Medical Cannabis for Pain: an Approach

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CSHP AGM

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Some slides adapted from Mike Boivin, BScPhm, CDE, CTE, CTH, (with permission)

Presenter Disclosure

- Presenter's Name: Roland Halil

- I have the Relationships with commercial interests:
  - Speaker/Consulting Fees: Invited Speaker at:
    - Walmart conference in Toronto, ON (Apr 2017)
    - Costco conference in Toronto, ON (May 2017)
  - Other:
    - Consultant with the Foundation for Medical Education at McMaster University (PBSG module consultant & reviewer)
    - Occasional consultant with Rxfiles
      - (Both are non-profit organizations)

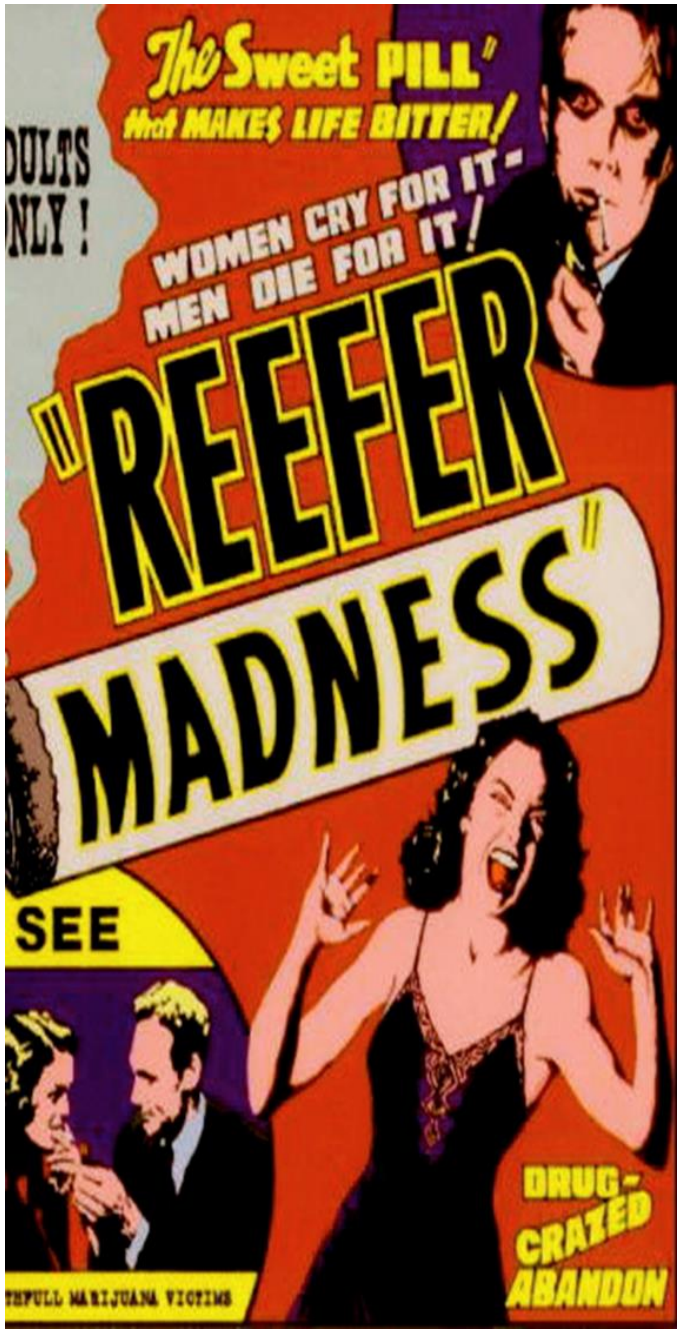
- Speaking Fees for current program:
  - I have received a speaker's fee from [CSHP] for this learning activity

Commercial Support Disclosure

- This program has received no financial or in-kind support from any commercial or other organization

Objectives

- Describe the regulatory framework around medical cannabis
- Describe the pharmacology of cannabis
- Describe an approach to prescribing and managing patients using medical cannabis
- Consider medical cannabis for a range of pain cases and manage therapy appropriately



History of Cannabis

- Used medicinally for >4000 yrs
- 1800's: for pain, vomiting, convulsions, spasticity
- 1920's: changed to *Marijuana*
  - more "un-American"
  - illegal since 1920's
- Canadian legislation uses *marihuana* spelling

Bostwick JM. Blurred Boundaries: The Therapeutics and Politics of Medical Marijuana. *Mayo Clin Proc*. 2012;87(2):172-186. doi:10.1016/j.mayocp.2011.10.003

Cannabis Regulation

2001 → **2014** → **2016** → **2018**

MMAR

Health Canada

MMPR

ACMPR

Legalization of *recreational* / OTC cannabis

Ref: A timeline of some significant events in the history of marijuana in Canada. The Canadian Press, 2014. http://cponline.thecanadianpress.com/graphics/2014/medical-marijuana-timeline/ Accessed Oct 24, 2017

21st Century: **MMAR**

Legal Rx therapy

[via Health Canada]

2014: **MMPR**

Legal Rx therapy

[via MD]

ACMPR will remain in effect for at least 5 more years (2018-2023)

(w/ same excise tax as recreational users; ~ $1/g)

Legal Rx therapy

[via MD]

20th Century:

Illegal CAM therapy

3000 B.C. to 1920 A.D.:

CAM tx

2018:

OTC Recreational/Medical &

Rx Medical strains

CAM: Complementary & Alternative Medicines

Health Canada Santé Canada

Your health and safety… our priority. *Votre santé et votre sécurité… notre priorité.*

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

Patient's Given Name and Surname:
Patient's Date of Birth (DD/MM/YYYY):
Daily quantity of dried marihuana to be used by the patient: grams / day
The period of use is ____day(s) _____week(s) _____month(s).

Note: The period of use cannot exceed one year

Health care practitioner's given name and surname:
Profession:
Heal
Full
(if di
Phor
Fax
Ema
Prov
Health Care Practitioner's Licence number:

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

Health Care Practitioner's Signature:
Date Signed (DD/MM/YYYY):

Health Canada requires LPs to publish an "**Equivalency Factor**" – to calculate the No. of grams of cannabis converted as **oil**
Eg. 1 gram dried cannabis = 3mL to 10 mL of cannabis oil (depending on brand)

Authorization

(Not a Rx)

No strength listed, only:

1. # of grams/day
2. Duration of therapy

- Maximum: 1 year
- Quantity: 30 days or 150 grams

Ref: Medical Document Authorizing the use of Cannabis for Medical Purposes under the Access to Cannabis for Medical Purposes Regulations. Health Canada. Date modified: 2017-03-23. https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-use-marijuana/licensed-producers/sample-medical-document-marihuana-medical-purposes-regulations.html Accessed Oct 24, 2017

Cannabis

Cannabis

Common hemp

Scientific classification

Kingdom:	Plantae
Clade:	Angiosperms
Clade:	Eudicots
Clade:	Rosids
Order:	Rosales
Family:	Cannabaceae
Genus:	***Cannabis*** L.

Species[1]

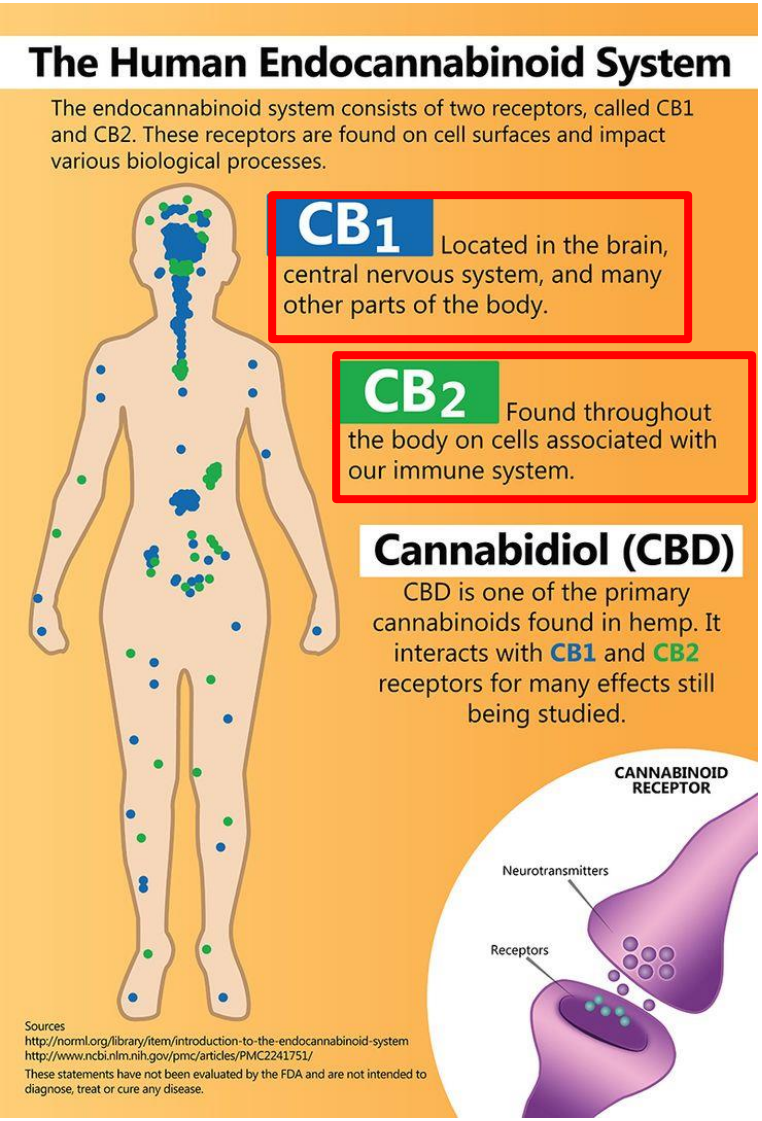
- *Cannabis sativa* L.
- *Cannabis indica* Lam.
- *Cannabis ruderalis* Janisch

- Over **100** different cannabinoids
  - Produced by trichomes in female plant (w/ terpenes & flavonoids)
1. **THC** (Δ-9 Tetrahydrocannabinol)
   - Main psychoactive agent
2. **CBD** (Cannibidiol)
   - Main non-psychoactive agent
   - May boost or block THC
- Average concentration (1980-1997):
  - THC = 3.1%
  - CBD = 0.3%

SATIVA INDICA

1. 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. doi:10.17226/24625.
2. University of Washington Alcohol & Drug Abuse Institute · Updated 6/2013 http://LearnAboutMarijuanaWA.org/factsheets/potency.htm Accessed Oct 24/2017

Endocannabinoid System



CB1 receptor	• Receptor in most organ systems • High distribution in CNS in areas – pleasure, movement, memory, learning and pain centers
CB2 receptor	• Mostly found in immune system • < CB1 • Thought to provide a general protective mechanism

Abramovici H, Chief H-O, Bureau R, et al. Information for Health Care Professionals. http://www.hc-sc.gc.ca/dhp-mps/marihuana/med/infoprof-eng.php .

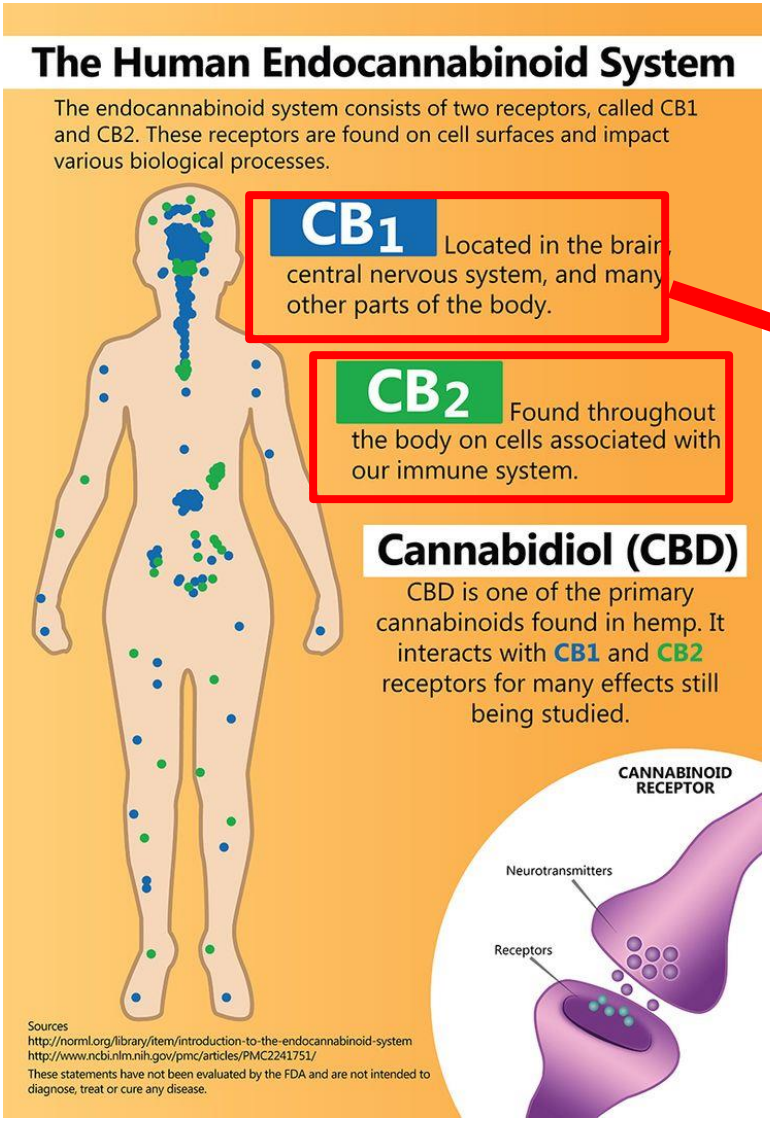
Mechoulam R, Parker LA. The Endocannabinoid System and the Brain. *Annu Rev Psychol*. 2013;64(1):21-47. doi:10.1146/annurev-psych-113011-143739.

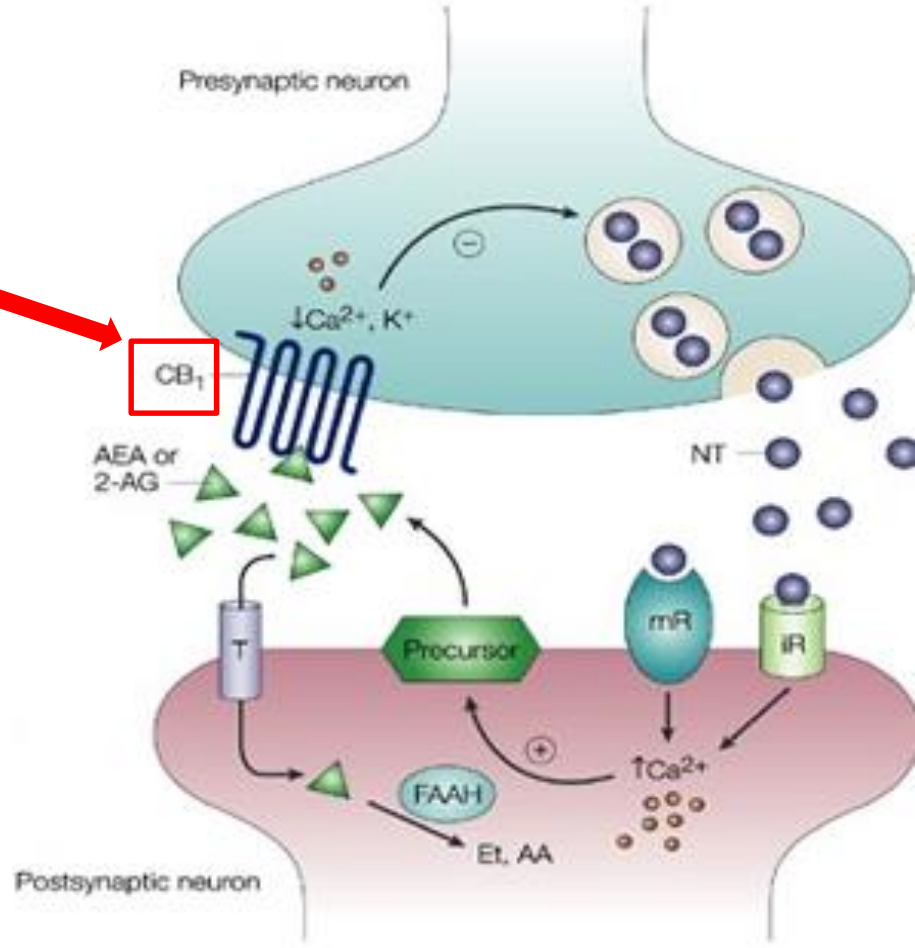
Breivogel CS, Sim-Selley LJ. Basic neuroanatomy and neuropharmacology of cannabinoids. *Int Rev Psychiatry*. 2009;21(2):113-121. doi:10.1080/09540260902782760

The Endocannabinoid System

Endocannabinoids function alongside **adrenergic**, **cholinergic** & **dopaminergic** systems via retrograde signalling

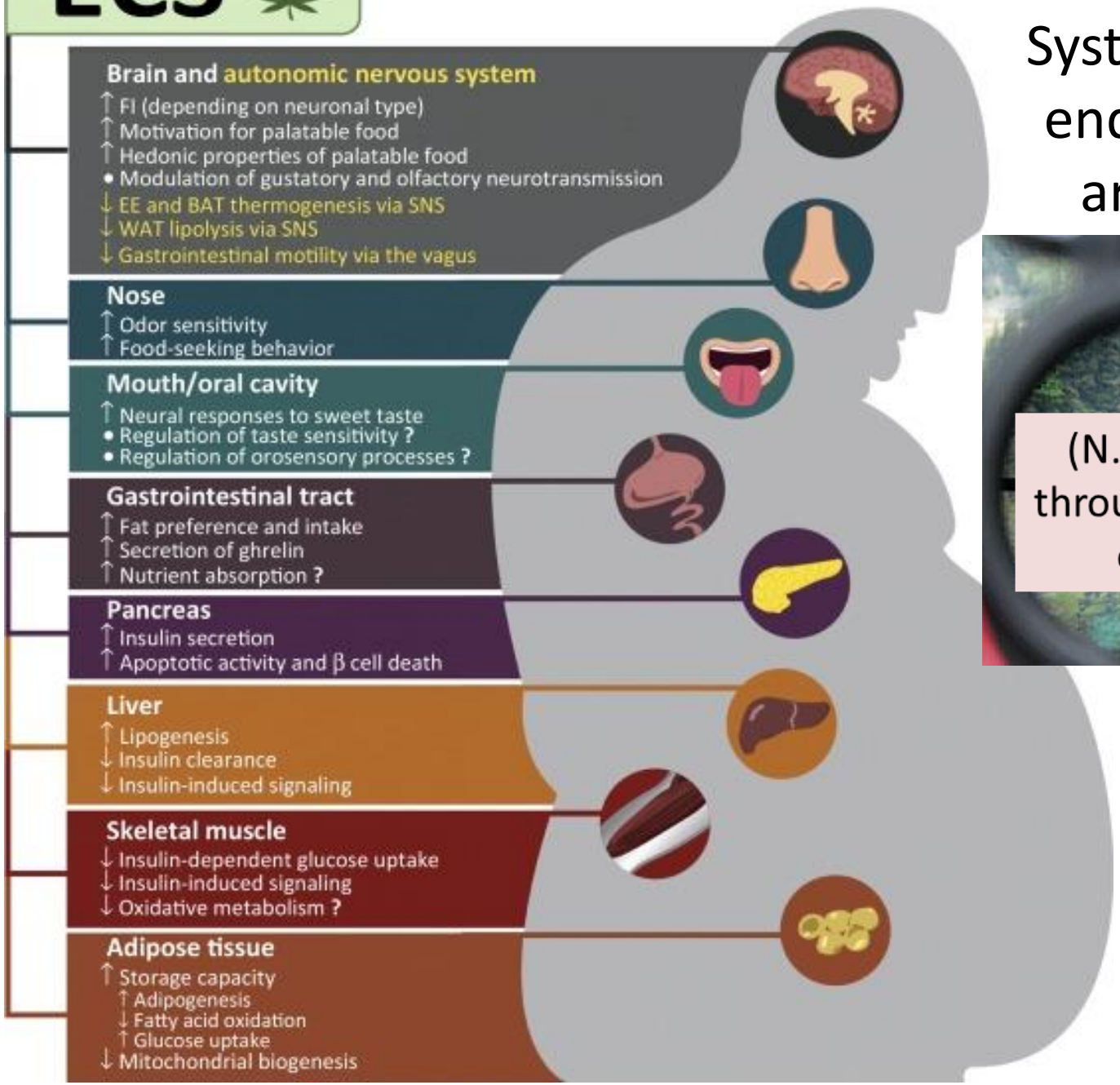
(Anandamide, 2-arachidonoylglycerol (2-AG))





Health Canada. Information for Health Care Professionals: Cannabis (marihuana, marijuana) and the cannabinoids [Health Canada, Feb 2013]. http://www.hc-sc.gc.ca/dhp-mps/marihuana/med/infoprof-eng.php . Accessed Oct 24, 2017

ECS



Systems affected by endocannabinoids are widespread

Trends in Endocrinology and Metabolism

Adverse Effects of Cannabis

- Impaired motor coordination and motor performance
- Dizziness
- Drowsiness
- Fatigue
- The smoke of cannabis can be irritating to conjunctival, nasopharyngeal, and bronchial tissue
- Gastrointestinal effects (diarrhea, nausea, dry mouth)
- Impaired short-term memory and information processing
- Altered judgment
- Decreased attention
- Tachycardia, orthostatic hypotension
- Muscle relaxation
- Increased appetite
- High doses (paranoia, anxiety)

Notcutt WG, Clarke EL, eds. Cannabinoids in Clinical Practice: A UK Perspective. In: *Handbook of Cannabis*. Oxford, United Kingdom ; New York, NY: Oxford University Press; 2014:415-432 Grotenhermen F, Müller-Vahl K. The Therapeutic Potential of Cannabis and Cannabinoids. *Dtsch Ärztebl Int*. 2012;109(29-30):495-501. doi:10.3238/arztebl.2012.0495.

Drug Interactions

Pharmacodynamic

- Look for additive, synergistic or antagonistic interactions with other drugs and diseases
- Clinically significant:
  - Additive CNS depression and psychomotor impairment
  - For Eg.
    - Sedative-hypnotics
    - Alcohol
    - Anti-psychotics
    - Anti-depressants
    - Etc

Pharmacokinetic

- Metabolism:
  - **THC** oxidized by CYP450-2C9, 2C19, 3A4
  - CBD oxidized by CYP450-3A4 (& others)
- CYP450 inhibitors ↑ **THC**:
  - Eg. fluoxetine, omeprazole, macrolides, ketoconazole, diltiazem, verapamil, HIV protease inh, amiodarone etc.
- CYP450 inducers ↓ **THC**:
  - Eg. rifampicin, phenytoin, St. John's Wort etc.
- THC inhibits CYP450 1A1, 1A2, 1B1
  - ↑ amitriptyline, caffeine, tamoxifen, warfarin etc.
- CBD inhibits CYP 2D6, 2C9, 2C19
  - ↑ clobazam etc

Abramovici H, Chief H-O, Bureau R, et al. Information for Health Care Professionals. http://www.hc-sc.gc.ca/dhp-mps/marihuana/med/infoprof-eng.php .
Kerstin Iffland et al. An Update on Safety and Side Effects of Cannabidiol: A Review of Clinical Data and Relevant Animal Studies. Cannabis Cannabinoid Res. 2017; 2(1): 139–154. Published online 2017 Jun 1. doi: [10.1089/can.2016.0034] PMCID: PMC5569602 PMID: 28861514

Drug Interactions

- These drugs may make THC **more** potent!
- These drugs may make THC **less** potent!
- **THC** may make these drugs **more** potent!

Pharmacokinetic

- Metabolism of THC:
  - oxidized by CYP450-**2C9**, **2C19, 3A4**

P450 inhibitors ↑ THC:
- Eg. fluoxetine, omeprazole, macrolides, ketoconazole, diltiazem, verapamil, HIV protease inh, amiodarone etc.

P450 inducers ↓ THC:
- Eg. rifampicin, phenytoin, St. John's Wort etc.

THC inhibits P450 1A1, 1A2, 1B1
- ↑ amitriptyline, caffeine, tamoxifen, warfarin etc.

Abramovici H, Chief H-O, Bureau R, et al. Information for Health Care Professionals. http://www.hc-sc.gc.ca/dhp-mps/marihuana/med/infoprof-eng.php.

When?

Rational Prescribing of Cannabis

Ginseng anyone?

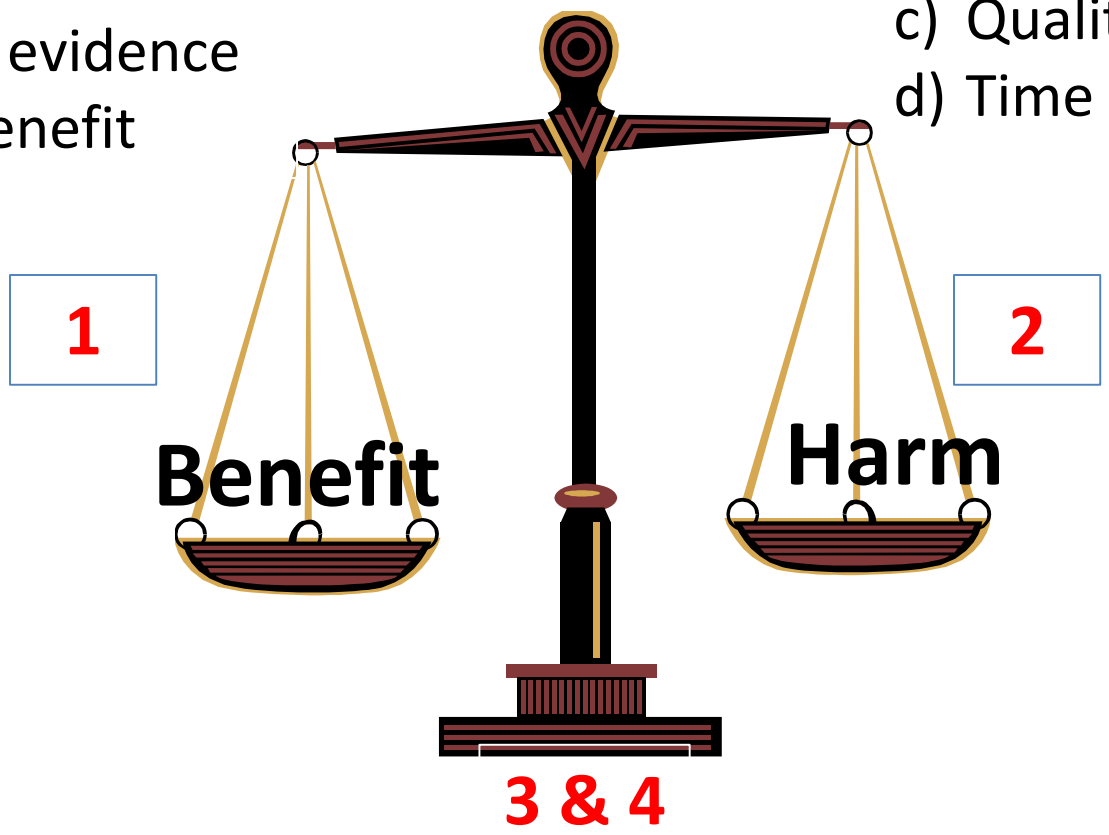
Rational Prescribing

Prioritize:

a) Type of benefit
b) Quantity of benefit
c) Quality of evidence
d) Time to benefit

Prioritize:

a) Type of harm
b) Quantity of harm
c) Quality of evidence
d) Time to harm

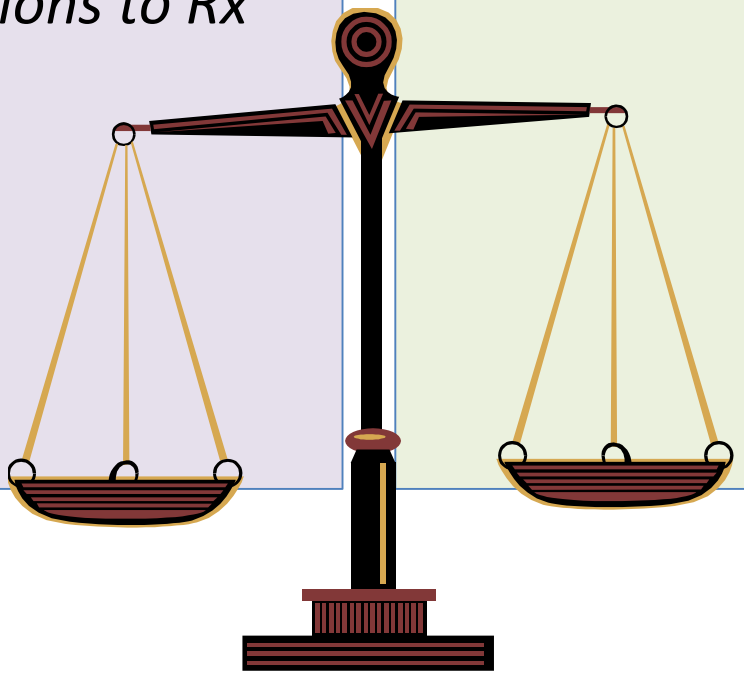


Cost & Convenience

Primum non nocere

- When EBM is ***strong***:
  - Benefit easily outweighs Harm
  - *Only specific contraindications to Rx*

- When EBM is ***weak***
  - It is easy for Harm to outweigh Benefit
  - *First, do no harm*



Harm: Safety Data

Rare & Severe **vs** Common & Bothersome

Conventional / Rx

b) Quality of evidence
- Wide spectrum of quality in methodologies
- Phase IV studies

c) Quantity of evidence
- Months to decades
- Relatively small amount of safety data

Higher manufacturing standards

CAM

b) Quality of evidence
- Narrower spectrum
  - Oral traditions
  - Anecdotal

c) Quantity of evidence
- Centuries to millennia
- Relatively large amount of safety data

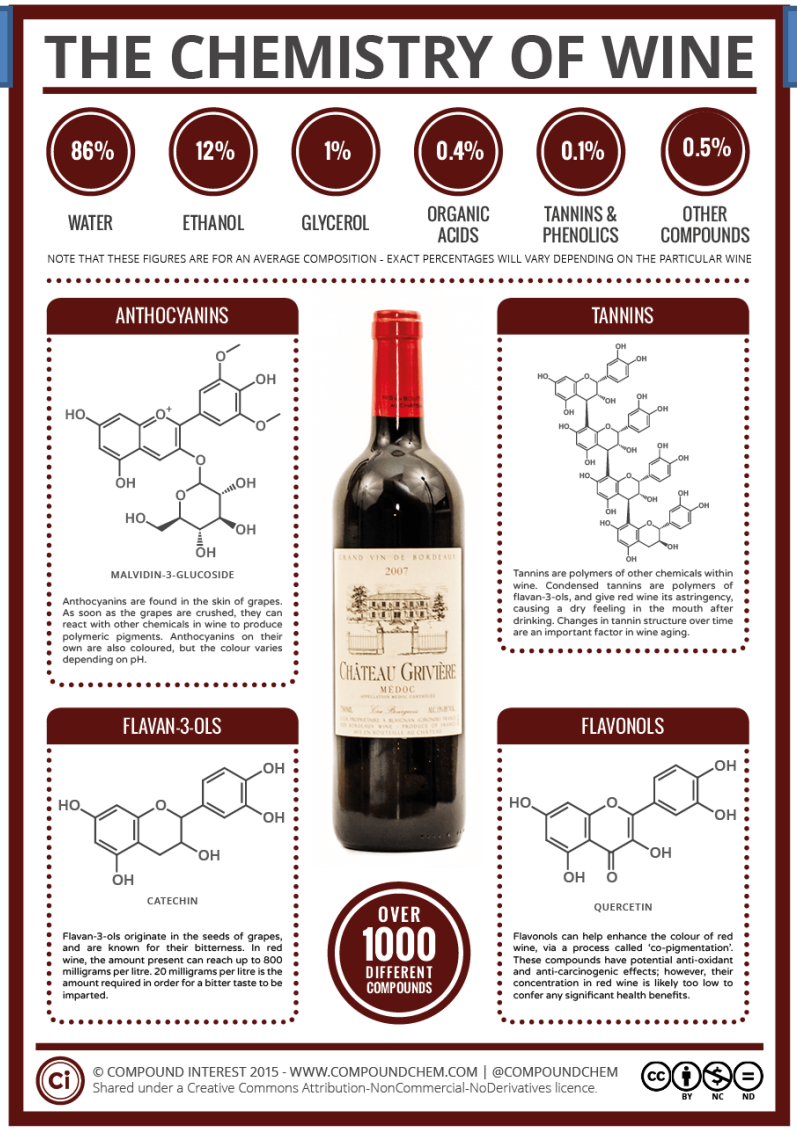
Lower manufacturing standards

Complementary & Alternative medicines (CAM)

Additional safety concerns secondary to manufacturing quality

Plonk

Vintage



Variations in Preparations

- Extraction process
- Dosage forms
- etc

Manufacturing Quality

- Adulterants
- Contaminants
- Undeclared ingredients

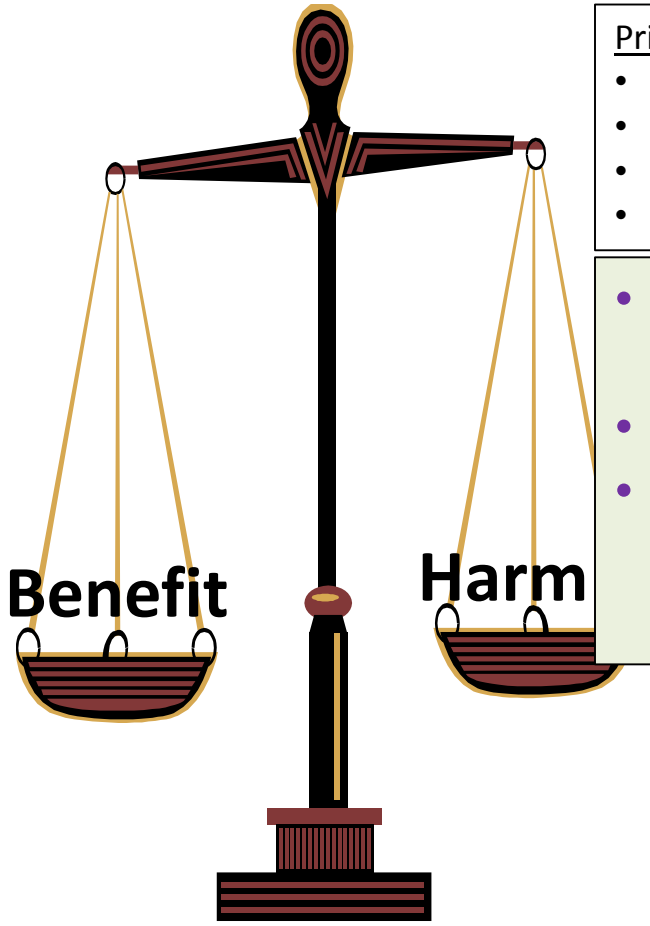
http://www.compoundchem.com/wp-content/uploads/2014/05/The-Chemistry-of-Wine-2015.png
http://www.pharmaceutical-journal.com/opinion/comment/setting-the-standards-for-medicines-the-british-pharmacopoeia/10005375.article

Rational Prescribing & **Cannabis**

When EBM is weak, and risk is lower than Rx options

Prioritize:
- Type of benefit
- Quantity of benefit
- Quality of evidence
- Time to benefit

- No mortality/ morbidity benefits
- Highly subjective quantity of benefit
- ++ Less RCT data
- Stat onset via inhalational route



Prioritize:
- Type of harm
- Quantity of harm
- Quality of evidence
- Time to harm

- Millennia of anecdotal / historical safety data
- Mental health morbidity
- Rare (<1%) risks
  - Often with years of chronic use

~~No~~ insurance coverage

Cost & Convenience

Shipped via the mail
No real PharmD/MD monitoring

New!: SunLife for limited indications:
(CINV, refractory pain, MS pain/spasticity, RA refractory pain)
Manulife – case by case basis

Cannabis & Weak EBM

Captain Obvious

Ps. “and smoking is bad for you.”

VS

Lost? Let me help you find your way

When patients need us the most

Rational Prescribing & CAM

No one stands on solid ground

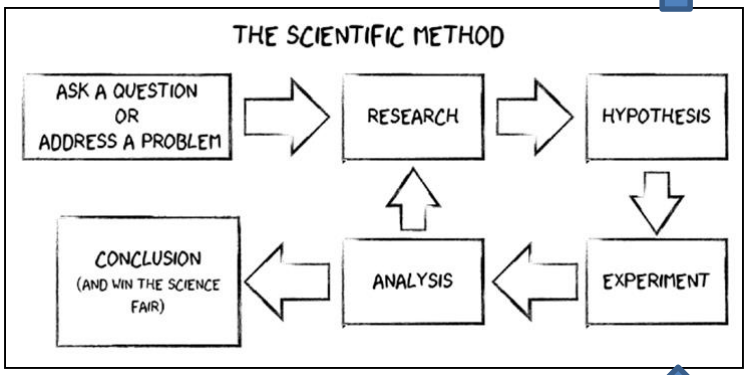
- All drugs are tools:
  - Not heroes nor villains
- Consider Cannabis when:
  a) EBM is weak
  b) Goal: Symptom relief
  c) Benefit outweighs Harm
  d) Risk is < Rx meds; <u>Consider</u>
     - N.B. The ice is thin!
     - "*Primum non nocere*"

How?

How?
Treat as: "n of 1"
(a Therapeutic Trial)

The Therapeutic Trial (n = 1)

A clinician's Scientific Method for Symptomatic Relief



1. **Select** best option via Rational Prescribing process
   - **1st** Exhaust interventions that reduce Mortality & Morbidity
     - Then, address symptoms/QoL
     - Test one option (variable) at a time
2. **Determine** the following:
   a) The Benefit (ie. Definition of success)
   b) Stop Date (ie. Time to benefit)
   c) Monitoring parameters (ie. Potential risks)
3. **Reassess** & adjust hypothesis
   - Start over

The Therapeutic Trial (n = 1)

Assessing Outcomes

↑Benefit	No Harm
Success Reassess: Continue Rx vs ↑Dose?	

No Benefit	No Harm
Reassess: Discontinue vs ↑Dose?	

↑Benefit	↑ Harm
Reassess: Discuss Benefit vs Risk with patient	

No Benefit	↑ Harm
Failure Discontinue Therapy	

Why?

Cannabis Therapeutics

Summary of Current Evidence

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. doi:10.17226/24625.

Weight-of-Evidence Categories

CONCLUSIVE EVIDENCE

- For therapeutic effects: There is strong evidence from randomized controlled trials to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.
- For other health effects: There is strong evidence from randomized controlled trials to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.
- For this level of evidence, there are many supportive findings from good-quality studies with no credible opposing findings. A firm conclusion can be made, and the limitations to the evidence, including chance, bias, and confounding factors, can be ruled out with reasonable confidence.

SUBSTANTIAL EVIDENCE

- For therapeutic effects: There is strong evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.
- For other health effects: There is strong evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.
- For this level of evidence, there are several supportive findings from good quality studies with very few or no credible opposing findings. A firm conclusion can be made, but minor limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

MODERATE EVIDENCE

- For therapeutic effects: There is some evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.
- For other health effects: There is some evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.
- For this level of evidence, there are several supportive findings from good- to fair-quality studies with very few or no credible opposing findings. A general conclusion can be made, but limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

LIMITED EVIDENCE

- For therapeutic effects: There is weak evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.
- For other health effects: There is weak evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.
- For this level of evidence, there are supportive findings from fair-quality studies or mixed findings with most favoring one conclusion. A conclusion can be made, but there is significant uncertainty due to chance, bias, and confounding factors.

NO OR INSUFFICIENT EVIDENCE TO SUPPORT THE ASSOCIATION

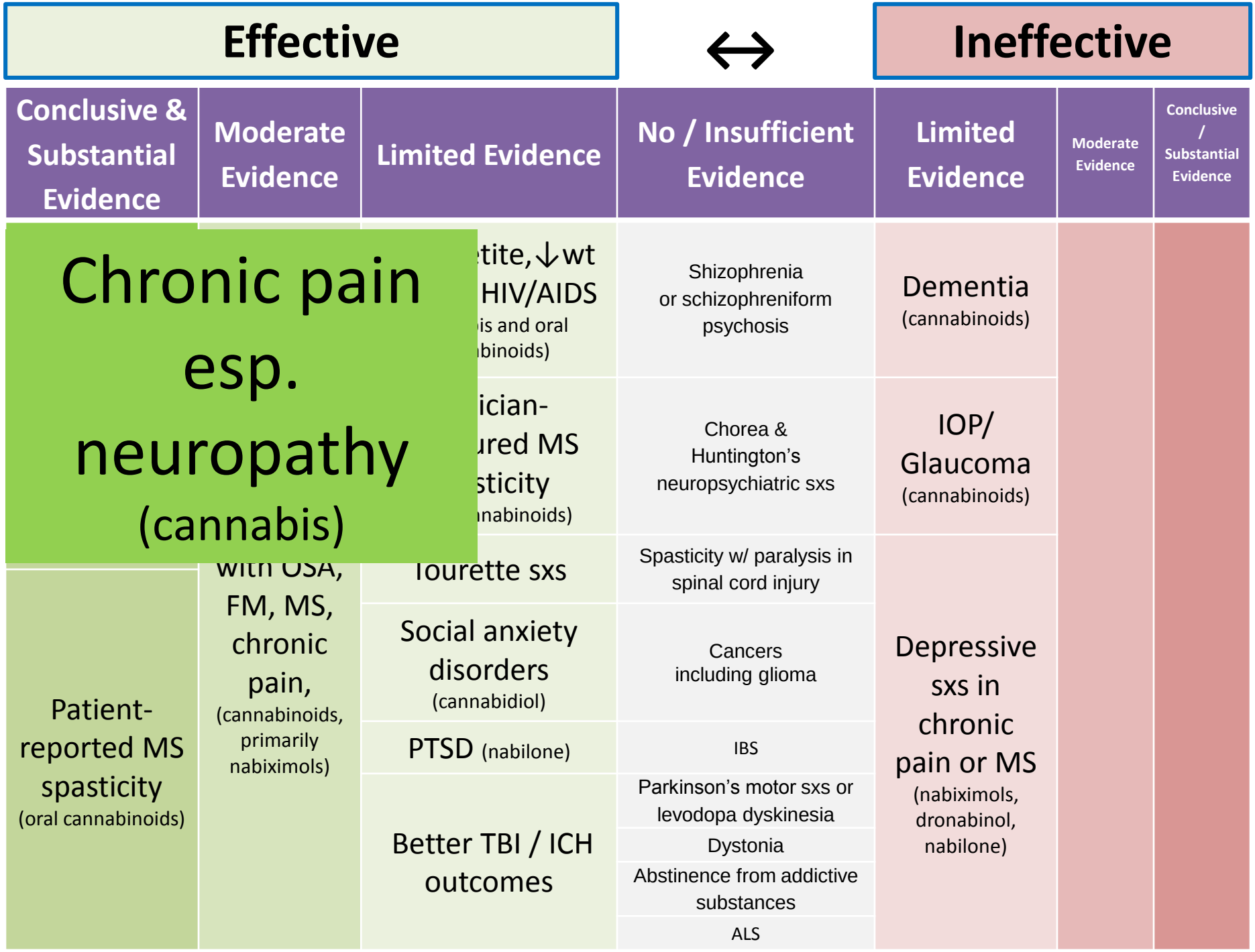
- For therapeutic effects: There is no or insufficient evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.
- For other health effects: There is no or insufficient evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.
- For this level of evidence, there are mixed findings, a single poor study, or health endpoint has not been studied at all. No conclusion can be made because of substantial uncertainty due to chance, bias, and confounding factors.

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. doi:10.17226/24625.

Effective			↔	Ineffective		
Conclusive & Substantial Evidence	**Moderate Evidence**	**Limited Evidence**	**No / Insufficient Evidence**	**Limited Evidence**	**Moderate Evidence**	**Conclusive / Substantial Evidence**
Chronic pain esp. neuropathy (cannabis)	Short-term sleep outcomes with OSA, FM, MS, chronic pain, (cannabinoids, primarily nabiximols)	↑Appetite, ↓wt loss w/ HIV/AIDS (cannabis and oral cannabinoids)	Shizophrenia or schizophreniform psychosis	Dementia (cannabinoids)		
Antiemetics for CINV (oral cannabinoids)		Clinician-measured MS spasticity (oral cannabinoids)	Chorea & Huntington's neuropsychiatric sxs	IOP/ Glaucoma (cannabinoids)		
Patient-reported MS spasticity (oral cannabinoids)		Tourette sxs	Spasticity w/ paralysis in spinal cord injury	Depressive sxs in chronic pain or MS (nabiximols, dronabinol, nabilone)		
		Social anxiety disorders (cannabidiol)	Cancers including glioma			
		PTSD (nabilone)	IBS			
		Better TBI / ICH outcomes	Parkinson's motor sxs or levodopa dyskinesia			
			Dystonia			
			Abstinence from addictive substances			
			ALS			

Harm			↔	Safety		
Conclusive& Substantial Evidence	**Moderate Evidence**	**Limited Evidence**	**No / Insufficient Evidence**	**Limited Evidence**	**Moderate Evidence**	**Conclusive / Substantial Evidence**
Male & smoking cigarettes: risk of **problem cannabis use (PCU)**	MDD: risk of PCU	Non-seminoma-type testicular germ cell tumors (current, frequent, or chronic cannabis smoking)			Anxiety, Personality, & Bipolar disorders are ***not*** risk factors for PCU	Stimulant treatment of ADHD in adolescence is ***not*** a risk factor for PCU
Early cannabis initiation is a risk factor for future PCU	Male: risk of PCU				Adolescent ADHD is ***not*** a risk factor for PCU	
					Neither alcohol nor nicotine dependence alone are risk factors for PCU	

Harm Associations			Safety Associations	
Conclusive & Substantial	**Moderate Evidence**	**Limited Evidence**	**Limited Evidence**	**Moderate Evidence**
↑Respiratory sxs & chronic bronchitis	Overdose injuries, incl. respiratory distress	↑ severity of PTSD sxs	↓ metabolic syndrome & diabetes	No assoc w/ lung cancer (cannabis smoking)
MVA	↓ Learning, memory, & attention (acute use)	↑ acute MI (cannabis smoking)	↓ inflam cytokines	No assoc w/ head & neck cancers
↓ Birth wt of the offspring	↑ Mania & hypomania in bipolar (regular use)	↑ CVA, SAH	↑ Pregnancy complications	Higher FVC
↑ Schizophrenia / other psychoses, (w/frequent users)	↑ Risk for depressive disorders	↑ prediabetes	No progression of hepatic dz w/ HCV (daily use)	Improved airway dynamic w/ acute, but not chronic, use
↑ Cannabis use frequency & ↑ problem cannabis use	↑ S.I. & attempts (highest w/ heavier users)	↑ COPD		Cannabis cessation: ↓ respiratory sxs
	↑ Suicide completion	↑ Admx to NICU		No worsening of negative sxs of schizophrenia
	↑ Social anxiety disorder (regular use)	↑ Positive symptoms of schizophrenia		↑ cognitive performance in psychotic disorders & Hx of cannabis use
		↑ Bipolar disorder, esp. regular or daily users		
		↑ Any type of anxiety disorder, except social anxiety disorder		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Chronic pain esp. neuropathy (cannabis)
tite, ↓wt
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with OSA, FM, MS, chronic pain, (cannabinoids, primarily nabiximols)
Tourette sxs
Social anxiety disorders (cannabidiol)
PTSD (nabilone)
Better TBI / ICH outcomes
Patient-reported MS spasticity (oral cannabinoids)
Shizophrenia or schizophreniform psychosis
Chorea & Huntington's neuropsychiatric sxs
Spasticity w/ paralysis in spinal cord injury
Cancers including glioma
IBS
Parkinson's motor sxs or levodopa dyskinesia
Dystonia
Abstinence from addictive substances
ALS
Dementia (cannabinoids)
IOP/ Glaucoma (cannabinoids)
Depressive sxs in chronic pain or MS (nabiximols, dronabinol, nabilone)

Cannabis & Chronic Pain

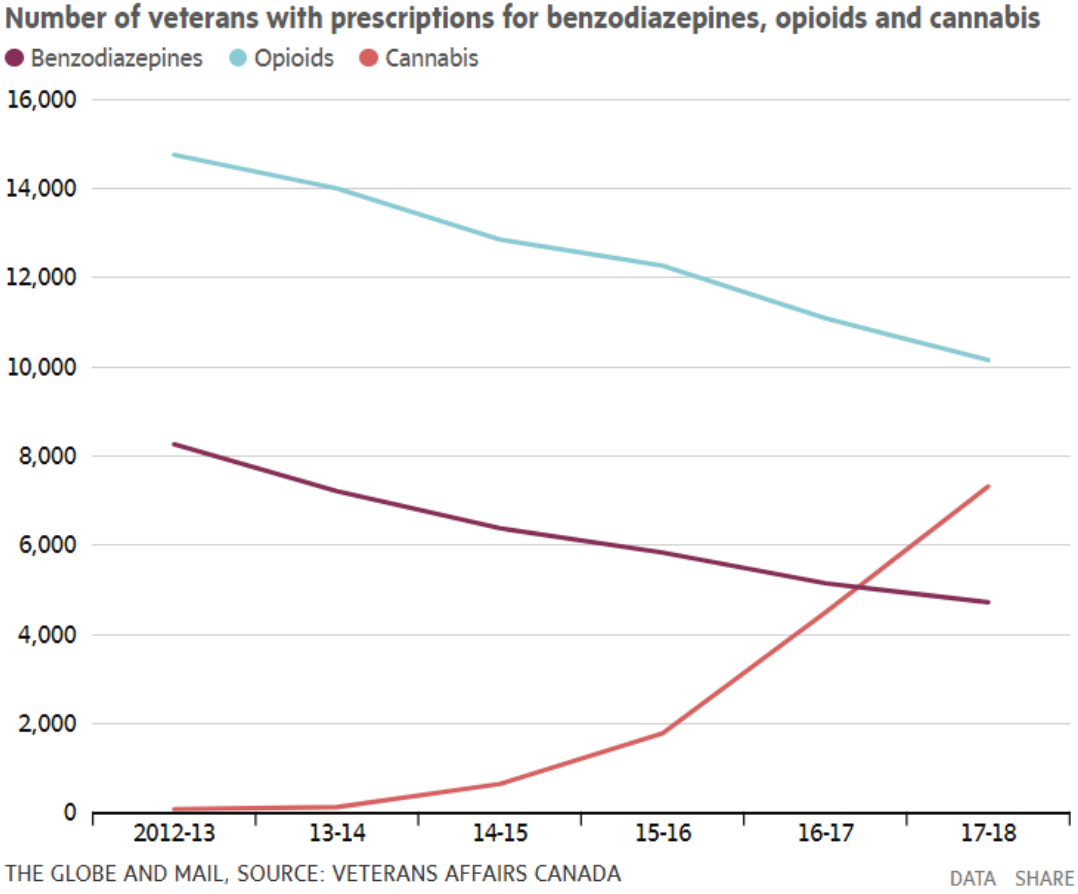
Associations

- The most common indication:
  - 94% of Colorado cannabis ID holders indicated “severe pain” as a condition
  - 87% of pts were seeking medical marijuana for pain relief (Ilgen, 2013)
- Cannabis may displace other pain meds, including opioids
  - 24.8% (95% CI[−37.5% to −9.5%] P = .003) reduction in annual opioid overdose mortality rate in states with medical cannabis laws (vs states without)
    - Association generally strengthened over 6 year time frame:
  - Reduction of conventional analgesic Rx’s (Bradford, 2016)
    - Annual No. of daily doses Rx’d per MD in states with medical MJ for Medicare Part D patients
    - 31810 vs 28165 (a reduction of 3645) ($p < 0.01$)
    - $165 million saving in 2013 (small potatoes for National Medicare)

1. 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. doi:10.17226/24625.
2. Bachhuber, MA et al. *Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999-2010*. JAMA Intern Med. 2014;174(10):1668–1673. doi:10.1001/jamainternmed.2014.4005
3. Bradford AC. et al. *Medical Marijuana Laws Reduce Prescription Medication Use In Medicare Part D.* Health Aff (Millwood). 2016 Jul 1;35(7):1230-6. doi: 10.1377/hlthaff.2015.1661.

Cannabis & Chronic Pain

Associations



Veterans Affairs Canada:
(2012 to 2017)

- No. of Benzo Rx's: 4,702 (43% decrease)
- No. of opioids Rx's: 10,130 (31% decrease)

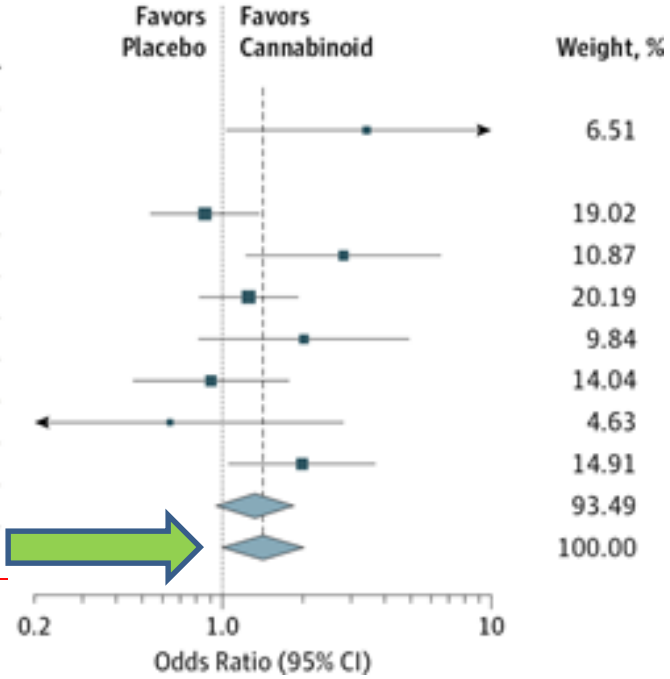
Ref: MIKE HAGER. Cannabis use among veterans soars as Ottawa cuts paybacks. PUBLISHED MAY 6, 2018
https://www.theglobeandmail.com/canada/british-columbia/article-number-of-veterans-using-opioids-declines-significantly-as-cannabis/

Cannabis & Chronic Pain

Efficacy – Whiting et al.

- Cannabinoids are *modestly effective* (esp. **neuropathies**)
  - 5 systematic reviews - consistent conclusions (28 trials; 2454 participants)
  - 41% improvement of pain vs control (Defined as >30% reduction in pain)
    - (OR = **1.41**, [95% CI] = 0.99–2.00; 8 trials)
    - Other conditions: [Cancer pain, MS, RA, MSK issues, & chemo-induced pain]

Improvement in Pain With Cannabinoid vs Placebo by Study	Cannabinoid Events No.	Cannabinoid Events Total No.	Placebo Events No.	Placebo Events Total No.	Odds Ratio (95% CI)
Tetrahydrocannabinol (smoked)					
Abrams et al,[77] 2007	13	25	6	25	3.43 (1.03-11.48)
Nabiximols					
GW Pharmaceuticals,[22] 2005	54	149	59	148	0.86 (0.54-1.37)
Johnson et al,[69] 2010	23	53	12	56	2.81 (1.22-6.50)
Langford et al,[65] 2013	84	167	77	172	1.25 (0.81-1.91)
Nurmikko et al,[76] 2007	16	63	9	62	2.00 (0.81-4.96)
Portenoy et al,[67] 2012	22	90	24	91	0.90 (0.46-1.76)
Selvarajah et al,[70] 2010	8	15	9	14	0.63 (0.14-2.82)
Serpell et al,[88] 2014	34	123	19	117	1.97 (1.05-3.70)
Subtotal $I^2 = 44.5\%$, ($P = .0.94$)	241	660	209	660	1.32 (0.94-1.86)
Overall $I^2 = 47.6\%$, ($P = .0.64$)	254	685	215	685	1.41 (0.99-2.00)

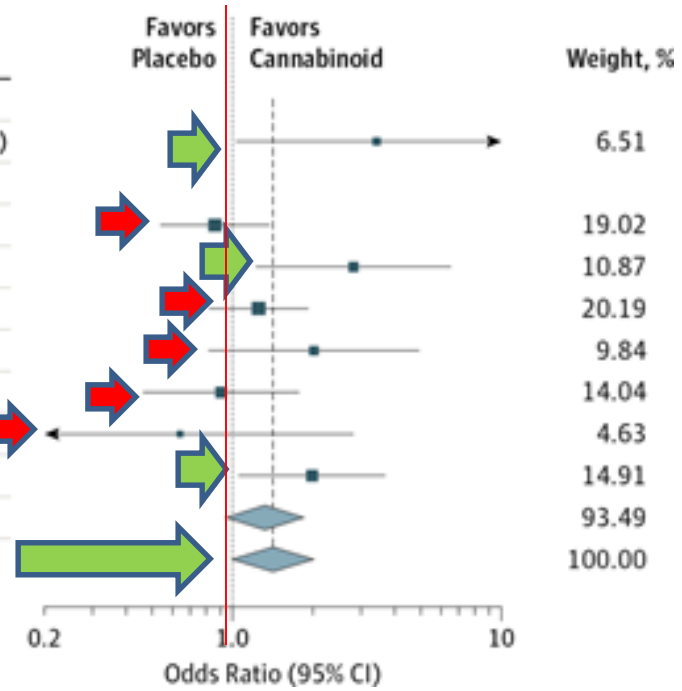


National Academies of Sciences, Engineering, and Medicine. 2017. *The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research.* Washington, DC: The National Academies Press. doi:10.17226/24625.
Whiting, PF et al. *Cannabinoids for Medical Use: A Systematic Review and Meta-analysis*. JAMA. 2015;313(24):2456–2473. doi:10.1001/jama.2015.6358

Cannabis & Chronic Pain

Efficacy – Whiting et al.

Improvement in Pain With Cannabinoid vs Placebo by Study	Cannabinoid Events No.	Cannabinoid Events Total No.	Placebo Events No.	Placebo Events Total No.	Odds Ratio (95% CI)	Weight, %
Tetrahydrocannabinol (smoked)						
Abrams et al,[77] 2007	13	25	6	25	3.43 (1.03-11.48)	6.51
Nabiximols						
GW Pharmaceuticals,[22] 2005	54	149	59	148	0.86 (0.54-1.37)	19.02
Johnson et al,[69] 2010	23	53	12	56	2.81 (1.22-6.50)	10.87
Langford et al,[65] 2013	84	167	77	172	1.25 (0.81-1.91)	20.19
Nurmikko et al,[76] 2007	16	63	9	62	2.00 (0.81-4.96)	9.84
Portenoy et al,[67] 2012	22	90	24	91	0.90 (0.46-1.76)	14.04
Selvarajah et al,[70] 2010	8	15	9	14	0.63 (0.14-2.82)	4.63
Serpell et al,[88] 2014	34	123	19	117	1.97 (1.05-3.70)	14.91
Subtotal $I^2 = 44.5\%$, ($P = .0.94$)	241	660	209	660	1.32 (0.94-1.86)	93.49
Overall $I^2 = 47.6\%$, ($P = .0.64$)	254	685	215	685	1.41 (0.99-2.00)	100.00



- *"Modestly effective"*
  - Variable effects
  - Variable indications [Cancer pain, MS, RA, MSK issues, & chemo-induced pain]
  - Variable preparations & doses (smoked vs nabiximols)

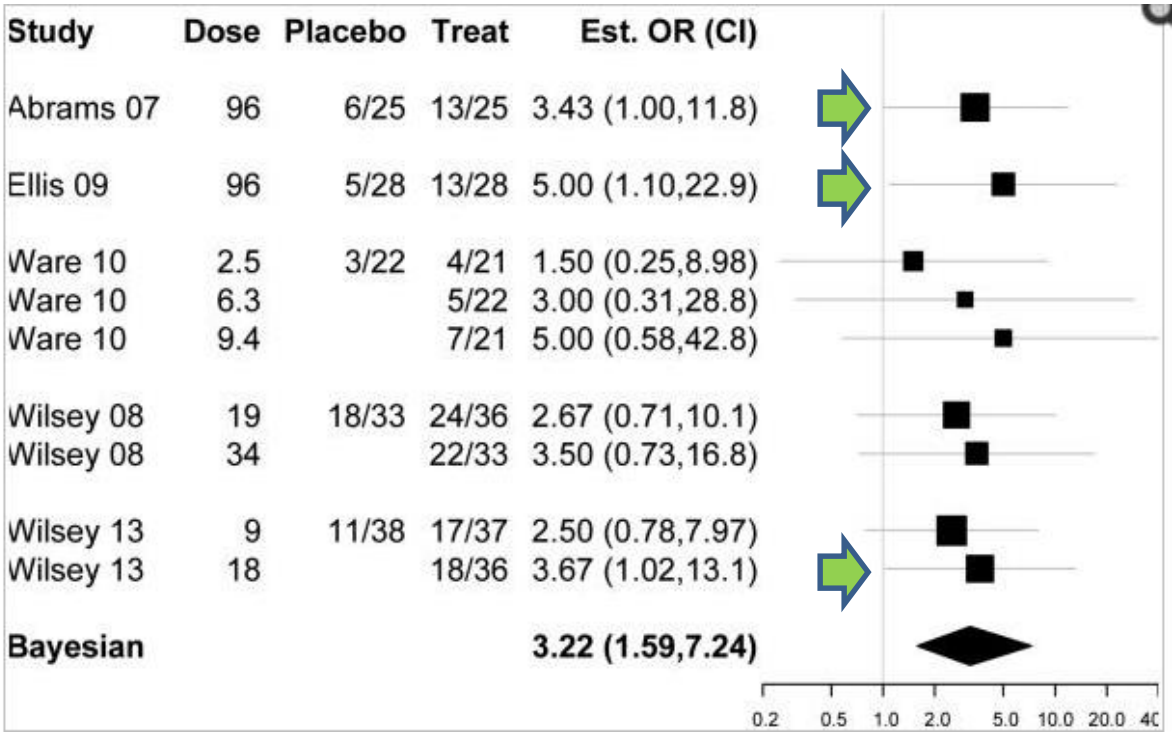
National Academies of Sciences, Engineering, and Medicine. 2017. *The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research.* Washington, DC: The National Academies Press. doi:10.17226/24625.

Whiting, PF et al. *Cannabinoids for Medical Use: A Systematic Review and Meta-analysis*. JAMA. 2015;313(24):2456–2473. doi:10.1001/jama.2015.6358

Cannabis & Chronic Pain

Efficacy – Andreae et al.

- Inhaled cannabinoids may be effective for neuropathies
  - 5 RCTs: 178 pts with 405 observed responses over days to weeks
    - Individual pt data Bayesian meta-analysis
  - Short-term reductions in chronic neuropathic pain
    - 1 in every 5 to 6 patients treated
    - **NNT = 5.6** (Bayesian 95% credible interval 3.4 - 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. doi:10.17226/24625.

Andreae MH, et al. *Inhaled cannabis for chronic neuropathic pain: an individual patient data meta-analysis.* The Journal of Pain . 2015;16(12):1221-1232. doi:10.1016/j.jpain.2015.07.009.

Cannabis & Chronic Pain

Efficacy

- From CAM to Mainstream:

(The ice thickens)

☑ Anecdotes

↓

☑ Suggestive results but:

Lower quality methodologies, smaller n#, variable indications

↓

☐ ?Home run RCTs, large n #

Stable preparations, GMP

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. doi:10.17226/24625.

Weak EBM

Primum non nocere

Patients need us <u>most</u> when:

- *Evidence is weak*
- *Confusion is high*
- *Risk can easily outweigh Benefit*

Guide them to good health

- Patient discussion of Benefit:Risk ratio
- Consider a Therapeutic Trial
  - n = 1

Workshop

Cannabis & Pain Management

Benefit

Harm(s)

Time

Set 3 Trial Parameters

Benefit

Harms

Time till R/A

n of 1®

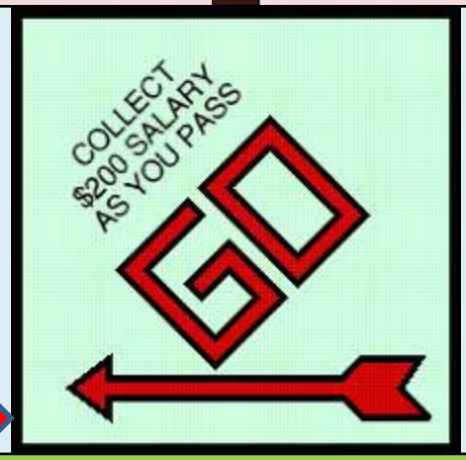
Family fun for everyone!

Results

YES

Indication

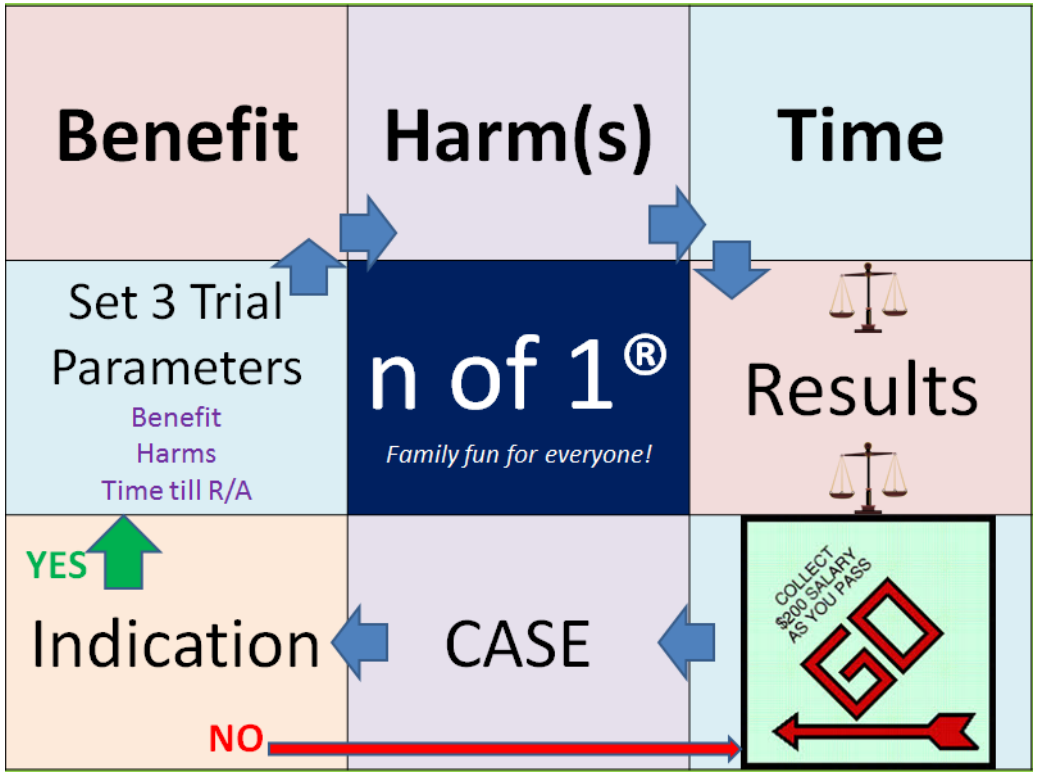
CASE



NO

Case #1

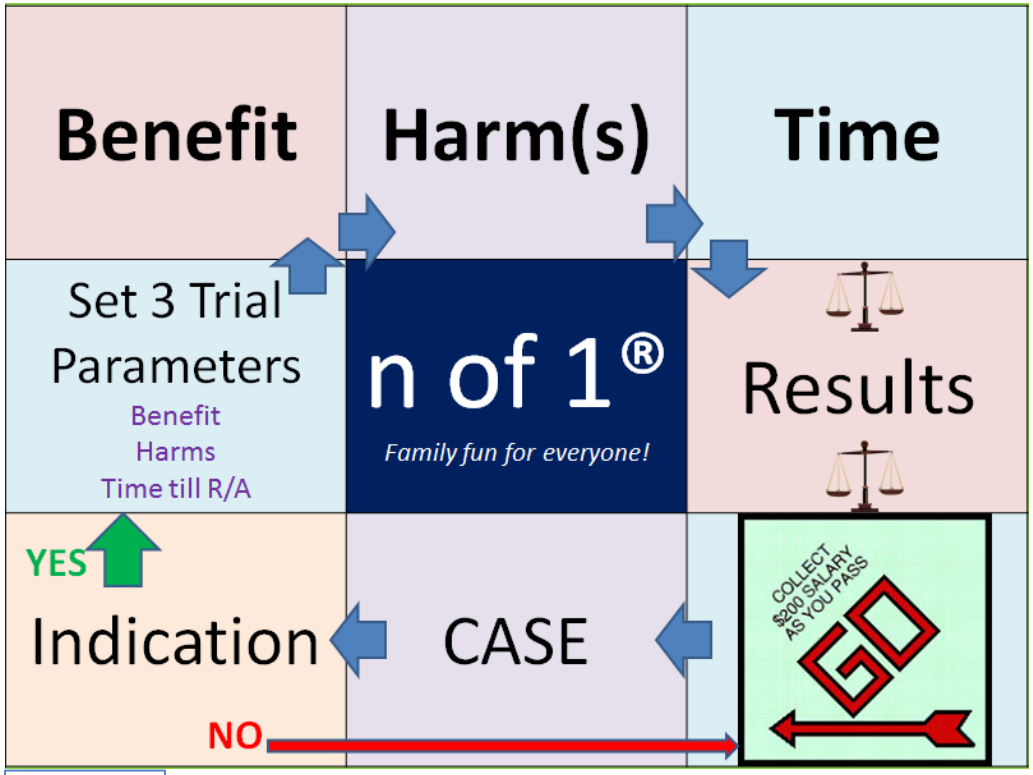
- Mr. DooB
  - 22y.o. arborist
  - CC: sore ankles from climbing trees all day
- Asking for medical cannabis
  - States it will help with his ankle pain and boredom at work
  - His brother has benefitted +++ from same
  - Important since his job depends on it!



Case #2

- Mrs. GK
  - 65y.o.
  - PMHx: CKD, HTN
  - CC: trigeminal neuralgia; Pain always 7/10 - 9/10
    - Chewing & dental care is very painful; Lost 16 lbs
- Asking for medical cannabis
  - Has tried and failed Gaba's, TCA's, SNRI's, Codeine under your supervision
  - Open to all options…

Options for Neuropathic Pain:
Choose: drug, dose, formulation



Define:

- Benefit: ↓in pain freq/severity/VAS, ↑in sleep/mood/fxn
- Time till R/A: 2 hours (pragmatically 1 week)
- Harm(s): ↓ Cognition; ↑ falls, dizziness, dry mouth, blurry vision

The Therapeutic Trial (n = 1)

Assessing Outcomes

Time till R/A = _1 wk dy/wk/mo/yr

Benefit: Type: ____ & ____0%

Harm: Type: ____ & ____0%

No Benefit	No Harm

Reassess:

Discontinue vs ↑Dose?

The Therapeutic Trial (n = 1)

Assessing Outcomes

Time till R/A = _1 wk dy/wk/mo/yr

Benefit: Type: ____ & ____60%

Harm: Type: ____ & ____20%

↑Benefit

↑ Harm

Reassess:
Discuss Benefit vs Risk with patient

The Therapeutic Trial (n = 1)

Assessing Outcomes

Time till R/A = _1 wk dy/wk/mo/yr

Benefit: Type: ____ & ____10%

Harm: Type: ____ & ____50%

↑Benefit

↑ Harm

Reassess:
Discuss Benefit vs Risk with patient

Reduce dose to previous week and maintain

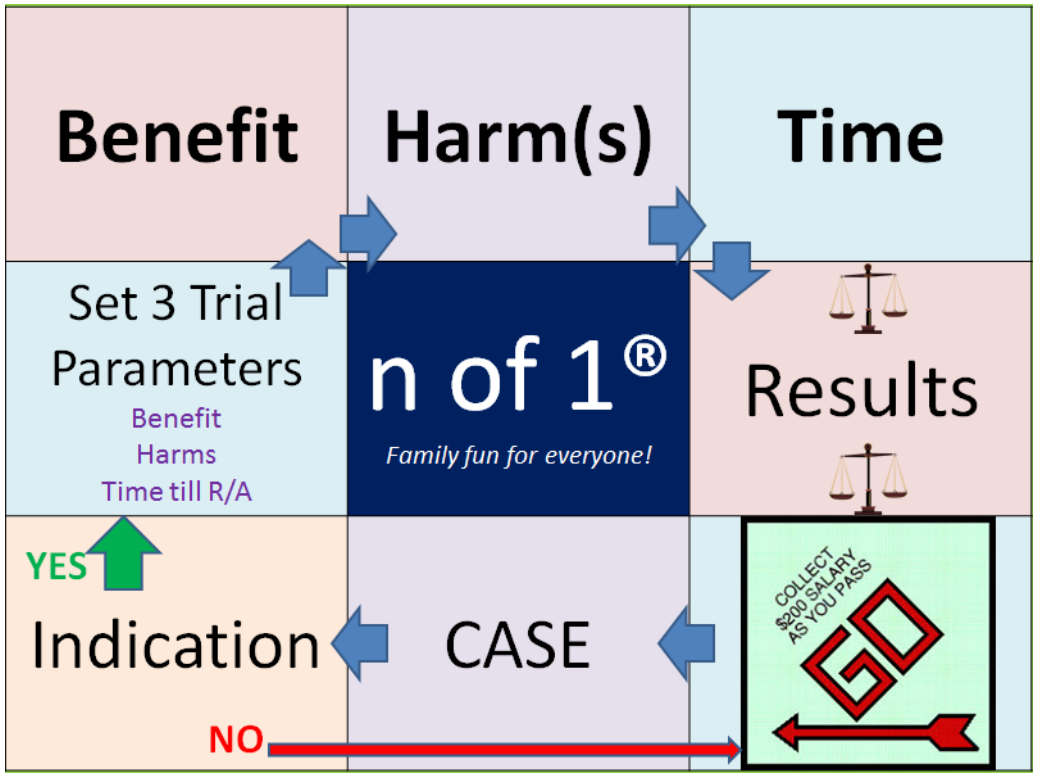
Reassess chronic status in 2-3 months

Case #3

- Mr. TS
  - 59y.o.
  - PMHx: scoliosis & spinal stenosis since childhood
  - CC: constant radiating pain down both legs;
    - VAS = 9/10 untreated
    - VAS = 3/10 w/ tx
- Asking for medical cannabis
  - Has smoked cannabis for fun & medicinally x 40yrs
  - Grows his own
  - Has never tried other therapies
    - Pre-contemplative for other options!

Indicated? Y/N

(If yes, choose: drug, dose, formulation)



Thanks for Playing 

!

Access

?OTC strains via www.OCS.ca or Rx via ACMPR?

1. Choose a **licensed producer**
   - By you or by patient
   - See list of Health Canada approved licensed producers (LP) here.
2. Find the **Medical Document** for Authorization
   - From Health Canada or the LP
   - Click here
3. Choose formulation
   - THC : CBD ratio
     (CBD preferred)
   - PO/SL vs inhaled
     (PO preferred, else Vaped)
   - If oral:
     - Find the **Equivalence Factor** for oils:dried bud
4. Complete the Authorization form
5. Mail or Secure Fax to LP

Cannabis Summary

- Quantity & Duration of authorization are your only leverage
- Cannabis is a complementary & alternative medicine (CAM) like any other:
  - Worthwhile for symptom relief when EBM is weak and risk is low vs. Rx meds
  - By definition, you are on *thin ice (first, do no harm)*

How?

- Start Low, Go Slow
- Consider a Therapeutic Trial:
  - Define your:
    1. Potential Benefit
    2. Time until reassessed
    3. Potential Harm(s) (monitoring parameters)
    4. Assess 4 possible outcomes

↑Benefit	No Harm
Success Reassess: Continue Rx vs ↑Dose?	

No Benefit	No Harm
Reassess: Discontinue vs ↑Dose?	

↑Benefit	↑ Harm
Reassess: Discuss Benefit vs Risk with patient	

No Benefit	↑ Harm
Failure Discontinue Therapy	

Resources

1. 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. doi:10.17226/24625. Click here
2. Health Canada. Information for Health Care Professionals: Cannabis (marihuana, marijuana) and the cannabinoids [Health Canada, Feb 2013]. http://www.hc-sc.gc.ca/dhp-mps/marihuana/med/infoprof-eng.php .
3. Allan, Michael G. et al. *Simplified guideline for prescribing medical cannabinoids in primary care*. Canadian Family Physician. Feb 2018 Vol 64. Click: here (**NEW**!)

Questions?

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2001
Medical Marihuana Access Regulations (MMAR)

- Supreme court decision 2001
- Health Canada:
  - Determined who qualified
  - Government production and distribution of bud or seeds
  - Access only for specific conditions (few)

Health Canada = Gatekeeper

Health Canada

Ref: A timeline of some significant events in the history of marijuana in Canada. The Canadian Press, 2014. http://cponline.thecanadianpress.com/graphics/2014/medical-marijuana-timeline/ Accessed Oct 24, 2017

2014

Marihuana for Medical Purposes Regulations (MMPR)

- Health Canada:
  - No production / distribution of cannabis/seeds
  - Only via Licensed Producers (LP's)
    - Corporate production
  - Illegal to grow your own

- **Prescribers** determine who gets cannabis
  - Eligibility is not determined by any one condition

Prescriber = Gatekeeper

Ref: A timeline of some significant events in the history of marijuana in Canada. The Canadian Press, 2014. http://cponline.thecanadianpress.com/graphics/2014/medical-marijuana-timeline/ Accessed Oct 24, 2017

2016

Access to Cannabis for Medical Purposes Regulations (ACMPR)

- Court ruling:
  - Allows patients to grow their own cannabis
  - Allows access to cannabis *oils* not just dried cannabis
- Seeds from Licensed Producers

Prescriber = Gatekeeper

Ref: A timeline of some significant events in the history of marijuana in Canada. The Canadian Press, 2014. http://cponline.thecanadianpress.com/graphics/2014/medical-marijuana-timeline/ Accessed Oct 24, 2017

André Picard. Access to medical cannabis regulation will remain in place at least five more years: Health Canada. Published October 12, 2018. https://www.theglobeandmail.com/cannabis/article-access-to-medical-cannabis-regulation-will-remain-in-place-at-least/