Cannabidiol, Ataluren & SUDEP: Mechanisms, Therapies & Preventions

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Cannabis sativa - used in China 8000 BCE
  - >420 compounds
  - 80 terpeno-phenol compounds, “cannabinoids”
Cannabis indica ~ 1700 BCE
Main ingredients
  - Cannabidiol (CBD) – not psychoactive (?GPR55 receptor)
  - Tetrahydrocannabinol (THC) – psychoactive; works on endocannabinoid system (CB1 receptor)
Challenges in Studying Medical Cannabis

- Naturalistic fallacy
- ↑ placebo rates in children (pain, asthma, psychiatry (anxiety, OCD, ADHD, depression) (Weimer et al, Ped Res 2013)
- Meta-analysis in TRE: children improved more with placebo than adults (19.9% v 9.9% in) but same response to meds (Rheims et al, PLoS Med, 2008)
- Children with ID & TRE - elevated placebo response rates.
  - Clobazam in LGS (mean, 12 yo): >=50% responder rate for drop seizures: 32% placebo, similar to clobazam. Avg weekly seizure frequency significantly lower in CBZ group (Ng et al, Neurology, 2011)
Challenges in Studying Medical Cannabis

- **Potential harms** (Volkow et al, NEJM 2014)
  - Short-term – impaired cognition, motor control, psychiatric disorders
  - Long-term – altered brain development, addiction, cognitive impairment, psychiatric disorders
    - **NOTE:** long-term effects unknown for FDA-approved AEDs in children and adults

- **Perceived therapeutic benefit**
  - Epilepsia poll – lay people: proof of efficacy/safety
  - Science of convenience
  - Entourage effect – nature knows how to mix an AED cocktail (ie, CBD, THC, THCA, CBG, CBN)
Cannabinoids: Anti-Seizure Efficacy

Whalley, 2014 American Herbal Pharmacopoeia; Rosenberg et al, 2015
Phase III Epidiolex (CBD) Trial: Dravet Syndrome

- USA & Europe
- 120 patients – pediatrics, ages 2-18 yo
  - 61 patients -- CBD 20 mg/kg titrated over 2 weeks (mean age 9.7 years)
  - 59 patients - placebo (mean age 9.8 years)
- Average of 3 concomitant AEDs
- Average of >4 prior AEDs
- Median baseline convulsive seizure frequency: 13 per month

Unpublished
Phase III Epidiolex Trial: Dravet Syndrome: SAFETY

- Overall well-tolerated
- Adverse events in >=10% of Epidiolex patients
  - somnolence, diarrhea, decreased appetite, fatigue, pyrexia, vomiting, lethargy, upper respiratory tract infection & convulsion
- 84% of Adverse events were mild or moderate
- Serious adverse events –
  - Epidiolex – 10, Placebo – 3

Unpublished
Phase III Epidiolex Trial: Dravet Syndrome: Efficacy

- 14 week treatment period (2 week titration/12 weeks on full dose CBD or placebo)
- Median reduction of Convulsive Seizures
  - Epidiolex – 39%
  - Placebo – 13%
- Statistical significance -- p = 0.01

Unpublished
Desperate Need in MMJ Studies in Epilepsy

- Largest pool of TRE are patients with focal epilepsy, but many hold THC key for Dravet and others
- 24 states have approved MMJ – parents and patients are self-titrating and defining THC/CBD concentrations
- Variable preparations and consistencies
- No systematic data on efficacy or safety
Challenges for MMJ Studies in Epilepsy

- Legal in states, illegal federally
- Need a supplier of a consistent product – appears possible with multiple companies
- Proposal – 3 or 4 arms
  - Placebo
  - CBD:THC 18:1 and 8:1
  - CBD only
Phase 2 Randomized, Double-Blind Placebo-Controlled Crossover Study of Ataluren for Epilepsy in Nonsense Mutation Dravet Syndrome
Ataluren: Pharmacology

- Not chemically similar to any currently used medications
- White powder for suspension
- Insoluble in water, readily absorbed in GI
- Peak levels 1-2 hrs after oral intake
- Half-life 2-6 hrs in normal volunteers
- Dosing: 10-10-20 mg/kg tid
Ataluren: Side Effects

- Nausea, abdominal pain, vomiting
- Headache
- Fever
- Rhinitis and sinusitis
- Elevated creatinine

Similar to Placebo (Kerem et al, Lancet Resp Med, 2014)
Mechanism of Action

- Selective read-through of premature mRNA stop codon (nonsense mutation)
- Produces full-length functionally active protein in appropriate cellular location
- Does not work on stop codons due to frameshift mutation
Ataluren binds to ribosome, enabling readthrough of premature stop codons ➔ functional protein

- High specificity for nonsense codon read-through without affecting normal termination codons
- The cellular target (the ribosome) is present in all cells, independent of tissue
- Orally bioavailable with low toxicity
Mechanism of Action

- Specific for translation
  - Doesn’t modify transcription or mRNA stability
  - Doesn’t modify levels of mRNA with stop codons or normal mRNA
Blood-BRAIN Barrier Penetration

- Nonsense-mediated Hurler mouse
- Pathological elevation of glycosaminoglycan (GAG)
- Tissue levels of ~1 to 20 µg/mL in brain as well as cell cultures, muscle, etc associated with read-through efficacy
Study Objectives

◆ Primary: characterize safety profile

◆ Secondary:
  ◆ evaluate changes in convulsive and drop seizure frequency
  ◆ determine changes in minor seizure types (absence, myoclonic, focal)

◆ Exploratory: evaluate changes in cognitive, motor, and behavioral function as well as QOL
Study Design

Double-masked placebo-controlled study

4 Wk Diary Screening → Dravet (N ≥ 8) → CDKL5 (N ≥ 8) → Ataluren (10,10,20 mg/kg) → Placebo

Open-label extension study

Period 1: 12 Weeks
Washout: 4 Weeks
Period 2: 12 Weeks
Mortality in Dravet Syndrome

- Status epilepticus – continuous seizure more than 10 mins or series of seizures without recovery
- Acute encephalopathy – consciousness +/- other neuro Sxs (eg, seizures) >24 h associated with infection.
- Sudden unexpected death in epilepsy (SUDEP) - ? Specific mechanisms with DS
  - Very similar issue in idic15
SUDEP: Mechanisms

- Environment
  - Lack of supervision
  - Lack of repositioning/stimulation

- Susceptible State
  - Sleep
  - Prone Position

- Seizure

- Postictal Early

- Postictal Late

- Death
  - Impaired Arousal
    - Central midbrain, Thalamus
    - Ach, NE, 5-HT

- Medulla
  - GABA, Glu, Adenosine, Gly, 5-HT

- Impaired Cardiorespiratory Function

- Susceptible Host
  - Non-adherence
  - Sleep Deprivation
  - Alcohol Withdrawal
  - AED Discontinuation

- Sympathetic Stimulation:
  - ↑ HR, ↑ BP, ↑ RR, ↑ EPI, ↑ NE, ↑ Cortisol,
    Pulmonary Edema

- Parasym pathetic Stimulation:
  - ↓ HR, ↓ BP

- Pathological Coactivation

Time
Mortality in Dravet Syndrome: Prevalence Sakachi et al (2011)

- Questionnaire – 91/246 hospitals w/kids
- 63/623 DS patients died (10.1%)
  - Ages 13 mos – 25 yo (median 6 yrs, 8 mos)
  - Risk of mortality high until age 12 yrs

Causes of death
- SUDEP – 53% (fever 26%; ↑Males)
- SE/Acute encephalopathy – 36% (fever 81%; ↑F)
  - Highest ages 1-3 years & early school (peak 6 yrs)
- Drowning – 10%
  - >age 7 yrs, bathing at home or hospital; 2 > age 18 yrs
Mortality in Dravet Syndrome: Prevalence Sakachi et al (2011)
Mortality in Dravet Syndrome: 
*Skluzacek et al (2011)*

- 833 pt sIDEA database
  - ? 193 responses
  - No medical records
- 31 deaths
  - SUDEP – 61% (1 – 8 yrs)
    - Detailed data on 9 cases; 8/9 in sleep
  - SE – 32% (10 mos – 17 yrs)
  - Ketoacidosis – 3%
  - Accident – 3%
Acute Encephalopathy Syndrome in Dravet: Okamura et al (2011)

- 15 cases in Japan; M=F
- Ages 8 mos – 15 years
- Most with URI, 2 roseola, 1 flu
- SCN1A mutations in 9 (truncation – 6; missense – 3)
  - 4 died
  - 9 with severe sequelae
  - 2 with moderate sequelae
Animal Models of Dravet Syndrome SUDEP (Kalume et al, 2013)

- Heterzygous Scn1a knockout (KO) mouse and conditional brain and cardiac KOs
- SUDEP after GTCSz
- Multiple GTCSz strong risk factor for SUDEP
  - 9.5 average in 24 hrs before SUDEP
- Decreased interictal Heart Rate Variability and ictal bradycardia with Tonic phase
- Prolonged atropine-sensitive bradycardia preceded SUDEP – brain not cardiac KO
Preventing SUDEP

◆ Control GTCSz – try for complete control
  ◆ Consider all effective therapies (eg, diet
  ◆ Lifestyle factors – avoid missed meds, illnesses, overheating, sleep deprivation
  ◆ If tendency for prolonged GTCSz, consider rescue benzodiazepine at seizure onset
◆ Antisuffocation pillows – Sleep Safe (unproven)
Preventing SUDEP

◆ Seizure monitors – unproven, life-saving
  ◆ Stop prolonged seizures/SE
  ◆ Stimulation and maintain airway after seizure

◆ Seizure monitors – types
  ◆ Wristwatch
    ◆ Empatica embrace
    ◆ Smartwatch
  ◆ Motion detector
    ◆ Under mattress – Emfit
    ◆ Video and motion detection - SAMi