hands of youth

Cannabis Legalization and Regulation [Internet]. Justice.gc.ca. 2020 [cited 6 September 2020]. Available from: https://www.justice.gc.ca/eng/cj-jp/cannabis/

What is Cannabis?

- 3 main species: Cannabis Sativa, Indica, and Ruderalis
- contains more than 500 compounds and over 100 cannabinoids.

Cannabinoid= any chemical that can bind to cannabinoid receptors in the body and brain to produce an effect.

There are 3 types:

- 1. Endocannabinoids (in the body)
- 2. Phytocannabinoids (from plants)
- 3. Synthetic cannabinoids (e.g. nabilone)

NIDA. "What is marijuana? ." *National Institute on Drug Abuse*, 13 Apr. 2020, https://www.drugabuse.gov/publications/research-reports/marijuana/what-marijuana Accessed 2 Sep. 2020.



The Human Endocannabinoid System

CBD, CBN and THC fit like a lock and key into existing human receptors. These receptors are part of the endocannabinoid system which impact physiological processes affecting pain modulation, memory, and appetite plus anti-inflammatory effects and other immune system responses. The endocannabinoid system comprises two types of receptors, CB1

THC

🕒 CBD

CBN

Tetrahydrocannabinol

Cannabidiol

Cannabinol

and CB2, which serve distinct functions in human harmand weil-being.

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Presynaptic (sending neuron) Cannabinoid

Receptor

CB1 receptors are primarily found in the brain and central nervous system, and to a lesser extent in other tissues.

CB1

CBD does not directly "fit" CB1 or CB2 receptors but has powerful indirect

effects still being studied.

CB2

CB2 receptors are mostly in the perepheral organs especially cells associated with the immune system.

Receptors are found on cell surfaces



Table 1. Physiological Effects of Δ 9-THC and CBD.^{9,10}

Δ9-THC		CBD	
•	Euphoria	•	Sedation
•	Hallucinations	•	Antidystonic
٠	Sedation	•	Antiepileptic
٠	Aggravation of psychotic states	•	Antiemetic
٠	Memory disturbance	•	Anti-inflammatory
•	Deterioration or amelioration	•	Anxiolytic
	of motor coordination	•	Antipsychotic
•	Analgesia		
٠	Orthostatic hypotension		
٠	Increase in oxygen demand		
٠	Tachycardia		
٠	Appetite stimulation		
٠	Delayed gastric emptying		
•	Antiemetic		

Can J Kidney Health Dis. 2019 Feb 22;6:2054358119828391.

The Diversity of Cannabis



- Origin: hot dry climates with long sunny days (e.g. Africa)
- Plant: long to mature.
- Ratio: high THC, low CBD.
- Effects: energizing, creative.



- Origin: harsh, dry and turbulent climates (e.g. India).
- **Plant:** grows faster than sativa.
- Ratio: low THC, high CBD.
- Effects: relaxing.

Administration Routes of Cannabis

- Smoked:
 - Joints or spliffs (cannabis +/tobacco rolled in paper)
 - Pipes and bongs
 - Blunts (fully or partially hollowed out cigar wrappers filled with cannabis)

Health Canada. About cannabis - Canada.ca [Internet]. Canada.ca. 2020 [cited 6 September 2020]. Available from: https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/about.html







Administration Routes of Cannabis

- Vaporized (heating till it is converted to gas and inhaling)
- **Dabbing** (inhaling hot vapors from heated concentrates)
- Ingested by drinking or eating (e.g. teas, baked goods, oil)

Health Canada. About cannabis - Canada.ca [Internet]. Canada.ca. 2020 [cited 6 September 2020]. Available from: https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/about.html

Outbreak of E-Cigarette Use or Vaping Associated Lung Injury (EVALI)

Dates of symptom onset and hospital admission for patients with lung injury associated with ecigarette use, or vaping — United States, March 31, 2019–February 15, 2020



Centers For Disease Control And Prevention, 2020, https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html#key-facts. Accessed 10 Sept 2020.

THC-containing e-cigarette or vape pens, particularly from informal sources were linked to most EVALI cases.

Vitamin E acetate, an additive in vaping products, is strongly linked to EVALI outbreak. Vit E when ingested does not cause harm, but when inhaled can affect lung function.

Cannabinoid Prescription Medications

• Schedule II medications (controlled substance), only 2 formulations available in Canada

Nabilone (Cesamet[®] capsules)- THC analogue

- Approved Use: severe N/V from chemo (CINV)
- Off-label use: AIDS-related anorexia, palliative or neuropathic pain (NeP)
- Onset: 60-90 mins, duration of effect: 8-12 hours
- Dosing & Cost (per 30 days):
 - Initial- 0.25-0.5mg po hs \$22-18
 - CINV- 1-2mg po daily to BID \$112-215
 - NeP- 1mg po BID \$112
 - Max- 6mg/d \$310
- Coverage: Pharmacare, occasional private insurance
- SE: drowsiness (52-66%), dizziness (59%), vertigo (52-59%), euphoria (11-38%), lack of concentration (12%), dry mouth (22-36%), visual disturbance (13%)



Cannabinoid Prescription Medications

Nabiximols (Sativex[®] oralmucosal spray) extracted THC 2.7mg/CBD 2.5mg per spray

- Approved Use: adjunctive therapy for advanced cancer pain or multiple sclerosis NeP or spasticity
- **Onset:** 20-150 mins, **duration of effect:** 6-8 hours
- Dosing & Cost (per 30 days):
 - Initial- 1 spray SL hs \$84
 - Usual- 1 spray SL q4h \$504
 - Max-12 sprays/day \$1008
- **Coverage:** none, occasional private insurance



 SE: dizziness (12-25%), drowsiness (8-15%), fatigue (13%), nausea (10-12%), Confusion (7%), vertigo (5-7%), intoxicated feeling (3%), vomiting (4-8%), dry mouth (6%), weakness (5-6%), oral mucosa ulcer (2%), oral candidiasis (3%)

SUMMARY OF EVIDENCE ON CANNABIS USE

Is there a Role for Cannabis in CKD?

Symptom burden is high in advanced CKD (stages 4 and 5):

- fatigue 81% (49-100%)
- drowsiness 75% (49-82%)
- pain 65% (38-90%)
- pruritus 61% (33-84%)
- dry skin 57% (42-72%)

The Problem with Opioids

- Can exacerbate symptoms such as nausea, anorexia, pruritus, and insomnia in CKD.
- Risk for fatal overdose, falls, and constipation
- Many active metabolites of opioids are renally excreted and can accumulate rapidly.

CKD stage 4 patients or those being treated conservatively report greater psychological symptoms such as anxiety, irritability, and depression.

Review of Cannabis Literature with a Focus on CKD



Canadian Society of Nephrology/ Société canadienne de néphrologie



CANADIAN JOURNAL OF KIDNEY HEALTH AND DISEASE Journal canadien de la santé et de la maladie rénale

Narrative Review

A Review of Cannabis in Chronic Kidney Disease Symptom Management

Canadian Journal of Kidney Health and Disease Volume 6: 1–14 © The Author(s) 2019 Article reuse guidelines: sagepub.com/journals-permissions DOI: 10.1177/2054358119828391 journals.sagepub.com/home/cjk



Claudia Ho^{1,2}, Dan Martinusen^{2,3,4}, and Clifford Lo^{2,4,5}

Due to limited studies in CKD, majority of studies identified in review were extrapolated from patients without renal impairment.

CJKHD. 2019 (6)1-14.

Focused on Conditions Common in CKD

IN SCOPE

- Non-synthetic cannabinoids
- Anorexia
- Chronic Pain
- Insomnia
- Nausea and vomiting
- Pruritus

OUT OF SCOPE

- Synthetic cannabinoids (e.g. nabilone)
- Behavioral symptoms in dementia
- Epilepsy
- Glaucoma
- Post-traumatic stress disorder
- Spasticity due to Multiple Sclerosis

Additional evidence included (non-specific to CKD)

- US National Academy of Sciences, Engineering and Medicine (NASEM).
- 2017 systematic review on "The Health Effects of Cannabis and Cannabinoids."

REPORT The Health Effects of Cannabis and Cannabinoids

The National Academies of

THE CURRENT STATE OF EVIDENCE AND RECOMMENDATIONS FOR RESEARCH



CLINICAL PRACTICE GUIDELINES

Simplified guideline for prescribing medical cannabinoids in primary care

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Abstract

Objective To develop a clinical practice guideline for a simplified approach to medical cannabinoid use in primary care; the focus was on primary care application, with a strong emphasis on best available evidence and a promotion of shared, informed decision making.

Methods The Evidence Review Group performed a detailed systematic review of 4 clinical areas with the best evidence around cannabinoids: pain, nausea and vomiting, spasticity, and adverse events. Nine health professionals (2 generalist family physicians, 2 pain management-focused family physicians, 1 inner-city family physician, 1 neurologist, 1 oncologist, 1 nuccelogist, 1 nu

Recommendations Recommendations include limiting medical cannabinoid use in general, but also outline potential restricted use in a small subset of medical conditions for which there is some evidence (neuropathic pain, palliative and end-of-life pain, chemotherapy-induced nausea and vomiting, and spasticity due to multiple sclerosis or spinal cord injury). Other important considerations regarding prescribing are reviewed in detail, and content is offered to support shared, informed decision making.

Conclusion This simplified medical cannabinoid prescribing guideline provides practical recommendations for the use of medical cannabinoids in primary care. All recommendations are intended to assist with, not dictate, decision making in conjunction with patients.

Editor's key points

This simplified prescripting guideline was developed with a primary care focus. Guideline contributors were selected based on
profession, practice setting, and location to represent a variety of key stakeholders (particularly primary care) from across the
country, as well as on the absence of financial conflicts of interest.

Although cannabinoids have been promoted for an array of medical conditions, the evidence base is challenged by bias and a lack of high-level research. Two large evidence synopses suggested that only 3 conditions have an adequate volume of evidence to inform prescribing recommendations: chronic pain, nause and vomiting, and spasticity.

• The guideline suggests that clinicians could consider medical cannabinoids for refractory neuropathic pain and refractory pain in palliative care, chemothenapy-induced nausea and vomiting, and spasticity in multiple sclerosis and spinal cord injury after reasonable trials of standard therapies have failed. If considering medical cannabinoids and criteria are met, the guideline recommends nabilone or nabizimols be tried first. Harms are generally more common than benefits are, and it is important to discuss the benefits and risks or medical cannabinoids with patients for whom they are being considered.

Vol 64: FEBRUARY | FÉVRIER 2018 4 Canadian Family Physician | Le Médecin de famille canadien 111

- The College of Family Physicians of Canada (CFPC).
- 2018 simplified guidelines for prescribing cannabinoids in primary care.

CJKHD. 2019 (6)1-14.

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. Can Fam Phys. 2018 (64)111-120.

Chronic Neuropathic Pain (NeP)

• No studies conducted in CKD patients (data extrapolated from non-CKD)

Ho et al. 2019: Non-synthetic cannabinoids have a moderate effect on reduction of NeP, which is a minimum of 30% pain reduction (systematic review of RCTs).

NASEM 2017: There is <u>conclusive or substantial evidence they are effective</u>.

CFPC 2018: We <u>recommend against medical cannabinoids as first- or second-line therapy in</u> <u>neuropathic pain</u> owing to limited benefits and high risk of harm.

Figure 2. Neuropathic pain: Pharmacotherapy treatment.

Outcome: Meaningful (approximately 30%) pain improvement Ordered by decreasing estimated efficacy



- Cannabinoids vs. placebo may ↓ chronic NeP with a NNT=11 for ≥30% reduction over 4 weeks.
- 9% of patients will experience improvement with cannabinoids, and 66% will not.

Bottom Line:

Cannabinoids have benefit in moderate reduction of NeP but should not be considered 1^{st} or 2^{nd} line. May consider if tried ≥ 3 drugs for NeP.

Can Fam Phys. 2018 (64)111-120.

*60-110 mg of oral morphine per day.

'Go to the full text of the article online and click on the CFPlus tab.

NNT= number needed to treat

Nausea and Vomiting

Chemotherapy-induced nausea and vomiting (CINV):

• No studies in CKD (data extrapolated from non-CKD).

Ho et al. 2019: Non-synthetic cannabinoids <u>may possibly be effective for CINV</u> <u>secondary to low-to-moderate emetogenic chemo regimens</u> (low quality RCTs).

NASEM 2017: There is conclusive evidence that oral cannabinoids are effective.

CFPC 2018: recommend against use of medical cannabinoids as first- or secondline therapy due to limited comparisons with first-line agents and known harms.

- For CINV, NNT=3 over ~ 1 day for cannabinoids
- Synthetic cannabinoids such as nabilone and dronabinol (not available in Canada) have comparable efficacy vs. prochlorperazine and metoclopramide for treating CINV. However cannabinoids have more adverse effects.
- Cannabinoids have not been studied for uremia-induced nausea and vomiting.

Bottom Line:

Cannabinoids may be effective in treatment of CINV but should not be considered 1st or 2nd line agents. Consider use if refractory to standard therapies for CINV.

Crawley A, LeBras M, Regier L, Jensen B. RxFiles. Saskatoon, Sask.: RxFiles; 2018. CJKHD. 2019 (6)1-14.

Anorexia and Cachexia

• Cannabinoids not studied in uremia-induced anorexia and cachexia.

Cancer-related anorexia-cachexia syndrome:

- Ho et al. 2019: Based on 1 RCT, ineffective for increasing appetite or \uparrow QoL.
- NASEM 2017: No evidence to support or refute use.

HIV associated wasting syndrome:

- Ho et al. 2019: Low quality evidence to suggest non-synthetic cannabinoids may be effective in increasing caloric intake and body weight in short-term.
- NASEM 2017: Limited evidence of effect

CJKHD. 2019 (6)1-14. 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. Bottom Line: weak and limited evidence to support use.

Insomnia

Bottom Line: Insufficient evidence to support cannabinoid use for primary insomnia.

Primary Insomnia:

• No studies in CKD (data extrapolated from non-CKD).

Ho et al. 2019:

• Insufficient evidence to support or refute use of non-synthetic cannabinoids for this indication.

NASEM 2017:

 Moderate evidence that nabiximols (Sativex) are effective for secondary insomnia (e.g. due to chronic pain, sleep apnea, fibromyalgia, multiple sclerosis).

Uremic Pruritus

Bottom Line: Insufficient evidence to support use of cannabinoids for uremic pruritus. Further investigation warranted.

Ho et al. 2019: Topical endocannabinoids may be associated with improvement of uremic pruritus in HD patients based on weak and limited evidence from a small observational study.

- Szepeitowski et al. 2015- uncontrolled observational study
 - o 23 IHD patients with mean 2.7 years of uremic pruritus
 - Intervention = cream containing N-acetylethanolamine (AEA), and Npalmitoylethanolamine (PEA) \rightarrow endogenous cannabinoids
 - At 21 days, 8 (38.1%) patients were free from itch and 17 (81%) patients had reduced xerosis.

Summary

- There is little to no evidence on medical cannabis in CKD.
- Based on extrapolated data from non-CKD population, compared to placebo, cannabinoids may be effective in reducing chronic neuropathic pain and CINV.
- Cannabinoids are not considered first- or second-line therapy for any indication and should be reserved for patients who have refractory conditions or have failed other therapies.

CLINICAL MANAGEMENI

Monitoring: Adverse Effects (AE)

- Very common and often underappreciated by patients
 - \sim 8-9 out of 10 patients will develop an AE
 - 1 in 10 patients will stop therapy due to AE
- Number needed to harm (NNH) for common AEs
 - e.g. NNH= 4 sedation

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.

Adverse Effects of the Central Nervous System

- Acute- sedation (up to 50%), dizziness (~32%), euphoria (15-35%)
- **Psychiatric disturbances** (17%, 27% with inhaled)
 - Schizophrenia unmasking, can hasten 1st psychotic episode by 2-6yrs
- Functioning- impaired memory and motivation, underachieve in education in youth, driving impairment
- **Behavioral** addiction (9% with non-medical use vs. 5.5% with opioids), irritability or agitation (9%), anger or aggression (5% with CBD)

Other Adverse Effects

Administration route matters! These AEs are specific to smoked cannabis.

- Respiratory: cough (7%), COPD, pulmonary aspergillosus, ?lung cancer (cannabis smoke contains carcinogens)
- CV: THR, postural hypotension, ? MI 1 hour after smoking, angina
- GI- dry mouth, decreased appetite (22% with CBD), ↑ appetite (28% with dronabinol) diarrhea (20%), vomiting (15% with CBD), cannabis hyperemesis syndrome (rare, severe cyclic vomiting, usually in chronic, high dose cannabis users)

Cannabis use disorder



9% of adults who use non-medical cannabis develop addiction.

In a 12 month period, watch for \geq 2 of the following:

- ↑ tolerance
- Consuming more than intended
- Unsuccessful attempts to quit
- A lot of time lost due to consuming or recovering
- Consuming despite persistent physical, psychological or social problems due to cannabis
- Failure to fulfill major roles at work, school or home
- Use in hazardous situations
- Strong cravings to consume

Screen for Contraindications

- **Patients <25 years of age** (brain not fully developed yet)
 - exposure prior to this can lead to lasting impact such as increased risk of impaired cognition, psychosis and cannabis use disorder
- Family history of psychosis

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- History of substance use disorders
- Pregnancy, contemplating pregnancy or breastfeeding
 - ↑NICU admission, ↓visual problem solving skills, & ↑stillbirth

Methods of Accessing Cannabinoids



Medical and application forms for medical cannabis can be found on the Health Canada website.





Indica-Dominant

CHARLEES ANGEL (SOUR DIESEL HYBRID)

by Redecan THC 14-17% CBD 0-0.4% (estimated potency)

\$16.97



High-THC strain (Sour Diesel hybrid) with notes of citrus and diesel.

Prominent terpenes

Caryophyllene

🔵 Humulene 💫 🔵

Myrcene

Product details Terpene Profile

Charlee Angel is an indica-dominant hybrid that resembles the Sour Diesel strain. The plant grows fast and stocky with a strong branch structure. It has an eight to eight-and-a-half week flower time and produces buds that are blanketed in white trichomes. It has a citrus aroma with overtones of diesel.

Produced in	Ontario Redecan	
Producer		
Street name	SOUR DIESEL HYBRID	
Туре	Indica-Dominant	
THC range	14-17% (estimated potency)	
CBD range	0-0.4% (estimated potency)	
Method of consumption	Inhalation	
Growing method	Greenhouse	
Harvesting method	Hand-harvested	

Where Can Patients be Referred to to Access Medical Cannabis?

- 1. Family physician (ideal for ongoing follow-up)
- 2. Private clinics (usually have additional service fees):
- Greenleaf Medical Clinic
 - Based in Langley and Abbotsford but offers telehealth
 - o (887) 513-4769, <u>https://greenleafmc.ca/</u>
- Apollo Cannabis Clinic (virtual clinic- Surrey, Abbotsford, Langley)
 - o (887) 560-9195, <u>https://apollocannabis.ca/</u>

Dosing

- No precise doses or established uniform dosing schedules for products such as fresh marijuana, smoked/vaporized marijuana, or cannabis oil.
- Start low and go slow:
 - **Dried cannabis** = 1 mg THC at HS
 - 1 puff of joint = 1 to 10 mg THC, with variability due to joint size, depth of inhalation, THC potency etc.
 - CBD oil = 2 to 3 mg PO HS
- Start on a weekend | 7 pm allows time for assessment.

Access to cannabis for medical purposes regulation – daily amount fact sheet (dosage). Health Canada. Accessed Sept 10, 2020.

Dosing

Target dose?

- THC as low as 2.5 to 3 mg/dose are associated with a therapeutic benefit and minimal psychoactivity.
- Median reported dose per day of THC (in studies) = 7 to 256 mg

Access to cannabis for medical purposes regulation – daily amount fact sheet (dosage). Health Canada. Accessed Sept 10, 2020.

Drug Interactions

- Not well studied and many are theoretical
 - \circ ? Increased INR and risk of bleeding with warfarin \rightarrow monitor
- THC and CBD have numerous CYP P450 drug interactions.
 - Both are metabolized by CYP 3A4→ strong inhibitors such as fluconazole, ketoconazole, clarithromycin, and verapamil can increase THC and CBD.
 - THC is metabolized by CYP 2C9→ inhibitors such as Septra, fluoxetine, and amiodarone can increase THC levels.

Drug Interactions

• Cannabis has many compounds besides THC and CBD and these may have unknown drug interactions → may be difficult to anticipate net effect.

Key Counseling Point:

 All cannabinoids have additive CNS effects (e.g. sedation, confusion, impairment) with alcohol, anticholinergics, anti-epileptic, benzodiazepines, opioids etc.

Consult a pharmacist if there are any concerns with drug interactions.

How to Stop a Trial of Cannabis?

- The concept of a trial of cannabis with exit strategy is important
- Optimal tapering regimen unknown, suggested regimen:
 - ↓ by 25% q 1-2 weeks as tolerated for most but if elderly, go slower (e.g. 10% q 1-2 weeks or 25% q 2-4 weeks)
- Monitor for withdrawal (onset 1-2 days, peak 2-6 days):
 - anger, aggression, appetite change, weight loss, anxiety, restlessness, cravings, sleep disturbance.
 - o May occur when used daily for weeks to months

Clinical Pearls

- Prescription cannabinoids (rather than cannabis) are preferred → standardized product approved by Health Canada, composition entirely known.
- Inhaled cannabis is NOT a preferred route due to unclear dosing, risk of adverse respiratory effects, and multi-component composition.
 - If cannabis must be used, edibles such as cannabis oil is a safer route.
 - If cannabis must be inhaled, consider vaping over smoked.

Clinical Pearls

- Use products with low THC content. High CBD: THC ratios typically carries less severe health risks (e.g. CNS effects, addiction or injuries).
- Key Counseling Point: Do not drive or operate dangerous machinery for at least 6 hours within consuming cannabinoids. Avoid combining cannabis with alcohol or sedatives.

THANK YOU Questions?

The team: Dr. Clifford Lo, PharmD Dr. Dan Martinusen, PharmD