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# *The Role of Cannabidiol in the Treatment of Refractory Pediatric Epilepsy*

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# Disclosures

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- *Consultant: GW Pharma, Zogenix, Eisai, Ovid*
- *Research grants: GW Pharma*
- *Clinical trials: GW Pharma, Zogenix*

# *The unmet need in refractory epilepsy: making a case for cannabidiol*

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- *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*

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- *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*

# *Making a case for cannabidiol: Use of cannabis in treating epilepsy*

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- *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*

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- *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*

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- *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*

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- *1996: California becomes first state to legalize medical marijuana*
- *2015: Medical marijuana legalized in 23 US states*
  - » Regulated at state level
  - » CBD specifically made legal in an additional 16 states
- *Increasing anecdotal reports about efficacy of medical marijuana, especially CBD-enriched formulations in the treatment of refractory pediatric epilepsy*

# *Cannabidiol: why a possible seizure treatment?*

## *Does it work via endocannabinoid receptors?*

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- *Cannabis is the only plant species with cannabinoids*
  - » THC, CBD, CBDv.....
- *Cannabinoid receptor family*
  - » CB(1) and CB(2)—CB(1) most abundant
  - » G protein coupled transmembrane receptor
    - Activate voltage-gated Ca channels
    - Enhances K channel conduction presynaptically

# *Cannabidiol: why a possible seizure treatment?*

## *Does it work via endocannabinoid receptors?*

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- *“Endocannabinoids”*
  - » 2-arachidonoylglycerol (2-AG) and anandamide
    - Endogenous lipid signaling molecules
    - Generated at cell membrane from phospholipid precursors
    - Modulate neuronal excitability

# *Cannabidiol: why a possible seizure treatment?*

## *Does it work via endocannabinoid receptors?*

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- *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
- *But cannabidiol does not exert main neural effects through activation of CB1R*
  - » May function as indirect antagonist at high levels

# *Cannabidiol: why a possible seizure treatment?*

## *What are other possible mechanisms of action?*

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- *Decreases presynaptic release of glutamate*
  - » By binding to members of TRP family of cation channels
- *Activates 5HT 1A receptors*
- *Inhibits adenosine reuptake*
- *Anti-inflammatory?*
- *Antioxidant?*
- *Modulation of mTOR pathway?*
- *?????*

# *Cannabidiol: why a possible seizure treatment?*

## *What have animal models shown?*

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- *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*

# *GW Pharmaceuticals: Epidiolex*

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- *99% pure oil based cannabidiol extract of constant composition*
- *100 mg/ml sesame oil-based solution*

# *GW Pharmaceuticals: Epidiolex*

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- *Expanded access program*
  - » 5 initial sites, several added—currently >1000 individuals in program (Devinsky et al, Lancet Neurol 2016)
  - » MGH enrolled 57, initial 25 started 4/2014
- *Dravet Syndrome*
  - » 2 RCT—results from first trial published (Devinsky et al, NEJM 2017)
- *Lennox Gastaut Syndrome*
  - » 2 RCT—results from both trials released
- *Tuberous Sclerosis Complex*
  - » RCT now enrolling



# *GWEP1423: Role of CBD in treating refractory epilepsy in Lennox Gastaut Syndrome*

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## **Key Inclusion Criteria:**

- *Patients aged 2-55 years*
- *Clinical diagnosis of LGS inadequately controlled by  $\geq 1$  current antiepileptic drug (AED), with a history of slow ( $< 3$  Hz) spike-and-wave pattern on electroencephalogram*
- *$\geq 2$  drop seizures (atonic, tonic, or tonic-clonic seizure that led, or could have led, to a fall or injury) each week during the 28-day baseline period*

## **Treatment groups:**

- *20 mg/kg/day of CBD (100 mg/mL) in oral solution or placebo as add-on to current AEDs*
- *Administered BID starting at 2.5 mg/kg/day and titrated to 20 mg/kg/day over 2 weeks, followed by a 12-week dose-maintenance period*

## **Primary Endpoint:**

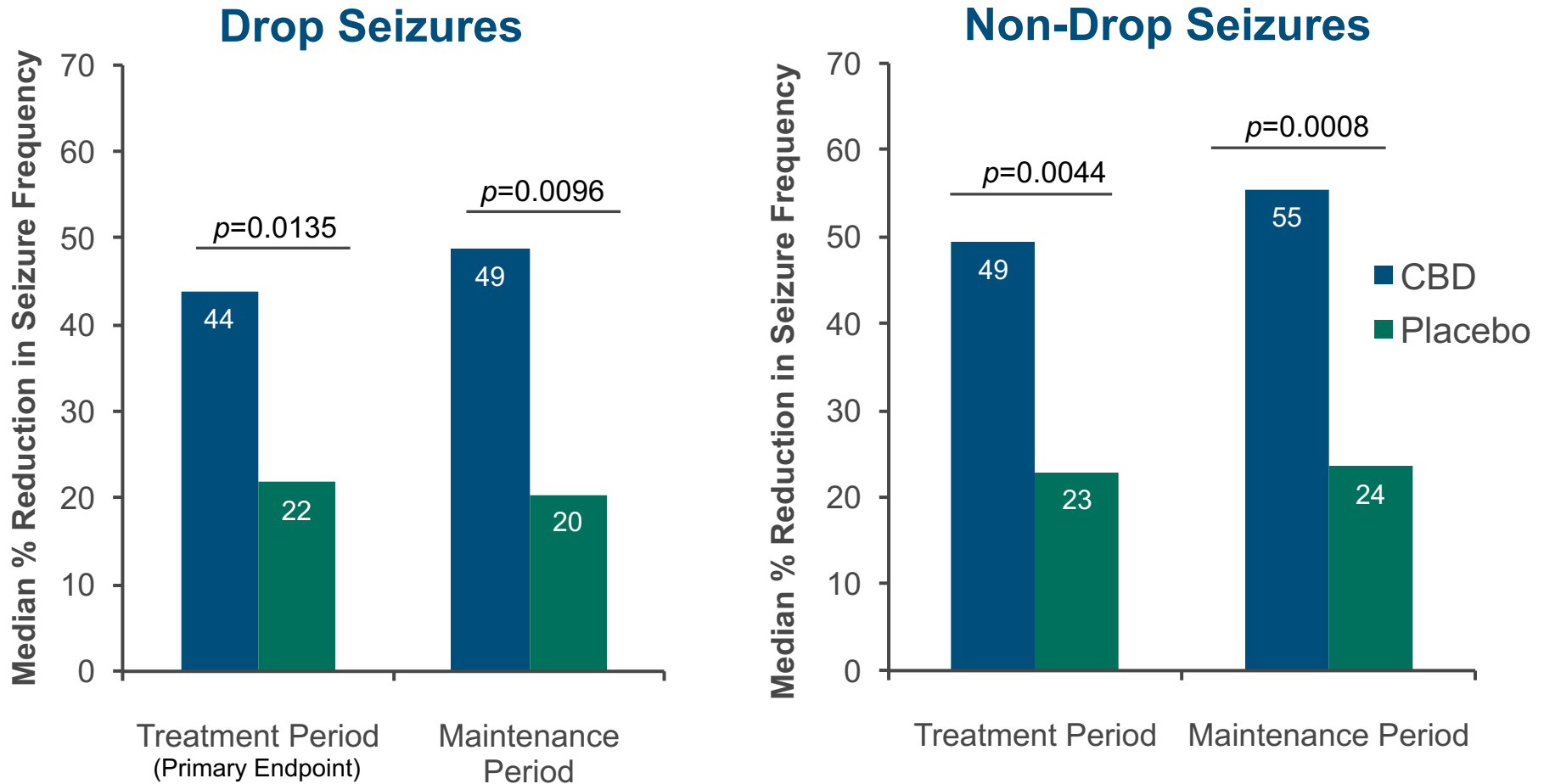
- *Percentage change from baseline in drop seizures over the 14-week treatment period*

# GWEP1423: Baseline Demographics

	<b>CBD (n=86)</b>	<b>Placebo (n=85)</b>
Mean age (min, max)	15.5 (2.7, 39.0)	15.3 (2.8, 45.1)
2-17 years [n (%)]	56 (65.1)	57 (67.1)
18-55 years [n (%)]	30 (34.9)	28 (32.9)
Male [n (%)]	45 (52.3)	43 (50.6)
Median number of prior AEDs (min, max)	6 (1, 18)	6 (0, 28)
Median number of current AEDs (min, max)	3 (1, 5)	3 (1, 4)
Median drop seizure frequency (per 28 days) during baseline (Q1, Q3)	71 (27.0, 156.0)	75 (47.3, 144.0)
Median total seizure frequency (per 28 days) during baseline (Q1, Q3)	145 (72.0, 385.7)	177 (68.6, 359.5)

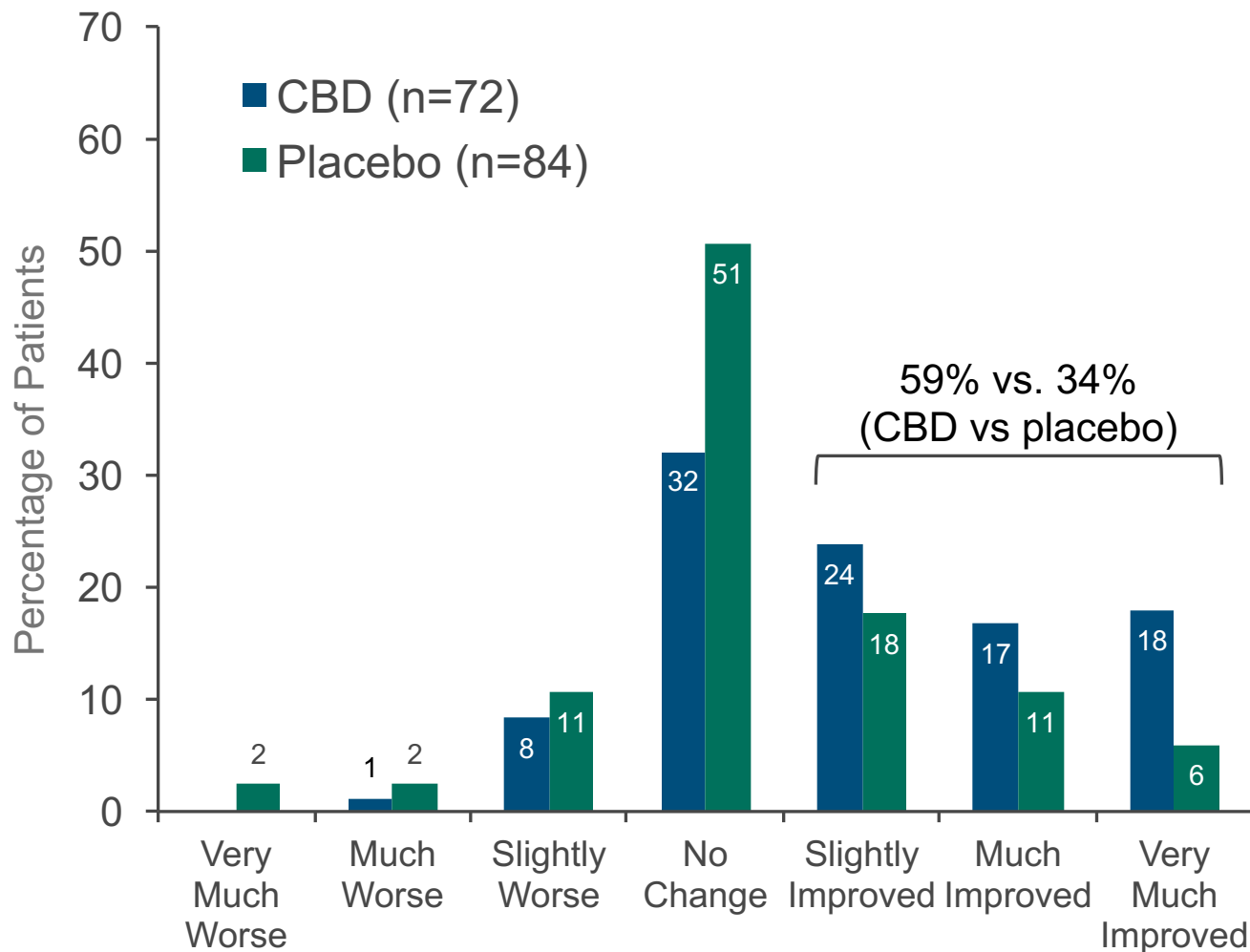
- *94% of patients were on multiple concomitant AEDs; most common were clobazam (49%), valproic acid (40%), and lamotrigine (37%)*

# Median Percent Reduction in Monthly Drop and Non-Drop Seizure Frequency



- The significant difference between groups was established in the first 4 weeks of maintenance period

# Subject/Caregiver Global Impression of Change (S/CGIC) From Baseline at Last Visit



- CBD caregivers/patients were significantly more likely to report an improvement in condition (OR=2.54;  $p=0.0012$ )

# GWEP1423: Key Safety Results

Treatment-Emergent Adverse Events (TEAEs)	CBD (n=86) n (%)	Placebo (n=85) n (%)
All-causality TEAEs	74 (86.0)	59 (69.4)
Treatment-related TEAEs	53 (61.6)	29 (34.1)
TEAEs leading to withdrawal	12 (14.0)	1 (1.2)
Serious TEAEs	20 (23.3)	4 (4.7)
Treatment-related serious TEAEs	9 (10.5)	1 (1.2)

## TEAEs reported in >10% of patients in either group by preferred term

Diarrhea	16 (18.6)	7 (8.2)
Somnolence	13 (15.1)	8 (9.4)
Pyrexia	11 (12.8)	7 (8.2)
Decreased appetite	11 (12.8)	2 (2.4)
Vomiting	9 (10.5)	14 (16.5)

## Laboratory Investigations

- Increases in ALT or AST (>3 × ULN) occurred in 1 placebo and 20 CBD patients
- 16 CBD patients with increases were on concomitant valproic acid
- No patient met standard criteria for drug-induced liver injury (Hy's law) with concurrent elevated bilirubin >2 × ULN
- 6 CBD patients withdrew from treatment; a 7th patient met criteria for withdrawal but was discontinued for noncompliance
- All elevations resolved

- There was 1 death in the CBD group, not deemed treatment-related
- Of those who reported a TEAE, 78% of CBD and 97% of placebo patients reported it as mild or moderate

# *Cannabidiol – Helpful or just reefer madness?*

## *What do we need to know?*

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- *All efficacy data to date until recently has been 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

# *Cannabidiol in refractory epilepsy: Where are we now?*

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- 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
- Zynerba Pharmaceuticals
  - » Transdermal CBD
  - » Refractory epilepsy, Fragile X
- *And what about medical marijuana?*

# MGH “CBD team”, or “village”

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- » 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



