

---

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

Elizabeth A. Thiele, MD, PhD

*Director, Pediatric Epilepsy Program*

*Massachusetts General Hospital*

*Professor of Neurology*

*Harvard Medical School*



# *Disclosures*

---

- *Consultant: GW Pharma (Greenwich Biosciences), Zogenix*
- *Research grants: GW Pharma*
- *Clinical trials: GW Pharma, Zogenix*

# *Epilepsy: Definitions*

---

- *Seizure: disturbance in the electrical activity of the brain*
- *Epilepsy: two or 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 resistant 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 refractory 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 Study PI
- » 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

Funding: GW Pharma