



Facts About Cannabidiol

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Disclosures

- ▶ None
- ▶ I have no financial interests or relationships with the pharmaceutical industry nor marijuana/CBD producers or distributors.

Motivation Behind the Talk



- ▶ Many patients, parents, and/or care providers are interested to know more about cannabis given recent media hype and anecdotal reports of treatment success.
- ▶ People may sense that marijuana is a more 'natural' product than anti-seizure medications prescribed by their physicians, hence may prefer it.
- ▶ Many people smoke marijuana for other reasons (recreational use, anxiety, problems sleeping, nausea, pain, etc).
- ▶ Recent human studies of CBD in epilepsy have been modestly encouraging.



Main points for discussion

1. Review some background information on marijuana/cannabis.
2. Talk about the reasons why cannabinoids could help to treat epilepsy.
3. Discuss the human research that has been done thus far regarding the use of cannabinoids to treat epilepsy and their safety profile.
4. Education around the current Canadian medical marijuana legislation, and upcoming anticipated changes.



Cannabis Background



Cannabis – Multiple Uses

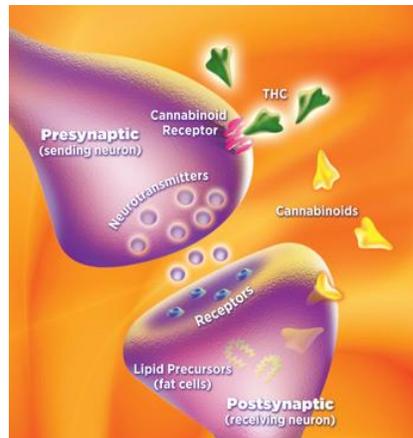
- ▶ **Cannabis** genus of flowering plants indigenous to Central and South America
- ▶ Used for millennia to make: hemp fiber for rope, clothing, bowstrings, paper, for seeds and oil, livestock feed, religious ceremonies, recreation and **medicine**.
- ▶ Hemp is now a worldwide crop: for cordage, construction materials, textiles, edible seeds, milk and oil.





Cannabinoids

- ▶ > 480 known compounds in the cannabis plant; >100 different cannabinoids
- ▶ **Cannabinoids:** chemical compounds which acts on the cannabidiol (CB) receptors
 1. **Phyto**cannabinoids – found in cannabis plant
 2. **Endo**cannabinoids – produced naturally in the body by animals
 3. **Synthetic** cannabinoids – manufactured artificially





Plant Derived Intoxicants



Plant	Intoxicant
Tobacco	Nicotine
Poppy	Heroin, opium
Coca	Cocaine
Grain	Beer, whisky
Grapes	Wine
Cannabis	Marijuana



Cannabinoids: Medicinal Use

- ▶ Two major neuroactive components of cannabis which are the most abundant and extensively studied are:
 1. **THC:** Δ^9 -tetrahydrocannabinol = psychoactive (may produce “high”)
 2. **CBD:** Cannabidiol = non-psychoactive





Cannabis: Two Main Species

1) *C. Sativa*

- ▶ Usually has higher THC:CBD ratio
- ▶ Traditionally used in medicinal preparations



2) *C. indica*

- ▶ Usually more sedating
- ▶ Higher CBD:THC ratio

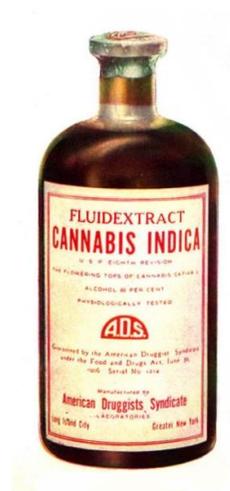




Cannabis: Medicinal History

- ▶ in China since ~2700BCE
- ▶ in medieval times by Islamic physicians
- ▶ Western medicine since 1800's
- ▶ Not mentioned in medical texts 19th- early 20th C
- ▶ THC & CBD structures elucidated in 1963-1964
- ▶ Most research then focused on THC x 30 years
- ▶ Focus more on CBD only in the last few years

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Cannabis: Varying Preparations

Intake by smoking, vaporizing, with food, or as an extract



Dried leaves/flower buds



Kief



Hashish (resin)



Tincture



Hash oil



Dairy butter



Pipe resin



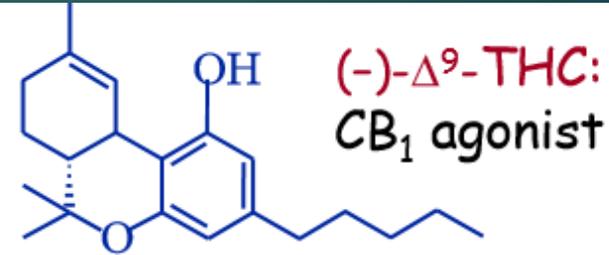
Medicinal Cannabis Use

- ▶ Best medical evidence is currently for:
 - ▶ painful HIV-associated neuropathy (smoked)
 - ▶ chronic pain (nabilone)
 - ▶ chemo induced nausea & vomiting (nabilone)
 - ▶ spasticity in MS patients (Sativex oral spray)



Why might cannabinoids
be used to treat
epilepsy?

Mechanisms of THC



- ▶ Binds to two cell membrane receptors named:
 - ▶ Cannabinoid type 1 (CB₁) and type 2 (CB₂) receptors
- ▶ Anandamide (CB₁) and 2-arachidonoylglycerol (CB₂) are naturally occurring molecules in the body which bind these receptors and are called **endocannabinoids**
- ▶ *These receptors are found in different parts of the body*
 - ▶ **CB₁**: brain (neocortex, hippocampus, basal ganglia, cerebellum > brainstem), spinal cord, peripheral nerves, and peripheral tissues
 - ▶ **CB₂**: immune and hematopoietic cells



The Human Endocannabinoid System

CBD, CBN and THC fit like a lock and key into existing human receptors. These receptors are part of the endocannabinoid system which impact physiological processes affecting pain modulation, memory, and appetite plus anti-inflammatory effects and other immune system responses. The endocannabinoid system comprises two types of receptors, CB1 and CB2, which serve distinct functions in human health and well-being.



Tetrahydrocannabinol



Cannabidiol



Cannabinol



CB1 receptors are primarily found in the brain and central nervous system, and to a lesser extent in other tissues.



CB2 receptors are mostly in the peripheral organs especially cells associated with the immune system.

CBD does not directly "fit" CB1 or CB2 receptors but has powerful indirect effects still being studied.

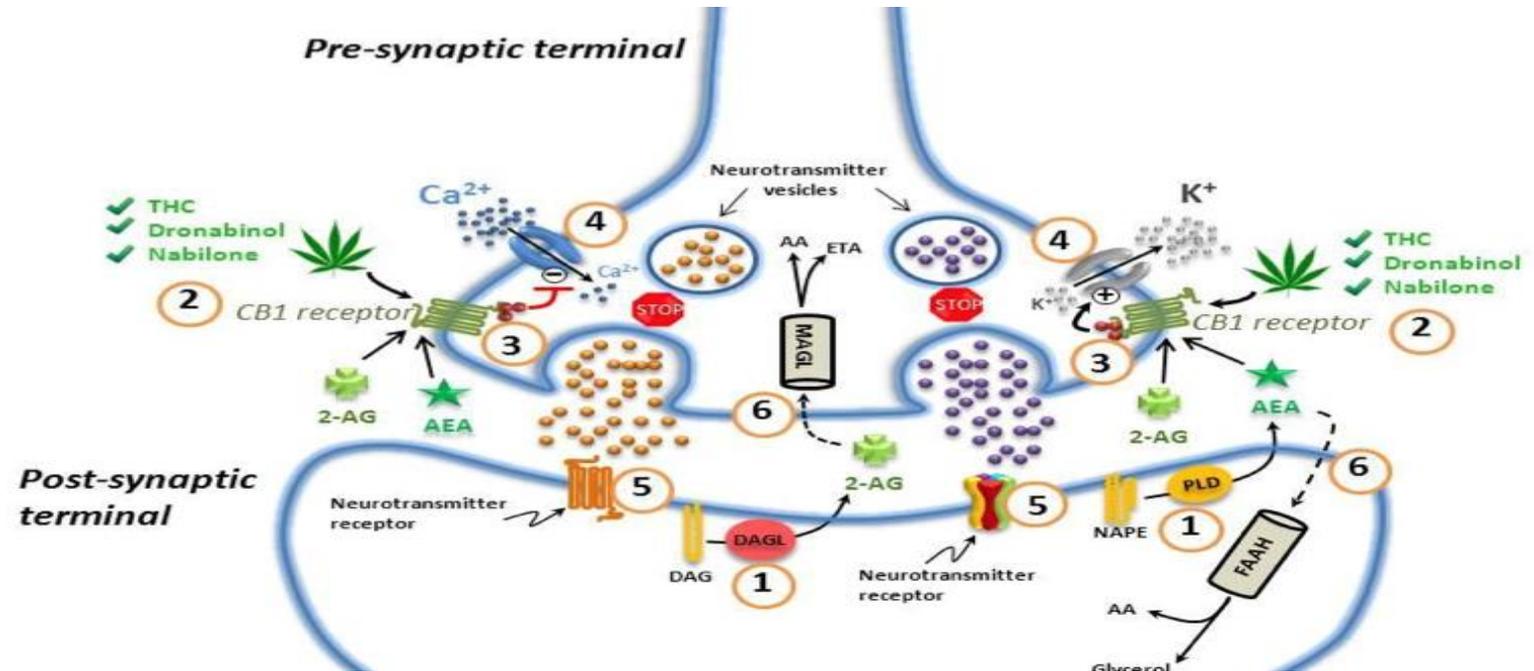
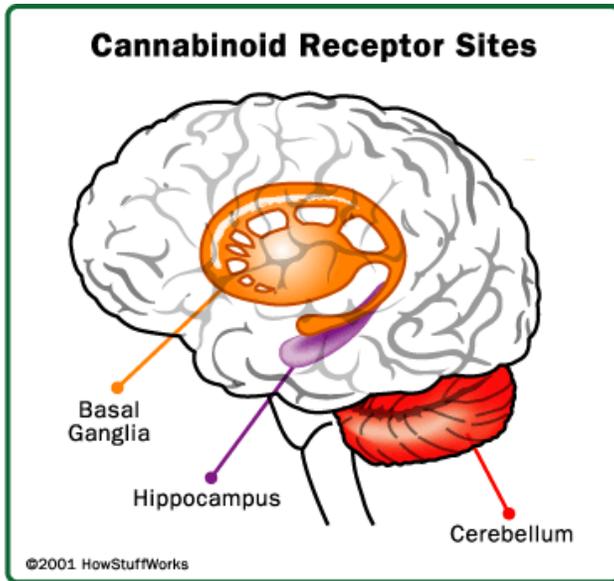
Receptors are found on cell surfaces



source: www.the-human-solution.org



Mechanisms of THC

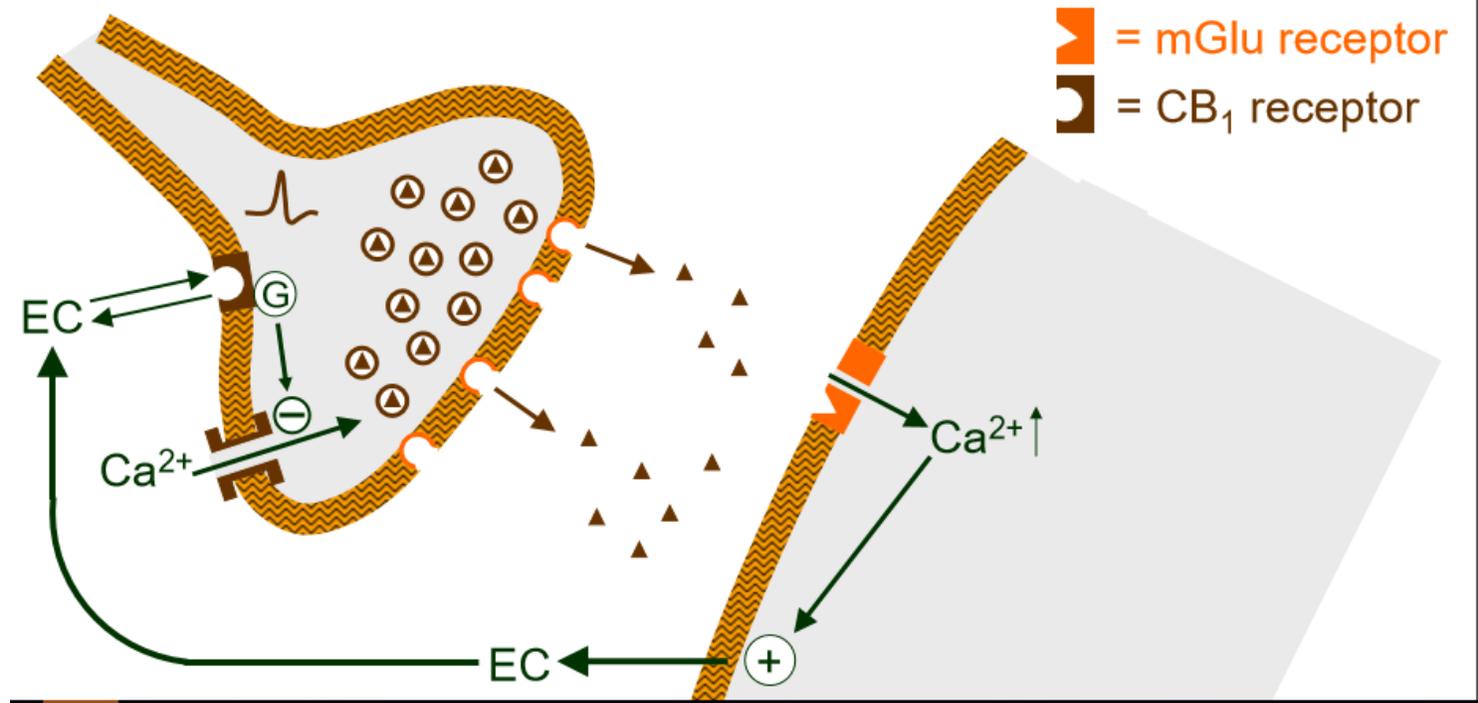


- CB1 receptors: are present in inhibitory GABAergic neurons and excitatory glutaminergic neurons
- May be excitatory or inhibitory, depending on which type of neuron it binds.



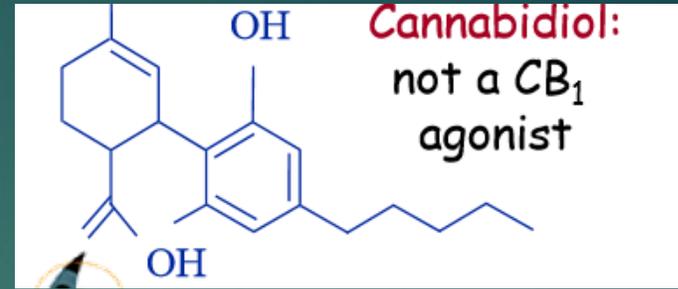
Endocannabinoid System - THC

Endocannabinoid (EC) retrograde signalling between e.g. cerebellar Purkinje cells and presynaptic glutamatergic granule cells (DSE)



Endocannabinoid feedback reduces transmitter release in many different systems

Mechanisms of CBD



- ▶ Does **NOT** activate CB1 or CB2 receptors (likely why it does not have psychoactive properties)
- ▶ Interacts with many non-endocannabinoid signaling systems: multi-target drug.
- ▶ Low concentrations: blocks orphan G Protein coupled receptor GPR55, enhances activity of 5HT1 α , α 3 and α 1 glycine receptors
 - ▶ High Concentrations: activate TRPV1 and 2 (important for pain). Potent antioxidant (neuroprotective?), bidirectional effect on intracellular calcium
- ▶ CBD can enhance or diminish the effects of THC.



Cannabinoid Effects in Preclinical Animal Models of Seizure and Epilepsy

(B) Plant cannabinoid	Animal Model	Efficacy
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 ^a
	Absence epilepsy (WAG/Rij)	N
	Partial seizures with secondary generalization (penicillin but not maximal dentate gyrus activation)	N ^a
	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

^aIndicates a proconvulsant effect.

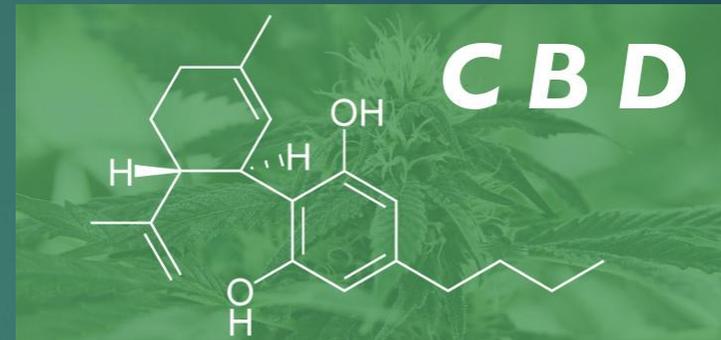


Conclusions from animal studies

- ▶ **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. Over 20 animal models of epilepsy have showed NO pro-convulsant properties. Some likely mechanisms:
 - ▶ Modulation intracellular calcium
 - ▶ Anti-inflammatory effects
 - ▶ Inhibition of adenosine (inhibitory neurotransmitter) reuptake



Cannabidiol Pharmacology





Possible Delivery Routes

- ▶ Inhaled (aerosolization or vaporization)- yield peak plasma concentrations in <10 min.
- ▶ Orally in oil based capsule (absorption from GI tract is erratic. Bioavailability from oral delivery estimated at 6% do to significant first pass liver metabolism.
- ▶ Oral mucosa/sublingual (sprays or lozenges (similar to oral route) but less variable (sativex).
- ▶ Transdermal(skin patch) not practical because of accumulation in the skin.



Distribution/Metabolism/Elimination

▶ Distribution:

- ▶ High fat solubility = rapid distribution in brain, adipose tissue, other organs.
- ▶ Possibility of accumulation in people with chronic use and high adiposity.

▶ Metabolism and Elimination:

- ▶ metabolized extensively by the liver by cytochrome P450 enzyme.
- ▶ Terminal $\frac{1}{2}$ life is 18-32hrs.



Physiologic Effects of Cannabis

Bodily effects of Cannabis

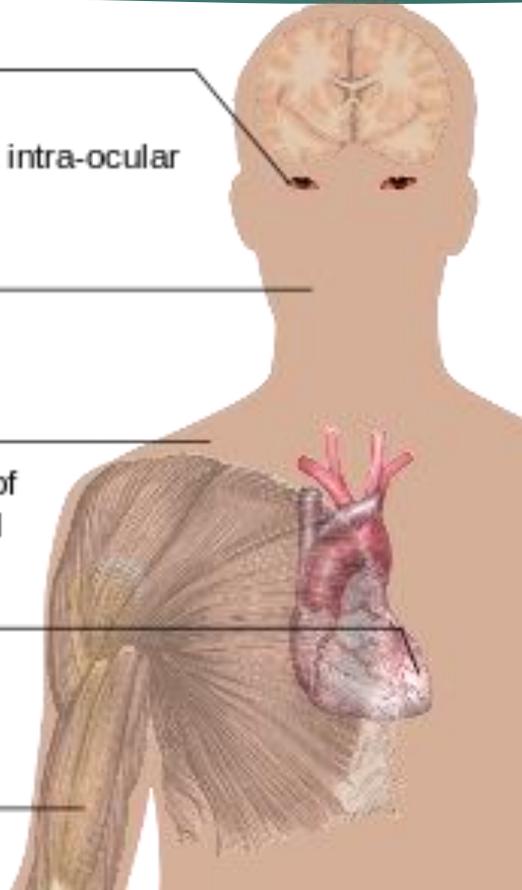
Eyes: ———
- Reddening
- Decreased intra-ocular pressure

Mouth: ———
- Dryness

Skin: ———
- Sensation of heat or cold

Heart: ———
- Increased heart rate

Muscles: ———
- Relaxation





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 following approval in Europe and Canada for MS.
- ▶ Theoretical risk of immunosuppression: CBD shown to suppress IL-8 and 10 production and to induce lymphocyte apoptosis in vitro.
- ▶ Drug-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.



Human Studies of Cannabidiol in Epilepsy

2014 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

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 an 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



▶ Author's Conclusions:

- ▶ **No reliable conclusions** can be drawn 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**.

Case Report → Media Storm



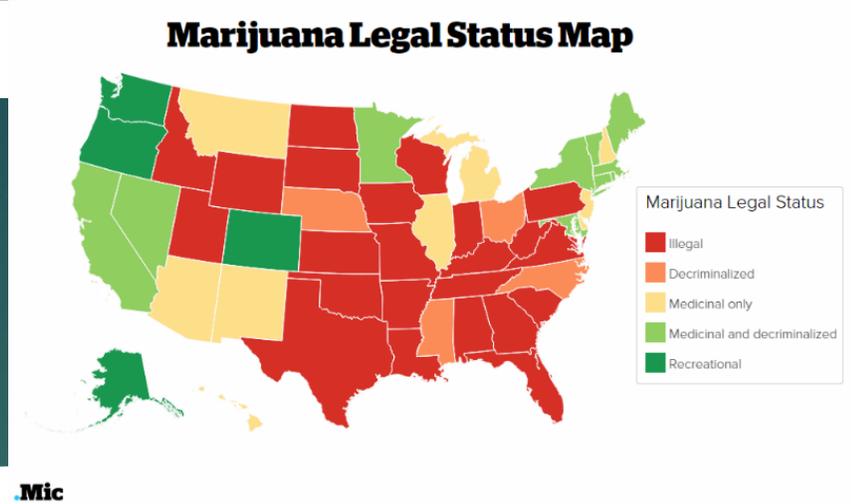
- ▶ Began having seizures at age 3 mo. Multiple sz types and frequent episodes of status. Dx with Dravet Syndrome
- ▶ By age 5: Failed all available medication and ketogenic diet. Significant cognitive and motor delays. Frequency of up to 50 sz per day.
- ▶ Mom found marijuana breeder who provided sublingual 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.”

Surveys Amongst Cannabinoid Users



- ▶ Facebook page for parents of 19 children with TRE using THC/CBD = **84%** improvement in seizure control & **11%** seizure free. (Porter and Jacobson 2013)
- ▶ Survey of 11 parents of children with TRE using CBD enriched cannabis = **100%** improvement in motor seizures & **73%** with complete or near complete seizure control. (Gedde and Maa 2013)
- ▶ Survey of 28 active cannabis smokers with epilepsy = **68%** improved seizure severity & **54%** improved seizure frequency. (Gross et al 2014)
- ▶ Survey of cannabis smokers (13 active; 297 ex-users) with epilepsy = only 2 active users reported improved seizures; 7 ex-users reported worsening of their seizure control. (Hamerle et al 2014)

Changing US Political Scene



- ▶ Media storm around Charlotte's Web and children with refractory epilepsy has fueled political pressure to allow medical marijuana in different forms & strains.
- ▶ Recent unprecedented lay person driven movement has led to approval of medical marijuana in 25 states, with many others have some form of legislation that allows access.
- ▶ Washington and Colorado have legalized marijuana for recreation as well.
- ▶ Yet scientific evidence at the time remained limited.
- ▶ Epilepsia Issue (2014) calls for an urgent need for more studies.



Interval Human Research Focus on CBD

1. CHILDHOOD ONSET TREATMENT REFRACTORY EPILEPSY (TRE)
2. FEBRILE INFECTION-RELATED EPILEPSY SYNDROME (FIRES)
3. STATE SPONSORED TREATMENT PROGRAM OF TRE
4. TRE IN TUBEROUS SCLEROSIS COMPLEX (TSC)



Open Label Trial of Cannabidiol in Severe Treatment Resistant Epilepsy

METHODS

- ▶ **214 patients** aged 1-30 yo with severe (≥ 4 motor component seizures/week) intractable childhood-onset treatment resistant epilepsy who were also on stable ongoing antiseizure medications (mean 3 other agents) +/- ketogenic diet and/or VNS
- ▶ Enrolled across 11 US epilepsy centres
- ▶ Given oil-based oral 99% pure **CBD extract** of constant composition (Epidiolex, GW Pharmaceutical, London, UK) at 2-5mg/kg/day titrated up to 25mg-50mg/kg/day or intolerance of side effects



Open Label Trial of Cannabidiol in Severe Treatment Resistant Epilepsy

SAFETY RESULTS (162 pts had sufficient data)

- ▶ Adverse events reported in 128 pts (**79%**)
 - ▶ Somnolence (25%) *
 - ▶ Decreased appetite (19%)
 - ▶ Diarrhoea (19%)
 - ▶ Fatigue (13%) *
 - ▶ Convulsion (11%)

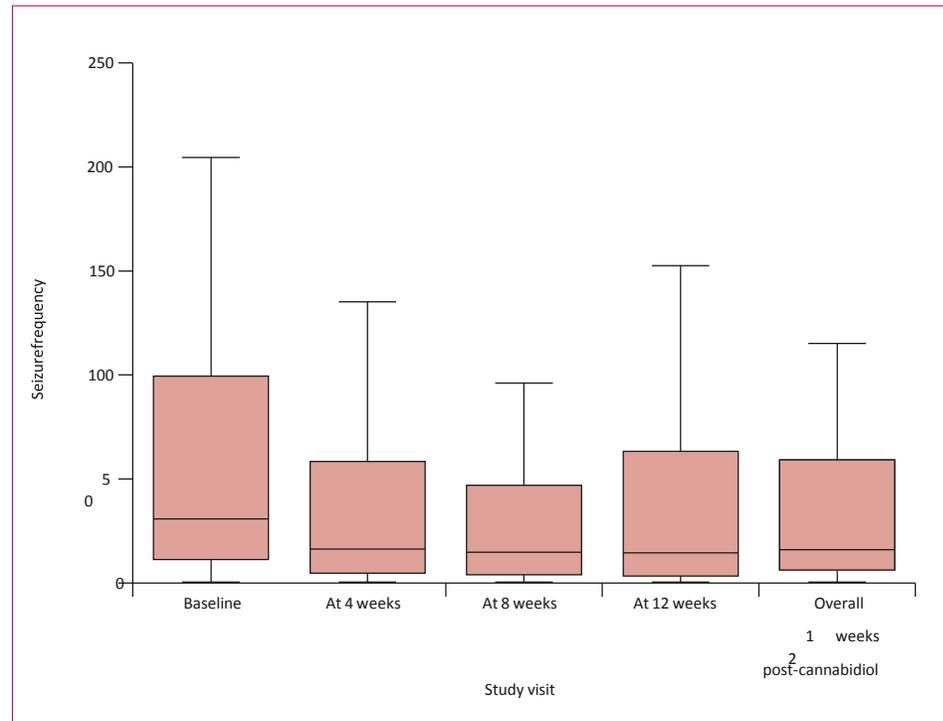
* 50% of those taking clobazam experienced increased somnolence or fatigue
- ▶ Serious adverse events felt to possibly related to CBD in 20 pts (**12%**)
 - ▶ Status epilepticus = most common
 - ▶ Increased liver function abnormalities in those also on valproic acid
- ▶ 3 pts (**5%**) stopped treatment due to serious adverse events



Open Label Trial of Cannabidiol in Severe Treatment Resistant Epilepsy

EFFCACY RESULTS (@ 3 months)

- ▶ Median reduction in monthly motor seizures = **36.5%**
- ▶ **50%** on clobazam had a $\geq 50\%$ seizure reduction
- ▶ 20% had LGS and 20% had Dravet Syndrome
- ▶ Only 20 pts (**12%**) were on CBD > 25mg/kg/d at end
- ▶ 15 pts (**7%**) were motor seizure free in last 4 wks
- ▶ **2%** were free of all seizure types over 12 weeks



Lancet Neurology, 2016



Lancet Study Limitations

- ▶ Unblinded study with no control population
- ▶ Other studies have showed that placebo rates in this population are high
 - ▶ 20% in children and 10-15% in adults
- ▶ Higher placebo rates expected given media attention/many relocated
- ▶ Increased serum concentrations of other AEDs may account for benefit

CBD Therapy in State Sponsored TRE Treatment Program



- ▶ 51 pts (half children) with TRE studied for 6 months on max 50mg/kg/d Epidiolex
- ▶ Statistically significant benefit at dose 25-50mg/kg/day
- ▶ >50% seizure reduction in 56% of adults

CBD for TRE in Tuberous Sclerosis Complex



- ▶ Genetic disease causing epilepsy in 85% of patients, 2/3 have TRE
- ▶ 18 pts studied for 3 months on Epidiolex max 50mg/kg/d
- ▶ Median reduction in weekly seizure frequency = 49%
- ▶ One or more adverse effects in 2/3 (67%)



CBD Use in FIRES

- ▶ Febrile Infection-Related Epilepsy Syndrome
- ▶ Case series of 7 children with very difficult to control status epilepticus
- ▶ Seizure frequency and duration improved in 6/7 patients
- ▶ Publication bias



Canadian Pediatric Studies Underway

- ▶ Open label unblinded, not placebo-controlled
- ▶ Oral CBD (Epidiolex not available in Canada; to apply for FDA approval)
- ▶ Children with refractory epilepsy



Phase 3 Preliminary RCT Study Results

Lennox Gastaut Syndrome

- ▶ 171 pts with LGS on Epidiolex 20mg/kg/d
- ▶ Percentage change in monthly drop attacks: CBD 44% vs. placebo 22%
- ▶ Serious adverse events in 23% CBD vs. 5% placebo
- ▶ Open label extension ongoing



RCT of CBD in Dravet Syndrome

- ▶ 120 children (aged 2 to 18 yo) with refractory epilepsy and confirmed Dravet
- ▶ 20mg/kg CBD vs. placebo x 14 weeks
- ▶ CBD decreased convulsive seizures by around **20 %** compared to placebo
- ▶ Responder rate ($\geq 50\%$ decreased convulsions) **43%** (CBD) vs **27%** (placebo)
- ▶ 3 patients (**5%**) were seizure free on CBD vs. none in the placebo group
- ▶ Caregiver global impression of change scale improved **62%** (CBD) vs **34%** (placebo)
- ▶ Adverse events ($>10\%$): GI (diarrhea, vomiting, decreased appetite), fatigue, lethargy, somnolence, fever, convulsions
- ▶ Study sponsored by industry with one involved MD holding patents.



CBD in Epilepsy Conclusions in 2017

- ▶ CBD is the most promising component of marijuana in terms of seizure prevention, with the role of adjuvant THC remaining unclear.
- ▶ There are subsets of patients with refractory epilepsy who have shown improved seizure control (and rarely even complete seizure freedom) with better quality of life relating to CBD use.
- ▶ CBD seems to be relatively safe, although carries a significant side effect profile (decreased appetite, diarrhea, vomiting, sedation, fatigue), and convulsions may be increased in some.



Cautions Regarding Medical Cannabis

- ▶ Patients should inform their physicians of cannabis use due to drug interactions.
- ▶ Marijuana withdrawal seizures are speculated to occur in some with abrupt cessation.
- ▶ Recent study results can not be extrapolated to:
 - ▶ Patients with milder forms of epilepsy
 - ▶ Non-purified variabilities in CBD preparations and/or additional potential THC effects
 - ▶ A 2015 FDA analysis showed that 33% of OTC cannabidiol preparations contained no cannabinoid.

THC Formulations Carry Different Risks



- ▶ The safety and efficacy of THC (either alone or in various ratios with CBD) remains to be defined in patients with epilepsy.
- ▶ THC has been associated with increased risks of psychosis in teens and young adults.
- ▶ Marijuana use in pregnancy is a/w increased risk of pre-term labor and low birth weight.
- ▶ Long-term negative cognitive effects have been seen to children born to mothers and even fathers who have used marijuana in the year prior to conception.



What is the current Canadian Stance on Cannabis?



The Current Canadian Situation

- ▶ Since the early 20th C, most countries have had laws forbidding the production, sale or transfer of cannabis.
- ▶ The medical use of cannabis is currently legal in:
 - ▶ Australia, Belgium, Canada, the Netherlands, Spain, and 23 US states
 - ▶ “In Canada, it is against the law to possess, sell, give away, or grow marijuana without legal permission from Health Canada. People who have certain health problems can buy a limited amount of marijuana for their own use, and licensed people can grow and provide medical marijuana to those who need it.”



The Current Canadian Situation

“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.”

ACMPR

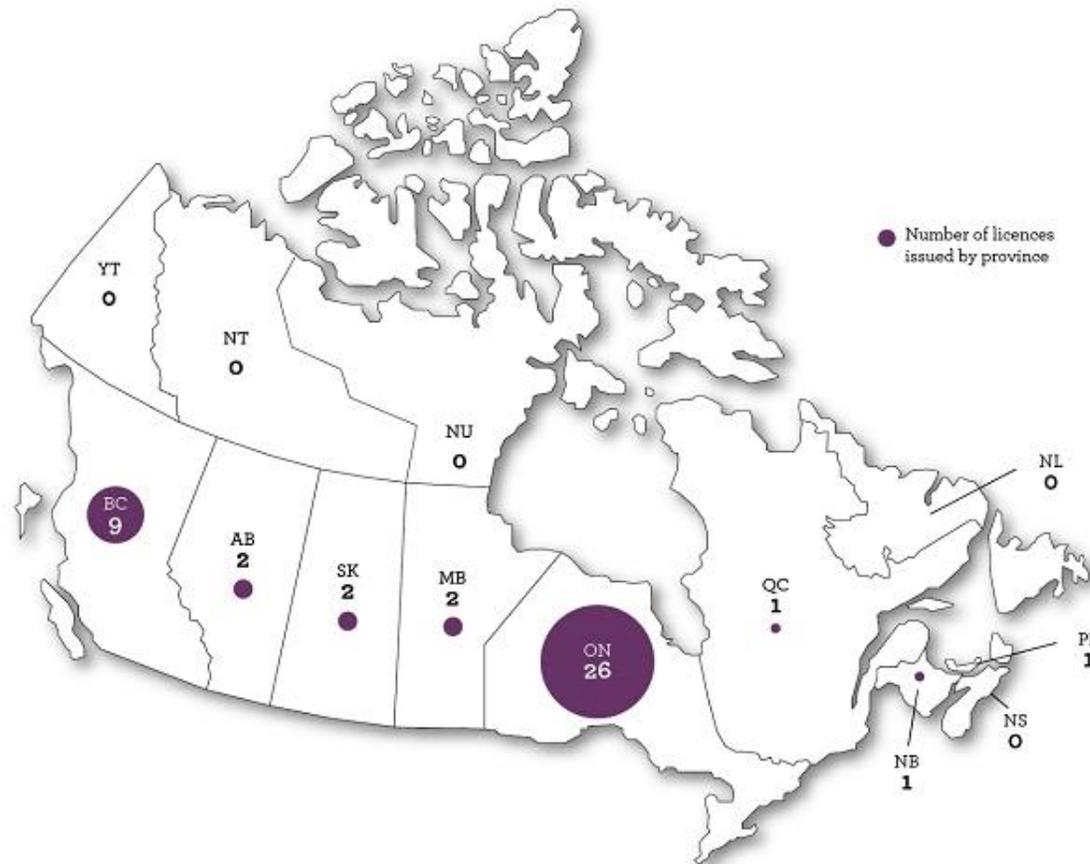


- ▶ **Access to Cannabis for Medical Purposes Regulations (ACMPR)** – Aug 2016
- ▶ Replace the prior Marijuana for Medical Purposes Regulations (MMPR)
- ▶ “Under the ACMPR, Canadians who have been authorized by their health care practitioner to access cannabis for medical purposes will continue to have the option of purchasing safe, quality-controlled cannabis from one of the [producers licensed](#) by Health Canada. Canadians will also be able to produce a limited amount of cannabis for their own medical purposes, or designate someone to produce it for them.”
- ▶ Marihuana Medical Access Program at 1-866-337-7705

<http://www.hc-sc.gc.ca/dhp-mps/marihuana/about-a-propos-eng.php>



Health Canada Authorized Licensed Producers for Medical Purposes



<http://www.hc-sc.gc.ca/dhp-mps/marihuana/info/list-eng.php>

Liberal to announce marijuana will be legal by July 1, 2018





Summary of Facts about Cannabidiol

What we know	What we don't know
The brain has CBD1 receptors, where THC acts	The exact mechanism of action of CBD
Purified CBD is a compound with promise in epilepsy	The effects of CBD in combination with THC in epilepsy
CBD has been a/w modest short term improvements in seizure control	The longer lasting effects of CBD on seizure control
Children with severe refractory epilepsies (Dravet, Lennox Gastaut) may have some benefit from CBD use	Whether there is any potential benefit in those with milder better controlled epilepsy



Questions?

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Special thanks to Dr. Tiffany Townsend for having shared her prior slides on this topic.

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