Cannabinoid Prescribing Information 2018

Contents

Toward Optimized Practice

Alberta College of Family Physicians

Physician Learning Program

PEER Patients Experience Evidence Research

University of Alberta Faculty of Medicine & Dentistry Department of Family Medicine

Part 1: Recommendations and Policy Statements from governing and Health Organizations within Canada regarding Medical Cannabinoid Prescribing

National or Specific Province	Organization	Policy Statement	Web-link
National	College of Family Physicians of Canada	Authorizing Dried Cannabis for Chronic Pain or Anxiety	http://www.cfpc.ca/uploadedFiles/Resources/_PDFs/Authorizing%20Dried%20Cannabis%20for%20Chronic%20Pain%20or%20Anxiety.pdf
	Canadian Medical Association (CMA)	CMA Response: Health Canada's Medical Marihuana Regulatory Proposal	https://www.cma.ca/Assets/assets-library/document/en/advocacy/Proposed-Medical-Marihuana-Regulations_en.pdf
	Health Canada	Information for Health Care Professionals: Cannabis (Marihuana, Marijuana) and the Cannabinoids	http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/marihuana/med/infoprof-eng.pdf
	Government of Canada: Department of Justice	Access to Cannabis for Medical Purposes Regulations	http://laws-lois.justice.gc.ca/PDF/SOR-2016-230.pdf
	Government of Canada: Department of Justice	Marijuana for Medical Purposes Regulations	http://www.laws-lois.justice.gc.ca/PDF/SOR-2013-119.pdf
	Canadian Medical Protective Association	Medical Marijuana: Considerations for Canadian Doctors	https://www.cmpa-acpm.ca/en/advice-publications/browse-articles/2014/medical-marijuana-new-regulations-new-college-guidance-for-canadian-doctors
Alberta	College of Physicians and Surgeons of Alberta	CPSA Standard of Practice re medical marijuana	http://www.cpsa.ca/standardspractice/cannabis-for-medical-purposes/
British Columbia	College of Physicians and Surgeons of British Columbia	Cannabis for Medical Purposes	https://www.cpsbc.ca/files/pdf/PSG-Cannabis-for-Medical-Purposes.pdf
Manitoba	College of Physicians and Surgeons of Manitoba	Bylaw 11 (p.20): Standards of Practice of Medicine	http://cpsm.mb.ca/cjj39alckF30a/wp-content/uploads/ByLaws/By-Law-11.pdf

National or Specific Province	Organization	Policy Statement	Web-link
New Brunswick	College of Physicians and Surgeons of New Brunswick	Medical Act, Regulations and Guidelines: Medical Marijuana	http://www.cpsnb.org/en/medical-act-regulations-and-guidelines/guidelines/444-medical-marijuana
Newfoundland and Labrador	College of Physicians and Surgeons of Newfoundland and Labrador	Advisory to the Profession and Interim Guidelines: Marihuana for Medical Purposes	http://imis.cpsnl.ca/web/files/CPSNL%20%20Medical%20Marihuana%20%20March%202014%20rev%201_0.pdf
Nova Scotia	College of Physicians and Surgeons of Nova Scotia	Professional Standard Regarding the Authorization of Marijuana for Medical Purposes	http://www.cpsns.ns.ca/DesktopModules/Bring2mind/DMX/Download.aspx?PortalId=0&TabId=129&EntryId=52
Ontario	College of Physicians and Surgeons of Ontario	Marijuana for Medical Purposes	http://www.cpso.on.ca/Policies-Publications/Policy/Marijuana-for-Medical-Purposes
Prince Edward Island	College of Physicians and Surgeons of Prince Edward Island	Prescribing of Medical Marijuana	http://cpspei.ca/wp-content/uploads/2017/03/Marijuana-Prescribing-Nov-3016.pdf
Quebec	Collège des médecins du Québec	Guidelines Concerning the Prescription of Dried Cannabis for Medical Purposes	http://www.cmq.org/publications-pdf/p-1-2014-04-01-en-directives-concernant-ordonnance-cannabis-seche-fins-medicales.pdf?t=1455740574019
Saskatchewan	College of Physicians and Surgeons of Saskatchewan	Prescribing Medical Cannabis: Information for Patients and Physicians	http://www.cps.sk.ca/iMIS/Documents/Programs%20and%20Services/Prescribing%20Medical%20Cannabis.pdf
		Part 6: Practice Standards 19.2 Standards for Prescribing Marihuana	https://www.cps.sk.ca/iMIS/Documents/Legislation/Legislation/Regulatory%20Bylaws%20-%20August%202017.pdf
	Pharmacy Association of Saskatchewan	Medical Cannabis	http://www.cps.sk.ca/iMIS/Documents/Programs%20and%20Services/Prescription%20Review%20Program/Medical%20ParMarihuana/PAS-Medical%20Cannabis%20Summary%20(April%202017).pdf

Part 2: Summary of Provincial Legislations for Prescribing Medical Cannabis (Valid as of October 17, 2017)

Province	British Columbia	Alberta	Saskatchewan	Manitoba	Ontario
Registering Process with College	Do not need to register.	Prescribers must register with College of Physicians and Surgeons of Alberta (CPSA) to authorize (prescribe) cannabis for medicinal purposes.	Do not need to register.		
Prescription Length	Must fill out authorizing document for medical cannabis on an annual basis.		Length prescribed follows the same provincial legislations for prescriptions of controlled substances.		
Details Required	Patient Information (DOB, Health Care Number, Relevant Medical Condition) Prescriber Information (Clinic Information, Registration Number, Signature) Cannabis Usage (daily quantity of dried cannabis to be used in grams per day and the period of use)				
Keeping & Sending Documentation	Retain copy as per normal patient document keeping.	Must retain copy and send medical document to CPSA within one week of completing document.	Retain copy as per normal patient document keeping.		
Other Comments	Must assess addiction or risk of addiction using a tool.	Must follow up every 3 months once patient is stabilized.	Must have patient sign a written treatment agreement.		Must have percentage of THC marijuana contains on the medical document.
Registering Process with College	Physician must be part of a research project.	Do not need to register			

Province	British Columbia	Alberta	Saskatchewan	Manitoba	Ontario
Prescription Length	N/A	Length prescribed follows the same provincial legislations for prescriptions of controlled substances.			
Details Required	Patient Information (DOB, Health Care Number, Relevant Medical Condition) Prescriber Information (Clinic Information, Registration Number, Signature) Cannabis Usage (daily quantity of dried cannabis to be used in grams per day and the period of use)				
Keeping & Sending Documentation	Retain copy as per normal patient document keeping.				
Other Comments*			Physicians only need to specify maximum daily amount of cannabis to be used. Document gives a general guideline of patients usually requiring 1g (or less) to 5g per day.	Written patient consent form with discussion of risks of side effects. Patient must be informed that medical marijuana has not been scientifically verified.	Must assess patient risk for addiction using a risk tool.

In Quebec, medical cannabis can **only be prescribed within a **research framework**.*

Health Canada Example Medical Form Available: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/marihuana/info/med-eng.pdf

The Canadian regulations allow patients to obtain medical cannabis in one of three ways:

1. Submitting the medical document directly to a licensed commercial producer.
2. Registering with Health Canada to produce a limited amount of cannabis for one's own medical purposes.
3. Registering with Health Canada to designate someone else to produce the cannabis for them.

Note: Nurse Practitioners are not permitted to prescribe cannabis at the present time, based on the recommendations of the College & Association of Registered Nurses of Alberta.

College and Association of Registered Nurses of Alberta (CARNA). Prescribing Standards for Nurse Practitioners (NPs). June 2017. http://www.nurses.ab.ca/content/dam/carna/pdfs/DocumentList/Standards/NP_PrescribingStandards_June2017.pdf (Accessed Dec 13, 2017).

Part 3: List of Authorized Licensed Producers of Dried and Fresh Marijuana, and Cannabis Oil for Medical Purposes, last accessed October 16, 2017

The below list, generated by Health Canada under the Access to Cannabis for Medical Purposes Regulations (ACMPR), indicates licensed producers who are authorized to produce and sell to registered persons/clients who wish to access cannabis for medical purposes. Health Canada requires the following information to be completed on the Medical Document by the applicant's health care practitioner:

- Patient's name and date of birth
- Daily quantity of dried marijuana to be used by the patient
- Period of use: days, weeks or months – cannot exceed one year
- Health care practitioner's contact information and signature

Licensed Producer, Contact Information	Province*	Patient Registration	Medical Document	Allows Prescribing Clinicians to Provide Directions for Use
ABcann Medicinals Inc. 1-855-322-2266 info@abcann.ca	ON	https://www.abcann.ca/registration.php	https://www.abcann.ca/docs/ABcann-MedicalDocument.pdf	N/A
Aphria 1-844-427-4742 info@aphria.com	ON	https://aphria.ca/registration/patient/	https://aphria.ca/wp-content/uploads/2017/02/08.01.02-Aphria-Registration-Forms.pdf	N/A
Aurora Cannabis Enterprises Inc. 1-844-928-7672	AB	https://register.auroramj.com/registrations/new	https://auroramj.com/forms/medical-document.pdf	N/A
Broken Coast Cannabis Ltd. 1-888-486-7579 info@brokencoast.ca	BC	https://sign.signority.com/signRegister.html?iid=1865ee52-4558-4e49-b6ad-cd3af632d940&lang=en	https://www.brokencoast.ca/pdfs/MedicalDocBrokenCoast.pdf	N/A

Licensed Producer, Contact Information	Province*	Patient Registration	Medical Document	Allows Prescribing Clinicians to Provide Directions for Use
Canada's Island Garden Inc. 1-844-470-5500	PEI	https://canadasislandgarden.com/register/	https://canadasislandgarden.com/wp-content/uploads/2017/02/CIG-Registration-Kit-2017-02-13.zip	N/A
Canna Farms Ltd. 1-855-882-0988, info@cannafarms.ca	BC	https://www.cannafarms.ca/register	https://static1.squarespace.com/static/565211aae4b058e88fc9eb8d/t/581a4282c534a52382e3689d/1478115971523/Canna_Farms_Medical_Document_V2.0.pdf	N/A
CanniMed Ltd. 1-855-787-1577, info@cannimed.com	SK	http://files.cannimed.ca/CanniMed-Application-For-Medical-Marijuana-Form-A.pdf?l=328	http://files.cannimed.ca/CanniMed-Medical-Document.pdf?l=328	May indicate medical diagnosis and specific physician directions.
CannTrust Inc. 1-855-794-2266, customerservice@canntrust.ca	ON	https://canntrust.ca/register/	https://canntrust.ca/wp-content/uploads/2017/08/Medical-Document-28.07.2017.pdf	May indicate medical diagnosis and special instructions.
Delta 9 Bio-Tech Inc. 1-855-245-1259, info@delta9.ca	MB	https://www.delta9.ca/forms/Delta9_ApplicationForm.pdf	https://www.delta9.ca/forms/Delta9_MedicalDocument.pdf	N/A
Emblem Cannibis Corp. 1-844-546-3633	ON	https://emblemcannabis.com/online-registration/	https://emblem.blob.core.windows.net/content/2017/08/emblem-medical-document-2017.pdf	May indicate product recommendations, patient diagnosis and additional comments.

Licensed Producer, Contact Information	Province*	Patient Registration	Medical Document	Allows Prescribing Clinicians to Provide Directions for Use
Emerald Health Botanicals Inc. 1-800-757-3536, info@emerald.care	BC	https://www.emerald.care/the-emerald-experience/	https://www.emerald.care/wp-content/uploads/2016/09/cannabis-registration-medical-document.pdf	N/A
Green Relief Inc. 1-855-841-2009, clientcare@greenrelief.ca	ON	https://www.greenrelief.ca/wp-content/uploads/2017/08/GR-0010-16-Registration-Form-R6-00000002.pdf	http://www.greenrelief.ca/wp-content/uploads/2017/04/GR-0010-16-Medical-Document-R5_03.13.17.pdf	N/A
Hydropothecary 1-844-406-1852, info@thehydropothecary.com	QC	http://www.thehydropothecary.com/register	https://s3.amazonaws.com/hydropothecary-forms/Hydropothecary+-+Medical+Document+V2.2.pdf	May indicate medical condition, maximum THC %, and maximum CBD %.
Indiva Inc. 1-888-649-6686, learn@indiva.ca	ON	https://indiva.ca/media/Patient-Registraion.pdf	https://indiva.ca/media/Medical-Document.pdf	N/A
Maricann Inc. 1-844-627-4226, info@maricann.ca	ON	https://www.maricann.com/embedded-forms	https://static1.squarespace.com/static/58992d6320099e826d2aade8/t/58ff799486e6c0d96519c5a6/1493137816735/FR-1101-02.06+Medical+Document+-+ACMPR_%28EN%29.pdf	May indicate optional information after consent received from patient.
MedReleaf Corp. 1-855-473-5323, askus@medreleaf.com	ON	https://shop.medreleaf.com/register-with-medreleaf	https://shop.medreleaf.com/app/uploads/2017/06/MR_Medical_Document_may29_2017.pdf	N/A

Licensed Producer, Contact Information	Province*	Patient Registration	Medical Document	Allows Prescribing Clinicians to Provide Directions for Use
Mettrum Ltd. 1-866-920-2009, info@mettrum.com	ON	https://csr.mettrum.com/sign-up/	https://csr.mettrum.com/application/assets/pdf/Medical-en.pdf	May indicate medical diagnosis, optional notes, choice of dried or oil product, and THC %.
OrganiGram Inc. 1-855-961-9420	NB	https://www.organigram.ca/client-registration-form/	https://www.organigram.ca/assets/Uploads/Medical-Document-V2.pdf	May indicate medical condition.
Peace Naturals Project Inc. 1-888-647-3223	ON	https://secure.rightsignature.com/signers/77afa06a-347b-413b-9446-28465dda1112/sign?access_token=yxdx8FHPNaJWzzWE4L9S	https://peacenaturals.com/forms/Peace-Naturals-Medical-Form.pdf	N/A
Redecan Pharm 1-844-892-6788 info@redecan.ca	ON	https://shop.redecanpharm.ca/#/new-registration	https://www.redecan.ca/download/forms/RedeCan-Pharm_Medical-Document.pdf	N/A
THC Biomed Ltd. 1-844-842-6337 info@thcbiomed.com	BC	https://shop.thcbiomed.com/signup	http://thcbiomed.com/wp-content/uploads/2017/06/Medical-Document-English_Electronic.pdf	May indicate medical diagnosis and special instructions.
Tilray 1-844-845-7291	BC	https://customer.tilray.ca/en/Signup	https://www.tilray.ca/files/EN-MedicalDocument-Interactive-20170406.pdf	N/A

Licensed Producer, Contact Information	Province*	Patient Registration	Medical Document	Allows Prescribing Clinicians to Provide Directions for Use
Tweed Main Street 1-855-558-9333,Hi@TweedMainStreet.com	ON	https://www.tweedmainstreet.com/account/register	http://d3pmlt4a1agi09.cloudfront.net/TMS_Docs/TMS_Medical_Doc_en.pdf	May indicate diagnosis, choice of dried or oil product, and additional guidance.
WeedMD 1-844-933-3646 sendmeinformation@weedmd.com	ON	https://www.weedmd.com/register-as-a-patient-with-weedmd/	https://www.weedmd.com/forms-medical-document/	May indicate THC % limit and primary condition
Whistler Medical Marijuana Corp. 1-604-962-3440 info@wmmc.ca	BC	https://whistlermedicalmarijuana.com/register/	https://whistlermedicalmarijuana.com/wp-content/uploads/2015/02/WMMC_Registration_Package.pdf	May indicate medical diagnosis.

* AB=Alberta; BC=British Columbia; MB=Manitoba; NB=New Brunswick; ON=Ontario; PEI=Prince Edward Island; QC=Quebec; SK=Saskatchewan.

Part 4: Additional Questions from the Guideline Committee

Part 4a: Pulmonary Aspergillosis and Smoked Marijuana

Question: Have there been any cases of pulmonary aspergillosis, and if so was the cannabis smoked or vaporized?

Study Selection: Case reports and cohort studies regarding pulmonary aspergillosis and marijuana use were included.

Answer:

There is no cohort data available but there have been several case reports that involved an infection with Aspergillus species and marijuana use.[1-10] Most of these cases involved using marijuana through smoking and some cases were able to culture Aspergillus from the patient's cannabis sample.[3,10] There was one report of vaporized marijuana use. This case involved a 29-year-old male with type 1 diabetes using marijuana daily for neuropathic pain who developed pulmonary aspergillosis.[5]

In Canada, medical cannabis must adhere to quality standards as outlined on the federal government's website.[11] This includes ensuring the microbe count is below a certain threshold. Thus, the concern for aspergillosis may not apply to medical marijuana obtained legally in Canada. However, we may still want to be cautious as marijuana use is still a new concept and proper long term safety data is still lacking in this area.

References

1. Cescon DW, Page AV, Richardson S, Moore MJ, Boerner S, Gold WL. Invasive pulmonary aspergillosis associated with marijuana use in a man with colorectal cancer. J Clin Oncol. 2008 May;26(13):2214-5.
2. Gargani Y, Bishop P, Denning DW. Too many moudly joints – marijuana and chronic pulmonary aspergillosis. Mediterr J Hematol Infect Dis. 2011;3(1).
3. Llamas R, Hart DR, Schneider NS. Allergic bronchopulmonary aspergillosis associated with smoking moldy marihuana. Chest 1978 Jun;73(6):871-872.
4. Marks WH, Florence L, Lieberman J, Chapman P, Howard D, Roberts P. Successfully treated invasive pulmonary aspergillosis associated with smoking marijuana in a renal transplant recipient. Transplantation. 1996 Jun;61(12):1771-4.
5. Remington TL, Fuller J, Chiu I. Chronic necrotizing pulmonary aspergillosis in a patient with diabetes and marijuana use. CMAJ. 2015 Nov;187(17):1305.
6. Sakkour A. A 56-year-old woman with COPD and multiple pulmonary nodules. Chest 2008 Feb 1;133(2):566-569.
7. Salam AP, Pozniak AL. Disseminated aspergillosis in an HIV-positive cannabis user taking steroid treatment. Lancet Infect Dis. 2017 Aug;17(8):882.
8. Schwartz IS. Marijuana and fungal infection. Am J Clin Pathol. 1985 Aug;84(2):256.

9. Sutton S, Lum BL, Torti FM. Possible risk of invasive pulmonary aspergillosis with marijuana use during chemotherapy for small cell lung cancer. Drug Intell Clin Pharm. 1986 Apr;20(4):289-291.

10. Szyper-Kravitz M, Lang R, Manor Y, Lahav M. Early invasive pulmonary aspergillosis in a leukemia patient linked to aspergillus contaminated marijuana smoking. Leuk Lymphoma. 2001;42(6):1433-1437.

11. Health Canada. Technical Specifications for Testing Dried Marihuana for Medical Purposes. Available from: https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/marihuana/info/techni-eng.pdf. Accessed on September 1, 2017.

Part 4b: Effects Concerning Proportions of Tetrahydrocannabinoil (THC) and Cannabidiol (CBD)

Background:

Cannabidiol (CBD) is believed to have a lower risk of psychoactive properties than tetrahydrocannabinol (THC), and many individuals think that changing THC:CBD ratios, or using CBD alone, will negate some of the side effects of medical cannabinoids. There is also a belief that CBD is more effective for many symptoms. As with any claims, we must be vigilant in the use of high quality evidence for clinical decisions in the patients we treat, and not rely on proposed mechanisms of action or surrogate markers.

Question:

Does the evidence support a consistent differential effect (benefit or harm) with varying concentrations (or presence) of CBD and THC or its individual components?

Answer:

We found four RCTs that allowed comparison of THC versus CBD or CBD versus THC/CBD or THC versus THC/CBD. We also included a high-quality RCT of CBD versus placebo to assess adverse events. Evidence comparing the combination of THC/CBD to either THC or CBD alone is limited. Unfortunately, the majority of studies are severely underpowered (small sample sizes, multiple intervention arms) and often used in healthy people with a history of using, and therefore tolerating, cannabinoids.[1]

A cancer pain study[2] found that THC/CBD was more effective at achieving a 30% pain reduction compared to THC alone (43% versus 23%, fisher test p=0.045). Adverse effects were similar between the two agents and are outlined in Table 1.

Two RCTs found the efficacy of the combination of THC/CBD similar to THC alone.[3,4] First, an anorexia-cachexia RCT[3] found the combination of THC/CBD similar to THC for appetite and quality of life. Adverse events between the two agents were similar but both were significantly higher compared to placebo. Out of a total of 526 adverse effects reported, 45.2% were from the THC/CBD arm, 37.5% from the THC only arm and 17.3% from placebo. Second, a neuropathic pain RCT[4] found THC/CBD versus THC to be equally as effective for treating pain in patients with brachial nerve injury. This crossover trial found THC/CBD had a number needed to treat (NNT) of 9 versus placebo and THC had a NNT of 8 versus placebo for a 30% reduction in pain. The most commonly reported adverse events are outlined in Table 2.

Finally, a four arm 'n-of-1' trial studied THC, CBD, the combination of THC/CBD and placebo in 24 patients with stable chronic pain and unresponsive to pain management.[5] The crossover study was completed in 8 weeks with all patients using each arm for at least two, seven day periods. The authors included an open-label 14 day run-in with the combination of THC/CBD. On a weekly basis, patients were asked to compare the medication they were on to the run-in and state which was more effective with symptom control. Most patients found more effective symptom control with THC/CBD and THC alone (38% and 33%) and less response to CBD alone (17%) when compared to the run-in treatment of THC/CBD. Infrequent adverse events included time distortion (numbers not given), hallucinations (n=1), vasovagal episode (n=1), and a change in neural function (n=2; decreased reflex and loss of sensation). Most common adverse events reported and Fisher test

comparisons of agents are outlined in Table 3. The most significant limitation of this study is that 59% of patients were previous cannabis users. This leads to significant bias as most users are able to differentiate the interventions they are on and are often more tolerant to side effects. However, based on the results we see a euphoria/dysphoria less often reported when patients are using CBD only.

We found one high quality RCT that studied CBD alone compared to placebo. Devinsky et al. assessed the effect of cannabidiol (20 mg/kg) versus placebo in the management of symptoms in children and young adults (n=120) with Dravet syndrome.[6] The primary outcome, frequency of seizures, was significantly reduced in the treatment group versus placebo during the 14-week trial, compared to the 28-day baseline period (Median Difference: -22.8%; 95% CI -41.4%, -5.4%). Adverse events were more common in patients receiving cannabidiol (93%) versus those receiving placebo (75%). Specific adverse events are reported in Table 4.

Conclusion:

Overall, the evidence we found was inconclusive. One RCT found THC/CBD superior to THC alone, two RCTs found effectiveness similar for THC/CBD versus THC and one RCT found THC alone or THC/CBD superior to CBD. While it is not clear adding CBD improves effectiveness, CBD may have slightly less adverse events than THC based on one 24-person study with two weeks on therapy. In other comparison studies of THC/CBD versus THC there was no consistent difference in adverse events. In the highest quality study of CBD, it is clear CBD had more adverse events than placebo.

Based on the best available data, it is unknown if using different ratios of THC:CBD or using its individual components alone would lead to improved efficacy or reduced adverse events (compared to other cannabinoid research).

Table 1: Most commonly reported adverse events in Johnson et al.

Harm	THC:CBD N (%)	T)HC N (%	Placebo
Somnolence	8(13)	8(14)	6(10)
Dizziness	7(12)	7(12)	3(5)
Confusion	4(7)	1(2)	1(2)
Nausea	6(10)	4(7)	4(7)
Vomiting	3(5)	4(7)	2(3)
Hypotension	3 (5)	0	0

Table 2: Most commonly reported adverse events in Berman et al.

	Agent: Number of patients reported adverse event		
Adverse Events	**Placebo**	**THC**	**THC:CBD**
Dizziness	4	11	9
Somnolence	5	6	7
Dysgeusia	1	5	10
Nausea	3	5	1
Feeling Drunk	0	4	4

Table 3: Most commonly reported events and associated chi squares in Notcutt et al.

Agent	**Most Commonly Reported Adverse Events: Frequencies**		
	Dry Mouth	Drowsiness	Dysphoria/Euphoria
THC	18/24	20/24	12/24
CBD	15/24	9/24	4/24
THC:CBD	20/24	14/24	12/24
Placebo	11/24	8/24	1/24
Comparison of Agents	**Most Commonly Reported Adverse Events: Fisher Test**		
	Dry Mouth	Drowsiness	Dysphoria/Euphoria
THC	18/24	20/24	12/24
CBD	15/24	9/24	4/24
THC:CBD	20/24	14/24	12/24

*Statistically significant at $p<0.05$

Table 4: Most commonly reported events in Devinsky et al.

Harm	Cannabididiol N (%)	Placebo N (%)
Diarrhea	19 (31)	6 (10)
Vomiting	9 (15)	3 (5)
Fatigue	12 (20)	2 (3)
Pyrexia	9 (15)	5 (8)
URTI	7 (11)	5 (8)
Decreased Appetite	17 (28)	3 (5)
Convulsion	7 (11)	3 (5)
Lethargy	8 (13)	3(5)

References:

1. Johnson JR, Lossignol D, Burnell-Nugent M, Fallon MT. An open-label extension study to investigate the long-term safety and tolerability of THC/CBD oromucosal spray and oromucosal THC spray in patients with terminal cancer-related pain refractory to strong opioid analgesics. J Pain Symptom Manage. 2013 Aug;46(2):207-18.
2. Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, Fallon MT. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. J Pain Symptom Manage. 2010 Feb;39(2):167-79.
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4. Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. Pain. 2004;112(3):299-306.
5. Notcutt W, Price M, Miller R, Newport S, Phillips C, Simmons S, Sansom C. Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 'N of 1' studies. Anaesthesia. 2004 May;59(5):440-52.

6. Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. N Engl J Med. 2017 May 25;376(21):2011-2020

Part 4c: Cannabinoids for Appetite Stimulation

Question: What is the evidence on medical cannabinoids for appetite stimulation?

Study Selection: Systematic reviews were included. Three relevant articles were found.

Answer:

A 2015 systematic review identified four randomized control trials (RCTs) (n=255) comparing dronabinol either to placebo, active therapy or both for weight gain and appetite stimulation in patients with HIV/AIDS.[1] The review concluded that dronabinol use, compared to placebo, may be associated with an increase in patients' weight. One RCT comparing dronabinol to active therapy (megestrol acetate) found more weight gain with the latter. Appetite changes were assessed by visual analogue scales (VAS) in two RCTs, which found an increase in appetite with dronabinol compared to placebo. Results from the four RCTs addressed in the systematic review are presented in Table 1.

Table 1: RCTs in Systemic Review[1]

Study	Study Type Interventions	Participants Duration	Results	Biases
Abrams et. al (2003)[2] USA HIV-1	3-armed RCT Marijuana Dronabinol Placebo	n=67 21 days	Weight Gain (median, 95% CI): Marijuana: 3.0kg (0.75 to 8.6kg)* Dronabinol: 3.2kg (1.4 to 7.6 kg)* Placebo: 1.1kg (1.4 to 5.2kg)	No blinded control arm for smoked marijuana; short duration; small sample size
Timpone et. al (1997)[3] USA HIV	Open label RCT (4 arms) Megestrol acetate (M) Dronabinol	n=52 12 weeks	Weight Change (mean): M 750 mg: +6.5 +/- 1.1kg* M 750 mg+Dronabinol: +6.0 +/- 1.0kg* M 250mg+Dronabinol: -0.3 +/- 1.0kg Dronabinol: -2.0 +/- 1.3kg	Small sample size; lack of blinding; no placebo
Struwe et. al (1993)[4] USA HIV-infected males	Crossover RCT Dronabinol Placebo	n=5 5 weeks (2 week wash out)	Weight Change (median only): Dronabinol: +0.5kg Placebo: -0.7kg Caloric Intake (kcals/kg/24 hours) Dronabinol: +3.48 Placebo: +0.84 Appetite (VAS 0=extreme hunger, 100=no hunger) Dronabinol: -19.6 Placebo: -5.7	Very small sample; short study duration; unblinding (participants could identify phases of crossover)
Beal et. al (1995)[5] USA	RCT Dronabinol Placebo	n=139 (n=88 evaluated)	Appetite (VAS 0=no appetite, 100=extreme hunger): Dronabinol: 37% Increase*	Majority male (93%); 10 people in placebo group broke protocol (used marijuana) and could not be evaluated

Study	Study Type Interventions	Participants Duration	Results	Biases
AIDS		6 weeks	Placebo: 17% Increase Weight Gain (mean): Dronabinol: +0.1kg Placebo: -0.4kg	

*Statistically Significant result

A systematic review was published in 2016 to review the role of cannabinoids in palliative care.[6] For appetite-related outcomes, cannabinoids were compared to placebo and active controls. Relevant results from the four RCTs reporting on these outcomes in this systematic review are presented in Table 2.

Table 2: RCTs in Systematic Review[6]

Study	Study Type Interventions	Participants Duration	Results	Biases
Strasser et al. (2006)[7] Germany/Switzerland/ Netherlands Cancer-related anorexia-cachexia syndrome	3-armed RCT Cannabis Extract (CE) THC Placebo	n=243 6 weeks	Mean Appetite Change (VAS 0mm=worst/no appetite, 100=best): CE: 5.4mm THC: 0.6mm Placebo: 5.8mm Appetite Increase (Self-Reported): CE: 75% THC: 60% Placebo: 72%	2 week run: 289 screened, 243 enrolled; 67% follow-up over 6 weeks
Brisbois et al. (2011)[8] Canada Advanced cancer	Pilot study Dronabinol Placebo	n=21 22 days	Appetite (SLIM Appetite Score) (0=fullness, 100=extreme hunger): Dronabinol: +11.3* Placebo: -0.8 Calorie Intake: Dronabinol: +132 kcal/day Placebo: +104 kcal/day	Per-protocol analysis of those who completed the study (n=21) (n=46 randomized); small sample and short study duration; pilot study- may limit generalizability
Johnson et al. (2010)[9] Europe Cancer	3-armed RCT THC:CBD THC Placebo	n=177 2 weeks	Appetite Numeric Rating Scale (NRS 0=more hunger, 10=less hunger): THC:CBD: +0.24* THC: +0.06* Placebo: -0.59	Funded by GW Pharmaceuticals; short study duration; used patient diary data (potential for errors)

Study	Study Type Interventions	Participants Duration	Results	Biases
Jatoi et al. (2002)[10] USA Cancer	3-armed RCT Dronabinol Megestrol acetate (M) Combination therapy (Combo)	n=469 70 days (median)	Appetite Increase (Self-Reported): Dronabinol: 49% M: 75%* Combo: 66% Weight Gain >10% (Self-Reported): Dronabinol: 3% M: 11%* Combo: 8% Weight Gain >10% (Physician-Collected): Dronabinol: 5% M: 14%* Combo: 11%	Relied on self-reported data for appetite increase; short study duration; randomization and allocation concealment process not described

* Statistically Significant result

The authors concluded that due to insufficient and low-quality evidence, no recommendations on the utility of medical cannabinoids for palliative patients, including use for appetite stimulation, could be made.

Another 2016 systematic review looking at the usefulness of medical cannabinoids in gastroenterology included only one RCT examining the effectiveness of medicinal hemp for appetite stimulation in patients with Crohn's disease.[11] The RCT was a small (n=21), eight week crossover study from Israel. The authors concluded additional high-quality evidence was needed before recommendations for medicinal hemp use in gastroenterology could be made. The results of the RCT are presented in Table 3.

Table 3: RCT in Systematic Review[11]

Study	Study Type Interventions	Participants Duration	Results	Biases
Naftali et al (2014)[12] Israel Crohn's disease	RCT Cigarette with THC Cigarette without THC (placebo)	n=21 8 weeks	Appetite Increase (Numerical Rating Scale 1-7): Cannabis: +4 (No SD) Placebo: +2 (No SD)	Small sample; short duration, potential conflict of interest (author was employee of company which provided cannabis and placebo)

SD: Standard Deviation

While RCTs trend towards an increase in appetite and weight gain in patients taking medical cannabinoids (dronabinol), most are subject to serious biases, including: short study durations, underpowered sample sizes, unblinding, and lack of placebo. Secondly, many RCTs looked at

cannabinoids for appetite stimulation in HIV patients, particularly in males. This may limit the generalizability of results to other patient populations. Thirdly, dronabinol failed to cause significant weight gain in patients, when compared to active treatment. Finally, no studies examined nabilone or nabiximols, the current pharmaceutical cannabinoids available in Canada for appetite stimulation or weight gain.

In summary, weak evidence supports medical cannabinoids as an application to treat cachexia in select populations. Harms should be stressed when initiating a conversation around cannabinoid therapy.

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Part 4d: Cannabinoids for Seizures

Question: Do cannabinoids reduce seizure frequency in patients with epilepsy?

Study selection: Systematic reviews and randomized, controlled trials (RCTs) on cannabinoids and seizures or epilepsy were included. Two systematic reviews and one RCT were found.

Answer:

A 2014 Cochrane systematic review aimed to the efficacy and safety of cannabinoids for patients with epilepsy of any type.[1] The authors found four very small RCTs of low quality, including one unpublished cross-over study abstract and one letter to the editor. Sample sizes ranged from 9-15, and all used daily oral cannabidiol (CBD) 200-300mg for a duration of four weeks to six months while patients' background anti-epileptic therapy was continued. Uncontrolled temporal lobe epilepsy was the primary seizure type in the trials; however, baseline characteristics were neither reported nor compared.

The primary outcome of seizure freedom at one year or three times the longest seizure-free interval was not reported in any of the trials.[1] One RCT of 15 adult patients showed benefit for the primary outcome in four patients with CBD compared to one placebo patient; however, the time to achieve seizure freedom was not reported. Another RCT of nine patients reported two patients treated with CBD achieved seizure freedom at three months compared to zero placebo patients; however, the authors did not specify whether patients' anti-epileptic doses were changed during trial period.

The Cochrane review did not find information provided in the four included trials on the secondary outcome of ≥50% reduction in seizure frequency. Information on the additional secondary outcome of quality of life measured with objective data was also not provided in the included trials. With the exception of mild drowsiness in one controlled trial of 12 institutionalized, mentally challenged patients with frequent seizures, the authors found no difference in adverse effects in the trial reports.

Another 2014 systematic review investigated whether cannabinoids decrease seizure frequency in epilepsy.[2] Unlike the Cochrane review above, the authors found no controlled trials in the literature.

A 2017 RCT investigated the use of cannabinoids in 120 pediatric patients with treatment-resistant epilepsy and Dravet syndrome.[3] CBD significantly reduced seizure frequency by ~23% more than placebo (38.9% with cannabidiol, 13.3% placebo). However, there was no significant difference for number of patients experiencing a 50% reduction in seizures [OR 2.00 (95%CI 0.93, 4.30)]. Somnolence (36% cannabinoids vs 10% placebo), decreased appetite (28% vs 5%) and diarrhea (31% vs 10%) and fatigue (20% vs 3%) were found to be more common in patients using CBD. Potential limitations of this study include a very defined population and adjusting for unknown factors in the calculation of seizure frequency.

While there may be some evidence for CBD use in treatment-resistant pediatric Dravet syndrome, there is a lack of RCT data on the use of cannabinoids for other seizure types.

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Part 4e: Cannabinoids for Headaches

Question: Can cannabinoids be used to treat headaches?

Study Selection: Systematic reviews and randomized, controlled trials (RCTs) on the use of cannabinoids in headache were included.

Answer:

Only one RCT was found. This small (n=30) crossover RCT compared nabilone 0.5mg/day to ibuprofen 400mg/day for the reduction of pain and frequency of headache in adults with long-standing, intractable medication overuse headache (MOH).[1] After eight weeks of treatment with each, nabilone was found to be significantly more effective than ibuprofen in reducing pain intensity on Visual Analogue Scale (5.7 ± 1.9 vs 6.6 ± 2.2 on VAS, $p < 0.05$), and the number of concurrent daily analgesic therapies (0.89 ± 0.5 vs 1.34 ± 0.9, $p < 0.05$). However, 30% of the patients enrolled had MOH secondary to NSAID use, further compounding the limitations of the small sample size and short study duration.

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Part 4f: Oral Cannabinoids for Pain

Question: What is the efficacy of oral cannabinoids in chronic pain?

Study selection: The two largest randomized, controlled studies (RCT) of nabilone from the Whiting systematic review were selected.

Answer:

The first RCT was an industry-sponsored, placebo-controlled trial of 40 fibromyalgia patients.[1] Nabilone 1mg PO BID for four weeks significantly reduced pain on a 10-point VAS by ~2.04 compared to baseline. However, when the differences in baseline pain are taken into account, this translates to an actual difference of ~1.46 compared to placebo. Intention to treat was not followed, and only about 83% of patients completed the trial.

The other RCT was a cross-over, double-blind trial of 96 patients with neuropathic pain.[2]

Tablets of 250µg nabilone or 30mg dihydrocodeine were used, titrated up to a maximum of 8 tablets a day. Attaining a 10 point drop in 100mm VAS score occurred in 19% of dihydrocodeine patients compared to 5% with nabilone. Dihydrocodeine reduced pain 6mm (95% CI, 1.4mm-10.5mm) more than nabilone. Quality of life and functional assessment were generally non-significant except for two results that conflicted (one in favor or nabilone, the other dihydrocodeine) but there was no adjustment for the multiple analyses, making any of these findings unreliable. The total number of adverse events were 334 for nabilone and 305 for dihydrocodeine. Only about 73% of patients were analyzed in the results.

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Part 5: Methods & Background Treatment Comparisons for Neuropathic Pain Infographic

Outcome: Meaningful Improvement in Pain

This tool was developed using cannabinoid data from our systematic review as well as data from Cochrane reviews of other neuropathic pain medications[1-7].

This tool can be used as a visual when helping patients with neuropathic pain make treatment decisions. Each block represents 100 people with neuropathic pain being treated with the above therapy.

Yellow faces: represent those that will have a meaningful improvement in pain **without** treatment.

Green faces: represent those who will have meaningful pain improvement because of the treatment.

Red faces: represent those that will not experience meaningful benefit regardless of being on treatment.

This tool was developed to encourage shared decision-making and conversation between physicians and patients around pain management. The selected outcome of a 'meaningful improvement in pain' ensures that patients will achieve a level a pain control that has a significant impact on their daily function and quality of life.

Table 1 below outlines the associated benefits and harms of pharmacotherapy options for treating neuropathic pain.

Table 1: Pharmacotherapy for Treatment of Neuropathic Pain: Benefits and Harms

Intervention	Relative Benefit (95% CI)	% Improved (clinically meaningful)	NNT* (clinically meaningful)	Mean Change in Pain on Scales	Harms (NNH* and costs)
Amitriptyline[3]	2.0 (1.5, 2.8)[?]	39% versus 20%	6		AE* (leading to cessation) (NNH=12) ≥1 AE (NNH=6)
Desipramine[2]	5.75 (2.2,15.1)	59% versus 10%**	3		Not Reported
Imipramine[2]	19 (4.0, 90.8)	97% versus 3%**	2		
Venlafaxine[2,8]	1.69 (1.25, 2.28)	52% versus 30%**	5		AE (leading to cessation) (NNH=17) Mild AE (NNH=9)
Duloxetine[1] (Cymbalta) 60 mg daily	1.53 (1.33,1.75)	64% versus 41%†	5		AE (leading to cessation) (NNH=18)
Gabapentin[4] 1800-3600 mg daily	1.62 (1.49, 1.76)	47% versus 28%***	6		AE (leading to cessation) (NNH=31) ≥1 AE (NNH=8)
Pregabalin[5] 300mg daily	1.65 (1.34, 2.04)	45% versus 28%	6		AE (leading to cessation) (NNH=14) ≥1 AE (NNH=7)
Opioids[6]	1.71 (1.33, 2.21)	57% versus 34%††	5	Change (versus placebo) on 100-point scale: 12/100	AE (leading to cessation) (NNH=12) Constipation (NNH=4) Dizziness (NNH=8) Somnolence (NNH=7) Nausea (NNH=6) Vomiting (NNH=12)
Cannabinoids[7]	1.37 (1.14, 1.64)	39% versus 30%	11		AE (leading to cessation) (NNH=19) ≥1 AE (NNH=6)

*NNT= Number Needed to Treat; NNH= Number Needed to Harm; AE= Adverse Event

** Global Improvement of Pain of Moderate or Better

***IMMPACT outcome of at least moderate improvement

† 30% Improvement of Pain

†† 33% Improvement of Pain

[?] Calculated from "third-tier" evidence, identified as "studies containing <200 participants and/or very short duration (<4 weeks), major heterogeneity, pitfalls in allocation concealment, major attrition or incomplete outcome data"[3]

A wide variety of placebo responses were reported in the systematic reviews, therefore, to facilitate conversation with patients around treatment options for neuropathic pain, we approximated a 25% placebo response rate2-6 in neuropathic pain to simplify comparability.

For the visual patient tool, relative benefits were used with a 25% placebo effect to recalculate treatment benefits.

An RCT from Saarto et al. (2007) on venlafaxine in neuropathic pain was retracted due to falsification of data. We recalculated an estimate of venlafaxine's effectiveness by meta-analyzing three studies that used dichotomous outcomes for pain control. Outcomes included "at least moderate", "≥30%", and "≥50%" pain improvement from the 2015 Cochrane review.

When risk ratios were not reported in the systematic reviews for moderate pain improvement, we completed our own meta-analyses. This occurred for opioids, pregabalin, and gabapentin.

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Part 6: Costs and Available Strengths of Dried and Ground Marijuana, and Cannabis Oil for Medical Purposes as Listed by Select Authorized Licensed Producers in Canada, last accessed October 30, 2017.

Licensed Producer	Location	Product Catalog	Dried Cannabis ($/g, %THC, %CBD)	Ground Cannabis ($/g, %THC, %CBD)	Cannabis Oil ($/bottle, THC mg/ml CBD mg/ml)
Tilray	BC	https://www.tilray.ca/en/products/?/	$8-14, THC: 15.7-26.2, CBD: 0.1-0.4	$8, THC: 14-15.6, CBD: 0.1	$45-60/25ml, THC: 4.1-16.9, CBD: 7.1-12
Aurora Cannabis Enterprises Inc.	AB	https://auroramj.com/strains/	$9, THC: 1-20, CBD: 0-12	N/A	$90/30ml, THC: 1.2-22.3, CBD: 0-27.7
CanniMed Ltd.	SK	https://www.cannimed.ca/collections/all	$4.46 – 8.99, THC: 0.7-22, CBD: 0.5 - 13	N/A	$129-169/60ml, THC: 1-18.3, CBD: 0.2-20
Delta 9 Bio-Tech	MB	https://www.delta9.ca/our_products.html	$4.25-11, THC: 6.29-26.6, CBD: 0-9	N/A	N/A
Tweed Main Street	ON	https://www.tweedmainstreet.com/collections/available	$6-12, THC: 2.3–22, CBD: 0.7-9.6	$6-8.5, THC: 0.23-14, CBD: 0-9	$60-90/40ml, THC: 0.7-10, CBD: 10- 15
Hydropothecary	QC	https://www.thehydropothecary.com/products	$7.25-15, THC: 0.57 – 20.98, CBD: 0-14.43	$8.5-15; THC: 0.46-15.3, CBD: 0-13.9	$89/15ml, THC: 25 – 28, CBD: 0
Canada's Island Garden Inc.	PEI	https://canadasislandgarden.com/products/	$8-9, THC: 1.05-17.7, CBD: 0-12.6	N/A	N/A
OrganiGram Inc.	NB	https://www.organigram.ca/products/	$6-11, THC: 10.8-20, CBD: 0.07	N/A	$99-129/50ml, THC: 1.08-21.7, CBD: 0.5-21.7

Kahan et al, 2014 recommends the following dosing for smoked cannabis:[1]

- starting dose: 1 inhalation 9%THC "joint" once per day
- maximum dose: 1 inhalation 9%THC "joint" four times a day (400mg per day or half of a joint per day)

Given the above costs of dried cannabis, at recommended doses as per Kahan et al, 2014, the monthly cost for smoked cannabis can range from $15 to $180 (CAD). Possession limits in Canada allow patients to possess up to 150 grams of dried marijuana at one time.[2] The monthly costs associated with possessing 150 grams of dried marijuana can range from $75 to $2250 (CAD).

Conversely, monthly costs for nabilone, the synthetic oral cannabinoid in capsule formulation, range from $94 to $305 before pharmacy dispensing fees. Generic nabilone capsules are covered by most provincial drug plans in Canada. Nabiximols, the oromucosal spray available as brand Sativex® in Canada, can range from $226 to $903 before pharmacy dispensing fees. Nabiximols is not listed on the provincial drug plans in Canada.

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