Medical cannabis: the evidence

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Disclosure

Financial interests: Lilly (moderator to program)

- **Health Canada**: Core member of Science Advisory Committee on Health Products Containing Cannabis (SAC-HPCC).
- **Australian** Centre for Cannabinoid Clinical and Research Excellence (ACRE): international advisory member
- **Arthritis Foundation US**: international advisor
- **Canadian Rheumatology Association**: lead for pragmatic approach to medical cannabis use for persons with rheumatic diseases

Objectives

- To understand the "cannabis landscape" in Canada

- To be informed of up-to-date evidence for medical cannabis use

- To know about the risks and contraindications for medical cannabis use

The Canadian cannabis context

- Medical cannabis legalized   2001

- Recreational legalization   2018

- 2019 Cannabis market
  - legal/illegal per year $6 billion (1/3 legal)
  - legal recreational cannabis $10.12 (dropping to $7.37/gm)
  - Illegal $5.73/gm

- 15% Canadians used cannabis in 3 months

Pattern worldwide is
medical legalization → decriminalization →recreational legalization

Some $ numbers pertaining to "evidence-based-medicine"

CIHR funding for cannabis research

- 2000-2020 $42.8 million

- Projected 2020 legal annual cannabis sale > $2 billion
- Veterans Affairs expenditure 2018-2019 $75 million

Cannabis industry has limited interest in the medical axis

The research climate (early 2020)

- Funding is mostly from federal government bodies
- Very limited funding from industry

  - Onerous regulations and prolonged delays for new projects
  - Permit required (the Cannabis Act) for any study of product
  - Funding from Govt. and industry has not kept up with demand
  - Funding directed to societal harm reduction (addiction, mental health) not effects of medical cannabis

Effect of legalization on medical cannabis use

- 1000 Rheumatology patients Montreal since recreational legalization[1]

    - Medical use tripled in 5 yrs
    - **13% have tried medical cannabis with ½ continuing to use**
    - Only 1 in 5 accessed entirely via legal medical route
    - Most had no knowledge of molecular contents
    - Only 1 in 3 disclosed use to rheumatologist

1. Fitzcharles et al. ACR Open May 2020

Keep in mind the complexities of the plant

- a 1000 strains, 1000 molecules

- Strains are not consistent from one cultivation to next
  - Growing conditions, harvesting, storage, preparation

- Plant material has contaminants
  - Pesticides, mycotoxins, heavy metals

Has there been a change in evidence in the last decade?

More systematic reviews and meta-analyses of medical cannabis than RCT's

Clinical science is LAGGING BEHIND
The same slide from 2017

- **All conditions**: 79 trials, 6462, **4/79 low bias,** + N&V, pain, spasticity [1]

- **Rheumatic disease**: 71 FM, 30 spine, 58 RA, poor quality, studies, inconsistent [2]

- **Fibromyalgia**: Cochrane. No convincing unbiased evidence for nabilone [3]

1. Whiting et al. JAMA 2015; 2. Fitzcharles et al. Schmerz 2016; 3. Walitt B et al Cochrane 2016;

Problems with cannabinoid RCT's & systematic reviews

- Heterogenous conditions (e.g. neuropathic pains)
- Fruit salad of treatments (pharma + medical cannabis)
- Mostly short duration
- Differing outcome measures

Studies of medical cannabis
- Often from dispensaries, grower's database
- Unknown concentrations of THC and CBD
- Various methods of administration
- Self report diagnoses

Clinical evidence is still lacking

- Pain (Cochrane, Nugent[2], Petze[3], Stockings) [1]
  - low strength evidence for neuropathic pain
  - Small effect on pain overall
  - NNT 20, NNH 3

- Sleep (Babson[4], Whiting[5])
  - CBD may help insomnia, REM sleep disorder, daytime sleepiness
  - Low quality evidence for help sleep disturbance

1. Minerbi. Drugs & Aging 2018. 2.Nugent S et al Annals Int Med 2017. 3. Petze F et al..Schmerz 2016;
4. Babson K. Curr Psychitry Rep 2017; 5.Whiting et al. JAMA 2015

Patients use medical cannabis for…

- Pain…mostly MSK (evidence is for neuropathic & MS pain)
- Mood….especially anxiety
- Sleep difficulties
- Comfort at the end of life

  - Nausea and vomiting related to chemotherapy
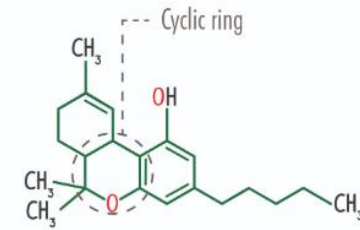 - Severe epilepsy in children

# So let us turn to 2020 and examine what is new

1. CBD

2. Drug interaction

3. Evidence for effects and harms
   - Mental health
   - Cardiovascular risks
   - Psychomotor effect
   - Young person and pregnancy
   - Cancer

1. CBD...why is there promise?

Tetrahydrocannabinol (THC) — Cyclic ring

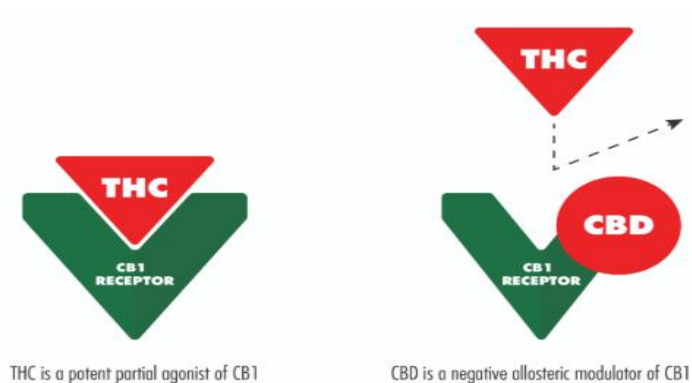Cannabidiol (CBD) — Hydroxyl group

- Anti-inflammatory, analgesic, anxiolytic, antioxidant, antiepileptic

- It can be rubbed onto joints, taken as a few drops, no need to smoke

- Safe ++++ even used in children with epilepsy

  - WHO ...pure CBD is safe, no abuse potential

THC is a potent partial agonist of CB1
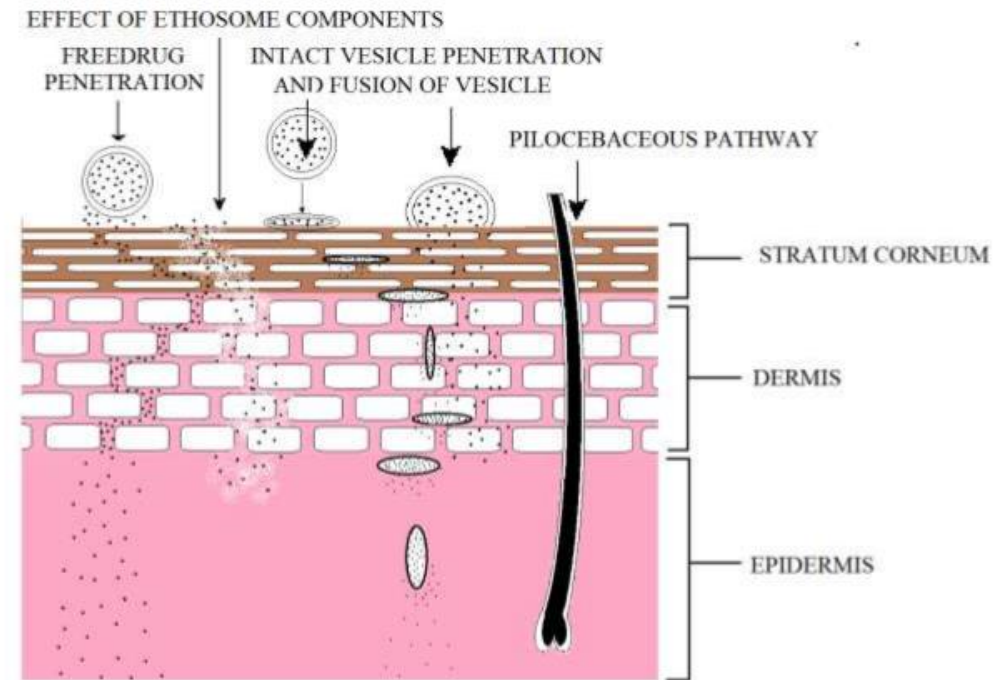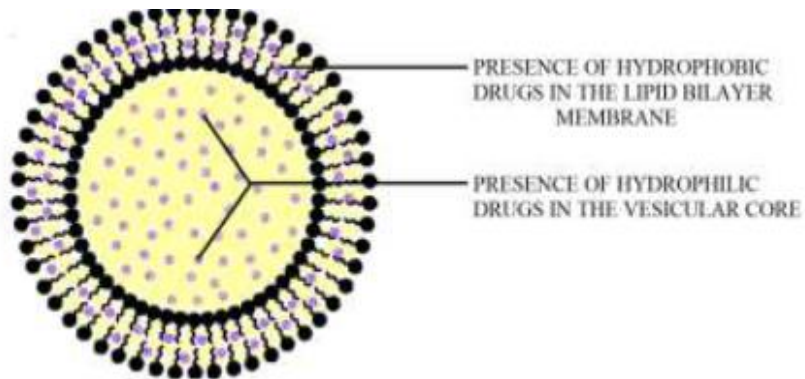
CBD is a negative allosteric modulator of CB1
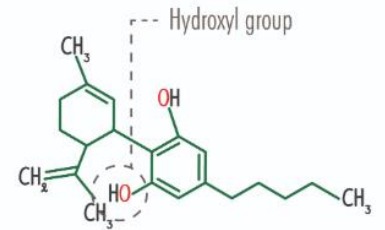
A perfect rubbing compound

- CBD is lipophilic

- Conc. In stratum corneum

- Ethosomal transport

1. Lodzki M et al. J Control Release 2003.

THE ONLY ARTHRITIS STUDY
Transdermal CBD in OA [1]

- Bid application: CBD total 250 mg/day, 500 mg/day, placebo

- 320 patients, mean age 62 yrs, 12 weeks, worst pain 6.9

Results

- Pain reduction not significant between groups -2.6, -2.8, -2.4

- Responder 250 mg CBD vs placebo, 53% vs 34% (p=0.016)

- Men responded better than women

1. Hunter D et al. Osteoarthritis Cartilage 2018

The CBD products

- CBD : OTC, wellness, dietary supplements, hemp oils

- Artisanal products
  - enriched with added cinnamon, cloves, turmeric etc
  - "pure" or boosted CBD up to 20%
  - "full-spectrum" with terpenes, flavonoids (entourage effect)

- **Inaccuracy labelling in US, Europe, Canada** [1,2,3]
  - 84 CBD commercial products analyzed [2]
  - 30% accurate
  - 21% contained THC
  - Mislabeling: vaping products 88%, oils 55%

- FDA warnings to vendors [4]

1. Hazekamp A. Med canna & cannabinoids 2018. 2. Bonn-miller MO et al. JAMA, 2017. 3. Pavlovic R et al. Molecules 2018. 4. FDA Warning letters and test results for Cannabidiol-Related products 2019

CBD dosing

The studies

- Clinicaltrials.gov:

    - opioid use disorder, mental health, epilepsy, Alzheimer's, pain

    - wide variation 20 mg/day to 25mg/kg/day (2000mg)

What patients are using

- A bottle of 30 ml, 10 mg/ml   (total 300mg /bottle)

- A few drops at a time   (2 drops=0.1 ml or 1mg)

Currently little evidence that OTC CBD products have health benefits, and safety has not been investigated [1]

1. Chesney E et al. Ther Adv in psychopharmacology 2020

2. Drug-drug interactions

Theoretical considerations only

- Cannabinoids metabolized via cytochrome P450[1]
  - Limited info in clinical practice
  - THC and CBD inhibit CYP2D6

- CBD is substrate for CYP2C19 and CYP3A4
  - CBD potential ↑antidepressants, ↑gabapentin, ↑tofacitinib, ↓clopidogrel
  - CBD can boost plasma levels of THC
  - Cannabis & tobacco induce CYP1A2..↓ TCA, ↓warfarin

1. Foster BC, et al. Cannabis and Cannabinoids: Kinetics and Interactions. Am J Med. 2019.

3. Evidence for effect and harms related to cannabis

Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis

- Meta-analysis 83 studies, 3067subjects [1]
  - Anxiety, depression, PTSD, Tourette, psychosis

- Results
  - scarce evidence for effect depressive or anxiety disorders, ADHD, PTSD, Tourette syndrome, or psychosis.
  - very low-quality evidence THC±CBD on anxiety with medical illness
  - insufficient evidence to provide guidance for cannabinoids in mental disorders.

1. Black N et al. Lancet Psychiatry Dec 2019

The evidence for harms

The blind men and the elephant: Systematic review of systematic reviews of cannabis use related health harms

- 44 systematic reviews, 1,053 studies

- Evidence shows a **clear association** between cannabis use and
  - Psychosis, affective disorders, sleep problems, anxiety, cognitive failures, respiratory events, CVS & GI disorders
  - Risk factor for MVA's, suicidal behaviour, partner and child violence

- Little info on dose dependency

Campeny E. et al. Eur. Neuropsychopharmacol April 2020.

Cannabis cardiovascular physiological effects 2020

- Activates sympathetic & parasympathetic nervous system
  - Low dose: vasodilatation, tachycardia, ↑myocardial oxygen demand
  - High dose: hypotension, bradycardia, ↓ cerebral blood flow
- Procoagulant effect…CB1 & CB2 platelets
- Vasoconstriction in coronary, cerebral and peripheral arteries
- Increased plasma volume..aldosterone effect
- Tolerance to CV effects occurs rapidly (after a few days) & is lost rapidly with cessation

1. *Latif Z et al. J of Clin Med 2020*

Cardiovascular risks of cannabis [1]

- Myocardial infarction
  - Pediatric reports of MI, cardiac arrest, vasospasm
  - Adults 3800 MI cases, risk ↑4.8-fold after smoking cannabis [2]
  - MI mortality ↑3-fold
  - More frequent use, greater risk of cardiac events
  - Thrombus formation, endothelial dysfunction (STEMI)

- Angina
  - ↓Threshold after cannabis...time to onset symptoms ↓by 50%

- Arrythmias
  - ↑ 2-fold
  - Atrial fibrillation (26%), ventricular fibrillation (22%)

1. Latif Z et al. J of Clin Med 2020. 2 Mittleman M et al. Circulation 2001

Acute psychotomimetic effects cannabis 2020

- Meta-analysis 15 studies, low risk of bias, 331 healthy subjects (mostly male, 20's) [1]
  - Acute cannabis administration…oral, inhaled IVI…tested over 1-2 hrs
  - **1.25-10mg (equivalent of a joint)**

- Results
  - Single use induces acute psychotic (positive), negative symptoms and other psychiatric symptoms with large effect sizes
  - Symptoms not moderated by dose or previous cannabis use
  - CBD did not moderate these effects for 3 of 4 studies

1. Hindley et al. Lancet Psychiatry April 2020

Cannabis and driving[1-2]

- ↑ Lane weaving
- Impaired reaction times
- Drive more slowly
- *Additive effects alcohol, other drugs + cannabis

1. Hartman. *Clin Chem 2013.*, 2.Bondallaz. *Forensic Science International 2016.*

Risk of MVA when driving + cannabis

McGill study (2018)[1]

- Complex driving-related performance was affected at all time points after cannabis use
- 2x ↑ in crash risk at post-cannabis time points
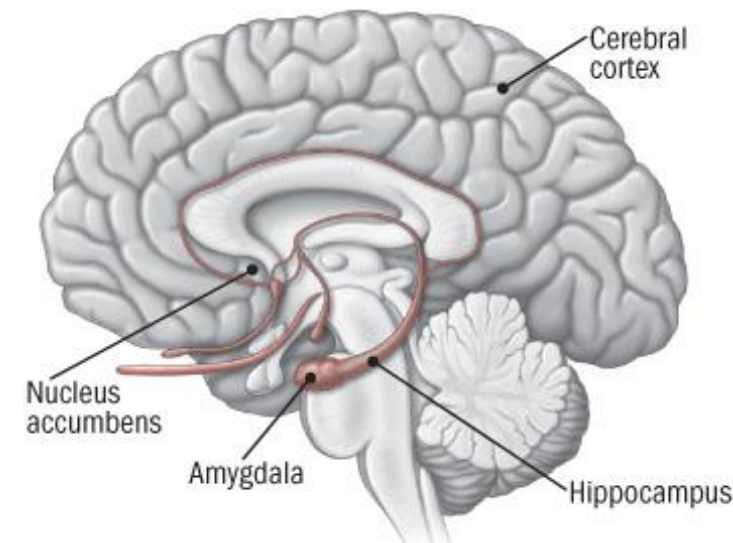- effects up to 5 hours after use

Motor Vehicle accidents

- Transport Canada (2013): Cannabis use 5x risk MVA crash[2]
- Meta-analysis 9 studies, 49,000 (fatalities or serious injuries)[3]
  - cannabis 2x risk fatal or serious MVA

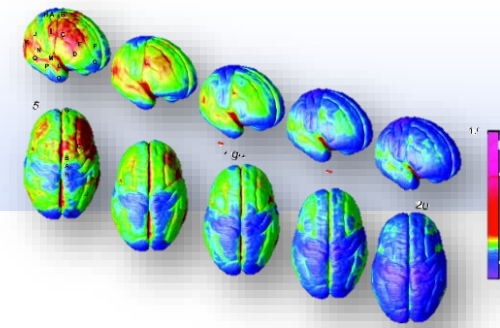1. Ogourtsova T. CMAJ 2018; 2 Beirness et al 2013.; 3. Asbridge M et al BMJ. 2012

Cannabis and dependence

via rewarding effects CB1 receptors & dopamine release in mesolymbic-dopamine reward pathway [1]

- 9% for all users, up to 50% daily users[2]

- MRI changes in **nucleus accumbens, amygdala, prefrontal cortex [3]**
    - young marijuana users (1/week vs.non-users)
    - controlled age, sex, alcohol, cigarettes

1 Cooper Z. Int. Rev. Psychiatry. 2009, 2. van der Pol P. Drug Alcohol Depend. 2013; 3. Gilman J. J of Neuroscience. 2014

Cannabis in the young person

- Less lifetime achievement…education, employment [1]
  - Australia/New Zealand longitudinal 30 yr f/u, 3765 persons
  - ↓high school completion, ↓degree attainment
  - ↑canna dependence (OR 18), other drugs (OR 8), suicide att (OR 7)

- Brain development into 20's
  - CB1 receptor in maturation neurones & brain circuitry [2]

- Risk to trigger psychosis (bidirectional)

1. *Silins et al. Lancet Psych 2014.* 2. *Njoo et al, PloS Biol 2015*
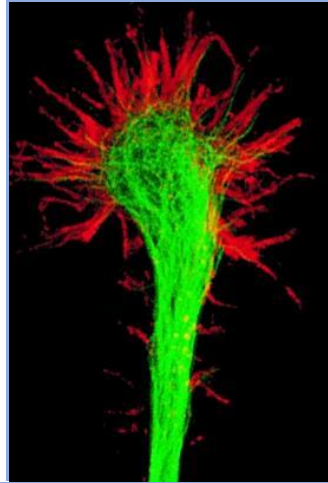
Cannabis in pregnancy.

- US data (Kaiser) 4-7% pregnant women using cannabis
  - 50% by toxicology screen

- Perception safety....65% pregnant women using cannabis reported "no risk"

- Seldom advice from MD....69% Colorado dispensaries suggest use in pregnancy: over 80% staff have no medical training [2]

1. Metz, Borgelt. Obstets Gynecol 2018; 2. Dickson B. Obstets Gynecol 2018

Cannabis in pregnancy…..to think about

- Endocannabinoid system:
  - implantation, blastocyst CB1 receptors on blastocyst [1]
  - CB1 receptor role in differentiation into neurones and glia, axonal migration, synaptogenesis

- Rats + THC (pregnancy/lactation):
  - ↑motor activity, ↓cognition, ↓long term memory, ↓emotional reactivity

- Human pregnancy [2]
  - More anemia, preterm birth, birth weight <2500gm, ↑NICU
  - Stillbirth but not perinatal death [2]

- Offspring
  - More psychopathology in middle childhood [3]

1. Metz, Borgelt. Obstets Gynecol 2018; 2. Gunn BMJ 2016; 3.Paul S. JAMA Psych 2020.

Cannabis and cancer: Checkpoint inhibitors

- 102 patients advanced cancers (lung, melanoma) starting immunotherapy
- 34 with cannabis, 68 no cannabis
- Mostly 20 gram/month, 28/34 inhaled

Results were significant for tumor progression and survival

	users	vs.	non-users
Time to tumor progression:	3.4	vs.	13.1 months
Overall survival:	6.4	vs.	28.5 months

"Collectively, cannabis consumption has considerable immunomodulatory effects, and its use among cancer patients needs to be carefully considered due to its potential effects on the immune system, especially during treatment with immunotherapy."

1. Bar-Sela et al. Cancers 2020

Medical cannabis and the opioid epidemic

Association between medical cannabis laws and opioid overdose mortality has reversed over time

Chelsea L. Shover[a,1], Corey S. Davis[b], Sanford C. Gordon[c], and Keith Humphreys[a,d]

- Bachbunder *JAMA Intern. Med.2014* [1]

  - States with medical cannabis laws ..1999-2010
    - 25% reduced death opioid overdose/100,000 population
    - Cited >350*   **medical cannabis can reverse opioid epidemic**

- Shover replicated the study in 2019 (same methods)[2]
    - similar findings up to 2010
    - after 2010 overdose mortality reversed from -21% to +23%
    - Medical cannabis correlated with use /misuse pain relievers

1. Bachbunder. JAMA2014. 2.Shover et al. Proc Natl Acad Sci 2019

Lessons learned from opioid studies
...applicable to cannabinoid study

- Efficacy in short term studies
  - extrapolating short term results to long term treatment
- Patient exclusions, comorbid illnesses, mental health
- Continued open-label studies...self selected

Canadian Rheumatology Association recommendations: contraindications and cautions [1]

Contraindicated	Caution advised
• <25 years • Allergy • Pregnancy and breastfeeding • History psychosis, substance abuse, suicide ideation/attempts	• Elderly • Unstable mental health • CVS or pulmonary disease • Working in setting requiring concentration, executive function and alertness • Concomitant sedative or psychoactive drugs

1. Fitzcharles M. J of Rheum 2019

If using…..how to use

- Medical cannabis from a licensed producer with known molecular content.

- Lower THC and higher CBD.

- The ideal dosing schedule is not known
  - start with night dose, may slowly increase (max 3 gram /day)
  - Most studies   THC   9% (max)
  - Most patients   1 g/day (a joint 500 mg)
  - Oils/oral   THC or CBD 2.5 mg at night
                            then ↑ 1.25-2.5 mg every 2 days
  - Inhalation   Not recommended

  - Doses > 20–30 mg/day may increase adverse events or induce tolerance

Summary

- Evidence based on RCT's remains limited

- Many studies assessed as "poor quality"

- Positive effects often based on anecdote, dispensary driven data

- Emerging evidence for harms based on population, ecological studies (often recreational users)

- The "industry" is loosing interest in the medical axis

- Cannabis "experts" are self-styled and base recommendations on "eminence" and not "evidence"

Conclusion

Medical cannabis may have a role in care of patients with various medical conditions, but sound evidence is needed.