Cannabinoids for Pediatric Epilepsy: Anecdotes vs. Evidence

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Anecdotes vs. Evidence

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Disclosures

• None

Outline

• General Info
• Illicit Use
• Mechanism
• Products
• Previous literature
• Myth vs Fact
• Current Studies
• Social Media
• Official Positions
• Conclusions
General Information

- Cannabis contains over 100 compounds
  - compounds called phytocannabinoids
  - unique to the plant
- Main cannabinoids are:
  - delta-9-tetrahydrocannabinol (THC)
    - responsible for producing most subjective effects of cannabis
  - cannabidiol (CBD)
    - lacks the psychoactivity of THC

Illicit Use

- WHO - 147 million people, or 2.5 percent of the world population, use cannabis (marijuana)
  - making it the world’s most widely cultivated, trafficked, and abused illicit substance
- Synthetic cannabinoids have emerged as a recreational drug with significant toxicity
  - synthetic compound is usually added to herbs or other plants to appear as a natural product
  - “K2,” “spice,” “crazy monkey,” “chill out,” “spice diamond,” “spice gold,” and “chill X”

Cannabinoids capable of targeting diseases across therapeutic areas
- Endocannabinoid system, TRP channels, adenosine uptake, serotonin receptors, etc.
Mechanism

- Endocannabinoids, including 2-arachidonoylglycerol (2-AG), activate presynaptic cannabinoid type 1 receptors (CB1R) on inhibitory and excitatory neurons, resulting in a decreased release of neurotransmitters
- Data indicate that the endocannabinoid 2-AG might be a promising target for an anti-epileptogenic approach


Mechanism (cont)

- Phytocannabinoids produce anticonvulsant effects through the endocannabinoid system
- Few adverse effects
- Cannabidiol and cannabidivarin should be tested in randomized, controlled clinical trials


Mechanism (cont)

- Investigated the effect of CBD and the structurally similar cannabinoid, cannabigerol (CBG), on voltage-gated Na⁺ (NaV) channels
- CBD effects on NaV channels were investigated using patch-clamp recordings from rat CA1 hippocampal neurons in brain slices, human SH-SY5Y (neuroblastoma) cells and mouse cortical neurons in culture
- CBG effects were also assessed in SH-SY5Y cells and mouse cortical neurons
- Effect of CBG on pentylenetetrazole-induced (PTZ) seizures was assessed in rat
- CBD and CBG are NaV channel blockers at micromolar concentrations in human and murine neurons and recombinant cells
- In contrast to previous reports investigating CBD, CBG had no effect upon PTZ-induced seizures in rat, indicating that NaV blockade per se does not correlate with anticonvulsant effects

Study Trial Products

• GW Pharmaceuticals leading to two product candidates:
  – Epidiolex® (CBD - cannabidiol) 50% of cannabinoid content within Sativex
  – GWP42006 (CBDV - cannabidivar) Structurally related to CBD; propyl instead of pentyl side chain
    • Anti-convulsant profile differs slightly from CBD
• Schedule I substance - regardless whether it is derived from “hemp” or some other cannabis strain that is higher in THC.

What does Schedule 1 mean?

• The drug or other substance has a high potential for abuse
• The drug or other substance has no currently accepted medical use in treatment in the US
• There is a lack of accepted safety for use of the drug or other substance under medical supervision

Compassionate Access, Research Expansion and Respect States (CARERS) Act

• Aims to protect medical marijuana patients, providers, and their families and allow states to control their own policies on the issue
• Amends the Controlled Substances Act to allow states to set their own policies in regard to medical marijuana
  – Patients, providers, and businesses that are acting in compliance with state law will no longer be considered in violation of federal law and vulnerable to federal prosecution.
Compassionate Access, Research Expansion and Respect States (CARERS) Act (cont)

- Allows families to obtain and possess cannabidiol (CBD)
- Reduces barriers to research
  - Three additional licenses will be granted to organizations to produce marijuana and marijuana-derivatives for federally approved research, breaking a NIDA monopoly that has stunted research
  - Bill ends a public health service review protocol that applies only to marijuana and no other illegal Schedule I or II drugs
- Overhauls restrictive banking laws
  - Allows banks to provide financial services to legal marijuana dispensaries working in compliance with state laws

PREVIOUS LITERATURE

Marijuana use and epilepsy: prevalence in patients of a tertiary care epilepsy center

- Telephone survey completed 2004 in Canada to determine the prevalence of marijuana use in patients with epilepsy
- 136 adults with epilepsy followed at a tertiary care epilepsy clinic
- 21% of patients reported active marijuana use
  - Of these, two-thirds believed that marijuana improved their seizure severity
- 24% of all subjects believed marijuana was an effective therapy for epilepsy
- Conclusion: Despite limited evidence of efficacy, many patients with epilepsy believe marijuana is an effective therapy for epilepsy and are actively using it.

Supportive Evidence

• Indirect evidence for the benefit of marijuana itself for human seizures
• Study demonstrated marijuana use was less common in patients admitted to an urban hospital for new onset seizures, than it was in a control group of patients admitted for other reasons.


Cochrane Review

• Searched for direct evidence that cannabinoids can prevent human seizures in studies using the only acceptable standard - randomized controlled trial
• Identified four studies - total of 48 patients randomized to placebo or to 200–300 mg of cannabidiol per day
• The four studies published between 1978 and 1990
  – not adequately powered (9-15 patients)
  – failed to provide evidence about cannabinoid efficacy in treating epilepsy
  – one of them being an unpublished abstract
• This particular cannabinoid has few psychotropic effects


Cochrane Review (cont)

• Overall, these studies demonstrate the short-term tolerability of this treatment
  – the only noted adverse effect being drowsiness in one study
  – Except for one study that reported two of four treated patients becoming seizure free for 3 months, the studies either reported no benefit, or the effect was not clearly stated
• Methods of randomization or determining outcome were inadequate or not clearly detailed
• Concluded: major shortcomings as an epilepsy treatment
  – Containing multiple compounds with unclear, possible, anti- or pro-convulsant effects, delivered in varying amounts from dose to dose
  – Long-term safety has not been adequately investigated
  – Evidence for efficacy in treating seizures does not meet the necessary standard to recommend it to patients.
Pro-Convulsant?

- other patients may report marijuana as a possible seizure precipitant

- may interfere with the way the body processes certain agents using the liver’s cytochrome P450 enzyme system
- Affect brain development?
- No guarantee of strength, purity or safety of products

MYTH VS FACT

It has already been well studied...

- MYTH
  Early clinical studies on the use of CBD and other cannabinoids for epilepsy had methodologic limitations
Dosage

- **Myth**: Giving any amount of CBD oil will improve seizures.
- **Fact**: Many effects of CBD follow a bell-shaped dose–response curve, suggesting that dose is a key factor in its pharmacology.

Availability

- **Myth**: Physicians are not prescribing CBD because they don’t want to use it.
- **Fact**: Clinical research on CBD in epilepsy has been limited by the legal restriction to use cannabis-derived medicine.

Online Purchase

- Large price range
- Multiple on-line sites are selling products ex. “hemp oil”
- No standardization
Marijuana is legal in VA

- **MYTH**
  - February 26, 2015 - Virginia Gov. Terry McAuliffe signed HB 1445 into law
  - Allows patients with intractable epilepsy to avoid a conviction — but not an arrest — for possessing certain medical cannabis oils
  - It does not provide for any in-state access
  - Provides an affirmative defense to patients who suffer from intractable epilepsy (and, for minors, their parents, or legal guardians) for the possession of marijuana extracts that contain at least 15% of either cannabidiol (CBD) or THC-A and no more than 5% THC

Marijuana is legal in VA (cont)

- Patients will probably have to travel to a state that allows out-of-state patients to obtain medical cannabis
- **What is an affirmative defense?**
  - Does not protect someone from being arrested, held in jail before trial, and made to stand trial
  - It is a defense that can be raised and proven in court after the person has been charged
  - Defense is that the defendant (or his/her minor child) has intractable epilepsy and physician issued a written certification within the past year

CURRENT STUDIES
AAN Abstract

- Epidiolex (Cannabidiol) in Treatment Resistant Epilepsy
  - Objective: Ten centers have independent FDA approved open-label Expanded Access Programs and have treated children and young adults with treatment-resistant epilepsies with pure CBD.
  - Background: Cannabidiol (CBD) is a component of Cannabis sativa with anticonvulsant activity in pre-clinical models of epilepsy, independent of activity at known endogenous cannabinoid receptors.
  - Design/Methods: Data has been collected on demographics, seizure counts, and safety through case report forms and tabulated in this series of open-label trials. Eligibility was determined and documented in protocols specific to each site after FDA and IRB review. Seizures were recorded as convulsive or non-convulsive. Atonic seizures were also specifically recorded. CBD (supplied by GW Pharmaceuticals) was given as a liquid and daily dose titrated up to 25mg/kg.
  - Results: Data were collected on 213 patients with treatment-resistant epilepsies for safety evaluation. 123 patients had at least 12 weeks continuous exposure and were included in efficacy calculations. Etiologies included Dravet and Lennox-Gastaut (LGS) syndromes as well as over 10 other conditions. Total convulsive and non-convulsive seizures showed a median percent reduction from baseline of 46% at week 12. Convulsive seizure frequency among Dravet patients treated for at least 12 weeks (N=23) was reduced by 51% at week 12. In patients with LGS treated for 12 weeks (N=10), atonic seizure frequency was reduced by a median -52% at week 12. Adverse events >10% were somnolence (21%), diarrhea (17%), fatigue (17%), and decreased appetite (16%). Nine patients (4%) discontinued for AEs.
  - Conclusions: CBD showed reductions in seizure frequency across multiple drug-resistant epilepsy syndromes and seizure types and was generally well tolerated in this open-label cohort. Controlled trials are indicated to characterize efficacy and safety.
  - Study Supported by: GW Pharmaceuticals.

Cannabidiol Oral Solution as an Adjunctive Treatment for Treatment-resistant Seizure Disorder - NCT02318602

- This is a multicenter, open-label trial to assess the long-term safety and efficacy of Cannabidiol Oral Solution as adjunctive therapy for pediatric and adult subjects with treatment-resistant seizure disorders, including Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS). All participants have rolled over from previous trials.
  - INSYS Therapeutics Inc
  - not yet open for participant recruitment

Cannabidiol Oral Solution in Pediatric Subjects With Treatment-Resistant Seizure Disorders - NCT02324673

- INSYS Therapeutics Inc
  - This is a Phase 1/2, open-label, trial designed to assess the pharmacokinetics, safety, tolerability, and preliminary efficacy of 3 multiple ascending doses of Cannabidiol Oral Solution in a sequential fashion.
  - Participants will be
    - pediatric (aged 1-17)
    - treatment-resistant seizures
  - currently recruiting
Epidiolex and Drug Resistant Epilepsy in Children NCT02397863

- 1 Year to 18 Years
- Sponsor/Collaborators: Georgia Regents University|State of Georgia
- Inclusion Criteria:
  - Patient should have history of trying at least four antiepileptic drugs (AEDs), including one trial of a combination of two concomitant drugs, without successful seizure control.
  - A State of Georgia resident.
- Exclusion Criteria:
  - Dravet Syndrome or Lennox-Gastaut Syndrome and eligible for a GW Pharmaceutical-Sponsored Clinical Trial.
- Start Date: December 2014
- Completion Date: January 2020
- No Study Results Posted

Cannabidiol (CBD) to 25 Patients (Aged 2 Years - 19 Years) With Drug Resistant Epilepsy -NCT02286986

- Recruiting
- Sponsor University of Utah
- Phase 1
- Study Designs:
  - Open Label
- Other IDs: IND 70871
- Outcome Measures:
  - Seizure Frequency
  - Drug Plasma Levels of Cannabidiol

Cannabidiol Expanded Access Study in Medically Refractory Sturge-Weber Syndrome - NCT0232655

- Recruiting
- Sponsor:
  - Anne Comi, MD
  - GW Pharmaceuticals Ltd.
  - Faneca 66 Foundation|Hugo W. Moser Research Institute at Kennedy Krieger, Inc.
- Study Designs: Phase 1/2 Open Label
- Outcome Measures:
  - Change in seizure frequency
  - Change in average seizure duration by seizure type
  - Change in the number of episodes of status epilepticus, defined as convulsive seizure lasting longer than 10 minutes
  - Change in the number of uses of rescue medication
  - Change in the number of ER visits/ hospitalizations
A Study to Investigate the Efficacy and Safety of Cannabidiol (GWP42003-P) in Children and Young Adults With Dravet Syndrome - NCT02224703

- Not yet recruiting
- Sponsor: GW Research Ltd
- Phase 3 Study Design:
  - Randomized
  - Double Blind
- Outcome Measures:
  - Mean percentage change from baseline in convulsive seizure frequency during the maintenance period
  - Number of subjects experiencing a ≥25% worsening, ≥25 to <50% change, 50-75% improvement, or >75% improvement in convulsive seizures from baseline
  - Number of subjects who are convulsive seizure free
  - Change in caregiver global impression
  - Caregiver Global Impression of Change (CGIC) at the end of treatment
  - The incidence of adverse events as measure of subject safety
  - The number of age-appropriate subjects with a treatment-emergent flag using the Columbia-Suicide Severity Rating Scale (C-SSRS) (Children's) during the course of the study

A Study to Investigate the Efficacy and Safety of Cannabidiol (GWP42003-P; CBD) as Adjunctive Treatment for Seizures Associated With Lennox-Gastaut Syndrome in Children and Adults - NCT02224560

- Not yet recruiting
- Sponsor: GW Research Ltd
- Placebo control
- Phase 3 Study Design:
  - Randomized
  - Double Blind
- Outcome Measures:
  - Mean percentage change from baseline in number of drop seizures (average per week) during the maintenance period
  - Mean percentage change from baseline in number of drop seizures (average per week) during the weeks 1-4, 5-8 and 9-12 of the maintenance period
  - Number of subjects experiencing a ≥10% worsening, ≥10 to <25% change, 25-50% improvement, or >50% improvement in drop seizures from baseline
  - Number of subjects who are drop seizure free
  - Mean percentage change from baseline in number of non-drop seizures (average per week)
  - Mean percentage change from baseline in the frequencies of sub-types of seizures (average per week)
  - Change from baseline in Quality of Life
  - Changes from baseline in the Caregiver Global Impression of Change (CGIC) score
  - The incidence of adverse events as measure of subject safety
  - The number of age-appropriate subjects with a treatment-emergent flag using the Columbia-Suicide Severity Rating Scale (C-SSRS) (Children's) depending on age during the course of the study

A Study to Investigate the Efficacy and Safety of Cannabidiol (GWP42003-P; CBD) as Adjunctive Treatment for Seizures Associated With Lennox-Gastaut Syndrome in Children and Adults - NCT02224690

- Not yet recruiting
- Sponsor: GW Research Ltd
- Phase 3 Study Design:
  - Randomized
  - Double Blind
- Outcome Measures:
  - Mean percentage change from baseline in number of drop seizures (average per week) during the maintenance period
  - Mean percentage change from baseline in number of drop seizures (average per week) during the weeks 1-4, 5-8 and 9-12 of the maintenance period
  - Number of subjects experiencing a ≥25% worsening, ≥25 to <50% change, 50-75% improvement, or >75% improvement in drop seizures from baseline
  - Number of subjects who are convulsive seizure free
  - Mean percentage change from baseline in number of non-drop seizures (average per week)
  - Mean percentage change from baseline in the frequencies of sub-types of seizures (average per week)
  - Mean change from baseline in quality of life
  - Changes from baseline in the Caregiver Global Impression of Change (CGIC) score
  - The incidence of adverse events as measure of subject safety
  - The number of age-appropriate subjects with a treatment-emergent flag using the Columbia-Suicide Severity Rating Scale (C-SSRS) (Children's) depending on age during the course of the study
An Open Label Extension Study of Cannabidiol (GWP42003-P) in Children and Young Adults With Dravet or Lennox-Gastaut Syndromes - NCT02224573

- Not yet recruiting
- Sponsor: GW Research Ltd
- Phase 3 Study Design:
  - Intervention Model: Single Group Assignment
  - Open Label
- Outcome Measures:
  - Mean percentage change in total convulsive seizure frequency, relative to the pre-randomization baseline of the Core Study
  - Mean percentage change in total non-convulsive seizure frequency, relative to the pre-randomization baseline of the Core Study
  - Mean percentage change in the number of drop seizures, relative to the pre-randomization baseline of the Core Study
  - Mean percentage change in the number of non-drop seizures, relative to the pre-randomization baseline of the Core Study
  - Number of subjects considered treatment responders, defined as those with a ≥25%, ≥50%, ≥75%, or 100% reduction in convulsive seizures, relative to the pre-randomization baseline of the Core Study.
  - Number of subjects experiencing a >25% worsening, −25 to +25% no change, 25-50% improvement, 50-75% improvement or >75% improvement in convulsive seizures, relative to the pre-randomization baseline of the Core Study
  - Mean percentage change in the number of drop seizures, relative to the pre-randomization baseline of the Core Study.
  - Mean percentage change in the number of non-drop seizures, relative to the pre-randomization baseline of the Core Study.
  - Mean percentage change in the number of sub-types of seizures, relative to the pre-randomization baseline of the Core Study.
  - Number of subjects considered treatment responders, defined as those with a ≥25%, ≥50%, ≥75%, or 100% reduction in drop seizures, relative to the pre-randomization baseline of the Core Study.

Antiepileptic Efficacy Study of GWP42003-P in Children and Young Adults With Dravet Syndrome - NCT02091375

- Recruiting
- Sponsor: GW Research Ltd
- Phase 3 Study Design:
  - Randomized
  - Placebo Controlled
  - Double Blind
- Outcome Measures:
  - Mean percentage change from baseline in convulsive seizure frequency during the maintenance period of the study
  - Number of subjects who experienced a 50% or more reduction in convulsive seizures from baseline
  - Mean change from baseline in usage of rescue medication
  - Mean change from baseline in Epworth Daytime sleepiness scale score
  - Mean change from baseline in Quality of Life in Childhood Epilepsy (QOLCE) score
  - Number of subjects who are convulsive-seizure free
  - Change from baseline in types of seizures
  - Mean change from baseline in number of inpatient hospitalizations due to epilepsy
  - The incidence of adverse events as measure of subject safety
  - Mean percentage change from baseline in convulsive seizure frequency

A Dose-ranging Pharmacokinetics and Safety Study of GWP42003-P in Children With Dravet Syndrome - NCT02091206

- not recruiting
- Sponsor: GW Research Ltd
- Phase 2 Study Design:
  - Randomized
  - Double Blind
- Outcome Measures:
  - The incidence of adverse events as measure of subject safety
  - The plasma concentration time curves for cannabidiol and its major metabolite following single and multiple doses of GWP42003-P
  - Plasma concentrations of clobazam and N-desmethylclobazam, if taken concomitantly with GWP42003-P, prior to single and multiple doses of GWP42003-P
Genetic Analysis Between Charlotte's Web Responders Versus Non-Responders in a Dravet Population NCT02229032

- Recruiting
- University of Colorado, Denver | Denver Health Medical Center

**Study Designs:**
- Observational Model: Cohort\Time
- Perspective: Cross-Sectional

**Outcome Measure:**
- genetic differences between patients with Dravet Syndrome (SCN1A gene mutation) who appear to respond to high concentration cannabidiol (CBD) oil therapy versus those who do not

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**Social Media**

- Online dispensaries
- Patient testimonials
- Blogs
- Physicians endorsing use ex Dr. Gedde

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**OFFICIAL POSITIONS**
At the present time, there are no data from controlled clinical trials to indicate that cannabinoids have any efficacy in the treatment of epilepsy.

CURE

• “At CURE, we believe that there must be more research done on marijuana rich in CBD. At the present time, regulatory hurdles make it difficult for researchers to gain access to marijuana rich in CBD”
• “CURE recognizes that CBD and/or medical marijuana are not an answer for all children with epilepsy”

American Epilepsy Society

• “The recent anecdotal reports of positive effects of the marijuana derivative cannabidiol for some individuals with treatment-resistant epilepsy give reason for hope. However, we must remember that these are only anecdotal reports, and robust scientific evidence for the use of marijuana is lacking.”
• “To increase clinical research into the effectiveness and safety of marijuana as a possible treatment for resistant epilepsy, the American Epilepsy Society urges that marijuana’s status as a Federal DEA Schedule 1 controlled substance be reviewed.”
• “AES’s call for rescheduling is not an endorsement of the legalization of marijuana...”
American Academy of Neurology

• systematic review of the medical literature
• “AAN found was that not enough clinical evidence exists to make general statements about either the efficacy or safety of medical marijuana for the neurologic conditions studied.”
• “However, the AAN did find enough evidence to suggest that certain forms of medical marijuana may have benefits in treating some symptoms of multiple sclerosis (MS).”

Conclusions

• More studies are needed
• It may be an effective treatment for pediatric epilepsy
• Long-term results are not known

QUESTIONS?