Medical Marijuana in the Treatment of Central Nervous System Disorders

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Disclosure

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Learning Objectives

- Describe the scientific rational for considering the use of medical marijuana for the treatment of certain central nervous system (CNS) disorders
- Evaluate the evidence for the use of medical marijuana for the treatment of certain CNS disorders
- Cite limitations of current evidence for the use of medical marijuana for the treatment of certain CNS disorders
Marijuana Basics

- Marijuana contains approximately 60 active compounds (cannabinoids)
- The ratio in botanical and pharmaceutical preparations determines the therapeutic vs psychoactive effects
- The higher the concentration of THC (Delta-9-Tetrahydrocannabinol) the greater the likelihood of psychoactive effects
- Cannabidiol (CBD) is a major non-psychoactive component

Why Consider Medical Marijuana for CNS Disorders

- The endocannabinoid system is distributed throughout the brain and spinal cord
- CB-1 receptors are concentrated in the hippocampus, association cortices, basal ganglia, cerebellum and spinal cord (especially dorsal root ganglia)
- CB-2 receptors are found in the periphery including lymph tissue as well as in lower amounts in the brain including the periaqueductal gray
- Activation of these receptors results in physiologic responses that would be expected from these regions

Why Consider Medical Marijuana for CNS Disorders-2

- Examples of such responses include: a feeling of well-being, psychosis, diminished locomotor functioning, impaired memory/cognition, **ANTINOCEPTION, SPASTICITY REDUCING, SLEEP PROMOTING**, and antiemetic.
- Receptor activation inhibits adenylate cyclase and subsequently the release of multiple neurotransmitters is inhibited when neuronal excitation is present.
- These neurotransmitters include glutamate, acetylcholine and dopamine.
- Other neuronal networks may be modulated by endocannabinoids through indirect effects on opiate, N-Methyl-D Aspartate (NMDA), and Gamma – amino- Butyric Acid (GABA) receptors.

Important Additional Considerations Regarding Medical Marijuana for CNS Disorders

- The concentration of THC as well as the ratio of THC to CBD in specific formulations is what limits (or not) THC’s psychoactive effects

- Key Examples: Dronabinol: 2.5mg THC; Nabilone: 100mg CBD; Nabiximols: ratio of THC 2.7mg/CBD mg/spray; Smoked marijuana: 4% THC

CNS Disorders to be Covered

- Multiple Sclerosis (MS): spasticity, central pain and painful spasms, bladder dysfunction, tremors and other involuntary movements
- Dyskinesias of Huntington disease (HD)
- Levodopa-induced dyskinesia of Parkinson disease
- Cervical dystonia
- Tics associated with Tourette syndrome
- Epilepsy
- Headache
MS- Oral Cannabinoids (Cannabis extract and THC)

- Neither oral cannabis extract (OCE) nor dronabinol had a greater effect in MS patients in reducing spasticity as measured by the Ashworth scale compared to placebo- this was the primary outcome measure of this study.

- HOWEVER: for certain secondary outcome measures in this study, including pain associated with spasticity, muscle spasms and sleep both treatment groups demonstrated greater improvement than placebo treated patients.

MS- Oral Cannabinoids (Cannabis extract and THC)-2

- In a randomized controlled study (RTC) of 249 MS patients treated with OCE, muscle stiffness was more likely to occur in treated pts compared with placebo (29.4% vs. 15.7%) and secondary outcomes including spasms, pain and sleep were more likely to occur in the treated group.
- Another RTC showed no difference in Ashworth scale scores OR subjective symptoms in each group.
- A RTC assessing the effect of OCE for tremor and bladder symptoms in MS patients did not show a significant difference between pts treated with cannabinoids and placebo.

MS- Oral Cannabinoids
(Cannabis extract and THC)-3

Based upon these findings the American Academy of Neurology (AAN) advises:

1. OCE is established as **effective** for reducing patient-reported spasticity symptoms and pain

2. THC is **probably effective** for reducing patient-reported symptoms of spasticity and pain

3. OCE and THC are **probably ineffective** for reducing objective spasticity measures and tremors

MS- Oromucosal Cannabinoid Spray

- A 6 week RTC including 160 MS pts evaluated the effect of the oromucosal cannabinoid spray (OCS) on spasticity: no objective measured difference was seen between groups
- A 5 week RTC in 66 pts with MS related central neuropathic pain demonstrated that the OCS was superior in reducing mean pain intensity compared to placebo
- A 10 week RTC in 135 pts with MS related urinary incontinence did not show improvement with OCS; HOWEVER, the daily # of voids did decrease significantly in the treatment group

Based upon these findings the American Academy of Neurology (AAN) advises:

1. OCS is *probably effective* for improving subjective spasticity symptoms, pain and urinary frequency
2. OCS is *probably ineffective* for reducing objective spasticity measures or bladder incontinence
3. OCS is *possibly ineffective* for reducing MS-related tremor

MS-Smoked Cannabis

- 1 crossover study in 37 MS patients reported spasticity reduction; the primary outcome measure (using a modified Ashworth scale) in the cannabis group
- Pain, a secondary measure, also improved in the cannabis group
- Cognitive performance was measured and was REDUCED after cannabis treatment

In a separate study of 20 MS pts and normal controls, both groups demonstrated reduced measures of posture and balance after smoking one marijuana cigarette.

Based upon these findings the American Academy of Neurology (AAN) advises:

1. **Data are not adequate** to determine the safety or efficacy of smoked cannabis used for spasticity or pain relief.

MS – Additional Thoughts

- The reported studies were of short duration, the longest 15 weeks
- Central side effects of the active agent could have unmasked subject
- The Ashworth scale may be insensitive to spasticity changes in these studies
- The cannabinoids were associated with serious adverse events including death- mild-moderate side effects were more common (50-80%) including dizziness, lightheadness, increased appetite, nausea, emesis, cystitis, dehydration, transient psychosis, hallucinations and cognitive impairment

Cannabinoids and Huntington Disease

- A crossover study evaluated nabilone in 37 HD pts., two, 5-week treatment periods separated by a 5-week washout period

- No significant difference was seen on the primary outcome measure with treatment— the Unified Huntington Disease Rating Scale

- A separate study examining the efficacy of CBD capsules (10mg/kg/d in 2 divided doses) did not show any changes in HD symptoms but was noted to be underpowered

Koppel BS, Brust JCM, Fife T, et al. Systematic Review: Efficacy and safety of medical marijuana in selected neurologic disorders
Neurology 2014;82:1556-1563
Cannabinoids and Huntington Disease-2

- Based upon these findings the American Academy of Neurology (AAN) advises:

1. Available studies are underpowered to detect differences; thus, no conclusions can be made

Cannabis and PD

- A Double Blind Crossover study evaluated the effect of CBD in the treatment of levodopa-induced dyskinesias in 19 PD pts (Average daily dose = 0.146mg/kg/d), primary outcome measure was the dyskinesia section of the Unified Parkinson’s Disease Rating Scale.

- The treatment group trended towards WORSENING on this measure.

- A second study (non blinded) showed improvement in 7 PD pts.

Cannabis and PD-2

- Based upon these findings the American Academy of Neurology (AAN) advises:

1. OCE is *probably ineffective* for treating levodopa-induced dyskinesias in PD pts

Cannabis and Tourette Syndrome

- 12 pts were studied in a placebo-controlled, crossover study-treatment was a single dose of THC capsules (5, 7.5, 10mg); no reliable conclusions could be drawn
- 24 pts were studied in a placebo-controlled study to determine effect of up to 10mg/day of oral THC over 6 weeks; no significant differences seen

Cannabis and Tourette syndrome

Based upon these findings the American Academy of Neurology (AAN) advises:

1. *Data are insufficient* to support or refute efficacy of THC for reducing tic severity

Cannabis and Cervical Dystonia

- Dronabinol has been evaluated in CD in one study - the study was underpowered and no conclusion could be drawn
- Based upon these findings the American Academy of Neurology (AAN) advises:
  1. Data are insufficient to support or refute the efficacy of dronabinol in CD

Cannabinoids and Epilepsy

- Two poor quality studies have not demonstrated any significant benefit nor adverse effects (CBD)
- A Cochrane Database analysis also noted that CBD had been safely administered to small numbers of patients for short periods but no “reliable conclusions” could be drawn regarding the efficacy or safety of CBD as a treatment of epilepsy

Cannabinoids and Headache

- Earliest case reports of use of cannabis for migraine date back to late 19th century- in 1890 Sir John Russell Reynolds, then President of the British Medical Association, published his 30 years of experience using cannabis for migraine, neuralgia, and dysmenorrhea.

- Sir William Osler advocated for use of cannabis to treat migraine in his medical textbook.

Cannabinoids and Headache-2

- No blinded studies involving the assessment of the efficacy of cannabinoids for headache have been published.
- There is a report of cessation of daily marijuana use being associated with the development of headache.
- An endogenous cannabinoid anandamide, has been shown to inhibit dural blood vessel dilatation after electrical stimulation as well as after nitric oxide, capsaicin and calcitonin gene related peptide administration.

Final Thoughts-2

- Obviously, very limited research has been completed.
- Further research with randomized controlled studies is needed.
- Given the current scheduling of marijuana (I), research in the United States will be difficult for the present.
- There is a great urgency in studying cannabinoids in a manner similar to other medications so that these substances can be used as appropriately as possible - the matter is urgent given the action of 20 states and the District of Columbia, which have legalized the use of medical marijuana.
Final Thoughts

- Analysis of published studies regarding the use of cannabinoids for CNS disorders suggest 6.9% of the patients discontinued use due to adverse effects.

- Nausea, weakness, mood changes, suicidal ideation, hallucinations, dizziness, psychosis, dysphoria, feeling intoxicated and anxiety were reported adverse effects in multiple studies.

- Psychosis, dysphoria and anxiety were associated with higher concentrations of THC.