Cannabinoids and Epilepsy

The science behind the hype

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Disclosures

- Honorarium from UCB Pharma.
- No financial interests in Pharmaceutical or Medical Marijuana provider companies or organizations.

Motivation for the Talk

- Explosion of interest
- Daily questions in clinic from interested patients and families
- Not just people with difficult to control seizures

Motivation for the Talk

- Young person, newly diagnosed, who wants to try this as a first medication.
- Individuals who would smoke marijuana even if they didn't have epilepsy
- Individuals using it to help with other epilepsy or medication-related conditions: anxiety, headache, sleep disturbances, nausea, or just to help them relax at the end of the day.

Common Themes

Need for education around 3 main topics :

1. Reasons for thinking cannabinoids could be useful in treatment of epilepsy.

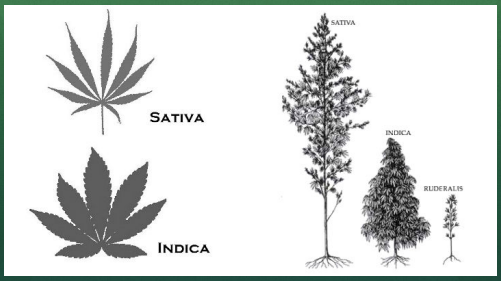
2. What is the state of the evidence we have for cannabinoids as substances that can treat epilepsy, and their safety profile.

3, Need for some education around the Health Canada MMPR regulations.

Cannabinoids: Brief History of Medical Uses

- *Cannabis* genus of flowering plants are mainly comprised by the *Sativa* and *Indica* species.
- Indigenous to Central and South America

Types of Cannabis



Uses for Cannabis

- Used for millennia to make:
  - Hemp fiber for rope and clothing
  - Bowstrings
  - Paper
  - Seeds and oil
  - Livestock feed
  - Medicine
  - Religious ceremonies and recreation.

Cannabinoids: Brief History of Medical Uses

- Two major neuroactive components of cannabis are:
  - Δ^{9}- tetrahydrocannabinol (THC)- psychoactive (I.e: can produce "high"
  - Cannabidiol (CBD)- non-psychoactive
- THC:CBD ratio is thought to be higher in *Indica* species but this is variable and *Sativa* strains can also be have relatively high THC content.
- Cannabis *Indica* is more sedating.

Cannabinoids: Brief History of Medical Uses

- C. *Sativa* has been used in medicinal preparations
  - in China since ~2700BCE,
  - in medieval times by Islamic physicians,
  - Western medicine since 1800's

Cannabinoids: Use for Epilepsy in the Modern Era

- Anecdotal use by 19th Century neurologists Reynolds and Gowers.
- No mention in any texts during 19th C or early 20th C.
- Research begins again in 1960s

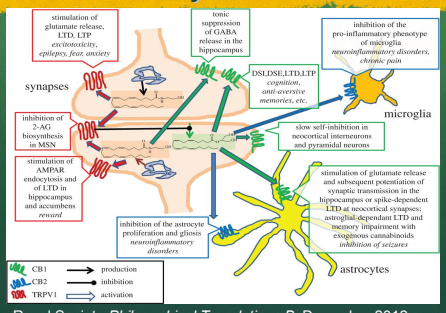
Pharmacology and Mechanisms of Action

- C. *Sativa* produces more than 80 compounds called cannabinoids.
- Present in varying relative proportions depending on the strain.
- Highly lipophilic compounds
- THC isolated first, then CBD was isolated in 1940 and molecular structure elucidated in 1964 and 1963 respectively.
- Most research over the next 30 yrs focused on THC because of its psychotropic effects.

Mechanisms of THC

- Binds to two cell membrane receptors: Cannabinoid type 1 (CB_1) and type 2(CB_2) receptors.
- Why do we have receptors for cannabis in our bodies?
  - We have molecules called *endocannabinoids* naturally occurring in our bodies. Bind CB1 and CB2 and other receptors.
    - Anandamide (CB_1)
    - 2-arachidonoylglycerol (CB_2)

Complex Endocannabinoid System



The Royal Society-*Philosophical Translations B*, December 2012 Volume: 367 Issue: 1607

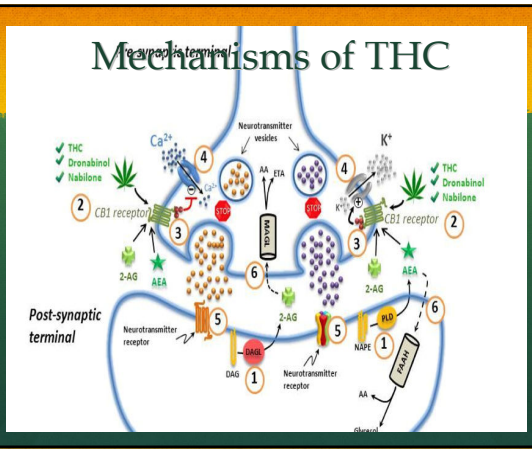
Mechanisms of THC

- CB_1 receptors found in brain (neocortex, hippocampus, basal ganglia and cerebellum>brainstem, spinal cord and peripheral nerves) and peripheral tissues
- CB2 receptors mainly found in immune system (including glial cells in brain) and hematopoietic (blood producing) cells

Mechanisms of THC

- CB1 receptors: are present in
  - inhibitory GABAergic neurons
  - excitatory glutaminergic neurons

Mechanisms of THC



Mechanisms of CBD

- Does NOT activate CB1 or CB2 receptors (likely why it does not have psychoactive properties)
- Interacts with many signaling systems: multi-target.
  - Low concentrations: blocks orphan G Protein coupled receptor GPR55, enhances activity of 5HT1a, a3 and a1 glycine receptors
  - High Concentrations: activate TRPV1 and 2 (important for pain). Potent antioxidant (neuroprotective?), bidirectional effect on intracellular calcium
- May modulate some of THC effects by reducing psychoactive effects.

Summary of THC and CBD actions

- THC
  - Binds to CB1 and CB2 receptors on neurons throughout the brain
  - could be excitatory or inhibitory depending which type of neuron it binds to
  - Produces "high", associated with increased risk psychosis
- CBD can modulate effects of THC (enhance or diminish)
- CBD through action on immune cells in the brain could have an effect on brain inflammation (in theory)

Cannabinoid Effects in Animal Models of Seizure and Epilepsy

Animal Studies with Whole Cannabis or Extracts

- Rat maximal electroshock model (MES) (cannabis resin 17% THC) used: suggested that modulation of serotonergic system mediated anticonvulsant effect (didn't know % or other cannabinoids).
- Dog penicillin –induced model of epilepsy suggested that THC lowered seizure-threshold.

Cannabinoid Effects in Preclinical Models of Seizure and Epilepsy

(B)		
Δ^9-Tetrahydrocannabinol (Δ^9-THC)	Generalized seizure (e.g., MES, PTZ, 6 Hz, 60 Hz, nicotine, and strychnine)	Y
	Temporal lobe epilepsy	Y
Synthetic CB1R agonists (e.g., WIN55-212)	Generalized seizure (MES, PTZ, amygdala kindling)	Y
	Partial seizure with secondary generalization (penicillin and maximal dentate gyrus activation)	Y
	Temporal lobe epilepsy	Y
	Absence epilepsy (WAG/Rij)	Mixed effect
Synthetic CB1R antagonists (e.g., SR141716A)	Generalized seizure (MES and PTZ)	N*
	Absence epilepsy (WAG/Rij)	N
	Partial seizures with secondary generalization (penicillin but not maximal dentate gyrus activation)	N*
	Epileptogenesis (juvenile head trauma but not kainic acid)	Y
Δ^9-Tetrahydrocannabivarin (Δ^9-THCV)	Generalized seizure	Y
Cannabidiol (CBD)	Generalized seizure (MES, PTZ, 6 Hz, 60 Hz, picrotoxin, isonicotinic acid, bicuculline, hydrazine, limbic kindling (electrical), and strychnine but not 3-mercaptopropionic acid)	Y
	Temporal lobe convulsions/status epilepticus	Y
	Partial seizures with secondary generalization (penicillin but not cobalt)	Y
Cannabidivarin (CBDV)	Generalized seizure (MES, PTZ, and audiogenic)	Y
	Temporal lobe convulsions/status epilepticus	Y
	Partial seizures with secondary generalization (penicillin only)	Y
Cannabinol (CBN)	Generalized seizure (MES only)	Y

*Indicates a proconvulsant effect.

Conclusions of animal studies

- THC: activation of CB1 receptors with THC or synthetic CB1 agonists is likely pro-convulsant or at least lowers the seizure threshold. Unlikely to yield therapeutic benefits in epilepsy
- CBD: Good anticonvulsant properties in acute models of seizure. Less evidence in preclinical models of chronic epilepsy. Some likely mechanisms:
  - Modulation intracellular calcium,
  - Anti-inflammatory effects (modulation TNFa release),
  - Inhibition of adenosine reuptake.

Media Storm

Charlotte's Web

- Began having seizures at age 3 mo. Multiple sz types, frequent episodes of status.
- Diagnosed with Dravet Syndrome (SCN1A gene mutation)
- By age 5: Failed all available medication and ketogenic diet.
- Significant cognitive and motor delays. Frequency of up to 50 sz per day.

Charlotte's Web

- Mom found marijuana breeder who provided sublingual extract of a high CBD strain.
- Went from >300sz/week- after 3 months had >90% reduction in GTCs, behaviour has improved and she was starting to walk and talk at 20 months into treatment.
- Strain of marijuana dubbed "Charlotte's web".

Changing Political Scene In USA

- More than half of the States have some law allowing medical marijuana to some extent.
- Washington and Colorado have legalized it for recreation as well.
- Media storm around Charlotte's Web and children with refractory epilepsy has fueled political pressure to allow medical marijuana in different forms, strains.
- Call for more studies/ Epilepsia issue.

Cannabidiol in Humans

Cochrane Review: Cannabinoids for Epilepsy

- Main Results:
  - 4 randomized trial reports that included a total of 48 patients, each of which used cannabidiol as a treatment agent.
  - One was and abstract and one was letter to the editor
  - No investigation as to whether treatment and control group were similar
  - All reports were low quality
  - The 4 reports only answered the secondary outcome re: adverse effects- none.

Cochrane Review: Cannabinoids for Epilepsy

- Objectives: To assess the efficacy and safety of cannabinoids when used as monotherapy or add-on treatment for people with epilepsy.
- Secondary Outcomes: responder rate at 6 mo or more, adverse events, objective quality of life data
- Selection Criteria: RCTs, blinded or not

Table 1. Clinical trials of cannabidiol in epilepsy

Study	Treatments (subjects per group)	Duration	Outcome	Toxicity	Limitations
Mechoulam and Carlini, (1978)[72]	TRE– CBD 200 mg/day (4) TRE– Placebo (5)	3 months	CBD: 2 seizure free; 1 partial improvement; 1 no change	None	No baseline seizure frequency, no definition of improvement; unclear if AEDs were changed; small N/limited power; not truly randomized-blinded; unknown if groups were matched
Cunha et al. (1980)[73]	TRE-TLE CBD (7)[a] TRE-TLE Placebo (8)[a,b]	200–300 mg/day for 3–8 weeks	Last visit: 4 CBD, 1 placebo	Somnolence	Not clearly blinded, since one patient transferred groups and doses were adjusted in CBD, but no mention of this in placebo group and CBD group received had longer average treatment
Ames and Cridland (1986)[74]	IDD–TRE CBD (16)[c] IDD–TRE Placebo (16)[c] × 4 weeks	CBD 300/day × 1 week; 200/day × 3 weeks	No difference between CBD v. Placebo	Somnolence	This was a letter to the editor and details are lacking
Trembly and Sherman (1990)[75]	TRE (10 or 12)[d]	3 months baseline; 6 months placebo Randomized to either 6 months placebo v. CBD 100 t.i.d.; then crossover for 6 months on alternative treatment	No change in seizure frequency or cognitive/behavioral tests	None	Only truly double blind study. Unclear why sample size differed in two reports. Data reported is incomplete

TRE, treatment-resistant epilepsy; TLE, temporal lobe epilepsy; IDD, intellectual developmental disability.
[a]Frequent convulsions for >1 year—1 GTCSs per week.
[b]One patient transferred from placebo to treatment after 1 month.
[c]12 subjects were divided into two groups, but distribution uncertain.
[d]Abstract and subsequent book chapter have different N's (10 and 12).

Cochrane Review: Cannabinoids for Epilepsy

- Author's Conclusions:
  - No reliable conclusions can be drawn at present regarding the efficacy of cannabinoids for the treatment of epilepsy
  - The dose of 200-300mg daily of cannabidiol was safely administered in small numbers of pts. for short periods (months) of time.
  - The safety of long-term cannabinoid treatment cannot be reliably assessed.

Clinical Trial of CBD in Pediatric Epilepsy NYU and UCSF

- Phase I, Observational study of Cannabidiol as a new treatment for Drug Resistant Epilepsies (began Jan. 2014)
- Objectives: Determine tolerability and optimal dose of CBD as an adjunct to treatment of children and young adults with severe drug-resistant epilepsy. Secondary goal: change in seizure frequency.
- Number of subjects: 25
- All subjects will be on the study drug (viscous liquid in dropper 98% pure synthetic CBD) x 1 year after reaching max. dosage. Seizure diaries will be kept.

Clinical Trial of CBD in Pediatric Epilepsy NYU and UCSF

- Preliminary Results: 12 week safety study
- 27pts (age 3-18, avg 10), treatment-resistant epilepsy
- CBD added to other AEDS
- 48% had 50% reduction in sz frequency compared to 4 week baseline.
- 15% seizure-free at end of 12 weeks
- No withdrawal due to side-effects
- Side-effects: somnolent, fatigue, diarrhea, appetite

Clinical Trial of CBD in Pediatric Epilepsy NYU and UCSF

- Study will continue given signal of possible efficacy and good safety.
- There will be separate study specifically for Dravet Syndrome and possibly Lennox-Gastaut

In The Meantime…

- Licensed producers
- Illegal unregulated marijuana dispensaries
- Unknown risks of all the products

Safety in Humans

- Multiple small short-term studies (placebo controlled and open) have demonstrated CBD as well-tolerated across wide dosage range (up to 1500mg/day).
- Many patient years of exposure to Nabiximols (Sativex) following approval in Europe and Canada for MS.

Distribution/Metabolism/ Elimination

- Metabolism and Elimination: metabolized extensively by the liver by cytochrome P450 (CYP3A and CYP2C families).
  - Further metabolism and excreted in feces and to lesser extent in urine.
  - Terminal ½ life is 18-32hrs

Safety in Humans

- Theoretical risk of immunosuppression: CBD shown to suppress IL-8 and 10 production and to induce lymphocyte apoptosis in vitro.
- Drug Interactions:
  - CBD potent inhibitor of CYP2C and CYP3A
  - Many AEDS are substrates for CYP3A
  - CBD metabolized by CYP3A, it is likely that enzyme inducing AEDS could reduce serum CBD levels.

Safety in Pregnancy and Breastfeeding

- Several studies looking at marijuana use during pregnancy have shown increased risk of pre-term labour, low birth weight
- Cannabis is secreted (including CBD) in breastmilk at high concentrations
- Studies also showing long-term negative cognitive effects to children born to mothers and even fathers who have used marijuana in the year prior to pregnant up to ages 10 and 16. No info. Re: CBD alone.
- More research is now being done given legalization of marijuana in many US states.

Safety: Psychiatric

- Many studies of varying quality have shown increased risk of psychosis in adolescents and young adult individuals who have ever used cannabis, dose-dependent risk
- No definite association with mood or anxiety disorders (like depression, anxiety)

Safety: Driving

- You are not supposed to drive while under the influence of marijuana- THC is main focus
- Recent public health study found that motor vehicle accidents related to marijuana use were the most important public health issue to focus on

Health Canada Medical Marijuana Program

Current State of MMPR

- **"Dried marijuana is not an approved drug or medicine in Canada. The Government of Canada does not endorse the use of marijuana, but the courts have required reasonable access to a legal source of marijuana when authorized by a physician."**
- Indication for Medical Marijuana Use for the Treatment of Epilepsy
  - "The current Marihuana Medical Access Regulations (MMAR) allow the use of dried marihuana in the context of epilepsy in patients who experience seizures and who have either not benefited from, or would not be considered to benefit from, conventional treatments (384)."

What are the Canadian Regulations?

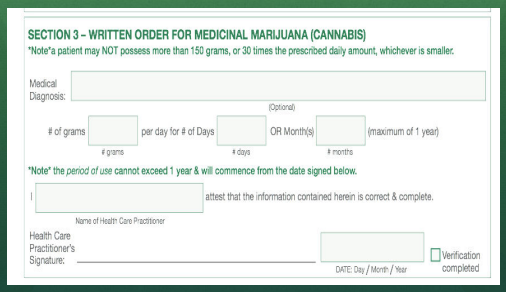
- MMPR is in transition and change is being delayed by the courts.
- The *only* legal medical marijuana in Canada used to be the kind you ordered directly from health Canada (dried or plants).
- All the other marijuana dispensaries are technically illegal, although police tend to turn a blind eye. New regulations: "storefront or retails operations will not be permitted"
- With the new system there are now going to be licensed producers: currently only 18. One based here in Whistler: Whistler Medical Marijuana Corp.

- https://whistlermedicalmarijuana.com

What are the Canadian Regulations?

- They will only be able to access dried marijuana from the producer (no oils, tinctures, capsules, sprays).
- Physician or NP has to fill out a form. Max 150g /month.
- Cost: 7.50$/g +shipping. 2g/day=450$/mo +shipping.

Physician Form



SECTION 3 – WRITTEN ORDER FOR MEDICINAL MARIJUANA (CANNABIS)

*Note*a patient may NOT possess more than 150 grams, or 30 times the prescribed daily amount, whichever is smaller.

Medical Diagnosis: (Optional)

# of grams (# grams) per day for # of Days (# days) OR Month(s) (# months) (maximum of 1 year)

Note the *period of use* cannot exceed 1 year & will commence from the date signed below.

I (Name of Health Care Practitioner) attest that the information contained herein is correct & complete.

Health Care Practitioner's Signature: DATE: Day / Month / Year Verification completed

Dr. Anna Reid
President, Canadian Medical Association
July 2013

- "Asking physicians to prescribe drugs that have not been clinically tested runs contrary to their training and ethics. Expecting doctors to write prescriptions for marijuana without the existence of such evidence is akin to asking them to work blindfolded and potentially jeopardize the safety of patients".

Conclusions

- 1. There are scientific reasons to think that CBD may be a useful anti-convulsant
- 2. There is now preliminary safety data on a pediatric population that pure synthetic CBD is safe and possibly effective for treatment resistant epilepsy and further Phase 2 and 3 studies are ongoing.
- 3.Health Canada MMPR is in flux and court proceedings underway.
- All storefront medical marijuana dispensaries are illegal and unregulated.

References

- 1. Devinsky et al, "Cannabidiol: Pharmacology and Potential Therapeutic Role in Epilepsy and other Neurpsychiatric Disorders",*Epilepsia*,5(6) 791-802, 2014
- 2. Cochrane Collaboration, "Cannabinoids for Epilepsy (A Review)",The Cochrane Library (Issue 3) 2014
- Health Canada Information for Health Professionals: Cannabis and the Cannabinoids