The Yin and Yang of Cannabis: The Yang

Gregory L. Holmes, MD
Chair, Department of Neurological Sciences
Larner College of Medicine
University of Vermont
Burlington, Vermont
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.
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
- 2016: 29 states and the District of Columbia currently have laws legalizing medical marijuana in some form.
- Eight states and the District of Columbia have adopted more expansive laws legalizing marijuana for recreational use.
- Increasing anecdotal reports about efficacy of medical marijuana, especially CBD-enriched formulations in the treatment of refractory pediatric epilepsy.
6 yr old Charlotte Figi stops 300 seizures per week with marijuana. No side effects, diminished risk of SUDEP, intractable seizures, or any other disorder. Reduced life expectancy and balance issues will not outgrow.
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 infantile spasms or Lennox-Gastaut syndrome
- 85% reported reduction in seizure frequency
  - 14% seizure free
  - Many reported improved sleep, alertness and mood

Hussain et al, Epilepsy & Behav, 2015
Medical marijuana: is it effective in treating refractory epilepsy?

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

Porter, B. E. & Jacobson, C. Epilepsy Behav 2013
Hussein et al, Epilepsy Behav 2015
Cannabidiol: why a possible seizure treatment? Does it work via endocannabinoid receptors?

- Cannabinoid receptor family
  - CB(1) and CB(2) (CB(1) most abundant)
  - G protein coupled transmembrane receptor
  - Activate voltage-gated Ca\(^{2+}\) channels

- Endocannabinoids
  - 2-arachidonoylglycerol (2-AG) and anandamide
  - Endogenous lipid signaling molecules
  - Modulate neuronal excitability

- Synapses
  - Inhibition of 2-AG biosynthesis in MSN
  - Stimulation of AMPAR endocytosis and LTD in hippocampus and accumbens reward
  - Inhibition of the astrocyte proliferation and gliosis
  - Neuroinflammatory disorders

- Astrocytes
  - Inhibition of LTD at neocortical synapses; astroglial-dependent LTD and memory impairment with exogenous cannabinoids
  - Inhibition of seizures

- Microglia
  - DSI, DSE, LTD, LTP
cognition, anti-aversive memories, etc.
  - Slow self-inhibition in neocortical interneurons and pyramidal neurons

- Inhibition of the pro-inflammatory phenotype of microglia
  - Neuroinflammatory disorders, chronic pain

- Stimulation of glutamate release, LTD, LTP, excitotoxicity, epilepsy, fear, anxiety
Cannabidiol: why a possible seizure treatment?
Does it work via 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

CBD blocks NMDA receptor – like antiepileptic drugs
CBD enhances GABA receptor – like antiepileptic drugs
CBD stabilizes ion channels – like antiepileptic drugs

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

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
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
GW Pharmaceuticals: Epidiolex

- Expanded access program
  - 5 initial sites, several added
  - UVM is a study site
- 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 13 sz/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?
Cannabidiol – Helpful or just reefer madness?
What do we need to know?

- All efficacy data to date is 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
Case reports and limited studies have addressed the efficacy of marijuana based products in treating various neurologic disorders. A recent evidence based guideline by the AAN provided support for the use of specific oral and oromucosal forms of cannabis to improve some symptoms in patients with multiple sclerosis.

A subsequent AAN systematic review of medical marijuana for neurologic disorders concluded that oral cannabis extracts are probably ineffective for treating levodopa-induced abnormal involuntary movements in Parkinson’s disease, but it did not find evidence for or against the use of oral cannabinoids for several other conditions.

These and other reviews emphasize the need for further research. Importantly, there is no evidence to support the use of smoked cannabis.
Conclusions: Cannabis

- Likely to have considerable medical benefit in treatment of neurological disorders.
- Unlikely to be the silver bullet for the treatment of neurological disorders.
- Like other pharmaceuticals is likely to have some adverse effects.
- Benefit to risk ratio needs to be evaluated.
- Like other pharmaceutical agents, urgent need for accurate measurement of CBD and other ingredients is critical.
- Cost is a major issue for our patients.