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 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
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 worldwide: > 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

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
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