Considerations for Recommending Medical Marijuana in Practice

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Background

- The plant is: *Cannabis sativa*
- Made up of 500 compounds
- Unique compounds are called cannabinoids
- Main active ingredient is the cannabinoid 9-tetrahydrocannabinol (THC) (psychoactive)
- Cannabinol and cannabidiol are other cannabinoids (non-psychoactive)
History

- First use in the treatment of complications from gastrointestinal disorders, rheumatologic symptoms, pain, and epilepsy
- In the 1800s, the well-known English neurologist, W.R. Gowers, reported the use of a marijuana based product to treat seizures.
- Many of the studies performed in various neurological disorders thus far have been using products with a relatively high content of THC.
- The psychoactive properties of *Cannabis sativa* have been attributed to THC due to its binding within the brain to two G-protein-coupled receptors names CB₁ and CB₂.
- Many other components of the plant such as CBD do not bind to these receptors which may explain the lack of euphoric properties within this compound.

DEA Schedule I

- Must obtain a schedule I DEA license for research purposes before can prescribe legally
- IND can be filed with FDA for use in epilepsy treatment
- Other studies ongoing
- Government currently evaluating status of product(s) for re-classification to lower schedule
- This does not apply to current approved products
Limited forms of legislation

- Alabama, Utah, Kentucky, Mississippi and Wisconsin passed very limited forms of legislation related to Cannabinoids (also called CBD legislation), which authorizes the physician supervised use of varieties of cannabis and/or extracts high in the non-psychotropic cannabinoid oil
- Does not account for supply of medication
- Alabama only permits the use of CBD by prescription during the course of an FDA-approved clinical trial
- Wisconsin limits those who may legally dispense CBD to only include those physicians who have obtained an FDA-issued investigational drug permit to prescribe it

Federal Legislation

- Congressman Scott Perry (R-PA) introduced a medical marijuana bill specifically geared towards seizures in children
- Called the “Charlotte’s Web Medical Hemp Act of 2014”
- Press release states that it is “to ensure that children and individuals with epilepsy and other debilitating seizure disorders have access to life-changing Cannabidiol (CBD) Oil and therapeutic hemp”
- The bill is bipartisan and has 10 co-sponsors
Medical use

• Anecdotal evidence for many illnesses:
  ▪ nausea related to chemotherapy
  ▪ anorexia and wasting from AIDS
  ▪ glaucoma
  ▪ muscle spasticity
  ▪ Tourette syndrome
  ▪ multiple sclerosis
  ▪ epilepsy

Possible consequences of legalization

• Annals of Emergency Medicine Article:
  ▪ The call rate in non-legal states to poison centers showed no change from 2005 to 2011
  ▪ The call rate in decriminalized states increased by 30.3% from 2005 to 2011
  ▪ Low numbers overall
• Survey showed that 28% of parents and 55% of teens thought legalization for medical purposes would make it easier for teens to abuse
Possible consequences of legalization

- Study from Colorado showed unintentional marijuana ingestions by young children (8 months to 12 years)
- 0 of 790 to 14 of 588 (before decriminalization to after)
  - Nine patients had lethargy, 1 had ataxia, and 1 had respiratory insufficiency
  - Eight patients were admitted, 2 to the intensive care unit
  - Eight of the 14 cases involved medical marijuana, and 7 of these exposures were from food products

Other studies

- 2014 study reviewing drug use and the perceptions of adolescents found that legalizing medicinal marijuana at the state level causes no measured increase in youth marijuana use
- Editorials discounted the methodology
- Study showed that 43% of patients with a positive urine drug screen for THC had MSLT findings consistent with narcolepsy
Facts

Synthetic cannabinoids dronabinol (Marinol) and nabilone (Cesamet) are approved in adults for: nausea and vomiting associated with cancer chemotherapy appetite stimulation in patients with wasting diseases such as AIDS.

Currently allowed to prescribe a CBD product, Epidiolex, for use to treat seizures from epilepsy in children via an investigational new drug (IND) application or the FDA approved studies.

- Dravet Part A complete
- Dravet Part B, Open label, and Lennox Gastaut Studies soon

Sativex is a medication with a higher THC component being tested for nausea and vomiting associated with chemotherapy.

FDA approval

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Why is this a hot topic now?

Because of this guy!
Story – part I

- Dr. Gupta highlighted a little girl named Charlotte with Dravet Syndrome
- She had a remarkable reduction in seizures
- She was given an oil that is low in THC and high in CBD
- Company now calls the oil Charlotte’s Web

Part II

- Second one showed a follow up
- Charlotte’s mother has been speaking at many states about trying to legalize efforts for epilepsy use
- Charlotte continues to do well, but is NOT seizure free
- Toured the GW pharmaceutical plant in London
- Interviewed Orrin Devinsky, MD from NYU Medical Center
Reasons to use CBD treatments

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

How does it work?

- Full mechanism of action is unknown
- Based on animal studies, it appears two theories likely:
  - NMDA receptor antagonist
  - Potential calcium channel modulation
  - Possible serotonin properties
  - Possible positive effects on memory and learning
  - Decrease inhibition of aberrant inhibitory cells (GABA)
What does the evidence show?

Cochrane Review 2014

• Included all randomized controlled trials blinded or unblinded, letter to editor, and abstract
• All other study formats were excluded
• All ages, sex, and epilepsy type considered
• Use of any marijuana product including THC, cannabinol and cannabidiol
Outcome measures

• Primary measure was seizure freedom
  ▪ No seizures for 12 months or 3 times longest seizure free interval

• Secondary measures were:
  ▪ 50% or more reduction in seizure frequency from baseline
  ▪ Adverse events requiring medication change or emergency department visit
  ▪ Improvement in quality of life

Outcome measures

• No primary measures
• No information about two of secondary measures (responder rate at least 6 months or objective quality of life)
• All four trials reported no toxic effects with 200 to 300 mg of treatment
• One case of mild drowsiness reported
Summary

• No reliable conclusions can be made
• However, the dose of 200 to 300 mg of daily cannabidiol may be safe
• No major adverse events reported
• Small number treated in a short period of time
• Low quality studies
• High risk of bias

Other neurological diseases

• Headache
• Movement disorder
• Multiple sclerosis
• Stroke
Other disease states

• Chronic Pain:
  ▪ Suggests that cannabis treatment is moderately efficacious for treatment of chronic pain
  ▪ More evidence from larger, well-designed trials is needed to clarify the true balance of benefits to harms.

• Celiac Disease:
  ▪ Potential to treat GI associated inflammation
  ▪ HIV/AIDS anorexia: 2013 Cochrane Review states more data on safety and efficacy needed

Headache

• No randomized controlled trials have been performed
• Reports dating back to the late 1800s with J.R. Reynolds describing use of marijuana to treat migraine and various other forms of neurological pain and headache
• Other case reports suggesting benefit
• A case report exists of successful treatment of cluster headaches in a 19 year old patient using both recreational marijuana and a synthetic high THC based product
Mechanism of Action

• Proposed mechanisms of actions of CBD acting on serotonin receptors

• Potential impact for headache related disease has been proposed within the medical literature by various authors through targeting of the endocannabinoid signaling system within the brain

• It is within this system that potential benefit from pain in general has been found

• More data needed

Movement Disorders

• Trials containing a small number of patients suggested improvement in tics and obsessive compulsive symptoms with the youngest patient being 18 years of age

• AAN Guidelines states:
  • Data is insufficient to support or refute efficacy of THC for reducing tic severity

• Limited poorly powered data exists that suggests that marijuana based products are not effective in reducing chorea related to Huntington disease and levodopa-induced dyskinesia seen in Parkinson Disease (PD)

• Recently, a study suggested potential benefit from CBD in quality of life for patients with PD without dementia symptoms
**Multiple Sclerosis**

- AAN Guideline Paper:
  - For patients with spasticity from MS, oral extract and synthetic preparations are probably effective when evaluating subjective measures with unclear benefit with the evaluation of objective measures.
  - Smoked preparations are of no benefit.
  - Oral extracts contain a similar proportion of THC and CBD.
  - For pain and spasms related to MS:
    - The oral extracts are effective.
    - THC and other synthetic derivatives may be effective for treating pain and spasms related to MS.
    - For bladder dysfunction related to MS, nabiximol, is probably effective for void reduction.
    - In patients with tremor, all marijuana-based preparations are probably not effective in addressing tremor-related complications from MS.

**Stroke**

- Stroke as a complication related to recreational and synthetic marijuana products high in THC reported.
- No long term adverse effects have been reported from products with a high content of CBD and a low content of THC.
American Academy of Neurology Guideline – Summary

• “Oral cannabinoids are of unknown efficacy in non-chorea-related symptoms of HD, Tourette syndrome, cervical dystonia, and epilepsy.”

• https://www.aan.com/Guidelines/home/GetGuidelineContent/650

AAN Position Statement

• Supports all efforts to conduct rigorous research to evaluate the long-term safety and effectiveness of marijuana-based products

• For research purposes, requests the reclassification of marijuana-based products from their current Schedule 1 status

• Does not advocate for the legalization of marijuana-based products for use in neurological disorders at this time

• May be potential use for these agents in the treatment of some neurological disorders
AAN Position Statement

• Not sufficient evidence to make any definitive conclusions regarding the effectiveness of marijuana-based products
• It is not appropriate to extrapolate the results of trials of standardized preparations to other, non-standardized, non-regulated cannabis products
• Effectiveness of a non-standardized product is not equal to that of standardized products that are studied in clinical trials
• Most currently available marijuana-based products are not regulated by any agency and may not contain the products mentioned by labeling

Summary

• No current monitoring of “street-based” products
• No substantial data on efficacy and long term risks
• It is not natural, nor is it marijuana (medication)
• Not enough evidence
• More research is needed to know if effective
• Would not recommend prescribing unless go through proper channels

Summary

• Studies are ongoing
• State legislation is not likely needed at this time
  • May confuse situation
• Careful of available products
• Pure CBD is not psychoactive
• THC is more controversial due to psychoactive properties
Thank you!

References


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References


