Alternative Therapies in Autism and Epilepsy

John Gaitanis, M.D.
September 9th, 2017

Disclosures

* None
J, a 9 year-old boy with autism

- He consistently had 30 to 50 aggressions in a school day, with a one-time high of 300
- “J had 300 aggressions today”
- “He began to bite and to smack the glasses off my face”
- The teachers were wearing tae-kwon-do arm pads to protect themselves against his biting
- For a year, his individual education plan at his special-needs school was full of blanks, recording “no progress” because he spent his whole day an “irritated, frustrated mess”
Following Treatment

- After starting cannabis, he began having days—sometimes one after another—with zero aggressions
- After two years of treatment, his mother wrote:
  “I would call our experiment a qualified success. Not because cannabis has cured J, who's now 11, or anything near it. But it's alleviated some of his severest symptoms so that he, my husband, and I can actually enjoy each other, rather than being held hostage by his autism in a house full of screams, destruction, and three very unhappy people”

Autism and Aggression
Autism and Aggression

✶ Among 1,380 children with ASD
✶ 68% of the children had previously behaved aggressively towards caregivers
✶ 49% towards non-caregivers
✶ Aggressive behavior has been documented in only 7-11% of people who have intellectual disability (ID) but not autism


Autism and Aggression

✶ Comparing aggressive behaviors in 23 children with autism and 23 typically developing children
✶ Typical children use aggression to achieve social goals, such as getting attention or avoiding adults' demands
✶ Children with autism become aggressive when
   ✶ adults interfere with a repetitive behavior
   ✶ someone takes away an item they need for a repetitive routine
   ✶ trying to escape uncomfortable sensory input

Autism and Aggression

- Forty-six placebo-controlled RCTs of pharmacologic treatments of aggression in youth age 2 to 17 years with ASD
- Compared with placebo, 3 compounds resulted in significant improvement in ABC-I at the end of treatment.
- Risperidone and aripiprazole were found to be the most effective, with the largest effect sizes.
- Sedation, extrapyramidal side effects, and weight gain were common side-effects


Autism and Aggression

- Families dealing with aggressive behavior struggled with
  - social isolation
  - concerns about the safety of people and property
  - lack of respite care
  - limited professional supports
  - families were concerned about being able to find alternate housing for their child with autism as they aged
- Parents described an “unbearable” level of exhaustion, with at least one mother comparing her situation to being in “jail for life.”

Autism and Aggression

✶ My own observations:
  ✶ Aggression is most common in boys with past history of developmental regression around 1 to 2 years of age
  ✶ More common with history of epilepsy/EEG abnormalities
  ✶ Develops in pre-adolescence to adolescence
  ✶ (? Role of testosterone)
  ✶ Increased stimming and aggression sometimes precede seizures
  ✶ Multifactorial
    ✶ OCD
    ✶ Pain
    ✶ Sensory integration
    ✶ Communication
    ✶ Infection/Inflammation

Epilepsy and Autism
Epilepsy and Autism

- Epilepsy occurs in 8 to 20% of children with autism spectrum disorders
- Autism occurs in up to 30% of children with epilepsy
  - It is more common when seizures develop within the first three years

Epidemiology

- There are two peaks for diagnosis of epilepsy
  - Early (Infantile spasms, Dravet)
  - Late (BECTS, primary generalized)
Root Causes

Neurotransmitter Disorders
Fragile X

- Rat models of Fragile X syndrome
  - blockade of cannabinoid receptors
    - normalize hippocampal development
    - correct cognitive deficits
    - improve seizures
    - reduce pain sensitivity.
  - Enhancing endocannabinoid signaling
    - correct abnormal synaptic plasticity in the prefrontal cortex
    - improvement in hyperlocomotion and anxiety-related behaviors


m-TOR disorders

- Tuberous Sclerosis
- Neurofibromatosis
- Cowden Disease
- Bannayan-Riley-Ruvalcaba
Channelopathies

Immunologic
Role of Inter-ictal spikes?

Awake

Asleep

Cannabinoids for Epilepsy
Cannabis sativa

- Medicinal use of cannabis
  - Originates in ancient China
  - Shen Nung (the “red emperor,” 2838–2698 BC), considered the father of all herbalists, is said to have suggested its use in his book “The Herbal”

- The first record of medical marijuana as a treatment for epilepsy comes from ancient Indian literature in 1000 BC.

- The Irish physician William O’Shaughnessy is credited with introducing the therapeutic use of cannabis to Western medicine in the 1830s
Charlotte Figi
What exactly is in it?

Cannabis sativa

- Over 421 chemical compounds
- more than 80 terpeno-phenol compounds named “cannabinoids”
- Not found in other plants
- present in varying relative proportions depending on the plant
THC

- Accounts for most psychoactive effects
- Δ9-THC was isolated and characterized in 1964
- Δ9-THC binds to specific cell membrane receptors named cannabinoid (CB1 and CB2) receptors
- The discovery of cannabinoid receptors was followed by the identification of their endogenous ligands termed “endocannabinoids”
  - anandamide
  - 2-arachidonoylglycerol

Cannabidiol

- Independent of endocannabinoid system
- Does not exert main effects through cannabinoid receptor-1
- At high levels, may actually block cannabinoid receptor-1
- Binds to TRP family of cation channels
- Decreased release of glutamate
- Anti-oxidant and anti-inflammatory effects
Cannabinoid Receptors

**Cannabinoid receptor 1 (CB1R)**
- Presynaptic, G-protein–coupled receptor
- Activates voltage-gated calcium channels and enhances potassium-channel conduction in presynaptic terminals
- Endogenous ligands
  - 2-arachidonoylglycerol (2-AG)
  - Anandamide
- Modulates neuronal excitability

<table>
<thead>
<tr>
<th>Cannabinoid</th>
<th>Structure</th>
<th>Central Nervous System Targets</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ⁹-Tetrahydrocannabinol</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>CB₁ R (microglia)</td>
<td>Partial agonist</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TRPV₁, TRPV₂, TRPM₈, α₁β₂γδR</td>
<td>Agonist</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S-HT₄₅₆, PPARI, GPR₅₅</td>
<td>Antagonist</td>
</tr>
<tr>
<td>Cannabidiol</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>CB₁ R (microglia)</td>
<td>Antagonist</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GPR₅₅, TRPV₁–₂, TRPV₄</td>
<td>Agonist</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TRPM₈, S-HT₄₅₆₇₈, α₁γδR</td>
<td>Agonist</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PPARI–γ, C₉₁₀ ion channel</td>
<td>Enhancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adenosine reuptake</td>
<td>Inhibitor</td>
</tr>
<tr>
<td>Cannabidivarin</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>TRPV₁, TRPV₄, TRPV₁–₂</td>
<td>Agonist</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DAGL-α</td>
<td>Agonist</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Antagonist</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Agonist</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inhibitor</td>
</tr>
</tbody>
</table>
Pre-clinical studies in Epilepsy

Cannabinoid Receptors

- Patients with temporal-lobe epilepsy have significantly lower levels of anandamide in cerebrospinal fluid
- Tissue from patients undergoing surgery for epilepsy have lower levels of CB1R messenger RNA
Cannabinoid Receptors

- Cannabinoid receptor-1 blockers cause seizure like discharges in neuronal cell cultures
- Mice that lack cannabinoid receptor-1 have more severe and prolonged seizures

Cannabinoid Receptors

- Activation of cannabinoid receptor-1 using THC has reduced seizures in most animal models.
- In four animal studies, THC had a pro-convulsant effect at certain doses
Clinical studies

Clinical Trials

- Cunha, Carlini, Mechoulam 1980
- Double-blinded trial of cannabidiol
  - 200-300 mg cannabidiol for 4 to 5 months
  - 15 medically refractory patients
  - 8 patients treated with cannabidiol
    - 4 patients seizure free
    - 3 patients with partial improvement
    - 1 no improvement
- 7 placebo patients
  - 1 showed improvement

Chronic administration of cannabidiol to healthy volunteers and epileptic patients. Pharmacology. 1980;21(3):175-85
Clinical Trials

- A 2013 survey of caregivers of 19 children with severe epilepsy who were receiving cannabidiol-enriched cannabis extracts
  - 2 of the children had become seizure-free
  - 8 others had a reduction in the frequency of seizures of 80%


---

Clinical Trials

- 2015 survey of 75 parents whose children were treated with oral cannabis extracts in Colorado
  - parents reported that one third of the children had a reduction in seizures of more than 50%.
  - electroencephalograms were obtained for 8 of these children before and after the administration of cannabis, and none showed improvement in background activity

Clinical Trials

- Epidiolex (a purified cannabis extract containing 99% cannabidiol and less than 0.10% ∆9-THC)
- Produced by GW pharmaceuticals

Epidiolex Phase I

- A preliminary report from this open-label study, initiated by investigators to assess the safety and dosing of cannabidiol
- Among 137 patients who had received at least 12 weeks of treatment, the median reduction in the number of seizures was 54%

Epidiolex Phase III—Dravet Syndrome

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

Unpublished

CBD and THC at 20:1 ratio

- Retrospective study of 74 patients (age range 1-18 years) with intractable epilepsy resistant to >7 antiepileptic drugs
- CBD and tetrahydrocannabinol at a ratio of 20:1 dissolved in olive oil. The CBD dose ranged from 1 to 20 mg/kg/d
- 89% reported reduction in seizure frequency
  - 13 (18%) reported 75-100% reduction
  - 25 (34%) reported 50-75% reduction
  - 9 (12%) reported 25-50% reduction
  - 19 (26%) reported <25% reduction
- Five (7%) patients reported aggravation of seizures which led to CBD withdrawal

Tzadok et al. (CBD-enriched medical cannabis for intractable pediatric epilepsy: The current Israeli experience. Seizure. 2016 Feb; 35:41-4)
CBD and THC at 20:1 ratio

- Improvement in behavior and alertness, language, communication, motor skills and sleep
- Adverse reactions included somnolence, fatigue, gastrointestinal disturbances and irritability leading to withdrawal of cannabis use in 5 patients


Cannabinoids for Autism
Neuroligin-3

- Neuroligins are postsynaptic cell-adhesion molecules. Mutations in neuroligins predispose to autism and impair tonic endocannabinoid signaling.
- Alterations in endocannabinoid signaling may therefore contribute to autism pathophysiology.

Fragile-X

Blockade of the endocannabinoid system is a potential therapeutic approach in Fragile X syndrome.

CB1R regulation of synaptic strength is altered in Fmr1 (Fragile X) knockout mice.

CB1R blockade in male Fmr1 knockout mice normalizes cognitive impairment, nociceptive desensitization, and susceptibility to audiogenic seizures.

Pharmacological blockade of CB2R normalizes anxiolytic-like behavior.


Clinical Studies
Case Reports


My Observations

✱ Cannabidiol
 ✱ Minimal to no sedation
 ✱ Reports of improved focus/attention
 ✱ Rare insomnia or increased anxiety
 ✱ Not helpful for self-injurious behaviors

✱ THC/THCA
 ✱ More sedating
 ✱ Stronger anxiolytic effect
 ✱ Stronger pain effect
 ✱ Can work acutely in buccal mucosa

✱ Ideal ratios are different than for epilepsy
Autism and Aggression

※ Difficult to treat with single agent since many factors contribute
  ※ Pain
    ※ Migraine
    ※ Neuropathic-pain
    ※ Abdominal
  ※ OCD/Anxiety/Transitioning
  ※ Sensory Integration
  ※ Communication
  ※ Sleep disturbances
  ※ Mood
  ※ Epilepsy
  ※ Infection/Inflammation

Autism and Aggression

※ Pain
  ※ Migraines
    ※ Topiramate, gabapentin, tricyclic anti-depressants, magnesium, butterbur, feverfew
  ※ Abdominal
    ※ Cyproheptadine, tricyclic anti-depressants
  ※ Anxiety/OCD
    ※ N-acetylcysteine, magnesium, SSRI, hydroxyzine

※ Epilepsy
  ※ Topiramate, valproic acid, lamotrigine, gabapentin
  ※ Avoid levetiracetam, zonisamide

※ Sleep
  ※ Melatonin, magnesium, suvorexant, hydroxyzine

※ Infection/Inflammation
  ※ Antibiotic Course, NSAIDs, steroids
Side-effects

Effects on Cognition

![Graph showing the effects of marijuana use on Full Scale Intelligence Quotient (IQ) over time. The graph compares 'Never used marijuana' and 'Persistent marijuana use'. The x-axis represents age groups: 13-17 years and 38 years, and the y-axis represents IQ scores ranging from 85 to 110.]
Effects on Cognition

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cognitive</th>
<th>Brain Structure</th>
<th>Brain Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meier et al., 2012</td>
<td>↓ intelligence quotient (IQ)</td>
<td>↓ prefrontal cortex volume</td>
<td>↑ left superior prefrontal cortex MRL blood oxygen level dependent (BOLD) signal during working memory task</td>
</tr>
<tr>
<td>Pope et al., 2003</td>
<td>↓ attention</td>
<td>↓ white matter integrity in prefrontal cortex</td>
<td>↓ anterior cingulate MRL blood oxygen level dependent (BOLD) signal during inhibition task</td>
</tr>
<tr>
<td>Ehrenreich et al., 1999</td>
<td>↓ visual search</td>
<td>↓ superior prefrontal cortex thickness</td>
<td>↑ prefrontal cortex MRL blood oxygen level dependent (BOLD) signal during novel stimulus presentation in working memory task</td>
</tr>
<tr>
<td>Huestegge et al., 2002</td>
<td>↓ executive functioning</td>
<td>↓ total gray matter, ↑ total white matter</td>
<td></td>
</tr>
<tr>
<td>Fontes et al., 2011</td>
<td>↑ impulsivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Churchwell et al., 2010</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gruber et al., 2011</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopez-Larson et al., 2011</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilson et al., 2000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Becker et al., 2010a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gruber et al., 2012</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jager et al., 2010</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Psychiatric Effects

### Depressio

<table>
<thead>
<tr>
<th>Study (use)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHIS (as weekly)</td>
<td>1.70 (1.03-2.79)</td>
</tr>
<tr>
<td>Colombia</td>
<td>1.31 (0.95-1.80)</td>
</tr>
<tr>
<td>ECA</td>
<td>4.00 (1.23-12.90)</td>
</tr>
<tr>
<td>N-MHMS*</td>
<td>1.99 (0.32-6.00)</td>
</tr>
<tr>
<td>NMBS (dependence)</td>
<td>0.83 (0.52-1.36)</td>
</tr>
<tr>
<td>HF state (women)</td>
<td>1.02 (0.77-1.36)</td>
</tr>
<tr>
<td>Victoria (as weekly: men)</td>
<td>0.47 (0.37-1.36)</td>
</tr>
<tr>
<td>Victoria (as weekly: women)</td>
<td>1.90 (1.10-3.29)</td>
</tr>
<tr>
<td>Overall</td>
<td>1.49 (1.17-1.94)</td>
</tr>
</tbody>
</table>

### Psychosis

<table>
<thead>
<tr>
<th>Study (use)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHIS (daily)</td>
<td>1.56 (1.20-2.03)</td>
</tr>
<tr>
<td>ECA (daily)</td>
<td>2.04 (1.72-2.45)</td>
</tr>
<tr>
<td>EDSP (daily)*</td>
<td>2.23 (1.30-3.80)</td>
</tr>
<tr>
<td>NMBS (weekly)*</td>
<td>6.81 (1.79-25.91)</td>
</tr>
<tr>
<td>NMBS (dependence)*</td>
<td>1.47 (0.85-2.53)</td>
</tr>
<tr>
<td>Swedish (+511 sessions)</td>
<td>2.09 (1.54-2.84)</td>
</tr>
</tbody>
</table>

Overall
Ethical considerations

Ethical Considerations

- Potential benefits must outweigh the risks of therapy
  - Difficult to establish with limited data
  - Requires close observation of seizures and side-effects to evaluate for improvement/worsening
  - Consider prolonged EEG for objective data
- No financial conflict of interest
- Adequate trials of standard therapy to prove patient is refractory
- Consider need for video EEG to confirm seizures
- Reliability of care givers
- Agreement among all care givers
- Involve pediatrician in decision making
Legal considerations

Physician Certification

- Physicians are not allowed to "prescribe" cannabis
- They may only "recommend" its use or "advise consideration"
- In 2002, the U.S. Court of Appeals held that the First Amendment, which protects free speech, allows physicians to discuss and perhaps recommend medical marijuana use without punishment
Legal Concerns

DEA targets doctors linked to medical marijuana

By Kay Lazar and Shelley Murphy | GLOBE STAFF JUNE 06, 2014

US Drug Enforcement Administration investigators have visited the homes and offices of Massachusetts physicians involved with medical marijuana dispensaries and delivered an ultimatum: sever all ties to marijuana companies, or relinquish federal licenses to prescribe certain medications, according to several physicians and their attorneys.

The stark choice is necessary, the doctors said they were told, because of friction between federal law, which bans any use of marijuana, and state law, which voters changed in 2012 to allow medical use of the drug.

The DEA's action has left some doctors, whose livelihoods depend on being able to offer patients pain medications and other drugs, with little option but to resign from the