CNF Symposium: Cannabis in Epilepsy
State of Science: Cannabis

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Disclosures

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The unmet need in refractory epilepsy: making a case for cannabidiol

- *Not a new idea - what can history teach us?*
- *Do possible mechanisms of action make sense?*
- *What do the preclinical studies suggest?*
- *What is the clinical "data"?*
- *What do we need to know?*

The unmet need in refractory epilepsy: making a case for cannabidiol

- *Cannabis used as medical treatment for thousands of years*

  - 2200 BCE, Sumaria
    first documented use in epilepsy
  - 1100 CE, *al-Mayusi*
    nasal treatment with cannabis leaf for seizures
  - 1400's CE, *al-Badri*
    regular use of cannabis for epilepsy

Making a case for cannabidiol: Use of cannabis in treating epilepsy

- *1842: O'Shaughnessy reported cannabis reduced infantile convulsions, hydrophobia (rabies), lockjaw (tetanus) and rheumatism*

- *1856: McMeans reported successful use of tincture of cannabis indica in 4 children with epilepsy, including 7 week female*

Ley, Provincial Medical and Surgical Journal, 1842
McMeens, Western Lancet 1856

Making a case for cannabidiol: Use of cannabis in treating epilepsy

- *1881: William Gowers reported cannabis had been recommended for epilepsy by Russell Reynolds in 1861 as "sometimes, though not very frequently, useful…small value as an adjunct to the bromide, but is sometimes of considerable service given separately…"*

- *Gowers administered cannabis in many cases, with the effect of delaying paroxysms and mitigating the severity in some individuals*

Gowers WR (1881) Epilepsy and other chronic convulsive disorders. Churchhill, London 223-224.

Making a case for cannabidiol: Use of cannabis in treating epilepsy

- *1851: US Dispensary*
  Cannabis compounds suggested for neuralgia, depression, hemorrhage, pain relief and muscle spasm, convulsive disorders and other ailments

- *1860: Ohio Medical Society Committee on Cannabis Indica: Efficacy claimed for infantile convulsions, epilepsy and many other disorders*

Making a case for cannabidiol: Use of cannabis in treating epilepsy

- *1911: Massachusetts first state to outlaw cannabis (in setting of prohibition of alcohol)*
  - » Other states quickly followed with marijuana prohibition laws

- *1970: US Controlled Substances Act passed, classifying marijuana as a drug with "no accepted medical use."*

Making a case for cannabidiol: Use of cannabis in treating epilepsy

- *1996: California becomes first state to legalize medical marijuana*
- *2015: Medical marijuana legalized in 23 US states*
  - » Regulated at state level
  - » CBD specifically made legal in an additional 16 states
- *Increasing anecdotal reports about efficacy of medical marijuana, especially CBD-enriched formulations in the treatment of refractory pediatric epilepsy*

Medical marijuana: is it effective in treating refractory epilepsy?

- *Solicited data from an online Facebook survey of 150 families whose children were using cannabidiol-enriched cannabis to treat drug resistant seizures*

- *19 responses (12.7%): 13 Dravet syndrome, 4 Doose syndrome, 1 Lennox-Gastaut syndrome, 1 idiopathic epilepsy*
  - Average of 12 prior AEDs

Medical marijuana: is it effective in treating refractory epilepsy?

- *Overall, 84% noted decreased seizure frequency on CBD:*
  - » 2 (11%) had complete remission
  - » 8 (42%) had >80% reduction in seizure frequency
  - » 6 (32%) had 25-60% reduction

- *Cannabidiol was associated with adverse events:*

  Drowsiness: 37%, Fatigue: 16%

- *and with some side benefits:*

  Better mood: 79%,Increased alertness: 74%

  Better sleep: 68%

Medical marijuana: is it effective in treating refractory epilepsy?

- *Online survey of parents of children with epilepsy who had used CBD products*
  - 117 responses
    - Mean latency from epilepsy onset to CBD use 5 years
    - Mean of 8 prior medication trials
  - Included 53 with IS or LGS

- *85% reported reduction in seizure frequency*
  - 14% seizure free
  - Many reported improved sleep, alertness and mood

Medical marijuana: is it effective in treating refractory epilepsy?

- *Survey study limitations:*
  - Subject to participation bias
  - Unknown formulations
  - No control group

Cannabidiol: why a possible seizure treatment? Does it work via the endocannabinoid receptors?

- *Cannabis is the only plant species with cannabinoids*
  - » THC, CBD, CBDv….
- *Cannabinoid receptor family*
  - » CB(1) and CB(2)—CB(1) most abundant
  - » G protein coupled transmembrane receptor
    - – Activate voltage-gated Ca channels
    - – Enhances K channel conduction presynaptically

Cannabidiol: why a possible seizure treatment? Does it work via the endocannabinoid receptors?

- *"Endocannabinoids"*
  - » 2-arachidonoylglycerol (2-AG) and anandamide
    - – Endogenous lipid signaling molecules
    - – Generated at cell membrane from phospholipid precursors
    - – Modulate neuronal excitability

Cannabidiol: why a possible seizure treatment? Does it work via the endocannabinoid receptors?

- *Is there evidence?*
  - » Lower levels of anandamide in CSF of patients with newly diagnosed temporal lobe epilepsy
  - » Tissue resected during epilepsy surgery with lower levels of CB1R mRNA and reduced expression of enzyme responsible for synthesis of 2AG
- *But cannabidiol does not exert main neural effects through activation of CB1R*
  - » May function as indirect antagonist at high levels

Romigi et al Epilepsia 2010
Ludanyi et al, J Neurosci 2008

Cannabidiol: why a possible seizure treatment? What are other possible mechanisms of action?

- *Decreases presynaptic release of glutamate*
  - » By binding to members of TRP family of cation channels
- *Activates 5HT 1A receptors*
- *Inhibits adenosine reuptake*
- *Anti-inflammatory?*
- *Antioxidant?*
- *Modulation of mTOR pathway?*
- *?????*

Cannabidiol: why a possible seizure treatment? What have animal models shown?

- *CBD shown to be effective in several acute seizure models*
  - » PTZ-induced seizures
  - » MES-induced seizures
  - » Pilocarpine-induced temporal lobe seizures
  - » Penicillin-induced partial seizures
- *Less convincing data in chronic seizure models*
- *CBD increases after-discharge (AD) threshold and reduces AD amplitude, duration and propagation in electrically kindled limbic seizures in rats*

Cannabidiol (Epidiolex, GW Pharmaceuticals): US Expanded access compassionate use program

- *214 patients (ages 1-30 yr) with >12 weeks of CBD treatment between 1/2014 and 1/2015*
  - » To determine safety and tolerability as well as efficacy of CBD
    - – 12 wk safety, tolerability data on 162 (76%)
    - – Efficacy data on 137 (64%)
  - » 11 pediatric epilepsy centers
  - » Compassionate use, open label---not controlled trial
  - » All patients with significant medically refractory epilepsy
  - » Shared trial design to allow data to be pooled
    - – Initial 2.5-5mg/kg/day, increasing weekly to 25 or 50 mg/kg/day
    - – 4 week baseline, minimum of 4 seizures
    - – All AED, diet, VNS stable for month prior to enrollment
    - – Parents maintained detailed daily seizure diaries

Devinsky et al, Lancet Neurol 2016

Epidiolex USA EAP: Safety and tolerability

- *Adverse events in 128 patients (78%)*
  - Somnolence n=41 (25%)
  - Decreased appetite n=31 (19%)
  - Diarrhea n=31 (19%)
  - Fatigue n=21 (13%)
  - Convulsion n=18 (11%)
- *Serious adverse events in 20%*
  - Status epilepticus most common, n=9 (6%)
  - Diarrhea, weight loss
- *5 (3%) discontinued treatment due to adverse event*

Devinsky et al, Lancet Neurol 2016

Epidiolex USA EAP Efficacy

- *36.5% median reduction of motor seizures over 12 wk treatment period (49.8% in DS patients)*
  - » 5 patients seizure free of all motor seizures
- *54 (39%) with >50% reduction in motor seizures*
  - » 29 (21%) with >70% reduction
  - » 12 (9%) with >90% reduction
- *32 patients with atonic seizures*
  - » 18 (56%) with >50% reduction
  - » 5 (16%) became seizure free

Devinsky et al, Lancet Neurol 2016

Cannabidiol – Helpful or just reefer madness? What do we need to know?

- *All efficacy data to date until recently has been anecdotal or open label*
  - » Need for randomized controlled trial data
- *Cannabidiol is NOT medical marijuana!*
  - » Significant variability in “artisanal” medical marijuana preparations
  - » And what about those >500 other chemicals in cannabis?
    - – Could some of them or some combination be more effective? Be more toxic?
  - » Need for reproducible, “vetted” CBD

GW Pharmaceuticals: Epidiolex

- *Expanded access program*
  - » 5 initial sites, several added
  - » MGH enrolled 57, initial 25 started 4/2014
- *Dravet Syndrome*
  - » 2 RCT—results released from first trial
- *Lennox Gastaut Syndrome*
  - » 2 RCT—results from both trials released
- *Tuberous Sclerosis Complex*
  - » RCT now enrolling

GW Pharmaceuticals Epidiolex: Dravet Syndrome RCT

- *120 patients randomized*
  - » 20 mg/kg/day CBD or placebo
  - » 4 week baseline, 14 week treatment phase
- *Average age 10 years*
  - » 30% less than 6 years
- *Median baseline seizure frequency 13sz/mo*
- *39% median reduction in seizure frequency*
  - » Vs 13% in placebo group (p=0.01)

Cannabidiol in refractory epilepsy: Where are we now?

- CBD may be effective and well tolerated epilepsy treatment for some/many
- GW Pharmaceuticals Epidiolex
  - » CBD purified from cannabis (biologic derivative)
  - » Ongoing/completed RCT in Dravet syndrome, Lennox Gastaut syndrome, Tuberous Sclerosis Complex
- Insys Pharmaceuticals
  - » Synthetic CBD
  - » Planned/enrolling trials in Dravet syndrome, Lennox Gastaut syndrome, infantile spasms
- *And what about medical marijuana?*

MGH "CBD team", or "village"

» Tricia Bruno RN	Nurse coordinator
» Lauren Skirvin RN	Nurse coordinator
» Jan Paolini RN	Nurse coordinator
» Christina Anagnos RN	Nurse coordinator
» Amy Morgan PhD	Neuropsychologist
» Emma Wolper	Research assistant
» Evan Hess	Research assistant
» Daniel Lubarsky	Research assistant
» John Vetrano	Research pharmacy
» Cherylann Reilly-Trembley	Research pharmacy

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