Cannabis in the treatment of Autism: Are we ready?

Deb Karhson, PhD and Lawrence Fung, MD, PhD
Cannabis Anecdotal Data: Comparing Epilepsy and Autism+
Science of Cannabinoids: Endocannabinoid System

Receptor Distribution

CNS/Brain

Immune

Cannabinoids Bind to Cannabinoid Receptors

CB1

CB2

Leafly

Stanford Medicine
Science of Cannabis: Definition of terms

- Current studies are focused on “top-down” action of cannabis
  - Is there an impact on behavioral symptoms of autism?

- Cannabis is $\geq 480$ components
  - $20$ identified Flavonoids (Flores-Sanchez and Verpoorte, 2008)
    - Aromatic molecules
    - Cannaflavins are pharmacologically active
  - $\geq 200$ Terpenes / terpenoids (Rothschild et al., 2005; Brennisen, 2007)
    - Responsible for cannabis odor and flavor
  - $\geq 100$ identified Cannabinoids in literature
    - Phytocannabinoids (Mechoulam R. BJP 2005. 146, 913-915)

- Major Cannabinoids: $\Delta^9$-tetrahydrocannabinol and Cannabidiol (THC and CBD)
  - New Kids on the Block: CBDV, CBDA, CBN, CBG, CBC, THCA, THCV
Science of Cannabinoids: Polypharmaceutical

- **Therapeutic workhorse: CBD**
  - Limited action at CB1 Receptors
  - Stress Response
  - Neuroinflammation

- **Entourage Effect**
  - THC+CBD more effective than THC alone
    - 100mg synthetic CBD ≠ 100mg whole plant extract
  - Terpenoid above [0.05%] are pharmacologically relevant (Adams and Taylor, 2010)

- **Chemistry is power!**
  - Not all artisanal products have advertised cannabinoids

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**Research Letter**

November 7, 2017

**Labeling Accuracy of Cannabidiol Extracts Sold Online**

Marcel O. Bonn-Miller, PhD; Mallory J. E. Loflin, PhD; Brian F. Thomas, PhD; et al

Author Affiliations

Science of Cannabinoids: Biochemistry of Consumption

- **Ingestion**
  - Difficult to titrate
  - Conversion of THC to 11-OH-THC by liver enzymes
    - 11-OH-THC is more potent than THC, higher blood levels
    - Peak effect ~2-4hrs post ingestion
  - Weight, metabolism, gender, and diet modulate effects

- **Sublingual**
  - Typically with decarboxylated cannabis
  - Increased density of blood vessels → direct uptake by bloodstream

- **Combustion**
  - Smoking
    - Associated with lung inflammation and bronchitis in humans
    - Δ⁹-THC via blood directly to brain, initial effect within minutes
    - peak effect ~30 minutes post smoking, psychoactive effects last 2 to 3 hours
  - Vaporization: permits inhalation while avoiding noxious smoke
    - rapid onset, direct delivery into the bloodstream, ease of self-titration
Industry Interactions: GW Pharmaceuticals

- Host of Cannabinoid-based therapeutics
  - Sativex for MS spasticity
    - 1:1 ratio of THC to CBD
  - Epidiolex for Epilepsy
    - 99% CBD formulation
  - Unnamed compounds: GWP42006, GWP42003, GWP42002, etc.

- Focus of R&D: **orphan** neurologic conditions
  - Orphan "autisms": Rett Syndrome and Fragile X

- GWP42006 – Cannabidivarin (CBDV)
  - Different profile from Epidiolex in 4 ways:
    - Efficacy profile in seizure models
    - Metabolic profile
    - Pharmacological profile
    - Different physicochemical characteristics
Industry Interactions: Zynerba

- **Synthetic** cannabidiol (CBD)
  - “Permeation-enhanced” gel
    - transdermal delivery
  - In clinical trials for Fragile X
    - Started February 2016
    - Phase 2 results in Sept. 2017

- Preliminary results in Epilepsy
  - Does not produce impairment in cognitive functioning
  - Non-affected participants: No decline in psychological health

http://zynerba.com/in-development/cbd-gel-zyn002/

http://zynerba.com/in-development/
Major Questions in Human Research

- **Is cannabis treating core or associated symptom?**
  - What patient population benefits the most, autism, autism+, seizures in autism?

- **“Whose on First?”**
  - What cannabinoids (phyto- or endo-) are performing what action?
  - Are the medical benefits of cannabinoids separable and comparable?

- **Are the mechanisms of action for cannabis treatment transdiagnostic?**
  - Do/Should we treat “The Autisms” the same way we treat
    - Dravet Syndrome or TSC or Fragile X?
    - None of the above?

- **Path forward: Patient-centered precision psychiatry**
Give me the evidence.

- Dr. Isabelle Rapin

From On the Move: A Life" (2015)
Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial

- Patients with severe, intractable, childhood-onset, treatment-resistant epilepsy
- Age 1–30 years
- 214 patients were enrolled
- CBD at 2–5 mg/kg/day, up-titrated until intolerance or to a maximum dose of 25-50 mg/kg /day
- 162 (76%) patients who had at least 12 weeks of follow-up after the first dose of CBD were included in the safety and tolerability analysis
- 137 (64%) patients were included in the efficacy analysis.

## Adverse Events

<table>
<thead>
<tr>
<th>Adverse events (reported in &gt;5% of patients)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>41 (25%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>31 (19%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>31 (19%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>21 (13%)</td>
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<tr>
<td>Convulsion</td>
<td>18 (11%)</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>14 (9%)</td>
</tr>
<tr>
<td>Status epilepticus</td>
<td>13 (8%)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>12 (7%)</td>
</tr>
<tr>
<td>Weight increased</td>
<td>12 (7%)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>10 (6%)</td>
</tr>
<tr>
<td>Drug concentration increased</td>
<td>9 (6%)</td>
</tr>
</tbody>
</table>

• 120 children and young adults with the Dravet syndrome and drug-resistant seizures
• 4-week baseline, 14-week CBD treatment at 20 mg/kg/day, in addition to standard antiepileptic treatment
### Adverse Events

<table>
<thead>
<tr>
<th>System Organ Class and Preferred Term</th>
<th>Cannabidiol (N = 61)</th>
<th>Placebo (N = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients (%)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19 (31)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9 (15)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>12 (20)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>9 (15)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Infections: upper respiratory tract infection</td>
<td>7 (11)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Metabolism: decreased appetite</td>
<td>17 (28)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Nervous system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convulsion</td>
<td>7 (11)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>8 (13)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>22 (36)</td>
<td>6 (10)</td>
</tr>
</tbody>
</table>

Drug–drug interaction between clobazam and cannabidiol in children with refractory epilepsy

Clobazem (CLB)
(active)

Norclobazem (nCLB)
(inactive)

4-hydroxydesmethylclobazam

CYP2C19

CBD
(active)

Subject 1

ClB level (ng/mL)

Weeks on CBD

Take-home message

- The science of cannabis-related treatments is highly complex
- Many non-pharmaceutical grade products have variable and sometimes inaccurate CBD and THC contents
- CBD clinical trials for epilepsy and related disorders (especially Dravet syndrome) provided the strongest evidence
- Somnolence, decreased appetite, and diarrhea are the most common adverse events caused by CBD
- CBD interacts significantly with some anti-seizure medications
- Efforts in developing cannabis-related treatments for ASD and other neurodevelopmental disorders are on-going
ON-GOING RESEARCH STUDIES (1)

Pregnenolone Treatment Trial for Individuals with Autism

Participants must:

• Be diagnosed with an Autism Spectrum Disorder
• Be between the ages of 14 and 25 years
• Be willing to take Pregnenolone for at least 14 weeks and provide blood samples
• Be willing to participate in behavioral and cognitive testing
• Have no serious medical problems

For More Information, Call or Email: 650-723-7547, azaleal@stanford.edu
ON-GOING RESEARCH STUDIES (2)

Adults with Autism Spectrum Disorder or Asperger’s Disorder

Participation in the study will involve:

• Traveling to Stanford for 3 days
• Remaining still in a simulated scan session
• Cognitive testing
• Preparation for PET imaging
• Completion of a combined 1hour PET/MRI scan

The subject must be:

• Between 18 and 55 years of age
• Diagnosed with Autism Spectrum Disorder or Asperger’s Disorder
• IQ greater than 70

For more information, or to enroll in this exciting opportunity, please contact: lkfung@stanford.edu (650) 498-9392
Thank you for attention!
Clinical Trial 1: International @ Shaare Zedek Medical Center (Israel)

- Cannabinoids for Behavioral Problems in Children With ASD
  - PI: Drs. Adi Aran and Varda Gross

- 12-week Double Blind, Randomized, Placebo-controlled Trial With Crossover
  - Intervention: CBD to THC ratio oil
    - 20:1 or 1:1 ratio
  - Estimated Enrollment: 120 participants with behavioral problems, aged 6 - 30 yrs
    - 53 participants by July 2017
  - Study ends **July 2019**

- Primary Outcome
  - Answers: Does CBD-enriched cannabinoid mixes improve “refractory behavioral problems” in autism?

- Secondary Outcomes
  - Communication difficulties and anxiety in Autism
  - Autism Parenting Stress Index
Clinical Trial 2: US @ Albert Einstein Medical College

- Cannabidivarin (CBDV) vs. Placebo in Children With ASD
  - PI: Dr. Eric Hollander

- 12-week double-blind, randomized, placebo-controlled trial
  - Intervention: 10mg/kg/day CBDV (no dose escalation)
  - Estimated enrollment: 100 participants, aged 5 -18 years
  - Starts Oct. 2017 – Not Yet Recruiting

- Primary Outcome
  - Answers: Does CBDV improve irritability in autism?

- Secondary Outcomes
  - Repetitive Behaviors, Social Withdrawal, Quality of Life, Adaptive Behaviors and Clinical Global Improvement