Treatments for Epilepsy: A large unmet need Is there a role for cannabidiol?

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- Clinical trials: GW Pharma, Zogenix

Epilepsy: Definitions

- Seizure: disturbance in the electrical activity of the brain
- Epilepsy: two of more unprovoked seizures occurring greater than 24 hours apart
- Epilepsy is a spectrum of disorders:
 - » Many different types of seizures
 - » Many causes
 - » Many syndromes and types of epilepsy

Epilepsy: Definitions

• Medically intractable seizures

- » Seizures that are not controlled by anticonvulsant medications, or are controlled only by medications that have significant side effects.
- » 1/3 of children with epilepsy will develop medically intractable epilepsy

Epilepsy syndromes: Dravet Syndrome and Lennox Gastaut Syndrome

Dravet Syndrome:

- » severe infantile-onset and highly treatment resistent epilepsy due to sodium channel mutation
- » Onset first year of life in previously healthy infants; typically develop multiple types of seizures and severe ID

• Lennox Gastaut Syndrome:

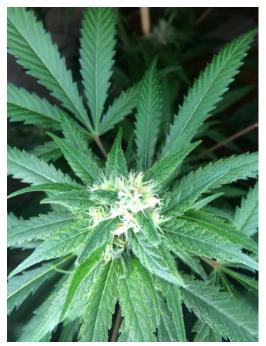
- Highly treatment resistant epilepsy with peak onset between 3-5 years of age
- » Typically multiple seizure types including drop seizures, and most with some degree of ID, often severe.

Treatments for Epilepsy: a large unmet need

- Incidence of epilepsy in US per year: ~150,000 new cases
- Prevalence of epilepsy in US: ~2.2 million people
- Prevalence of epilepsy world wide: > 65 million people IOM report on epilepsy, 2012
- Estimate of prevalence of <u>refractory</u> epilepsy:
 - » US: 730,000 people
 - » Worldwide: 21.7 million people

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



- 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

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

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

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

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

GW Pharmaceuticals Epidiolex: Dravet Syndrome RCT (GWPCARE1)

• 120 patients randomized

- » Mean age 10 yr (29% less than 6 yr)
- » Median convulsive seizure frequency per 28 days was 12.4 and 14.9
- » Patients had previously tried a median of 4 AEDs, were currently taking a median of 3
- 39% median reduction in convulsive seizure frequency (vs 13% in placebo group (p=0.01))
- 43% of CBD patients had a >50% reduction in convulsive seizures (vs 27% of placebo)

GW Pharmaceuticals Epidiolex: LGS Syndrome RCT (GWPCARE4)

- 171 patients randomized (86 to CBD, 85 to placebo)
 - » Mean age 15 yr (34% were 18 years or older)
 - » Median drop seizure frequency per 28 days was 74
 - » Patients had previously tried a median of 6 AEDs, were currently taking a median of 3
- 44% median reduction in drop seizure frequency (vs 22% in placebo group (p=0.0135) during 14 wk treatment period
- 86% of CBD and 69% of placebo patients had AE; in CBD group 78% were mild or moderate

MGH "CBD team", or "village"

- » Elizabeth Thiele, MD PhD
- » Tricia Bruno RN
- » Lauren Skirvin RN
- » Jan Paolini RN
- » Christina Anagnos RN
- » Amy Morgan PhD
- » Emma Wolper
- » Evan Hess
- » Daniel Lubarsky
- » John Vetrano
- » Cherylann Reilly-Trembley

Funding: GW Pharma

Study PI Nurse coordinator Nurse coordinator Nurse coordinator Nurse coordinator Neuropsychologist Research assistant Research assistant Research assistant Research pharmacy Research pharmacy