Cannabis use in child neurology: *Looking forward*
Anup Patel, MD

• Associate Professor Neurology and Pediatrics
• Director Complex Epilepsy Clinic
• Associate Medical Director Partners for Kids
• Nationwide Children’s Hospital and the Ohio State University College of Medicine
Disclosures

- Webinar Development: American Academy of Neurology
- Consultant: GW Pharmaceuticals
- Scientific Advisory Board - Supernus
- Research Grants: Pediatric Epilepsy Research Foundation (PERF), GW Pharmaceuticals, Upsher-Smith Pharmaceuticals, Brain Sentinel
Medical Marijuana

- Defined as whole plant marijuana (cannabis) that is used to treat disease or alleviate symptoms of disease
Cannabidiol

• Also called CBD
• A prominent non-psychoactive cannabinoid component of Cannabis. It has low affinity for the cannabinoid receptor types 1 (CB₁) and 2 (CB₂)
Law

- Currently, it is illegal for physicians (even in states where medical marijuana is legal) to **prescribe** the drug because it is schedule 1 drug
- Prescribing it would constitute aiding and abetting the acquisition of marijuana
- Could result in revocation of DEA licensure and even prison time
- States that have legalized are **STILL NOT immunized** from federal law
Reasons to use “Medical Marijuana”

- Family desperation
- Limited treatment options
- Toxicity of current treatment options
- Lengthy FDA approval process
Limited Efficacy of Current Treatments

• 30% patients remain treatment resistant despite all available treatments
• Efficacy of current treatments unchanged since 1857
• First treatment, Bromides, now again used
• Potential toxicity from many treatments (felbamate, valproate, etc.)
Medical Marijuana Use

• Anecdotal evidence for many illnesses:
  • Nausea related to chemotherapy
  • Anorexia and wasting from AIDS
  • Glaucoma
  • Epilepsy
  • Muscle spasticity
  • Tourette syndrome
  • Multiple sclerosis
  • Many others
Epidiolex Double Blind LGS Study

- 2-55 years
- The trial randomized 171 patients into two arms, where Epidiolex 20mg/kg/day (n=86) or placebo (n=85) was added to current AED treatment
- The median baseline drop seizure frequency per month was 74
- A median reduction in monthly drop seizures of 44 percent compared with a reduction of 22 percent in patients receiving placebo (p=0.0135)
- Safety profile similar to open label study (86% with AE compared to 69% in placebo group)
- No major adverse effects related to medication
Another LGS Double Blind Placebo Study

- Average age of trial participants was 16 years
- In the 20 mg/kg CBD group: the median drop seizure frequency reduction was 42% compared with 17% in the placebo group (p=0.0047)
- In the 10 mg/kg CBD group, the median drop seizure frequency reduction was 37%, compared with 17% in the placebo group (p=0.0016)
- Difference between Epidiolex and placebo emerged during the first month of treatment and was sustained during the entire treatment period
- Similar side effect profile as other studies
Tuberous Sclerosis

• Phase 3 trial comparison of Epidiolex versus placebo in a total of approximately 200 patients
• To assess its safety and efficacy as an adjunctive antiepileptic treatment
• Primary measure of this trial is the percentage change from baseline in seizure frequency during the treatment period
• Primary endpoint seizures include focal motor seizures with or without impairment of consciousness or awareness and generalized convulsive seizures
Infantile Spasms

• GW plans on doing a feasibility study of Epidiolex (CBD) for treatment of infantile spasms refractory to first-line medications
• Pilot trial schedule for 2017
• Larger multicenter study planned to follow
New Drug Application (NDA)

- GW met with FDA in July 2016
- Included data from Dravet studies and some discussion of data from the first Phase 3 LGS trial
- Plan to submit a single NDA that includes Phase 3 data from one Dravet trial and two LGS trials
- On track for a submission in the first half of 2017
- Hope is for simultaneous decision on both indications
- Not expecting to wait for results from the second trial in Dravet syndrome prior to submission
What if CBD were FDA Approved?

- Would be for Dravet and/or LGS
- If FDA approved, no law needed changed for use
- Will then be available via prescription in all states
- Will not be schedule I medication
- Will be regulated, consistent, and truth in labeling (FDA requirement and oversight)
- Would likely be used off-label as other anti-seizure medications are used
United Kingdom

• Based on promising study results of CBD
• Unregulated vernacular CBD sales have been halted
• UK now recognizing CBD as a medication based on trials
• Huge problem with use of non-consistent CBD projects
• Rule to stop those taking advantage of patients and families
Looking Forward for Epidiolex

- Epilepsy/Autism
- Hypoxic Ischemic Encephalopathy (HIE)
- Glioma
- Schizophrenia
Synthetic CBD

- Insys Pharmaceuticals
- Phase I and II trials in epilepsy complete
- Plans for LGS trials
- UCLA partnering to do infantile spasm study
- Also studying affect on withdrawal from cocaine dependency
Israeli Study of CBD Enriched Cannabis

- Studied as an Oil
- Retrospective Study of 20:1 CBD to THC formula with 74 children (1-18 years of age)
- Dosage: 1-20 mg/kg/day
- Children with treatment resistant epilepsy
- Parental report of seizure frequency
Results

- 89% reported a reduction in seizure frequency
- 18% reported 75-100% reduction
- 34% reported 50-75% reduction
- 12% reported 25-50% reduction
- 26% reported <25% reduction
- 7% patients reported aggravation of seizures which led to medication withdrawal
- Observed improvement in behavior and alertness, language, communication, motor skills and sleep
- Adverse reactions included somnolence, fatigue, gastrointestinal disturbances and irritability
Survey

- Experiences of children with IS and/or LGS who have been treated with CBD-enriched cannabis preparations
- Survey respondents included 117 parents of children with epilepsy (including 53 with IS or LGS) who had administered CBD products to their children
- 85% of all parents reported a reduction in seizure frequency
- 14% reported complete seizure freedom
- Median duration was 6.8 months
- Median dose was 4.3mg/kg/day
- 30% reported increased appetite
- 53% reported improved sleep
- 71% reported improved alertness
- 65% reported improved mood
Tic Disorder & Tourette Syndrome

• Cochrane review for Tourette syndrome suggested not enough evidence to know
• However, another article recommends THC the treatment of TS in adult patients who fail first line treatments
• Other studies have shown reduction of tics and frequency of tics
Multiple Sclerosis

• Meta-analysis stated cannabinoids including the cannabidiol/THC buccal spray are effective in treating neuropathic pain in multiple sclerosis
• THC may be effective in decreasing patient-centered and objective measures in MS
• Oral Cannabis Extract (OCE) shown effective to decrease spasticity
• Nabiximols (Sativex) may be effective in decreasing patient-centered and objective measures in MS
• Can use existing FDA approved synthetic THC medications
  • Nabilone (Cesemet)
  • Dronabinol (Marinol)
Central pain or painful spasms

- Oral cannabis extract – effective
- THC – probably effective
- Nabiximols – probably effective
Headache

• No good studies in children validating effectiveness of THC or CBD to decrease pain from headache
• Retrospective adult migraine study suggested some possible benefit
  • Frequency decreased from 10.4 to 4.6 headaches per month (p<0.0001)
  • Most patients used more than one form of marijuana
  • Most used it daily for prevention of migraine headache
• Possible use of CBD for migraine based on proposed mechanism of action (MOA) of CBD
  • 5 HT1α receptor agonist
  • Needs studies performed
### AAN review of efficacy of medical marijuana

<table>
<thead>
<tr>
<th>Product</th>
<th>Indication</th>
<th>Overall Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>*OCE</td>
<td>Multiple sclerosis</td>
<td>Decreased spasticity</td>
</tr>
<tr>
<td>OCE</td>
<td>Central pain, painful spasms</td>
<td>Effective</td>
</tr>
<tr>
<td>OCE</td>
<td>Urinary dysfunction</td>
<td>Probably ineffective</td>
</tr>
<tr>
<td>OCE</td>
<td>Dyskinesias in Parkinson’s</td>
<td>Probably ineffective</td>
</tr>
<tr>
<td>OCE</td>
<td>Non-chorea related symptoms of Huntington disease, Tourette syndrome, cervical dystonia, epilepsy*</td>
<td>Unknown efficacy</td>
</tr>
<tr>
<td>THC</td>
<td>Multiple sclerosis</td>
<td>May be effective in decreasing patient-centered and objective measures in MS</td>
</tr>
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*OCE: Oral Cannabis Extract; ^Sativex
Looking Forward

• Basic information is needed about the available products
  • Study of products claiming to have CBD showed 50% had zero CBD
• Testing and validation of available products needed
• Testing in other diseases states outside of epilepsy
• More work on mechanisms of action
• More work on potential negative effects on developing brain (i.e. THC)
  • Upcoming manuscript in Pediatric Neurology showing brain pathology changes from chronic marijuana use
Looking Forward

• Need more data on efficacy in other populations
• Need to evaluate possibility of other chemicals from cannabis plant that may have therapeutic effect
  • CBDv, etc.
• Need to provide answers to these questions on behalf of patients and their families
Is There a Way Forward?

• Work with state legislators to ensure safety and proper regulation of products is there
• Partner with companies that are making the products to study properly
  • “Money where your mouth is”
• Apply for funding to study in proper scientific fashion
• Lobby for further study and de-regulation for research purposes
  • See policy statements from AAN
Legalization of Marijuana

• Lines blurred between recreation and medicine
• Potential for patient or caregiver self treatment & administration
• Increase in unregulated products
• Unknown drug to drug interactions
• Unknown dosing
• More potential for misinformation
Summary

• More research is needed to know if effective
• Studies in epilepsy are ongoing
• Hopefully FDA evaluation for approval soon
• Careful of available products
• DEA appears to be loosening on allowing more research
Thank you!
References