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

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- *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

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