EPIDIOLEX®:
CASHING IN THE CANNABIS RAIN CHECK?

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H-E-B Pharmacy/UT Austin
Disclosures

• No conflicts of interest to disclose
Objectives

At the conclusion of this presentation, the learner should be better able to:

• Describe the difference between seizures and epilepsy
• Describe clinical trials which gained Epidiolex® FDA-approval
• Comment on the side effects, drug-drug interactions, and clinical pearls of cannabidiol therapy
• Educate patients and address questions regarding differences between Epidiolex® and OTC cannabidiol products
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Seizures

- **Seizure** - transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain

- Requires both neuronal
  1. Hyperexcitability
  2. Hypersynchronization

- Inhibitory synaptic currents break down and the excitability spreads, locally (focal seizures) or widely (generalized seizures)

---

Seizures

- Seizure ≠ epilepsy

<table>
<thead>
<tr>
<th>Provoked Seizures</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug overdose</td>
<td>Cocaine, TCA’s</td>
</tr>
<tr>
<td>Drug withdrawals</td>
<td>Alcohol, benzodiazepines</td>
</tr>
<tr>
<td>Acute neurologic events</td>
<td>Trauma, hemorrhage</td>
</tr>
<tr>
<td>Systemic illness</td>
<td>Hypoglycemia, eclampsia</td>
</tr>
<tr>
<td>Fever</td>
<td>Febrile seizures</td>
</tr>
</tbody>
</table>
Seizures – Terminology

• **Tonic** – muscles become tense or rigid
• **Atonic** – muscles become weak or limp
• **Clonic** – jerking movements
• **Myoclonus** – brief muscle twitches

• **Nonmotor symptoms** – symptoms that don’t affect movement
  • Changes in sensation, emotion, thinking
  • Changes in autonomic function (goosebumps, tachycardia)
  • Behavioral arrest (staring spells)
Seizures – Current Classifications

“NEW” CLASSIFICATION OF SEIZURE TYPES
International League Against Epilepsy, 2017

FOCAL ONSET
Aware | Impaired Awareness

GENERALIZED ONSET
Impaired Awareness

UNKNOWN ONSET

MOTOR
- Tonic-clonic
- Epileptic spasms (Generalized)
- Repeated automations (Focal)

NON-MOTOR
- Absence
- Autonomic function changes
- Change in emotions

Epilepsy

A disease of the brain defined by any of the following:

1. At least two unprovoked seizures occurring >24 h apart

2. One unprovoked seizure and probability of at least 60% for further seizures occurring over the next 10 years

3. Diagnosis of an epilepsy syndrome

Resolved epilepsy – seizure-free for 10 years with no seizure medications for the last 5 years
Classifications

Epilepsy Syndromes

- Benign Rolandic Epilepsy
- Doose Syndrome
- Juvenile Myoclonic Epilepsy
- West Syndrome
  - Lennox-Gastaut Syndrome
  - Dravet Syndrome
Lennox Gastaut Syndrome (LGS)

- Severe form of epileptic encephalopathy
- 2 cases out of 100,000 population
- Manifests by 8 years old, peak incidence at 3-5 years
  - Multiple seizure types – tonic, atonic, atypical absence; “drop attacks” common
  - Slow spike-and-wave activity on EEGs
  - Typically life-long with cognitive impairment
- 20-60% of patients have delayed cognitive development at disease onset, 75-95% become cognitively impaired with increasing age
Dravet Syndrome (DS)

- Genetic form of epileptic encephalopathy
- > 80% of cases due to mutations in the SCN1A gene
- 1 out of 20,000 – 40,000 population
- Seizures start within first year of life, with developmental slowing or regression at 1-2 years
  - Multiple seizure types – tonic, atonic, atypical absence
  - Nonspecific EEG features
  - Lifelong with developmental disabilities
# Treatment Options

<table>
<thead>
<tr>
<th>Lennox Gaustaut Syndrome</th>
<th>Dravet Syndrome*</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Felbamate (Felbatol®)</td>
<td><strong>First Line</strong></td>
</tr>
<tr>
<td>• Rufinamide (Banzel®)</td>
<td>• Clobazam (Onfi®)</td>
</tr>
<tr>
<td>• Clobazam (Onfi®)</td>
<td>• Valproate</td>
</tr>
<tr>
<td>• Clonazepam</td>
<td><strong>Second Line</strong></td>
</tr>
<tr>
<td>• Lamotrigine</td>
<td>• Stiripentol (Diacomit®)Δ</td>
</tr>
<tr>
<td>• Topiramate</td>
<td>• Topiramate</td>
</tr>
<tr>
<td>• Valproate^</td>
<td><strong>Third Line</strong></td>
</tr>
<tr>
<td></td>
<td>• Clonazepam</td>
</tr>
<tr>
<td></td>
<td>• Levetiracetam</td>
</tr>
<tr>
<td></td>
<td>• Zonisamide</td>
</tr>
<tr>
<td></td>
<td>• Ethosuximide</td>
</tr>
</tbody>
</table>

^Not FDA-approved for LGS, but commonly 1st line

*None are FDA-approved

Δ Available in Europe only
Treatment Options

- Treatment is aimed at controlling seizures
- Usually multiple medications are required
- Ketogenic diet or vagal nerve stimulation may be considered

LGS Prognosis

- 75% Survival
- 25% Mortality
- <10% seizure free

DS Prognosis

- 80% Survival
- 20% Mortality
- 11% seizure free

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DRUG REVIEW
Epidiolex® (Cannabidiol)

- The first naturally derived, FDA-approved *Cannabis* drug product
- Indicated for treating LGS and DS in patients 2+ years of age
- Strawberry flavored, clear to yellow color
- Gluten free, but does contain sesame oil
Epidiolex® (Cannabidiol)

• 100 mg/mL oral solution
• 100 mL stock bottle (NDC 70127-100-10)
• Recommended starting dose:
  • 2.5 mg/kg twice daily (5 mg/kg total daily dose)
• Maximum recommended dose:
  • 10 mg/kg/dose or 20 mg/kg/day
• Packaged with two 5 mL calibrated oral dosing syringes and a bottle adapter
HOW DOES IT WORK?
**Cannabis, a brief taxonomy**

- 2 species of plant: *Cannabis indica* and *Cannabis sativa*
  - Produce **cannabinoids**, terpenophenolic compounds exclusive to *Cannabis*

![Chemical structures of THC and CBD]

- There is a greater amount of CBD found in *C. sativa* and a greater amount of THC found in *C. indica.*

Cannabidiol MOA

- Cannabinoids interact with CB1 and CB2 receptors in the body
  - CB1 – neurons and glial cells
  - CB2 – immune system
- THC causes euphoria via CB1 receptors.
- CBD has little affinity for CB1 receptors, and when it does bind produces little to no effect

- Note: “hemp” is a legal and agricultural term referring to *C. sativa* with low THC content grown for industrial purposes
Cannabidiol MOA

• Cannabidiol (Epidiolex®) is a cannabinoid that naturally occurs in the *Cannabis Sativa* L. plant.

• The precise mechanisms by which cannabidiol exerts its anticonvulsant effect in humans are unknown
  • Does not appear to be via human cannabinoid receptors
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CLINICAL TRIALS
# Clinical Trials

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Study Design</th>
<th># of Patients</th>
<th>Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Thiele et al. (2018)</td>
<td>LGS</td>
<td>Randomized, double-blind, placebo-controlled trial at 24 clinical sites in the USA, Netherlands, Poland</td>
<td>N = 171 • CBD = 86 • PBO = 85</td>
</tr>
<tr>
<td>II. Devinsky et al. (2018)</td>
<td>LGS</td>
<td>Randomized, double-blind, placebo-controlled trial at 30 sites in the USA, Spain, UK, and France</td>
<td>N = 225 • CBD 10mg = 73 • CBD 20mg = 76 • PBO = 76</td>
</tr>
<tr>
<td>III. Devinsky et al. (2017)</td>
<td>DS</td>
<td>Randomized, double-blind, placebo-controlled trial at 23 sites in the USA and Europe</td>
<td>N = 120 • CBD = 61 • PBO = 59</td>
</tr>
</tbody>
</table>

Study Designs

Baseline
4 weeks

Treatment
2 week dose escalation*
12 week maintenance

Taper
10 days

Follow-Up
4 weeks

*Initial dose of 2.5 mg/kg in all 3 studies

Study I – Thiele et al. (2018)

“Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial”

**Primary Endpoint**

Percent change in monthly frequency of drop seizures from baseline

**Secondary Endpoints**

Proportion of patients with ≥ 50% ↓ in monthly frequency of drop seizures

Percent change in total seizure frequency from baseline

Patient or Caregiver Global Impression of Change from baseline (see Appendix B)
<table>
<thead>
<tr>
<th>Study I – Thiele et al. (2018)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion Criteria</strong></td>
</tr>
<tr>
<td>• Age 2-55 years</td>
</tr>
<tr>
<td>• Clinical diagnosis of LGS</td>
</tr>
<tr>
<td>• Refractory</td>
</tr>
<tr>
<td>• Taking 1-4 AEDs</td>
</tr>
<tr>
<td>• &gt; 1 type of generalized seizure, including drop seizures, for ≥ 6 months</td>
</tr>
<tr>
<td><strong>Exclusion Criteria</strong></td>
</tr>
<tr>
<td>• History of alcohol or substance abuse</td>
</tr>
<tr>
<td>• Recreational or medicinal cannabis users</td>
</tr>
<tr>
<td>• (+) urine THC screen</td>
</tr>
<tr>
<td>• Pregnant or lactating</td>
</tr>
<tr>
<td>• Significantly impaired hepatic function</td>
</tr>
<tr>
<td>• Felbamate within last year</td>
</tr>
<tr>
<td>• Corticotrophins in last 6 months</td>
</tr>
</tbody>
</table>
**Study I – Thiele et al. (2018)**

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 171</td>
</tr>
<tr>
<td>CBD = 86</td>
</tr>
<tr>
<td>PBO = 85</td>
</tr>
<tr>
<td>• Similar at baseline</td>
</tr>
<tr>
<td>• Mean age = 15.4</td>
</tr>
<tr>
<td>• Median of 6 previous AEDs</td>
</tr>
<tr>
<td>• Median of 3 concomitant AEDs during trial</td>
</tr>
<tr>
<td>• Median monthly frequency of drop seizures = 73.8</td>
</tr>
</tbody>
</table>
Study I – Thiele et al. (2018)

<table>
<thead>
<tr>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Endpoint</strong></td>
</tr>
</tbody>
</table>
| CBD = 43.9% ↓ (p = 0.0135)  \[
| • 71.4 to 31.4 drop seizures  \]
| PBO = 21.8% ↓  \[
| • 74.7 to 56.3 drop seizures  \]                                                                                                                              |
| **Secondary Endpoints**                                                                                                                                       |
| ≥ 50% ↓ in drop seizure frequency                                                                                                                              |
| CBD = 38/86 (44%, p = 0.0043)  \[
| PBO = 20/85 (24%)                                                                                                                                             |
| % Δ in total seizure frequency                                                                                                                                   |
| CBD = 41.2% ↓ (p = 0.0005)  \[
| PBO = 13.7% ↓  \]
| Improvement in GIC scale                                                                                                                                       |
| CBD = 49/84 (58%, p = 0.0012)  \[
| PBO = 29/85 (34%)                                                                                                                                             |
Study II – Devinsky et al. (2018)

“Effect of Cannabidiol on Drop Seizures in the Lennox–Gastaut Syndrome” (2 dose study)

**Primary Endpoint**
Percent change in monthly frequency of drop seizures from baseline

**Secondary Endpoints**
Proportion of patients with ≥ 50% ↓ in monthly frequency of drop seizures
Percent change in total seizure frequency from baseline
Patient or Caregiver Global Impression of Change from baseline

### Study II – Devinsky et al. (2018)

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age 2-55 years</td>
<td>• History of alcohol or substance abuse</td>
</tr>
<tr>
<td>• Clinical diagnosis of LGS</td>
<td>• Recreational or medicinal cannabis users</td>
</tr>
<tr>
<td>• ≥ 2 type of generalized seizure, including drop seizures, for ≥ 6 months</td>
<td>• (+) urine THC screen</td>
</tr>
<tr>
<td></td>
<td>• Pregnant or lactating</td>
</tr>
<tr>
<td></td>
<td>• Significantly impaired hepatic function</td>
</tr>
<tr>
<td></td>
<td>• Corticotropins in last 6 months</td>
</tr>
<tr>
<td></td>
<td>• Felbamate in last year</td>
</tr>
</tbody>
</table>
Study II – Devinsky et al. (2018)

<table>
<thead>
<tr>
<th>Patient characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 225</td>
</tr>
<tr>
<td>• CBD 10 mg = 73</td>
</tr>
<tr>
<td>• CBD 20 mg = 76</td>
</tr>
<tr>
<td>• PBO = 76</td>
</tr>
<tr>
<td>*mg/kg/day</td>
</tr>
<tr>
<td>• Similar at baseline</td>
</tr>
<tr>
<td>• Median of 6 previous AEDs</td>
</tr>
<tr>
<td>• Median of 3 concomitant AEDs during trial</td>
</tr>
<tr>
<td>• Most common AED was clobazam</td>
</tr>
<tr>
<td>• Median number of drop seizures = 85</td>
</tr>
</tbody>
</table>
# Study II – Devinsky et al. (2018)

## Results

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>Secondary Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CBD 10mg</strong> = 37.2% ↓ ((p = 0.005))</td>
<td>(\geq 50% \downarrow \textit{in drop seizure frequency})</td>
</tr>
<tr>
<td><strong>CBD 20mg</strong> = 41.9% ↓ ((p = 0.002))</td>
<td><strong>CBD 10mg</strong> = 26/73 (36%, (p &lt; 0.001))</td>
</tr>
<tr>
<td><strong>PBO</strong> = 17.2% ↓</td>
<td><strong>CBD 20mg</strong> = 30/76 (39%, (p = 0.003))</td>
</tr>
<tr>
<td></td>
<td><strong>PBO</strong> = 11/76 (14%)</td>
</tr>
</tbody>
</table>

\(\% \Delta \textit{in total seizure frequency}\)

| **CBD 10mg** = 36.4% ↓ (\(p = 0.002\)) | \(\textbf{CBD 10mg} = 48/73 \ (66\%, \ p = 0.002)\) |
| **CBD 20mg** = 38.4% ↓ (\(p = 0.009\)) | \(\textbf{CBD 20mg} = 43/75 \ (57\%, \ p = 0.04)\) |
| **PBO** = 18.5% ↓ | **PBO** = 33/75 (44%) |

\textit{Improvement in GIC scale}
Study III – Devinsky et al. (2017)

“Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome”

**Primary Endpoint**

Percentage change per 28 days from the 4-week baseline period in convulsive-seizure frequency

**Secondary Endpoints**

≥ 50% reduction in convulsive-seizure frequency per month

Reduction in total seizure frequency

Caregiver Global Impression of Change from baseline
### Inclusion Criteria
- Age 2-18 years
- Established diagnosis of DS
- Taking 1 or more AEDs
- ≥ 4 convulsive seizures during baseline

### Exclusion Criteria
- History of alcohol or substance abuse
- Recreational or medicinal cannabis users
- (+) urine THC screen
- Pregnant or lactating
- Significantly impaired hepatic function
Study III – Devinsky et al. (2017)

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 120</td>
<td></td>
</tr>
<tr>
<td>CBD = 61</td>
<td></td>
</tr>
<tr>
<td>PBO = 59</td>
<td></td>
</tr>
<tr>
<td>Similar at baseline</td>
<td></td>
</tr>
<tr>
<td>Mean age 9.8 years</td>
<td></td>
</tr>
<tr>
<td>Median of 4 previous AEDs</td>
<td></td>
</tr>
<tr>
<td>Median of 3 concomitant AEDs during trial</td>
<td></td>
</tr>
<tr>
<td>Median number of convulsive seizures/month = 13</td>
<td></td>
</tr>
</tbody>
</table>
**Study III – Devinsky et al. (2017)**

<table>
<thead>
<tr>
<th><strong>Primary Endpoint</strong></th>
<th><strong>Secondary Endpoints</strong></th>
</tr>
</thead>
</table>
| CBD = 38.9% ↓ \(p = 0.01\)  
  • 12.4 to 5.9 seizures  
  PBO = 13.3% ↓  
  • 14.9 to 14.1 seizures | \(\geq 50\% \downarrow\) *in convulsive seizure freq.*  
  CBD = 43% \(p = 0.08\)  
  PBO = 27%  
  \(\% \Delta \) *in total seizure frequency*  
  CBD = 28.6% ↓ \(p = 0.03\)  
  PBO = 9.0% ↓  
  *Improvement in GIC scale*  
  CBD = 37/60, 62%, \(p = 0.02\)  
  PBO = 20/58, 34% |

## Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CBD = 53/86 (62%)</td>
<td>CBD 10 mg = 56/67 (84%)</td>
<td>CBD = 57/61 (93%)</td>
</tr>
<tr>
<td>PBO = 29/85 (34%)</td>
<td>CBD 20 mg = 77/82 (94%)</td>
<td>PBO = 44/59 (75%)</td>
</tr>
<tr>
<td></td>
<td>PBO = 55/76 (72%)</td>
<td></td>
</tr>
<tr>
<td><strong>Common AE</strong></td>
<td><strong>Common AE</strong></td>
<td><strong>Common AE</strong></td>
</tr>
<tr>
<td>• Diarrhea, vomiting</td>
<td>• Diarrhea, vomiting</td>
<td>• Diarrhea, vomiting</td>
</tr>
<tr>
<td>• ↓ appetite</td>
<td>• ↓ appetite</td>
<td>• ↓ appetite</td>
</tr>
<tr>
<td>• Somnolence</td>
<td>• Somnolence</td>
<td>• Fatigue, lethargy</td>
</tr>
<tr>
<td>• Pyrexia</td>
<td>• Pyrexia</td>
<td>• URTI</td>
</tr>
<tr>
<td><strong>AE leading to withdrawal</strong></td>
<td><strong>AE leading to withdrawal</strong></td>
<td><strong>AE leading to withdrawal</strong></td>
</tr>
<tr>
<td>CBD = 12</td>
<td>CBD 10 mg = 1</td>
<td>CBD = 8</td>
</tr>
<tr>
<td>PBO = 1</td>
<td>CBD 20 mg = 6</td>
<td>PBO = 1</td>
</tr>
<tr>
<td></td>
<td>PBO = 1</td>
<td></td>
</tr>
</tbody>
</table>

- Somnolence was greater with concomitant clobazam; higher incidence of ↑ liver enzymes occurred with concomitant valproate

## Study Evaluations

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Adequate power achieved</td>
<td>• The sponsor (GW Pharmaceuticals) funded the study, supplied the drug and placebo; and assisted in data collection and writing of the studies</td>
</tr>
<tr>
<td>• Patient characteristics matching at baseline</td>
<td>• Poor ethnic diversity</td>
</tr>
<tr>
<td>• Sensitivity analyses of endpoints</td>
<td>• CBD was used as an add-on therapy, not stand-alone</td>
</tr>
<tr>
<td></td>
<td>• Patients or caregivers recorded #/type of seizures</td>
</tr>
<tr>
<td></td>
<td>• Small sample size</td>
</tr>
<tr>
<td></td>
<td>• Single dose of CBD was investigated in studies I/III</td>
</tr>
</tbody>
</table>

### Pearls and Implications

• Patients in CBD groups were more likely to experience ↑ liver transaminases, esp. if taking valproate concurrently (in Study II, 20 mg/kg > 10 mg/kg)

• CBD inhibits CYP2C19 and ↑ levels of the N-desmethyl metabolite of clobazam, which may have contributed to CBD efficacy and somnolence

## Package Insert

- Side effects include somnolence, ↓ appetite, diarrhea, transaminase elevations, fatigue, insomnia, infections
- Dosage adjustment recommended for hepatic impairment or concomitant valproate use
- Transaminase elevations are dose-dependent

<table>
<thead>
<tr>
<th>Hepatic Impairment</th>
<th>Starting Dosage</th>
<th>Maintenance Dosage</th>
<th>Maximum Recommended Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>2.5 mg/kg twice daily</td>
<td>5 mg/kg twice daily</td>
<td>10 mg/kg twice daily</td>
</tr>
<tr>
<td></td>
<td>(5 mg/kg/day)</td>
<td>(10 mg/kg/day)</td>
<td>(20 mg/kg/day)</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.25 mg/kg twice daily</td>
<td>2.5 mg/kg twice daily</td>
<td>5 mg/kg twice daily</td>
</tr>
<tr>
<td></td>
<td>(2.5 mg/kg/day)</td>
<td>(5 mg/kg/day)</td>
<td>(10 mg/kg/day)</td>
</tr>
<tr>
<td>Severe</td>
<td>0.5 mg/kg twice daily</td>
<td>1 mg/kg twice daily</td>
<td>2 mg/kg twice daily</td>
</tr>
<tr>
<td></td>
<td>(1 mg/kg/day)</td>
<td>(2 mg/kg/day)</td>
<td>(4 mg/kg/day)</td>
</tr>
</tbody>
</table>
## Concomitant Use of

<table>
<thead>
<tr>
<th>Inhibitors of CYP3A4, CYP2C19</th>
<th>Employ This Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ Dose of Epidiolex</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inducers of CYP3A4, CYP2C19</th>
<th>Employ This Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Dose of Epidiolex</td>
<td></td>
</tr>
</tbody>
</table>

| Substrates of UGT1A9, UGT2B7, CYP2C8, CYP2C9, CYP2C19 (Clobazam) | Consider dose reduction of substrate |

- Also note: based on animal data, may cause fetal harm
WHAT ABOUT OTC CBD?
Legal Issues – The DEA

• September 28, 2018 – DEA placed Epidiolex® into Schedule V
  o Specifically, FDA-approved drugs that contain CBD derived from *cannabis* and ≤ 0.1% THC

• All other cannabis/cannabis derivatives are still Schedule I
  • Loop-hole: Agricultural Act of 2014, AKA “The Farm Bill”
  • Very gray area, lots of confusion

Kux, L. Schedules of Controlled Substances. DEA. Federal Register: Vol. 83, No. 189; 48950-48953
The 2014 Farm Bill

- Hemp and its derivatives (CBD) are legal (?) to sell in all 50 states if grown under a licensed state pilot program
  - Hemp – cannabis with < 0.3% THC
  - License requires partnership with state department of agriculture or university
  - Texas does not have a license to grow hemp
  - DEA currently states that parts of hemp plant (not the entire plant itself) are legal to extract and sell from, but impractical due to negligible amounts of cannabinoids
- 2018 Farm Bill – hoping to clear up discrepancies
Products on the Market

• Most CBD products on the market are not isolates
  • “Full spectrum CBD”, “Hemp extracts”
• There is no regulatory body that enforces quality assurance
• Miller et al. (2017) analyzed 87 CBD products from 31 companies available for online purchase

21.43% Of samples had detectable THC levels
  • Mean of 0.45 mg/mL

26.19% Over
42.85% Under

Bonn-Miller et al. JAMA. 2017. 318 (17): 1708-1709
## Comparison

<table>
<thead>
<tr>
<th></th>
<th>Epidiolex®</th>
<th>OTC Cannabidiol*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strength</strong></td>
<td>100 mg/mL</td>
<td>66.66 mg/mL</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>~ $32,500/year</td>
<td>~ $13,650/year</td>
</tr>
<tr>
<td><strong>Efficacy established?</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Potency/purity guaranteed?</strong></td>
<td>Yes, per FDA</td>
<td>No, private testing</td>
</tr>
<tr>
<td><strong>Need a prescription?</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Patents?</strong></td>
<td>Yes, 5 “method of use”</td>
<td>No</td>
</tr>
</tbody>
</table>

*Online seller, $60 for 1000 mg (15 mL) bottle. Calculated using FDA-recommended maximum dosing of Epidiolex® for a 34-kg child.

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Pipeline

- Epidiolex® for Tuberous Sclerosis (Phase 3)
- CBDV for Epilepsy (Phase 2)
- CBDV for Autism Spectrum Disorders (Phase 2)
- IV CBD for Neonatal Hypoxic-Ischemic Encephalopathy (Phase 1)
- THC + CBD for Glioblastoma (Phase 2)
- CBD for schizophrenia (Phase 2)
- THC + CBD (Sativex®) for MS Spasticity (Phase 3 in the U.S.)
Conclusions

• Cannabidiol (Epidiolex®) is the first naturally derived, FDA-approved Cannabis product available in the U.S., indicated for severe epileptic syndromes: LGS and DS

• Pharmacists should emphasize FDA approval of Epidiolex®

• Be able to counsel on Epidiolex®
  • GI upset – nausea, vomiting, diarrhea
  • Increased LFT’s – with valproate
  • Somnolence and sedation – especially with concomitant clobazam
  • DDI’s – inducers, inhibitors, and substrates of CYP enzymes and UGTs

• Pharmacists should additionally be able to address patient questions between OTC cannabidiol products and Epidiolex®
Acknowledgements

• Nathan D. Pope, Pharm.D., BCACP, FACA
• Collin Hovinga, PharmD, MS, FCCP
QUESTIONS?
EPI DIOLEX®:  
CASHING IN THE CANNABIS RAIN CHECK?

Leila Petok  
PGY-1 Community Pharmacy Resident  
H-E-B Pharmacy/UT Austin
References

Appendices

Appendix A: Abbreviations

Appendix B: Patient and Caregiver Global Impression of Change Scale

Appendix C: Types of Epilepsy from the International League Against Epilepsy
Appendix A: Abbreviations

OTC = over-the-counter
TCA = tricyclic antidepressant
LGS = Lennox Gastaut Syndrome
DS = Dravet Syndrome
EEG = electroencephalogram
SCN1A = sodium channel, voltage gated, type I alpha subunit (gene)
FDA = (United States) Food and Drug Administration
mg = milligram
mL = milliliter
kg = kilogram
CBD = cannabidiol
THC = tetrahydrocannabinol
CB1/2 = Cannabinoid receptor type ½
PBO = placebo
AED = antiepileptic drug
CGIC = Caregiver Global Impression of Change scale
PGIC = Patient Global Impression of Change scale
AE = adverse effects
URTI = upper respiratory tract infection
IV = intravenous
CBDV = cannabidivarin
GI = gastrointestinal
DDI = drug-drug interactions
CYP = cytochrome P450 enzymes
LFTs = liver function tests
UGT = UDP-glucuronosyltransferase
Appendix B: Patient and Caregiver Global Impression of Change Scale

**CGIC:**
- Since your child started treatment, please assess the status of your child’s overall condition (comparing their condition now to their condition before treatment) using the scale below.

**SGIC:**
- Since you started treatment, please assess the status of your overall condition (comparing your condition now to your condition before treatment) using the scale below.

### TABLE 2. CGI-I guidelines

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Very much improved—nearly all better; good level of functioning; minimal symptoms; represents a very substantial change</td>
</tr>
<tr>
<td>2</td>
<td>Much improved—notably better with significant reduction of symptoms, increase in the level of functioning but some symptoms remain</td>
</tr>
<tr>
<td>3</td>
<td>Minimally improved—slightly better with little or no clinically meaningful reduction of symptoms. Represents very little change in basic clinical status, level of care, or functional capacity</td>
</tr>
<tr>
<td>4</td>
<td>No change—symptoms remain essentially unchanged</td>
</tr>
<tr>
<td>5</td>
<td>Minimally worse—slightly worse but may not be clinically meaningful, may represent very little change in basic clinical status or functional capacity</td>
</tr>
<tr>
<td>6</td>
<td>Much worse—clinically significant increase in symptoms and diminished functioning</td>
</tr>
<tr>
<td>7</td>
<td>Very much worse—severe exacerbation of symptoms and loss of functioning</td>
</tr>
</tbody>
</table>


Appendix C: Types of Epilepsy from the International League Against Epilepsy