Medical Marijuana

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Disclosure

- I have no conflict of interests
- No significant holdings in pharmaceutical or cannabis industry
Objectives

• Review the basic pharmacology of cannabinoids used for therapeutic benefit
• Compare NYS Medical Marijuana (MM) program to MM programs in other states
• Dissect pertinent primary literature to better understand the efficacy and safety of MM
• Propose evidence-based recommendations in guiding pharmacists managing patients enrolled in MM programs
Background

- Marijuana
  - Cannabis sativa
  - Cannabis indica

- Marijuana is the most widely abused illicit drug in Western societies
  - Rates of use have plateaued
  - Impression of risk declining

- Use
  - Inhalation (smoked vs. vaporized)
  - Ingestion

- Forms
  - Dried plant
  - Extracts (Hash Oil, Wax, resin)
  - Edibles (baked goods, candy)
  - Infusions (teas, energy drinks, fat/lipid rendering)

Question

- Marijuana has only recently been used in the United States to treat specific medical conditions
  - TRUE
  - FALSE
History

- Use described as far back as 3000 BCE
- Noted anxiolytic effects upon oral ingestion as early as 1000 BCE in India
- 19\textsuperscript{th} century – THC isolated from red oil extract of cannabis
- 1930s – THC structure elucidated
- 1937 – Marijuana Tax Act passed
- Mid-1980s – Cannabinoid receptors discovered (CB\textsubscript{1} and CB\textsubscript{2})
- 1992 – Endogenous cannabinoids, anandamide and 2-arachidonoyl glycerol, discovered

Endocannabinoid System

- Internal homeostatic regulatory system found in all vertebrates
- Influences multiple physiological processes
  - Pain modulation
  - Seizure threshold
  - Appetite
  - Digestion
  - Mood
- May play a role in other functions
  - Immune system regulation
  - Tumor surveillance
  - Fertility
  - Bone physiology
  - HPA axis
  - Intraocular pressure

Endocannabinoid System

- Noted to have two types of receptors
  - CB1 – mediates inhibition of neurotransmitter release
  - CB2 – modulates immune response
- Both G-coupled proteins
- Expressed throughout the central and peripheral nervous system
  - CB1 10x more prevalent than µ-opioid receptor

**Endogenous CB1/CB2 ligands**

<table>
<thead>
<tr>
<th><strong>Anandamide (AEA)</strong></th>
<th>CB₁ &gt;&gt; CB₂ agonist TRPV₁ agonist</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Anandamide structure" /></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>2-Arachidonoyl glycerol (2-AG)</strong></th>
<th>CB₁ ≈ CB₂ agonist</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="2-Arachidonoyl glycerol structure" /></td>
<td></td>
</tr>
</tbody>
</table>

- Derived from membrane phospholipid precursors and diacylglycerol
- Synthesized on demand
  - Release mechanism not well understood
- Uptake via active transport
- Degraded by Fatty Acid Amide Hydrolase (FAAH)

Anandamide

Anandamide biosynthesis

Phosphatase
phospho-AEA
NAPE-PLD
NAPE-PLC ?

Anandamide inactivation

Ethanolamine
+ arachidonic acid

2-AG

2-AG biosynthesis

Glycerophospholipid
+ phosphatidylethanolamine

Glycerol
+ arachidonic acid

MAGL

EMT

CB₁

CB₁
Endocannabinoid System

- Potential strategies
  - CB2 > CB1 for pain relief
  - CB1 + u-opioid agonist or NSAID for pain relief
  - Use CB1 ± CB2 agonist that do not cross BBB
  - Utilize CB1 ± CB2 agonist by intrathecal or transdermal/mucosal administration
  - Target FAAH to enhance endogenous endocannabinoids
  - Investigate role of transport proteins
Question

- Medical Marijuana has been evaluated for all of the indications below EXCEPT
  - A. Glaucoma
  - B. Epilepsy
  - C. Substance Abuse
  - D. IDB
  - E. Osteoporosis
  - F. None of the above
Evaluated Indications for Medical Marijuana

- Appetite stimulation
- Pain/Inflammation
- Neurotoxicity
- Dyskinesia
- Stroke
- Epilepsy
- Anxiety/Depression
- Glaucoma
- Cancer

- Insomnia
- Nausea/Emesis
- Drug Addiction
- Hypertension
- ACS
- Asthma
- IBD
- Arthritis
- Osteoporosis
## Commercially Available Cannabinoids

<table>
<thead>
<tr>
<th>Generic medication</th>
<th>Brand name(s)</th>
<th>Country</th>
<th>Licensed indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nabilone</td>
<td>Cesamet</td>
<td>U.S., Canada</td>
<td>Antiemetic (treatment of nausea or vomiting) associated with chemotherapy that has failed to respond adequately to conventional therapy[^2^]</td>
</tr>
<tr>
<td>Dronabinol</td>
<td>Marinol</td>
<td>U.S., Canada</td>
<td>Antiemetic (treatment of nausea or vomiting) associated with chemotherapy that has failed to respond adequately to conventional therapy[^2^]</td>
</tr>
<tr>
<td>Nabiximols</td>
<td>Sativex</td>
<td>Canada, New Zealand, eight European countries as of 2013</td>
<td>Limited treatment for spasticity and neuropathic pain associated with multiple sclerosis and intractable cancer pain[^2^]</td>
</tr>
</tbody>
</table>
Question

- The only active component of medical marijuana is THC
  - TRUE
  - FALSE
Cannabinoids

- Marijuana is composed of >60 active phytocannabinoids and terpenes
- Active at CB1 and CB2 receptors
- Modulate multiple neurotransmitters
THC

- Delta-9-tetrahydrocannabinol (THC)
- Identified in early 1930s
- Main psychoactive component of MM
- Concentration: 0.1-25% (dry weight)
- Metabolized via CYP2C9, 2C19, 3A4
- Properties:
  - Euphoriant
  - Analgesic
  - Anti-inflammatory
  - Antioxidant
  - Antiemetic

CBD

- Cannabidiol
- Identified in 1940
- Less psychoactive effects
- Concentration: 0.1 – 2.89% (% dry weight)
- Metabolized via CYP2C19 and 3A4
- Properties:
  - Anxiolytic
  - Analgesic
  - Antipsychotic
  - Antiinflammatory
  - Antioxidant
  - Antispasmodic

# Receptor Affinities

<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="image" alt="Structure" /></td>
<td>CB₁R, CB₂R (microglia), TRPA1, TRPV2, TRPM8, α₁β GlyR, 5-HT₁₃R, PPAR-γ, GPR18, GPR55</td>
<td>Partial agonist</td>
</tr>
<tr>
<td>Cannabidiol</td>
<td><img src="image" alt="Structure" /></td>
<td>CB₁R, CB₂R (microglia), GPR55, TPRA1, TRPV1–3, TRPV4, TRPM8, 5-HT₁₃R, 5-HT₂₃R, α₂GlyR, PPAR-γ, Caᵥ₃ ion channel, Adenosine reuptake</td>
<td>Antagonist</td>
</tr>
</tbody>
</table>
Figure 1. Pharmacological actions of non-psychotropic cannabinoids (with the indication of the proposed mechanisms of action).

Abbreviations: Δ⁹-THC, Δ⁹-tetrahydrocannabinol; Δ⁸-THC, Δ⁸-tetrahydrocannabinol; CBN, cannabinol; CBD, cannabidiol; Δ⁹-THCV, Δ⁹-tetrahydrocannabinivarin; CBC, cannabichromene; CBG, cannabigerol; Δ⁹-THCA, Δ⁹-tetrahydrocannabinolic acid; CBDA, cannabidiolic acid; TRPV1, transient receptor potential vanilloid type 1; PPARγ, peroxisome proliferator-activated receptor γ; ROS, reactive oxygen species; 5-HT₁A, 5-hydroxytryptamine receptor subtype 1A; FAAH, fatty acid amide hydrolase. (+), direct or indirect activation; ↑, increase; ↓, decrease.
Administration and Dosing

- Smoked/Vaporized
  - Vaporized components inhaled and absorbed via alveoli and readily cross BBB
    - Onset: 90 seconds
    - Tmax: 15-30 minutes
    - Effect: 2-3 hours
  - Dose titration more readily available
    - Space inhalations by 90 seconds
- Smoked
  - 40% active ingredients lost in combustion
  - Particulates can be irritating

Administration and Dosing

- Oral Ingestion
  - Onset: 90 minutes
  - Tmax: 2-3 hours
  - Effect: 4 – 12 hours
- THC has active metabolite 11-hyroxyl-THC
  - 4x greater psychoactivity
- Delayed onset and variable absorption makes dose titration difficult
  - Space doses by **2 hours**
  - High risk for intoxication due to excessive dose
  - Consider for treatment of chronic conditions

Administration and Dosing

- Oromucosal absorption
  - Spray inside of cheek or under tongue
    - Onset: 0.5 – 2.5 hours
    - Tmax: 1.5 – 4.25 hours
    - Effect duration: n/a
  - Generally faster onset than oral but still has active metabolite generation for THC
  - Less absorption than inhalation
  - Dosing titration easier than oral and preferred for treatment of nausea

Limitations

- No established dosing guidelines
  - Wide variation in products and routes of administration
  - Limited studies
  - Tolerance
  - Inter-patient variability in metabolism
  - Disease modification of endocannabinoid system
Recommendations

- Start low go slow
- Dose increase based on THC
  - Range: 2.5 mg – 120 mg
- Initiate with qhs dosing and increase frequency before dose
- Titrate based on patient response
  - Efficacy
  - Tolerability
- Average time to optimal dose: 1-2 weeks
Question

- There are no documented cases of marijuana-induced death
  - TRUE
  - FALSE
Adverse Effects

**Common**
- Asthenia
- Balance problems
- Confusion
- Dizziness
- Disorientation
- Diarrhea
- Euphoria
- Drowsiness
- Dry mouth
- Fertility issues (long-term)
- Somnolence
- Weight gain

**Serious**
- Cannabis Hyperemesis Syndrome
- Developmental issues
- Hypotension
- Psychotic Symptoms
  - Hallucination
  - Paranoia
- Tachycardia
Contraindications

- Hypersensitivity
- Pregnant or Breast feeding
- History of psychotic illness
- Active unstable ischemic heart disease
Precautions/Warnings

- Severe liver or kidney disease
- Pulmonary disease
- Concomitant use with sedatives/psychotropics
- Epilepsy or recurrent Seizure activity
- History of substance abuse

- Elderly or pediatric use
  - Use low doses and slower titration
Pharmacologic Interactions

- THC inhibits CYP2C & 3A4
- CBD induces CYP2B isoenzymes
- Smoked marijuana induces CYP1A2
Identifying Abuse

- Similar to other substance abuse disorders
  - History of abuse
  - Abuse & Dependance
  - Difficulty with Social and/or Occupational obligations
  - Reports of withdrawal effects
Medical Marijuana in US

NYS Medical Marijuana

• Compassionate Care Act – signed July 5, 2014
• Five (5) organizations responsible for cultivation/acquisition and dispensing at four (4) dispensaries each
• Physicians must complete a four hour course and register to certify patients
• Approved Indication:
  – Severe, debilitating or life threatening disease accompanied by an associated or complicating condition
  – NYS specific conditions include: cancer, AIDS, ALS, Parkinson’s, MS, spinal cord injury, epilepsy, IBD, Neuropathy, Huntington’s

NYS Medical Marijuana cont’d

• Available dose forms:
  – Liquid or oil or oromucosal/sublingual administration
  – Metered liquid or oil for vaporization
  – Capsules for oral administration

• Prepared edibles are not approved

• **SMOKING IS EXPRESSLY PROHIBITED**

• A low THC:CBD product and an equal THC:CBD product must be available
  • Must be within 95 – 105 % of labeled concentration of total THC or total CBD

• Maximum of 10 mg total THC per dose

## Selected Applicants

<table>
<thead>
<tr>
<th>Organization</th>
<th>Facility Type</th>
<th>County</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloomfield Industry Inc</td>
<td>Manufacturing</td>
<td>Queens</td>
</tr>
<tr>
<td></td>
<td>Dispensing</td>
<td>Nassau, New York, Onondaga</td>
</tr>
<tr>
<td>Columbia Care NY LLC</td>
<td>Manufacturing</td>
<td>Monroe</td>
</tr>
<tr>
<td></td>
<td>Dispensing</td>
<td>New York, Suffolk, Clinton, Monroe</td>
</tr>
<tr>
<td>Empire State Health Solutions</td>
<td>Manufacturing</td>
<td>Fulton</td>
</tr>
<tr>
<td></td>
<td>Dispensing</td>
<td>Broome, Albany, Westchester, Queens</td>
</tr>
<tr>
<td>Etain, LLC</td>
<td>Manufacturing</td>
<td>Warren</td>
</tr>
<tr>
<td></td>
<td>Dispensing</td>
<td>Albany, Ulster, Westchester, Onondaga</td>
</tr>
<tr>
<td>PharmaCann LLC</td>
<td>Manufacturing</td>
<td>Orange</td>
</tr>
<tr>
<td></td>
<td>Dispensing</td>
<td>Erie, Onondaga, Albany, Bronx</td>
</tr>
</tbody>
</table>
Appetite Stimulation/Weight Gain

- Well known side-effect of marijuana use
- Elevated anandamide levels noted in restricting anorexic patients
- Attributed to THC and CB1 agonism influencing leptin inversely
  - Confirmed with CB1 knockout animal models
- Weight gain noted even with normal caloric intake
  - Reduced metabolic activity
  - Increased adiponectin

## Literature review

<table>
<thead>
<tr>
<th>Author</th>
<th>Disease</th>
<th>Sample Size</th>
<th>Compound</th>
<th>Parameters</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regelson et al. (1976)</td>
<td>Cancer</td>
<td>54</td>
<td>THC</td>
<td>Appetite, weight</td>
<td>Improved both</td>
</tr>
<tr>
<td>Nelson et al. (1994)</td>
<td>Cancer</td>
<td>19</td>
<td>THC</td>
<td>Appetite, weight</td>
<td>Improved appetite</td>
</tr>
<tr>
<td>Beal, et al (1997)</td>
<td>AIDS</td>
<td>94</td>
<td>THC</td>
<td>Appetite, weight</td>
<td>Improved both</td>
</tr>
<tr>
<td>Timpone, et al. (1997)</td>
<td>AIDS</td>
<td>52</td>
<td>THC vs. Megestrol</td>
<td>Appetite, weight</td>
<td>THC less effective</td>
</tr>
</tbody>
</table>
Pain and Inflammation

- One of the earliest uses of cannabis
- Synergistic activity with NSAIDS
- Effective in mitigating chemical, mechanical, and thermal stimuli
  - Most effective in chronic and neuropathic pain
- CB1 and CB2 involvement in hyperalgesic activity via complex mechanisms affecting central and peripheral sensory nerves
  - May stimulate endogenous opioid release

Proposed targets for Anti-Inflammatory effects

Medical Marijuana in Pain Control

- Limited quality data
- Recent meta-analysis indicated moderate benefit in chronic pain and spasticity
  - evaluated 28 studies
  - 41% greater odds of achieving 30% reduction in pain
  - Average pain score reduction: -0.46 (95% CI: -0.80 - -0.11)
  - Twice as many patients reported pain improvement
  - No difference in quality of life scores

Epilepsy

- Used as early as 1800 BCE in Sumeria, cannabis tinctures used up until introduction of phenobarbital & phenytoin
- Endocannabinoid system strongly activated by seizures → upregulation of CB1 receptors
- Animal models
  - Anandamide levels increase post seizure
  - CB1 antagonists prolong seizure activity
- CBD may have alternate mechanism via TRPV1

Literature review

- Recent Cochrane Review evaluating cannabis in treatment of epilepsy concluded “no reliable conclusions can be drawn”
- Numerous case reports and patient surveys supporting use
- Case control study noted males with cannabis use 90 days prior to hospital admission were 64% less likely to present with new-onset seizure
- Four placebo-controlled studies utilizing cannabinoids performed
  - Half showed reduction in seizure frequency
- In 2013, an open-label trial in pediatric epilepsy evaluated 99% CBD (N=137)
  - Median reduction of seizures, 54%

Multiple Sclerosis/Spinal Cord Injury/ ALS

- Reports of cannabis use for spasms in ancient Greece, Rome, & China
- Suggested mechanism – endogenous cannabinoids released provide neuroprotection via negative feedback loop in microglial cells
- Reduction of muscle spasticity is debatable
  - Animal studies show reduced inflammation and improve neurologic outcomes with parenteral THC or exogenous anandamide
  - Anecdotal evidence of symptom relief in MM smokers but no change in spasticity scoring via Ashworth scale

## Literature review

<table>
<thead>
<tr>
<th># Studies (pts)</th>
<th>Cannabinoid</th>
<th>Outcome</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (519)</td>
<td>Nabiximols</td>
<td>50% Spasticity reduction</td>
<td>OR (95% CI) 1.4 (0.81 – 2.41)</td>
</tr>
<tr>
<td>2 (519)</td>
<td>Nabiximols</td>
<td>30% Spasticity reduction</td>
<td>OR (95% CI) 1.64 (0.95 – 2.83)</td>
</tr>
<tr>
<td>5 (1244)</td>
<td>Nabiximols</td>
<td>Spasticity</td>
<td>WMD (95% CI) -0.11 (-0.23-0.02)</td>
</tr>
<tr>
<td></td>
<td>THC/CBD Dronabinol</td>
<td>Ashworth scale</td>
<td>-0.32 (-1.59-0.95)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-0.94 (-2.37-0.49)</td>
</tr>
<tr>
<td>3 (698)</td>
<td>Nabiximols</td>
<td>Spasticity</td>
<td>WMD (95% CI) -0.76 (-1.38-0.14)</td>
</tr>
<tr>
<td></td>
<td>Nabilone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 (1433)</td>
<td>Nabiximols</td>
<td>ADLs</td>
<td>WMD (95% CI) -0.58 (-1.73-0.56)</td>
</tr>
<tr>
<td></td>
<td>THC/CBD Dronabinol</td>
<td>Barthel Index</td>
<td>0.23 (-0.13-0.59)</td>
</tr>
<tr>
<td>3 (461)</td>
<td>Nabiximols</td>
<td>Global Impression</td>
<td>OR (95% CI) 1.44 (1.074-1.94)</td>
</tr>
</tbody>
</table>

Parkinson’s Disease

- Characterized by resting tremor, muscular rigidity, and bradykinesia
- Animals models note overactivity of endocannabinoid system in striatum
  - Elevated tissue levels of endocannabinoids & CB1 receptors
  - Decrease rates of transport & FAAH-mediated degradation
- Increased CB1 receptor signalling in striatum may be compensation for dopaminergic loss
- CB1 augmentation may alleviate symptoms

Very limited data

- Studies showed improvement in tremor and potential for neuroprotection but do not affect bradykinesia
- CB1 antagonist rimonabant evaluated for bradykinesia – not significant
  - Dosing 10 fold lower than previous primate studies
  - Question if efficacious only in advanced disease
- 2 studies utilizing CB1 agonist (SR142801 & nabilone) for levodopa-induced dyskinesia
  - Sample size: 24 & 7 subjects evaluating motor symptoms
  - No significant improvement observed

Future studies

- Other cannabinoids of interest
  - Cannabinol (CBN)
  - Cannabichomene (CBC)
  - Cannabigerol (CBG)
  - Tetrahydrocannabivirin (THCV)
Limitations of Literature

- Small sample sizes
- Open-Label
- Blinding issues
- Most studies utilize isolated cannabinoids
  - Negates “entourage effect”
Hospital Issues

- Marijuana still remains a schedule I drug
- Legal implications of continuation of MM in an inpatient setting is complex
- Concern for withdrawal issues in high-dose regimens
- Complicates therapy in critically ill patients
  - Hypotension
  - Drug Interaction
  - Immune suppression
  - Sedation/Cognitive impairment
- Policies needed to address alternative therapies, consideration of use of patients’ supply, or justification of holding treatment
Summary

- Medical Marijuana has unique medical pharmacology and treatment modalities
- Limited number of quality studies evaluating its effectiveness and safety
- Dosing is patient directed and has high risk for therapy errors
- NYS MM program restricts the formulation and routes of administration
- Potential for expansive drug development targeting endocannabinoid system
Questions?