UNITY • STRENGTH • HOPE
JUNE 24-26 • EAGLEWOOD RESORT, ILLINOIS • 2016
RETT SYNDROME, MECP2 DUPLICATION, CDKL5 DISORDER, FOXG1 DISORDER
FAMILY CONFERENCE

Nothing replaces the experience
of meeting face-to-face
Medical Cannabis

Tim Feyma MD
Gillette Children’s Specialty Healthcare
Medical Cannabis: Agenda

• Introduction
• 2 Patients
• History
• Pharmacology
• Evidence / Experience
• 2 Patients Follow Up
• Summary
Medical Cannabis: Introduction
Medical Cannabis: Introduction

My personal introduction to the potential use of medical cannabis in 2006:

Esteemed emeritus professor: *Marijuana works for epilepsy it’s just a sh&#%! anti-convulsant.*
Marijuana stops child's seizures

Parents move to Colorado for medical marijuana

Pivotal Point Is Seen as More States Consider Legalizing Marijuana
3/20/2014 statement: The Epilepsy Foundation supports the rights of patients and families living with seizures and epilepsy to access physician directed care, including medical marijuana.
Medical Cannabis: 2 Patients
Medical Cannabis: 2 Patients

- 4yo CDKL5 female
  - Intractable focal / generalized epilepsy, history infantile spasms
  - Weekly seizures, rare rescue med dosage
  - On 2 anti-seizure meds / keto diet, failed 3 meds

- 17yo MECP2 female
  - Intractable focal and generalized seizures
  - Seizures weekly, needs up to 12 seizure rescue med doses per month
  - On 3 anti-seizure meds, failed 12 med trials
Medical Cannabis: History
Medical Cannabis: History

• Marijuana for medical purposes has been documented for centuries

From Library of King Ashurbanipal http://www.britishmuseum.org/
And more recently in Victorian times as seen in *Epilepsy and Other Chronic Convulsive Diseases* published in 1881 by WR Gowers MD:

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John K., aged 40, came under treatment in 1868, having suffered from fits for twenty-five years. They occurred during both sleeping and waking, at intervals of a fortnight. There was a brief warning, vertigo, then loss of consciousness, and tonic and clonic spasm followed by some automatism; —‘acts strangely and cannot dress himself.’ The attacks ceased for a time on bromide, but recurred when he discontinued attendance. He came again in October 1870; scruple doses of bromide of potassium three times a day had now no effect, and the fits, at the end of four months’ treatment, were as frequent as ever. Ext. cannabis indica gr. $\frac{1}{4}$, three times a day, was then ordered; the fits ceased at once, ‘a wonderful change’ the patient declared. He had no fit for six months, and then, having discontinued attendance, the fits recurred, but were at once arrested by the same dose of Indian hemp. He continued free from fits for some months, until, during my absence, bromide was substituted for the Indian hemp; the fits immediately recurred, and he left off treatment. He returned to the hospital in six months’ time, and on Indian hemp passed two months without an attack. In the third month another fit occurred, and the patient again ceased to attend, and did not return.
Medical Cannabis: History

• Small studies in the later 20th century were done on use of cannabidiol in epilepsy:

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatments (subjects per group)</th>
<th>Duration</th>
<th>Outcome</th>
<th>Toxicity</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechoulam and Carlini (1978)</td>
<td>TRE – CBD 200 mg/day (4)</td>
<td>3 months</td>
<td>CBD: 2 seizure free; 1 partial improvement; 1 no change</td>
<td>None</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>TRE – Placebo (5)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Gunha et al (1980)</td>
<td>TRE-TLE CBD (7)</td>
<td>200–300 mg/day for 3–18 weeks</td>
<td>Last visit: 4 CBD, 1 placebo</td>
<td>Somnolence</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>TRE-TLE Placebo (8)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ames and Cridland (1986)</td>
<td>IDD-TRE CBD (16)</td>
<td>CBD 300/day × 1 week; 200/day × 3 weeks</td>
<td>No difference between CBD v. Placebo</td>
<td>Somnolence</td>
<td>This was a letter to the editor and details are lacking</td>
</tr>
<tr>
<td></td>
<td>IDD-TRE Placebo (16)</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Tremblay and Sherman (1990)</td>
<td>TLE (110 or 12)</td>
<td>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</td>
<td>No change in seizure frequency or cognitive/behavioral tests</td>
<td>None</td>
<td>Only truly double blind study. Unclear why sample size differed in two reports. Data reported is incomplete</td>
</tr>
</tbody>
</table>

TRE, treatment-resistant epilepsy; TLE, temporal lobe epilepsy; IDD, intellectual/developmental disability.

*Frequent convulsions for ≥1 year; 1 GTCSx per week.

*One patient transferred from placebo to treatment after 1 month.

*12 subjects were divided into two groups, but distribution uncertain.

Abstract and subsequent book chapter have different N’s (10 and 12).
Medical Cannabis: History

• Interest was renewed in regard to Cannabis therapeutics with discovery a brain cannabinoid signaling system

Isolation and Structure of a Brain Constituent That Binds to the Cannabinoid Receptor

William A. Devane,*† Lumir Hanuš, Aviva Breuer, Roger G. Pertwee, Lesley A. Stevenson, Graeme Griffin, Dan Gibson, Asher Mandelbaum, Alexander Etinger, Raphael Mechoulam†
Medical Cannabis: History

• Medically intractable epilepsy combines with social media and marijuana interest
### Medical Cannabis: History

#### Uses for Neurologic reasons:

<table>
<thead>
<tr>
<th>Neurologic disorder</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spasticity</td>
<td>OCE is effective; THC and nabiximols are probably effective for patient-rated spasticity scores</td>
</tr>
<tr>
<td></td>
<td>OCE is probably ineffective for short-term reduction of objective spasticity scores</td>
</tr>
<tr>
<td></td>
<td>OCE and THC are possibly effective in reducing both patient-rated and objective spasticity measures at 1 y</td>
</tr>
<tr>
<td></td>
<td>Smoked marijuana is of uncertain efficacy for spasticity</td>
</tr>
<tr>
<td>Central/neuropathic pain and painful spasms of MS</td>
<td>OCE is effective in reducing central pain</td>
</tr>
<tr>
<td></td>
<td>THC and nabiximols are both probably effective in MS-related pain or painful spasms</td>
</tr>
<tr>
<td></td>
<td>Smoked marijuana is of uncertain efficacy for MS pain</td>
</tr>
<tr>
<td>Bladder dysfunction</td>
<td>Nabiximols is probably effective in reducing the number of bladder voids per day at 10 wk but is of unknown efficacy in reducing bladder complaints overall</td>
</tr>
<tr>
<td></td>
<td>THC and OCE are both probably ineffective in bladder complaints</td>
</tr>
<tr>
<td>Tremor in MS</td>
<td>THC and OCE are probably ineffective in MS-related tremor</td>
</tr>
<tr>
<td>Huntington disease</td>
<td>Nabilone and CBD are of uncertain efficacy in HD as the studies were underpowered</td>
</tr>
<tr>
<td>Dopamine-related dyskinesia in PD</td>
<td>Cannabinoids probably ineffective in PD dyskinesia</td>
</tr>
<tr>
<td>Tourette syndrome; cervical dystonia</td>
<td>THC efficacy for Tourette syndrome and dronabinol efficacy in cervical dystonia are both unknown</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>There is insufficient quality evidence regarding the efficacy of cannabinoids in reducing seizure frequency for patients with epilepsy</td>
</tr>
</tbody>
</table>

Abbreviations: CBD = cannabidiol; HD = Huntington disease; MS = multiple sclerosis; OCE = oral cannabis extract; PD = Parkinson disease; THC = delta-9-tetrahydrocannabinol.
Medical Cannabis: History

Marijuana Legalization Status

- **Medical marijuana legalized**
- **Marijuana legalized for recreational use**

Current May 2016 from:
Medical Cannabis: Pharmacology
Medical Cannabis: Pharmacology

- The *Cannabis* genera used most are *sativa* and *indica*

- More than 545 distinct compounds isolated from *Cannabis* species

- Most abundant chemicals are cannabinoids, >80 types of 21 carbon molecules. Delta-9-tetrahydrocannabinol (THC) and cannabidiol most abundant compounds.

Medical Cannabis: Pharmacology

- Major cannabinoid Brain receptor is cannabinoid receptor 1 (CB1R) that is a presynaptic, G-protein-coupled receptor that activates voltage-gated calcium channels & enhances potassium-channel conduction in presynaptic terminals.

- Studies have suggested that the endocannabinoid system plays a role in inhibition of seizures
Medical Cannabis: Pharmacology

- Cannabinoids are fat soluble

- Delivery routes have included smoked, aerosolized, oil based capsules, lozenges, and transdermal
  - Bioavailability from oral delivery is variable, but has been estimated to be 6% due to first pass metabolism. (Inhaled = 31%)

- Half life of cannabinoids can be 4 hours orally, cannabidiol specifically 2-5 days


Medical Cannabis: Pharmacology

- Extensively liver metabolized by hydroxylation via cytochrome P450 enzymes with many metabolites with eventual excretion mostly in stool and to a lesser extent in the urine. Metabolic substrates
  - CBD is a major substrate for CYP450 3A4 & 2C19
  - THC is a major substrate for CYP450 3A4 & 2C9

(Geffrey AL 2015 – 13 patients on cannabidiol and clobazam - mean increase in N-desmethylclobazam was 500 +/- 300%)
Medical Cannabis: Pharmacology

• Hypothetical 3A4 Interactions:
  - **Substrates**
    - Carbamazepine
    - Clobazam (documented)
    - Ethosuximide
    - Felbamate
    - Perampanel
    - Phenytoin
    - Tiagabine
    - Zonisamide
  - **Inducers**
    - Eslicarbazepine
    - Oxcarbazepine
    - Phenobarbital
    - Rufinamide
    - Topiramate

Medical Cannabis: Pharmacology

• Extracted cannabinoids versus botanicals, is one better?

• Beware:
  – In 2015 the FDA tested 18 over the counter products claiming to contain cannabidiol to help treat disease
  – 7/18 products contained no cannabidiol

http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm435591.htm
Medical Cannabis: Evidence / Experience
Medical Cannabis: Evidence / Experience

• Newer studies (Good):
  
  – Press et al 2015: retrospective case series of children cared for at epilepsy center with refractory epilepsy had >50% reduction in 33% of patients on oral cannabis extracts.
  
  – Devinsky et alia 2015: prospective open label 12 week trial of purified cannabidiol extract treating kids + young adults with severe childhood-onset epilepsy led to median reduction in monthly motor seizures by 36.5%.
Medical Cannabis: Evidence / Experience

• Newer Studies a closer look at Devinsky et alia 2015:

  – Adverse events were reported in 128 (79%) of 162 patients.
  • >10% of patients were somnolence, decreased appetite, diarrhea, fatigue, and convulsion
  • Serious adverse events in 30%, less than half of which here thought related to cannabidiol use, the most common of which was status epilepticus 6%
Medical Cannabis: Evidence / Experience

• Newer studies (Concerning):

  – Battistella G et alia 2014: Regular cannabis use is associated with gray matter volume reduction in the medial temporal cortex, temporal pole, parahippocampal gyrus, insula, and orbitofrontal cortex.

  – Knupp K et alia 2016 AAN abstract: If the family moved to CO for OCE, they were more likely to report benefit of OCE as compared to families who were already living in CO (68% vs 36%, p=0.004).
Medical Cannabis: Evidence / Experience

• The future:

| Recruiting | The Use of Medicinal Cannabinoids as Adjunctive Treatment for Medically Refractory Epilepsy |
| Condition: | Epilepsy, Unspecified, Refractory (Medically) |
| Intervention: | Drug: Medical Cannabis |

| Available | Epidiolex and Drug Resistant Epilepsy in Children |
| Condition: | Epilepsy |
| Intervention: | Drug: Cannabidiol (Epidiolex) |

| Recruiting | Cannabidiol (CBD) and Pediatric Epilepsy |
| Condition: | Epilepsy |
| Intervention: | |

| Recruiting | Genetic Analysis Between Charlotte's Web Responders Versus Non-Responders in a Dravet Population |
| Condition: | Dravet Syndrome |
| Intervention: | |
Medical Cannabis: Evidence / Experience

• Minnesota experience:
  – Lobbying by parents of children with severe epilepsy helped get medical marijuana law passed 5/29/14

  – 2 licensed manufacturers
    • Pills, oils or vaporizers but no dried leaves or plants
    • Patients agree to provide access to medical data for purposes of observational studies
Minnesota qualifying medical conditions:
- Cancer
- Glaucoma
- HIV/AIDS
- Tourette’s
- ALS
- Seizures
- Severe and persistent muscle spasms
- Crohn’s disease
- Terminal illness with life expectancy of under one year
- Chronic pain
Medical Cannabis: Evidence / Experience

- Patient has a qualifying condition
- Health care practitioner certifies condition
- Patient* registers information, proof of I.D. & payment
- Approved patient is added to registry
- Medical cannabis may now be obtained at any of the cannabis patient centers across the state

DID YOU KNOW THAT MINNESOTA IS THE FIRST STATE PROGRAM IN THE COUNTRY TO OFFER ONLY SMOKE-FREE MEDICAL CANNABIS?

- No smoke
- No plants
- Pill
- Liquid
- Oil

2 Manufacturers: Authorized regulated inspected

Cannabis patient centers:
- Hibbing
- Moorhead
- St. Cloud
- Minneapolis
- St. Paul
- Eden Prairie
- Eagan
- Rochester

*Care-giver may represent a patient by applying and meeting conditions including a background check.

MDH
Minnesota Department of Health
Medical Cannabis: Evidence / Experience

• I currently have 31 certified patients as of 6/24/2016

• 4 have found benefit.

• $$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$
Medical Cannabis: 2 Patients Follow Up
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Medical Cannabis: 2 Patients

• 4yo CDKL5 female
  – No benefit observed after a 2 month trial of cannabidiol oil that titrated to

• 17yo Rett female
  – Seizures lessened until an illness returned them to baseline
  – Benefits of increased alertness and better posture / walking sustained
Summary

• Medical cannabis holds promise as a potential helpful therapy

• It is not a miracle drug and can have impact on other meds being given

• Be mindful of your source should you try it
QUESTIONS?