Weeding out the Controversy: Cannabidiol in Drug Resistant Pediatric Epilepsy

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Seton Healthcare Family
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Objectives
• Compare and contrast the properties of tetrahydrocannabinol and cannabidiol
• Evaluate the observational and clinical literature regarding cannabidiol use
• Discuss cannabidiol’s potential place in therapy for resistant epilepsy

Epidemiology of Pediatric Epilepsy
• Lifetime prevalence of epilepsy: 10.2 per 1,000 (1%)
• Current epilepsy: 6.3 per 1,000 (0.6%)

Pediatric Epilepsy Syndromes
• Benign childhood epilepsy with centrotemporal spikes (BECTS)
• Childhood absence epilepsy
• Juvenile myoclonic epilepsy
• Lennox-Gastaut syndrome (LGS)
• Dravet syndrome (DS)
• Infantile spasms (IS)
• Myoclonic astatic epilepsy (MAE)

AED Review

Conflicts of Interest
• The author has no conflicts of interest to disclose.

* AED: antiepileptic drug

AEDs in LGS & DS

- Lennox-Gastaut syndrome
  - Clobazam
  - Felbamate
  - Rufinamide
  - Lamotrigine
  - Topiramate

- Dravet syndrome
  - Valproic acid
  - Topiramate
  - Clobazam
  - Stiripentol
  - Avoid: lamotrigine, carbamazepine

Efficacy of First AED in Newly Diagnosed Epilepsy

- 47-85% will become seizure free with 1st AED trial
- 14% will become seizure free with trial of 2nd or 3rd AED

Efficacy of AEDs in Lennox-Gastaut Syndrome

Drug Resistant Epilepsy

- Uncontrolled seizures are common in LGS & DS
  - LGS: 67% (1 seizure every 3 months for the past year)
  - DS: 84% (1 seizure within the past year)

Potential Consequences of Uncontrolled Seizure Activity

- Intellectual disability
- Physical injury
  - Lacerations
  - Fractures
  - Dental trauma
  - Concussions
- Decreased quality of life
- Sudden unexpected death
Charlotte Figi
- Diagnosed with Dravet syndrome at 3 months old
- Baseline of 300+ seizures per week
- Failed 8 AEDs and the ketogenic diet
- Collaborated with a company in Colorado to develop a cannabis extract, “Charlotte’s Web Oil”

Cannabinoids
- Pharmacological Actions
  - Anticonvulsant
  - Analgesic
  - Euphoria
  - Psychotropic
  - Cognitive modulation
  - Reduces muscle spasms
  - Reduces nausea
- Treated Conditions
  - Migraines
  - Neuropathic pain
  - Nausea
  - Parkinson’s disease
  - Multiple sclerosis
  - CRV
  - Cancer pain

Cannabinoid Mechanism of Action
- THC
  - CB1 & CB2
  - Anticonvulsant & Euphoria
- CBD
  - Blocks adenosine reuptake, inhibition of TRP channels, enhancement of serotonergic receptors
  - Anticonvulsant

Knowledge Check
- Cannabidiol is the component of marijuana that produces the “high” people seek when using it recreationally.
  - True
  - False

High CBD, Low THC Products
- 10-83 mg/mL CBD < 0.3% THC
- 100 mg/mL CBD < 0.1% THC

2017 Legislative Status of Cannabis in the United States
Myoclonic Responder

- 2015: SB 339
- Legalized CBD (THC < 0.5%) for patients with intractable seizures who have failed at least 2 AEDs
- Route of administration other than inhalation

### Observational Studies

**Survey**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Epilepsy syndrome</th>
<th>CBD dose (mg/kg/day)</th>
<th>2015, n=43</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-16</td>
<td>5</td>
<td>66</td>
<td>21</td>
</tr>
<tr>
<td>0.5-28</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Observational Studies: Side Effects**

<table>
<thead>
<tr>
<th>Negative SE</th>
<th>Porter</th>
<th>Hussain</th>
<th>Press</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowsiness</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fatigue</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>GI Symptoms</td>
<td>+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Positive SE**

- Improved mood: ++++ +++ +++
- Improved sleep: +++ +++ + +++
- Improved alertness: +++ +++ +++
- Decreased self stimulation: ++

### Press, 2015 - Other findings

- **Responder:** > 50% reduction in seizure frequency
- No difference in responder rates based on seizure types: e.g., generalized tonic-clonic, focal, absence, myoclonic
- Responder rate between epilepsy syndromes:
  - Lennox-Gastaut: 8/9 (89%)
  - Dravet: 3/13 (23%)
  - Myoclonic astatic epilepsy: 0/3 (0%)
- Responder rate was different between families who had moved to Colorado for treatment vs. already had established care in Colorado
  - 47% vs 22% (OR 3.16; 95% CI 1.16-8.59)
Most parents with children using cannabis products to aide in seizure control believe that it has a beneficial effect. Bias:
- Small sample sizes
- Voluntary response and confirmation bias
- Product and dose not standardized

Parents know their children best.

Knowledge Check

Many parents reported an increase in seizure frequency with the addition of cannabidiol to their child’s therapy.
- True
- False

Epidiolex® Clinical Trials: Summary

Clinical Trials

Epidiolex® Clinical Trials: Trial Characteristics

<table>
<thead>
<tr>
<th>Design</th>
<th>Inclusion Criteria</th>
<th>Intervention (mg/kg/day)</th>
<th>Duration</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Devinsky 2016, n=137</td>
<td>Open label</td>
<td>Epilepsy, ≥ 4 motor seizures in 4 weeks</td>
<td>Initial 2-5, max 25-50</td>
<td>12 weeks, titration not specified</td>
</tr>
<tr>
<td>Devinsky 2017, n=120</td>
<td>R, DB, PC</td>
<td>DS, ≥ 1 AED, 4 seizures in 4 weeks</td>
<td>20 titrated over 2 weeks, maintained for 12 weeks</td>
<td>Change in frequency of convulsive seizures</td>
</tr>
<tr>
<td>GW Pharm Jun 2016, n=171</td>
<td>R, DB, PC</td>
<td>LGS, uncontrolled on ≥ 1 AED</td>
<td>20 titrated over 2 weeks, maintained for 12 weeks</td>
<td>% change in monthly frequency of drop seizures</td>
</tr>
<tr>
<td>GW Pharm Sep 2016, n=225</td>
<td>R, DB, PC</td>
<td>LGS, uncontrolled on ≥ 1 AED</td>
<td>20 vs 10 titrated over 2 weeks, maintained for 12 weeks</td>
<td>% change in monthly frequency of drop seizures</td>
</tr>
</tbody>
</table>

GW Pharmaceuticals. Press Releases.

Epidiolex® Clinical Trials: Patient Characteristics

<table>
<thead>
<tr>
<th>Age, yrs. (median [range])</th>
<th>Epilepsy Type</th>
<th>Current AED (mean [range])</th>
<th>Failed AED (mean [range])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Devinsky 2016, n=137</td>
<td>10.5 (9.0-26.2)</td>
<td>DS 20%, LGS 19%, Other 61%</td>
<td>3 (0-3)</td>
</tr>
<tr>
<td>Devinsky 2017, n=200</td>
<td>9 (2.5-18)</td>
<td>DS 3 (1-5)</td>
<td>4 (0-26)</td>
</tr>
<tr>
<td>GW Pharm Jul 2016, n=171</td>
<td>15 (2.5-55)</td>
<td>LGS 3 (6)</td>
<td>6 (2-16)</td>
</tr>
<tr>
<td>GW Pharm Sep 2016, n=225</td>
<td>16 (2.5-55)</td>
<td>LGS 3 (7)</td>
<td>7 (2-30)</td>
</tr>
</tbody>
</table>

LGS: Lennox-Gastaut syndrome
DS: Dravet syndrome

Epidiolex® Clinical Trials: Results

<table>
<thead>
<tr>
<th>Pre/Post seizure frequency per month</th>
<th>CBD reduction in monthly seizure frequency</th>
<th>Placebo change in monthly seizure frequency</th>
<th>Responder rate (≥ 50% decrease in seizures)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Devinsky 2016, n=137</td>
<td>CBD 30-50</td>
<td>36.5%</td>
<td>33% for motor seizures, 37% for all seizure types</td>
</tr>
<tr>
<td>Devinsky 2017, n=120</td>
<td>CBD 12.4-19.5</td>
<td>36.9%</td>
<td>33.3%</td>
</tr>
<tr>
<td>GW Pharm Jun 2016, n=171</td>
<td>CBD 4% in placebo</td>
<td>27%</td>
<td>0.33-4.5 (p&lt;0.08)</td>
</tr>
<tr>
<td>GW Pharm Sep 2016, n=225</td>
<td>--</td>
<td>44% (p&lt;0.02)</td>
<td>22%</td>
</tr>
</tbody>
</table>

LGS: Lennox-Gastaut syndrome
DS: Dravet syndrome

Appendix A
GW Pharmaceuticals. Press Releases.
**Epidiolex® Clinical Trials: ADR**

<table>
<thead>
<tr>
<th>Study</th>
<th>ADR (%)</th>
<th>% Max. Mod. of CBD ADR</th>
<th>% Share of CBD ADR</th>
<th>ADR within 15% Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Devinsky 2016, n=137</td>
<td>CBD 79%</td>
<td>62.5%</td>
<td>37.5%</td>
<td>Fatigue, convolution, decreased appetite, diarrhea</td>
</tr>
<tr>
<td>Devinsky 2017, n=120</td>
<td>CBD 93%</td>
<td>CBD 84%</td>
<td>CBD 84%</td>
<td>Fatigue, convolution, URTI, vomiting, pyrexia, lethargy</td>
</tr>
<tr>
<td>GW Pharm Jan 2016, n=111</td>
<td>CBD 86%</td>
<td>Placebo 63%</td>
<td>78%</td>
<td>CBD 16% Placebo 5%</td>
</tr>
<tr>
<td>GW Pharm Sep 2016, n=225</td>
<td>CBD (20) 94%</td>
<td>CBD (10) 84%</td>
<td>CBD (20) 96% Placebo 96%</td>
<td>CBD (20) 6% Placebo 4%</td>
</tr>
</tbody>
</table>

**Epidiolex® Clinical Trials: Summary**

- Bias
  - All funded by GW Pharmaceuticals
  - Questionable application to epilepsy syndromes beyond LGS & DS
  - Titration schedules not clearly defined which limits patient application

- 37-44% decrease in monthly seizure frequency
- 37-43% experienced a reduction by > 50%

- High rates of ADRs reported, even in placebo group
- Most ADRs were mild-moderate in nature

**Knowledge Check**

- Clinical trials of Epidiolex® in pediatric patients with Lennox-Gastaut and Dravet syndrome have shown a reduction in seizure frequency in the interventional arm compared to the placebo arm.
  - True
  - False

**Drug-Drug Interactions**

- CBD inhibits CYP 3A4 and 2C19
- Significant changes in serum concentrations
  - Clobazam
  - N-desmethylclobazam
  - Esticarbazepine
  - Rufinamide
  - Topiramate

**Drug-Drug Interactions: A benefit?**

- Charlotte Figi
  - Completely weaned off clobazam after 1 month CBD therapy
- Porter et al.
  - 12/19 (63%) were able to discontinue at least 1 AED while on CBD
    - Clobazam 5/12 (42%)
    - Valproic acid 5/12 (42%)
    - Stiripentol 3/12 (25%)
Other Dilemmas

AED Discontinuation

Success of CBD oil in reducing seizures
Belief that "natural" products are safer and healthier
Abrupt AED discontinuation without physician knowledge

Unfair Expectations

- If hospitalized, asked to stop use of CBD oil
- Will this cause the patient’s seizures to become uncontrolled?
- Will the serum concentration of other AEDs decrease resulting in loss of seizure control?

Extrapolations

Hope from positive results
Stigma surrounding cannabis products
Initiation of therapy without physician knowledge

• Is this appropriate for anyone with uncontrolled epilepsy?

Looking ahead…

- New drug application currently in progress
  - Expected to be completed in October
- Future plans:
  - Expanding products to include other cannabinoid products
  - Research for other indications
    - Autism spectrum disorders
    - Rett Syndrome
    - Neonatal hypoxic ischemic encephalopathy
    - Glioblastoma
    - Partial onset epilepsy

Clinical Application of Epidiolex®

- Who: LGS or DS patients
- What: add on therapy
- When: after trial and failure of at least 2 AEDs
- How:
  - Initiate at 2.5 mg/kg/day divided into 2 doses
  - Increase by 2.5 mg/kg/day every 2 days
  - Up to a maximum dose of 20 mg/kg/day as tolerated
Acknowledgements

- Dr. Ronda Machen, Pharm.D., RD, BCPPS, BCNSP
- Dr. Carolyn Ragsdale, Pharm.D., BCPS, BCPPS
- Dr. Eimeira Padilla-Tolentino, Pharm.D., PhD
- Dr. Thanhhaa Ngo, Pharm.D., BCPPS

THANK YOU!
## Appendix A: Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AED</td>
<td>Antiepileptic drug</td>
</tr>
<tr>
<td>ADR</td>
<td>Adverse drug reactions</td>
</tr>
<tr>
<td>BCECTS</td>
<td>Benign childhood epilepsy with centrotemporal spikes</td>
</tr>
<tr>
<td>CB₁, CB₂</td>
<td>Cannabinoid receptor 1 &amp; 2</td>
</tr>
<tr>
<td>CBD</td>
<td>Cannabidiol</td>
</tr>
<tr>
<td>CINV</td>
<td>Chemotherapy induced nausea and vomiting</td>
</tr>
<tr>
<td>CLB</td>
<td>Clobazam</td>
</tr>
<tr>
<td>DB</td>
<td>Double blind</td>
</tr>
<tr>
<td>DS</td>
<td>Dravet syndrome</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>IS</td>
<td>Infantile spasms</td>
</tr>
<tr>
<td>LGS</td>
<td>Lennox-Gastaut syndrome</td>
</tr>
<tr>
<td>MAE</td>
<td>Myoclonic astatic epilepsy</td>
</tr>
<tr>
<td>PC</td>
<td>Placebo controlled</td>
</tr>
<tr>
<td>R</td>
<td>Randomized</td>
</tr>
<tr>
<td>SB</td>
<td>Senate bill</td>
</tr>
<tr>
<td>SE</td>
<td>Side effects</td>
</tr>
<tr>
<td>STP</td>
<td>Stiripentol</td>
</tr>
<tr>
<td>THC</td>
<td>Tetrahydrocannabinol</td>
</tr>
<tr>
<td>TRP channels</td>
<td>Transient receptor potential channels</td>
</tr>
<tr>
<td>URTI</td>
<td>Upper respiratory tract infection</td>
</tr>
<tr>
<td>VPA</td>
<td>Valproic acid</td>
</tr>
</tbody>
</table>
Appendix B: AED Review

Appendix C: 2017 Legislative Status of Cannabis in the United States
### Appendix D: Observational Studies

<table>
<thead>
<tr>
<th>Survey</th>
<th>Age (years)</th>
<th>Epilepsy syndrome (%)</th>
<th>CBD dose (mg/kg/day)</th>
<th>Reduction in seizures, n (%)</th>
<th>Complete resolution of seizures, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porter 2013, n=19</td>
<td>2-16</td>
<td>5 68 21 ? 6</td>
<td>0.5-28</td>
<td>16 (84%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Hussain 2015, n=117</td>
<td>3-10</td>
<td>21 13 4 39 23</td>
<td>2.9-7.5</td>
<td>100 (85%)</td>
<td>16 (14%)</td>
</tr>
<tr>
<td>Press 2015, n=75</td>
<td>0.5-18</td>
<td>12 17 4 ? 67</td>
<td>Not reported</td>
<td>43 (57%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Aguirre-Velazquez 2017, n=43</td>
<td>0.8-18</td>
<td>47 0 2 19 32</td>
<td>1-6.9</td>
<td>35 (81%)</td>
<td>7 (16%)</td>
</tr>
</tbody>
</table>

### Appendix E: Observational Studies: Side Effects

<table>
<thead>
<tr>
<th>Negative SE</th>
<th>Drowsiness</th>
<th>Fatigue</th>
<th>Decreased appetite</th>
<th>Increased appetite</th>
<th>GI Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Positive SE</th>
<th>Improved mood</th>
<th>Improved sleep</th>
<th>Improved alertness</th>
<th>Decreased self stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
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<td></td>
<td>++</td>
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</table>
### Appendix F: Epidiolex® Clinical Trials: Trial Characteristics

<table>
<thead>
<tr>
<th>Design</th>
<th>Inclusion Criteria</th>
<th>Intervention (mg/kg/day)</th>
<th>Duration</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Devinsky 2016, n=137</td>
<td>Epilepsy, ≥ 4 motor seizures in 4 weeks</td>
<td>Initial 2-5, ↑ weekly 2-5, max 25-50</td>
<td>12 weeks, titration not specified</td>
<td>Change in motor seizure frequency</td>
</tr>
<tr>
<td>Devinsky 2017, n=120</td>
<td>DS, ≥ 1 AED, ≥ 4 seizures in 4 weeks</td>
<td>20</td>
<td>titrated over 2 weeks, maintained for 12 weeks</td>
<td>Change in frequency of convulsive seizures</td>
</tr>
<tr>
<td>GW Pharm Jun 2016, n=171</td>
<td>LGS, uncontrolled on ≥ 1 AED</td>
<td>20</td>
<td>titrated over 2 weeks, maintained for 12 weeks</td>
<td>% change in monthly frequency of drop seizures</td>
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<tr>
<td>GW Pharm Sep 2016, n=225</td>
<td>LGS, uncontrolled on ≥ 1 AED</td>
<td>20 vs 10</td>
<td>titrated over 2 weeks, maintained for 12 weeks</td>
<td>% change in monthly frequency of drop seizures</td>
</tr>
</tbody>
</table>

### Appendix G: Epidiolex® Clinical Trials: Patient Characteristics

<table>
<thead>
<tr>
<th>Design</th>
<th>Age, yrs. median (range)</th>
<th>Epilepsy Type</th>
<th>Current AED mean (range)</th>
<th>Failed AED mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Devinsky 2016, n=137</td>
<td>10.5 (0.9-26.2)</td>
<td>DS 20% LGS 19% Other 61%</td>
<td>3</td>
<td>--</td>
</tr>
<tr>
<td>Devinsky 2017, n=120</td>
<td>9.1 (2.5-18)</td>
<td>DS</td>
<td>3 (1-5)</td>
<td>4 (0-26)</td>
</tr>
<tr>
<td>GW Pharm Jun 2016, n=171</td>
<td>15 (2-55)</td>
<td>LGS</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>GW Pharm Sep 2016, n=225</td>
<td>16 (2-55)</td>
<td>LGS</td>
<td>3</td>
<td>7</td>
</tr>
</tbody>
</table>
### Appendix H: Epidiolex® Clinical Trials: Results

<table>
<thead>
<tr>
<th></th>
<th>Pre/ Post seizure frequency per month</th>
<th>CBD reduction in monthly seizure frequency</th>
<th>Placebo change in monthly seizure frequency</th>
<th>Responder rate (≥ 50% decrease in seizures)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Devinsky 2016, n= 137</td>
<td>CBD 30 → 15.8</td>
<td>36.5%</td>
<td></td>
<td>39% for motor seizures, 37% for all seizure types</td>
</tr>
<tr>
<td>Devinsky 2017, n= 120</td>
<td>CBD 12.4 → 5.9 P 14.9 → 14.1</td>
<td>38.9%</td>
<td>13.3%</td>
<td>CBD 43% vs placebo 27% (OR 2; 95% CI 0.93-4.3; p=0.08)</td>
</tr>
<tr>
<td>GW Pharm Jun 2016, n= 171</td>
<td>--</td>
<td>44% (p&lt; 0.02)</td>
<td>22%</td>
<td>--</td>
</tr>
<tr>
<td>GW Pharm Sep 2016, n= 225</td>
<td>--</td>
<td>20-42% (p&lt; 0.01)</td>
<td>10-37% (p&lt; 0.01)</td>
<td>17%</td>
</tr>
</tbody>
</table>

### Appendix I: Epidiolex® Clinical Trials: ADR

<table>
<thead>
<tr>
<th></th>
<th>ADR (%)</th>
<th>% Mild- Mod of CBD ADR</th>
<th>% Severe of CBD ADR</th>
<th>ADR with ≥ 10% incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Devinsky 2016, n= 137</td>
<td>CBD 79%</td>
<td>62.5%</td>
<td>37.5%</td>
<td>fatigue, convulsion</td>
</tr>
<tr>
<td>Devinsky 2017, n= 120</td>
<td>CBD 93% P 75%</td>
<td>CBD 84% P 95%</td>
<td>CBD 16% P 5%</td>
<td>fatigue, convulsion, URTI, vomiting, pyrexia, lethargy</td>
</tr>
<tr>
<td>GW Pharm Jun 2016, n= 171</td>
<td>CBD 86% P 69%</td>
<td>78%</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>GW Pharm Sep 2016, n= 225</td>
<td>CBD 20 mg/kg/day 94% CBD 10 mg/kg/day 84% P 72%</td>
<td>CBD 20 88% CBD 10 89% P ---</td>
<td>CBD 20 6% CBD 10 6% P 4%</td>
<td>20 &amp; 10 URTI 20 pyrexia, vomiting, nasopharyngitis 10 status epilepticus</td>
</tr>
</tbody>
</table>
Appendix J: Bibliography


