

Cannabis use in child neurology: *Looking forward*



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Disclosures

- Webinar Development: American Academy of Neurology
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Medical Marijuana

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



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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 HT1 α receptor agonist
 - Needs studies performed

AAN review of efficacy of medical marijuana

Product	Indication	Overall Results
*OCE	Multiple sclerosis	Decreased spasticity
OCE	Central pain, painful spasms	Effective
OCE	Urinary dysfunction	Probably ineffective
OCE	Dyskinesias in Parkinson's	Probably ineffective
OCE	Non-chorea related symptoms of Huntington disease, Tourette syndrome, cervical dystonia, epilepsy*	Unknown efficacy
THC	Multiple sclerosis	May be effective in decreasing patient-centered and objective measures in MS
THC	Central pain, painful spasms	Probably effective
THC	Urinary dysfunction	Probably ineffective
+Nabiximols	Multiple sclerosis	May be effective in decreasing patient-centered and objective measures in MS
+Nabiximols	Central pain, painful spasms	Probably effective
+Nabiximols, +Sativex	Urinary dysfunction	Probably effective

*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!



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