CANNABINOIDS: Drug Comparison Chart [1,2]

L Regier BSP BA, B Jensen BSP Mar 2017

Cannabis contains 100s of compounds including ~70 cannabinoids, of which Delta-9-tetrahydrocannabinol (aka dronabinol or THC) is most psychoactive. Two less psychoactive cannabinoids are Delta-8-THC & cannabinol. Another active agent is cannabidiol (CBD), a potential analgesic & anti-inflammatory. These agents act at the Cannabinoid receptors (CB_1 & CB_2). General dosing considerations: start low & go slow.

GENERIC/TRADE (Strength & Formulations)	THERAPEUTIC USE/COMMENTS	CONTRAINDICATIONS CI/ADVERSE EVENTS AE/DRUG INTERACTIONS DI	INITIAL, USUAL & MAXIMUM DOSE	$/30 DAYS	ADDITIONAL INFORMATION
Dronabinol MARINOL χ⊗ PL 2.5, 5 mg cap (sesame oil) -synthetic THC **D/C 2012 in Canada** Syndros FDA'16: oral soln	✓Treat severe **N/V** from cancer chemo ✓Treat AIDS related **anorexia** **COMMENTS:** •Oral form – some abuse potential •Schedule III USA, was schedule II when available CDN •no effect on progression in progressive multiple sclerosis 104 **STORAGE:** Store in fridge	CI pregnant,breast feeding, ?sz, psychiatric hx AE N/V, ataxia, confusion, coordination problems, dizziness, somnolence, vertigo, red eyes, ↑or ↓BP, palpitations, ↑HR, flushing, panic rx, delusion of persecution, depersonalization, depression, thinking disturbance, euphoria, abuse potential DI 2C9,3A4 ↑AE: disulfiram,ethanol,fluoxetine,sedatives; ↓theophyll	**Initial**: 2.5mg po HS **Usual:** • chemo N/V: 2.5-5mg po TID-QID (~5mg/m²) • ↑ appetite: 2.5mg BID ac lunch & supper AIDS 3 **Maximum:** 20mg/d	$75 $205-505 $140 $505	**Canadian Society of Addiction Medicine Statement:** "Cannabis is classified as a **hallucinogen** in the category of psychoactive substances. Regular use is known to cause harmful health effects, including **addiction**, with its associated consequences, among susceptible individuals. Available literature & clinical experience indicate more risk than benefit in the use of cannabis products for medicinal purposes. Ongoing clinical research into possible medicinal uses of cannabis products is essential, using the same standards that are applied to any therapeutic agent before intro into general clinical practice." Oct, 1999
Marijuana [4] χ⊗ (Banji, Cannabis sativa, Grass, Pot, Weed etc.) PL Contains: •Delta-9-THC esp ♀ flowers & leaves ~9-20-30% THC, ?? **pesticides** present •Delta-8-THC, cannabinol & CBD {USA '16: 29 states & DC permit **medical;** 8 recreational use} •Average joint 0.5-1g cannabis WHO estimate •Trend towards much higher potency of products	**POSSIBLY EFFECTIVE**: ↑ appetite AIDS, ↓ glaucoma pressure, MS/neuropathic pain/spasm 118 & tics 20 (see **Category 1** MMAR list in Additional Info Column) **UNKNOWN EFFICACY**: dandruff, hemorrhoids, obesity, asthma, urinary infections, leprosy, preventing rejection after kidney transplants **COMMENTS:** •An euphoriant (recreational use). •In Canada, may be authorized to any patient for any medical indication. •Sometimes used in baking for medicinal effect without risks of smoking. •Potency/purity concern if unregulated •1 joint= ≤5 cigarettes from lung fx view 29; 70% more carcinogenic? •↑ risk of motor vehicle crashes 75	CI pregnant, breast feeding, ?seizures, ?psychiatric hx, (↑ periodontal disease) [Cannabis use & exposure to 2nd hand smoke associated with ↑ stillbirth.] AE **Psychiatric disturbance** 27% (e.g. depression, anxiety, euphoria, panic, paranoia, apathy, hallucination, ?psychosis 62,73), COMPASS headache 18%, nausea/vomit 17%, somnolence 13%, cough 7%, dry mouth, red eyes ?vision, heart 122, lung 29 & ↑ BP, ↑ weight & appetite, flashbacks, ?stroke, sedation, ?sexual problems, ?cancer testis; **gynecomastia;** ? ↑ steatosis with hepatitis C, impairment of driving accident ~ 2x as likely!, withdrawal, thrombophlebitis, hyperemesis syndrome, ↓ BMD. **Rare**: Lead adulteration to THC. DI 3A4, 2C9 ↑ AE: disulfiram, **ethanol**, fluoxetine, sleep meds. Theophylline ↓theophylline level, warfarin?	**Usual:** 65-195mg for smoking; Proposed as a daily amount •e.g. ≤ 5gram/day 10 (≤ 3gram/day for neuropathic pain) Med Let 2014 •Pain: 2.5gram/day on average (depending on THC%) via vaporizer/teas/baking (not smoking)  Hashish plant resin 16-65mg	~$10-20/gram **HC** Program ~12.5%THC $5-10/gram Production & distribution changes in progress 2014-2016 See **Regulations**. 2016: ~130,000 CDN people registered.	**REGULATIONS** **2001 to 2014**: *MMAR* → patients authorized for medicinal marijuana (e.g. compassionate end-of-life care, multiple sclerosis, spinal cord injury, cancer, AIDS, seziures) were able to grow own product at home. **2014 to 2016**: *MMPR* → any patient for any condition could be authorized for medicinal marijuana, but could only be purchased from a Licensed Producer. **Aug 2016 to ?**: *ACMPR* → see **Online Extras** 💻 for links to forms/agreements. 1. Complete medical documentation form. Complete treatment agreement form. 2. Submit documentation to Licensed Producer who delivers marijuana to pt. 3. **Or**, patients may apply to grow their own product at home (as per previous MMAR). 4. Medical documentation must be re-authorized at least once per year. 5. No set daily limit; max possession is lesser of 150g or 30 times daily amount. 6. Cannabis oil, buds, and leaves also acceptable as of July 2015. **Future regulations**: ?decriminalization fines vs criminal charges; ?legalization; ?penalties for grow-ops but not home growth; ?penalties for selling to minors ?penalties for driving while under marijuana influence
Nabilone ☎✆ **CESAMET,g** PL 0.5,1mg cap (0.25mg cap) χ✆ compound for low-dose e.g. simple syrup 5mg/50mL	✓Treat severe **N/V** from cancer chemo ☎ EDS Sask.=nausea/anorexia in AIDS **COMMENTS:** •Sleep benefit in small fibromyalgia trial[47] n=31 •Oral form – some abuse potential •Schedule II in USA & in Canada. •Not positive in urine drug screen!	CI pregnant, breast feeding, ?sz, psychiatric hx AE Drowsiness, vertigo, psych high/euphoria, dry mouth, depression, ataxia, ↑ HR, ↓ BP, blurred vision, hallucinations, sedation, headache & still an abuse potential DI ↑ AE: disulfiram, ethanol, fluoxetine, sleep meds. Theophylline ↓theophylline level	**Initial:** 0.25-**0.5mg** po HS ↑ by 0.5mg q2days **Usual:** 1-2mg daily-BID for chemo N/V **Maximum:** 6mg/day {Neuropathic pain ~2mg/day.}	$22-18g $36-61 $112-215 g $310 g $1200	
Tetranabinex/ nabidiolex [11] **SATIVEX** χ⊗ PL Buccal spray soln 10ml Natural extract contains: Delta-9-THC 2.7mg & CBD 2.5mg/spray peppermint flavour	✓**Adjunctive** relief of **advanced cancer pain**; & **MS neuropathic pain/spasticity** patients >18 years •Trial n=**66** 5week aided approval for this indication[18]; but product studied in 5 short trials with a total of 368 patients. •Trial n=38 10 wk in diabetic peripheral neuropathy; no better than placebo in patients with pain despite prior TCA tx.[54] ✓Approved as a narcotic April05 with conditions **COMMENTS:** May ↓voids/day if urinary dysfunction.[118] ✓Canada **first** country in the world to approve its use. **STORAGE:** •Unopened: Fridge •Room temp: stable 28days May help cannabis withdrawal symptoms [111]	CI allergy cannabinoids, propylene glycol, ethanol or peppermint oil, patients with severe heart, liver or kidney impairment, pregnant, ? psychiatric hx AE mouth irritation ~20% ,dizziness, ↑ HR, euphoric mood, changes in mood & concentration, drowsiness, bad taste, vertigo, reaction time DI ↑ AE: disulfiram, ethanol, fluoxetine,sleep meds. Theophylline ↓theophylline level; may ↑ levels of amitriptyline & fentanyl	**Buccal Adminstration** (Directed below the tongue/side cheek; Prime 2-3 times initially) **Initial:** 1 spray/day;↑q1-2 days Low dose: may spray into milk **Usual:** 1 spray q4h • MS: often use 4 - **5** sprays daily • Cancer: often use ≥8 sprays daily **Maximum:** ~12 sprays/day	 ~$252/vial	

New: THC 12.5mg & CBD 12.5mg/1mL in Medium Chain Triglcerides oil CANNTRUST χ ⊗ 1:1 Cannabis Drops; 40mL bottle ≈ 5g dried cannabis for about $90.

AIDS=acquired immunodeficiency syndrome **ac**=before meals **BP**=blood pressure **CBD**=cannabidiol **dx**=disease **fx**=function **HC=Health Canada HR**=heart rate **hx**=history **GP**=general practitioner **MP=** medical practitioner **MS**=multiple sclerosis **N/V**=nausea & vomiting **pt**=patient **sz**=seizures **rx**=reaction **TCA**=tricyclic antidepressant **THC**=delta-9-tetrahydrocannabinol **tx**=treatment **χ**=not Sask. formulary ⊗=not NIHB ▼=covered NIHB ☎=Exception Drug Status Sk ✆ =prior approval NIHB ♀=female ✓=official indication

BROADER CONSIDERATIONS

♦ **Pain** → based on very limited evidence: no more effective than codeine,↑AE & need larger trials [5] →cannabis may be moderately efficacious for chronic pain, benefits are offset by potential harms & complicated by the psychosocial aspects of chronic pain.[51,55] {Consideration: *Fourth line* analgesic for the tx of chronic neuropathic pain.} [50 Canadian Pain Society 2007] **Not recommended for**: age <25, substance use disorder, family hx of psychosis; smoked form not if CV or respiratory disease; mood/anxiety disorders; **MS**→modest therapeutic effect & risk of AE thus caution about using cannabinoids [7,8,9] {Small spasticity benefit & possible less disability & no major safety concerns in a 12 month CAMS MS n=502 follow up; patients felt these drugs helped their disease.} [12]

LIMITS OF THE EVIDENCE [2-4, 9, 12, 47, 51]

♦ Limited RCT's, small short trials, differing routes, forms & types of cannabinoids makes assessing efficacy almost impossible. One observational trial in patients with posttraumatic stress found an association with worse outcomes in those with ↑marijuana use.[194]

POSSIBLE APPROACH

A close review of 1) the indications, 2) what meds were previously used & 3) the context of the "therapeutic trial" of marijuana. These people should have 4) a random urine screen http://www.rxfiles.ca/rxfiles/uploads/documents/members/Urine-Drug-Screening-UDS-QandA.pdf & 5) an addictions assessment/addiction services, complete with 6) collateral information from family & others. Then 7) a focused case management discussion should be held, with all the assessors & care providers, before any decision is made. 8) Use a "treatment agreement" http://www.rxfiles.ca/rxfiles/uploads/documents/**Opiod**-Informed-Consent-And-Agreement.pdf, or see below online for Marihuana Treatment Agreement form 9) Start low dose at HS to minimize AE.
10) In the end the physician may say, " I am not comfortable prescribing smoked cannabis, because it has little evidence of efficacy for your condition & considerable evidence of harm." {Caution re driving within 6 hrs.}

Changing Legal Landscape CDN – Cautions: Potential for variety of unintended consequences {Trend towards higher potency & potential ↑ impairment; unintentional pediatric exposure common[232]; neuroplasticity; etc.}.

Cannabinoids: Online Extras 💻

Links for Prescribing of Medical Marijuana

1. Medical documentation (complete minimum of once per year, but may authorize for shorter durations): www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/marihuana/info/med-eng.pdf
2. List of Licensed Producers: www.hc-sc.gc.ca/dhp-mps/marihuana/info/list-eng.php
3. Application to grow marijuana at home: healthycanadians.gc.ca/drugs-products-medicaments-produits/buying-using-achat-utilisation/cannabis-medical/access-acces/personal-production-personnelle/index-eng.php
4. See College Bylaws below for Saskatchewan - must complete marijuana treatment agreement form (sample below). For other provinces, refer to here for guidance https://www.cmpa-acpm.ca/-/medical-marijuana-new-regulations-new-college-guidance-for-canadian-doctors

College of Physicians & Surgeons of Saskatchewan: The College's bylaw 2014-

The College's bylaw which regulates physician authorization of medical marihuana is now in effect. A summary of the bylaw follows:

1. The bylaw begins with a statement that there has not been sufficient scientific or clinical assessment to provide evidence about the safety and efficacy of marihuana for medical purposes. The bylaw begins with an acknowledgement that federal government regulations have authorized the use of marihuana for medical purposes.

2. A physician cannot authorize the use of marihuana for a patient unless the physician is also the treating physician
for the condition for which the patient is authorized to use marihuana. For example, if a patient is to be authorized to use medical marihuana to deal with symptoms of MS, the physician must also be the treating physician for the patient's MS.

3. A physician must review the patient's medical history, review relevant records pertaining to the condition for which the use of marihuana is authorized and conduct an appropriate physical examination before authorizing the patient's use of marihuana.

4. The patient must sign a written treatment agreement which contains the following:

A) A statement from the patient that the patient will not seek a prescription for marihuana from any other physician during the period for which the marihuana is prescribed;
B) A statement by the patient that the patient will utilize the marihuana as prescribed, and will not use the marihuana in larger amounts or more frequently than is prescribed;
C) A statement by the patient that the patient will not give or sell the prescribed marihuana to anyone else, including family members;
D) A statement by the patient that the patient will store the marihuana in a safe place;

5. The physician's record for the patient must include the requirements for all medical records and, in addition, contain the following:

A) The treatment agreement signed by the patient;
B) The diagnosis for which the patient was authorized to purchase marihuana;
C) A statement of what other treatments have been attempted for the condition for which the use of marihuana was prescribed and the effect of such treatments;
D) A statement of what, if anything, the patient has been advised about the risks of the use of marihuana;
E) A statement that in the physician's medical opinion the patient is likely to receive therapeutic or palliative benefit from the use of marihuana to treat the patient's condition.

6. The physician must retain a single record, separate from other patient records, which can be inspected by the College, and which contains:

A) The patient's name, health services number and date of birth;
B) The quantity and duration for which marihuana was prescribed;
C) The medical condition for which marihuana was prescribed;
D) The name of the licensed producer from which the marihuana will be obtained, if known to the physician.

7. Physicians who prescribe marihuana will be required to provide the College with the information referenced in paragraph 6:

A) Every twelve months if the physician has prescribed marihuana to fewer than 20 patients in the preceding 12 months;
B) Every six months if the physician has prescribed marihuana to 20 or more patients in the preceding 12 months.

8. The bylaw prohibits physicians from diagnosing or treating patients at the premises of a licensed producer;

9. The bylaw prohibits physicians who prescribe marihuana from having an economic or management interest in a licensed producer;

10. The bylaw prohibits physicians from storing or dispensing marihuana from any location where the physician practices medicine.

The bylaw is numbered Bylaw 19.2 of the regulatory bylaws of the College and is available at the College's website.

Sample treatment agreement to comply with the College Bylaw

I _____ understand that I will be receiving a medical document from Dr. _____ which will authorize me to purchase marihuana for a medical purpose. I agree to the following:

A) I will not seek to obtain a medical document to authorize me to purchase marihuana from any other physician during the period for which the marihuana is authorized;
B) I will utilize the marihuana as authorized in the medical document and I will not use the marihuana in larger amounts or more frequently than is authorized in the document;
C) I will not give or sell the prescribed marihuana to anyone else, including family members;
D) I will store the marihuana in a safe place;
E) I understand that if I break any of these conditions, Dr. _____ may refuse to provide any future medical authorization to purchase marihuana.

_____ _____
Patient's signature Date

Prepared by: Brent Jensen BSP, Loren Regier BSP BA for www.RxFiles.ca

Link to – Health Canada - Medical Marihuana: How to Apply: http://www.hc-sc.gc.ca/dhp-mps/marihuana/how-comment/applicant-demandeur/index-eng.php
Link to CFPC: http://www.cfpc.ca/Dried_Cannabis_Prelim_Guidance/

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1. Williamson EM, Evans FJ. Cannabinoids in clinical practice. Drugs. 2000 Dec;60(6):1303-14.
2. Use of Cannabis or Cannabinoids for Non-Malignant Chronic Pain Feb 2004. Alberta Heritage Foundation for Medical Research http://www.ahfmr.ab.ca/publications
3. Beal JE, Olson R, Laubenstein L, et al. **Dronabinol** as a treatment for anorexia associated with weight loss in patients with AIDS. J Pain Symptom Manage. 1995 Feb;10(2):89-97. n-139
4. Natural Medicines Comprehensive Database 2012
   May/09 **CNN:** The average potency of marijuana, which has risen steadily for three decades, has exceeded 10 percent for the first time, the U.S. government will report on Thursday. Scientists working for the government predict that potency, as measured by the drug's concentration of the psychoactive ingredient THC, will continue to rise. At the University of Mississippi's Potency Monitoring Project, where thousands of samples of seized marijuana are tested every year, project director Mahmoud ElSohly said some samples have THC levels exceeding 30 percent. Average THC concentrations will continue to climb before leveling off at 15 percent or 16 percent in five to 10 years, ElSohly predicted. The average THC for tested marijuana during 2008 was 10.1 percent, according to the government, compared to 1983 when it was reportedly under 4 percent. Even drugs seized at the United States' southwest border are showing increasing potency, the Office of National Drug Control Policy says. The median potency increased from 4.8 percent in 2003 to 7.3 percent in 2007. Marijuana from Mexico and other southern sources traditionally had lower THC content than other sources. http://www.whitehousedrugpolicy.gov/drugfact/marijuana/index.html
5. Campbell FA, Tramer MR, Carroll D, Reynolds DJ, Moore RA, McQuay HJ. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. BMJ. 2001 Jul 7;323(7303):13-6. Conclusion: Cannabinoids are no more effective than codeine in controlling pain and have depressant effects on the central nervous system that limit their use. Their widespread introduction into clinical practice for **pain management** is therefore undesirable. In acute postoperative pain they should not be used. Before cannabinoids can be considered for treating spasticity and neuropathic pain, further valid randomised controlled studies are needed.
6. Tramer MR, Carroll D, Campbell FA, et al. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. BMJ. 2001 Jul 7;323(7303):16-21. CONCLUSIONS: In selected patients, the cannabinoids tested in these trials **may be** useful as mood enhancing adjuvants for controlling **chemotherapy** related sickness. Potentially serious adverse effects, even when taken short term orally or intramuscularly, are likely to limit their widespread use.
7. Zajicek J, Fox P, et al.; UK MS Research Group. Cannabinoids for treatment of spasticity & other symptoms related to **multiple sclerosis** (**CAMS** study): multicentre randomised placebo-controlled trial. Lancet. 2003 Nov 8;362(9395):1517-26.n=630 15wk INTERPRETATION: Treatment with cannabinoids did **not** have a beneficial effect on **spasticity** when assessed with the Ashworth scale. However, though there was a degree of unmasking among the patients in the active treatment groups, objective improvement in mobility and patients' **opinion of an improvement in pain** suggest cannabinoids might be clinically useful.
8. Fox P, Bain PG, Glickman S, et al. The effect of cannabis on **tremor** in patients with **multiple sclerosis**. Neurology. 2004 Apr 13;62(7):1105-9. n=14 Cannabis extract does **not** produce a functionally significant improvement in MS-associated **tremor**.
9. Smith PF. The safety of cannabinoids for the treatment of **multiple sclerosis**. Expert Opin Drug Saf. 2005 May;4(3):443-56. Conclusion: given the modest therapeutic effects of cannabinoids demonstrated so far, & the risk of long-term adverse side effects, there is reason to be **cautious about their use** in the treatment of MS.
10. Marijuana Medical Access Division, Drug Strategy & Controlled Substances Program, AL: 3503B, Ottawa, On K1A 1B9 **1-866-337-7705**) or the **website** http://www.hc-sc.gc.ca/dhp-mps/marihuana/index-eng.php -Forms **B1** & **B2** & **Daily** Amount Fact Sheet Info for Health care professionals: www.hc-sc.gc.ca/dhp-mps/marihuana/how-comment/medpract/infoprof/information_e.html
    Marijuana Stakeholder **statistics** from Health Canada: http://www.hc-sc.gc.ca/dhp-mps/marihuana/stat/index-eng.php
    Marihuana for Medical Purposes Regulations- **MMPR**- http://www.laws-lois.justice.gc.ca/eng/regulations/SOR-2013-119/
11. Sativex Fact sheet Health Canada http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/sativex_factsheet_e.pdf Trial Info at www.gwpharm.com **& www.ccohta.ca**
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    http://www.rcplondon.ac.uk/pubs/books/cannabis/cannabis_summary.pdf
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16. Fergusson DM, Poulton R, Smith PF, Boden JM. Cannabis and psychosis. BMJ. 2006 Jan 21;332(7534):172-5.
17. Burns TL, Ineck JR. Cannabinoid analgesia as a potential new therapeutic option in the treatment of chronic pain. Ann Pharmacother. 2006 Feb;40(2):251-60. Epub 2006 Jan 31.
18 Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology. 2005 Sep 27;65(6):812-9.
19. Fergusson DM, Poulton R, Smith PF, Boden JM. Cannabis and psychosis. BMJ. 2006 Jan 21;332(7534):172-5.
20. Muller-Vahl KR. Cannabinoids reduce symptoms of Tourette's syndrome. Expert Opin Pharmacother. 2003 Oct;4(10):1717-25.
21. Mehra R, Moore BA, Crothers K, Tetrault J, Fiellin DA. The association between marijuana smoking and lung cancer: a systematic review. Arch Intern Med. 2006 Jul 10;166(13):1359-67.
22. Nabilone for Chemotherapy induced nausea & vomiting. Medical Letter Dec 4/18, 2006.
23. Lynch ME, Young J, Clark AJ. A case series of patients using medicinal marihuana for management of chronic pain under the Canadian Marihuana Medical Access Regulations. J Pain Symptom Manage. 2006 Nov;32(5):497-501. n=30 Doses of marihuana ranged from less than 1 to 5g per day via the smoked or oral route of administration. Ninety-three percent of patients reported moderate or greater pain relief. Side effects were reported by 76% of patients, the most common of which were increased appetite and a sense of well-being, weight gain, and slowed thoughts. (Ave dose = 2.5g/day).
24. Collin C, Davies P, Mutiboko IK, Ratcliffe S; Sativex Spasticity in MS Study Group. Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. Eur J Neurol. 2007 Mar;14(3):290-6. (n=189 6 weeks) The primary efficacy analysis on the intention to treat (ITT) population (n = 184) showed the active preparation to be significantly superior (P = 0.048). Secondary efficacy measures were all in favour of active preparation but did not achieve statistical significance. The responder analysis favoured active preparation, 40% of subjects achieved >30% benefit (P = 0.014). Eight withdrawals were attributed to adverse events (AEs); six were on active preparation and two on placebo. We conclude that this CBM may represent a useful new agent for treatment of the symptomatic relief of spasticity in MS.
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28. Pharmacist's Letter. **Sativex** for Advanced Cancer Pain. Sept 2007.
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