Medical Cannabis

Yasin Choudry, MD and Snehal Bhatt, MD
Department of Psychiatry and Behavioral Sciences
University of New Mexico
Nov. 4, 2017
Objectives

• Become familiar with the currently available evidence for medical cannabis for various medical conditions
• Become familiar with the endocannabinoid system
• Be able to explain the basic neurobiology of THC and cannabidiol
• Learn about some possible risks of cannabis
• Be able to weigh the risks and benefits of medical cannabis
History and Nomenclature
Medical Marijuana - A Historical Perspective

• Use dates back 12,000 years
• Started in central Asia and flourished in Southeast Asia and India
• 600 BCE: Earliest medical description of cannabis in Shennong Ben Cao Jin, compiled circa 100 CE from earlier oral traditions. Earliest archeological evidence of cannabis use dates to 600 BCE in Yanghai, China.
• Ancient China: malaria, constipation, rheumatic pain, female reproductive disorders
• Ancient India: euphoric properties [2000 BC], religious sacrament, fever reduction, promoting sleep, stimulating appetite, relieving headaches, curing VDs
• Azerbaijan: reports of medical marijuana in 9th century AD
Medical Marijuana - A Historical Perspective

• Introduced into the Americas in 1600s by English settlers and Spanish conquistadors
• 1616: Jamestown cultivates Cannabis sativa for hemp fibers
• 1842: O’Shaughnessy, a British army physician in India, produced a review of the use of cannabis in the treatment of various medical conditions
• Listed in the U.S. Pharmacopeia from 1850-1942
• Recreational use began to surge in 1930s during prohibition
• 1937: Marijuana Tax Act taxed and criminalized sale of marijuana. Medical use technically legal, but discouraged by taxes and regulations
• 1970: Controlled Substances Act places cannabis in Schedule I [high abuse liability, NO therapeutic potential]
Terminology

• “Marijuana” or “Marihuana”: exact meaning unknown; originates from Mexico; popularized in 1930s by Harry Anslinger, the first commissioner of Federal Bureau of Narcotics

• “Cannabis”: Genus name; originates from κάνναβις, written by Herodotus in 440 BCE

• Main segregates include *Cannabis sativa* and *Cannabis indica*

• “Hemp”:
  • Cannabis plant with a THC content less than 0.3%, grown for its seed and fiber
  • Has been used commercially in thousands of products for more than 12,000 years
  • Can describe any industrial or nutritional product from cannabis that is not used as a drug
Strains

• C. sativa, C. indica, and C. Ruderalis
• Often characterized by sativa having a “head” high vs. indica having a “body” high- not very accurate (McPartland, 2014)
• Hybrids dominate the market
• Cultivar names often mean little; instead rely on chemical profile
A Little Neurobiology

Why does cannabis, and not oregano, get us high
Endocannabinoid System

- Genomic and phylogenetic studies indicate that CB receptors evolved around 600 million years ago.
- CB receptors are present in every vertebrate investigated to date.
- CB receptors are absent in non-chordate invertebrates (insects, nematodes, Hydra), fungi, and plants.
- CB receptors existed long before cannabis evolved, ca. 25 million years ago.

“Classical” Endogenous Cannabinoid Agonists

- There are endogenous cannabinoids that the body synthesizes and degrades as needed.
- The two best-characterized endocannabinoids are anandamide (AEA) and 2-arachidonoylglycerol (2-AG), but “minor” endocannabinoids have been identified.
- They bind with and activate CB1 and CB2 receptors.
Endocannabinoids are Important!

1.) The role of our endocannabinoid system is largely to regulate activity of other neurotransmitters.

2.) "There is barely a physiological system in which endocannabinoids are not involved. Hence its importance is far beyond that of THC and marihuana....” - Mechoulam
Major Receptors

• **CB1 Receptors - 1988**
  – Hippocampus – Memory and Learning
  – Amygdala – Novelty, Emotion, Appetites
  – Basal Ganglia – Motor
  – Cerebellum – Real Time Coordination, Selective Attention and Time Sense
  – **Nucleus Accumbens - Reward Mechanism (Addiction)**
  – Cortex (Anterior > Posterior) – Frontal Lobe Executive Functions

• **CB2 Receptors - 1993**
  – Macrophages
  – Spleen, Intestines
CB 1 receptors

**CNS**
- Appetite ↑
- Cerebral Dilation ↑
- Core body temperature ↓

**CARDIOVASCULAR SYSTEM**
- Heart rate ↓
- Blood pressure ↓
- Myocardial contractility ↓
- Coronary dilation ↑

**LIVER**
- Lipogenesis
- Cerebral Adiponectin ↓
- Plasma triglyceride ↑
- HDL cholesterol ↓

**ADIPOSE TISSUE**
- Insulin and leptin resistance ↑
- Glucose tolerance ↓
- Thermogenesis ↓

**SKELETAL MUSCLE**

(Pacher et al 2008)
CB-2 Receptors

- CB2 is primarily expressed in peripheral tissues of the immune system (leukocytes, spleen, tonsils, thymus, bone marrow) and the gastrointestinal system.

- Cannabinoids have immunomodulating effects:
  - ↓ Th1 cytokines
    - IL-2, IFNγ, TNFα
  - ↑ Th2 cytokines
    - IL-5, IL-6, IL-10
  - ↓ Activity of mast cells, possibly neutrophils
  - ↑ Activity of macrophages
    (Pertwee 2014)
Exogenous cannabinoids

- There are 400 chemicals in the hemp plant
- At least 100 of them are cannabinoids [activate CB receptors]
- The cannabinoids with the most therapeutic interest are Delta-9 tetrahydrocannabinol [THC] and Cannabidiol [CBD]
- Terpinoids are organic aromatic compounds that give cannabis smell
- It is the overall chemical composition that often influences the effects of a particular cultivar of cannabis [“Entourage effect”]
Δ9-THC: Exogenous Cannabinoid
Δ9-THC: Exogenous Cannabinoid

- Δ9-tetrahydrocannabinol
- Purified in 1964
- The major psychoactive ingredient in marijuana
- Partial CB-1 and CB-2 agonist
- Major psychoactive effects and addiction through CB-1
- 11-OH-THC, formed during first pass metabolism, up to 4x more potent
Cannabidiol [CBD]

- Non-psychoactive
- Blocks formation of 11-OH-THC
- Non-competitive antagonist of CB-1
- Inverse agonist of CB-2
- Inhibits the reuptake and degradation of anandamide
- Little affinity for CB-1 and CB-2 receptors [100 fold less than THC]
- Antagonist at 5-HT1A receptor- possible antidepressant, anti-anxiety and pro-cognitive effects
- May counteract effects of THC [anxiety, tachycardia, panic attacks, psychosis] while enhancing therapeutic efficacy [Izzo 2009, Russell 2011]
- Neuroprotective
- Anti-inflammatory
Potential Therapeutic Applications
The Whole Plant as Medicine

• Derivatives of cannabis plant currently being used to treat over 50 conditions worldwide, but...

• Paucity of clinical trials showing efficacy of the whole plant for ANY specific condition (Koppel et al., 2014; Whiting et al., 2015; Madras, 2015)

• Challenges:
  • Variability of botanical products
  • Large number of compounds in whole plant
  • Variability in routes of administration
  • Variable risk benefit calculations in different populations
Current prescription forms

- Dronabinol (Marinol) and nabilone (Cesamet) indicated for chemotherapy-induced nausea and vomiting
- Dronabinol (Marinol) approved for HIV-associated anorexia
- Sativex: neuropathic pain in multiple sclerosis and cancer
- Other countries: nabiximols [“Sativex”]: oromucosal spray containing 1:1 ratio of THC: CBD approved for MS related pain/spasms
Whiting Review in JAMA 2015

- Moderate quality evidence for:
  - Chronic Pain
  - Spasticity due to MS or paraplegia

- Low Quality evidence for:
  - Nausea/vomiting due to chemotherapy
  - Appetite stimulation in HIV/AIDS
  - Sleep disorders
  - Tourette’s Syndrome

- Very low quality evidence for:
  - Anxiety Disorders

- Lack of evidence for:
  - Depression
  - Psychosis
  - Glaucoma
Whiting - Side effects

• Cannabinoids associated with:
  • significantly more short term adverse events [OR 3.03]
  • including serious adverse events [OR 1.41]
  • and withdrawals due to AE [OR 2.94]
Various Conditions
Chronic Pain Studies: vast majority of cards nationwide

• Whiting [2015][28 studies]: moderate quality evidence
  • Generally suggested improvements with cannabinoids, not all reached significance
  • Overall odds ratio for 30% improvement in pain 1.41 [37% vs 31%]
  • smoked THC OR 3.43
  • No difference between pain conditions

• Hill [JAMA, 2015]
  • 28 RCTs evaluated
  • “High quality evidence” for marijuana for chronic pain and neuropathic pain

• Hauser et al. [2017]- a review of 10 systematic reviews
  • Inconsistent findings on efficacy of cannabis for neuropathic pain, and for painful spasms in MS
  • Consistent findings showing insufficient evidence for rheumatic diseases and cancer pain
Chronic Pain Studies

• Nugent et al. [Annals of Internal Medicine, 2017]
  • Evaluated 27 trials of plant based cannabis preparations for chronic pain
  • **Low strength evidence** for neuropathic pain
  • Insufficient evidence for other pain conditions

• Boehnke et al. [2016]:
  • Retrospective survey of 244 patients on medical cannabis for chronic pain
  • 64% reduction in opiate use
  • Decreased number and side effects of medications
  • Improved quality of life

• Bachhuber et al. [2014]
  • States with medical cannabis laws had 24.8% lower mean annual opioid overdose mortality rate compared with states without medical cannabis laws
  • Passing of such laws was associated with a lower rate of overdose mortality that generally strengthened over time:
Spasticity due to MS/Paraplegia

- Whiting [2015]
  - 2 low risk of bias; 7 high risk of bias; 5 unclear risk of bias
  - Most favored cannabinoids, but not all reached significance
  - Moderate quality evidence for cannabinoids
Spasticity due to MS/Paraplegia

• Rovare et al. [2017]
  • 16 trials; N = 2597
  • Non-statistically significant improvement spasm frequency and severity
  • Non-statistically significant improvements in cognitive function, daily activities
  • Non-statistically significant reduction in spasticity
  • Moderate quality evidence
  • 3x risk of dizziness, dry mouth, somnolence
  • 2x risk of nausea
  • No increased risk of respiratory suppression
PTSD

• The single biggest indicator for medical marijuana in New Mexico
• Indication based on animal data that shows that THC administration helps rats forget aversive memories by acting on hippocampus plasticity
• Also based on anecdotal reports
• O’Neill et al. [2017]:
  • Systematic review of 2 reviews, and 3 observational studies; NO RCTs available- Insufficient evidence for cannabis
  • Medium to high risk of bias
• Two RCTs are ongoing
Medical Cannabis and Prescription Drugs

• Bradford & Bradford (2016):
  • Data on all prescriptions filled by Medicare Part D enrollees between 2010 and 2013
  • Once medical cannabis law was implemented, use of prescription drugs for eligible conditions dropped significantly
  • National overall reductions in Medicare program and enrollee spending estimated at $165.2 million per year in 2013 in states with medical cannabis
Areas of Further Research

- Alzheimer’s Disease
- Movement Disorders
- ALS
- PTSD
- Anti tumor properties: Results from in vitro and animal studies suggest cannabinoids and endocannabinoids inhibit tumour growth and the progression of several types of cancer
- Crohn’s [preclinical data supporting benefits]
- Opioid Use
- Epilepsy [CBD shows promise]
- Auto-immune conditions
- IDDM
Cannabidiol - The Future?

- Human studies do NOT show any worsening of psychopathology [Rong et al., 2017]
- Ample pre-clinical evidence showing efficacy in anxiety, depression, cognition
- Evidence for some types of epilepsy (Devinsky et al., 2016)
- Ongoing clinical trials for:
  - Anxiety
  - Psychosis
  - Schizophrenia
  - Behavior
  - Emotional stimuli
Cannabidiol - The Future?

• Khoury et al., 2017: Review of 6 case reports and 7 clinical trials
• Evidence as treatment for:
  • Cannabis withdrawal
  • Cannabis addiction
  • Positive symptoms in schizophrenia
  • Anxiety in social phobia
• No evidence for depression or bipolar disorder
Exciting Frontiers

• Exploring compounds that inhibit the activity of enzymes that break down endogenous cannabinoids (Blankman & Cravatt, 2013; Piomelli et al., 2006)
  • FAAH inhibitors have been shown in animal models and some human studies to reduce anxiety, depression, nicotine and cannabis intake, and to improve social behavior in Autism Spectrum Disorders (Blankman & Cravatt; 2013; Gunduz-Cinar et al., 2013; Marco et al., 2015; Scherma et al., 2008)
  • NO tolerance noted
Exciting Frontiers

• Selectively activating peripheral CB2 receptors using compounds that do not cross the blood brain barrier
  • Animal studies- such compounds can improve pain due to immune or PNS action (Pertwee, 2012; Rahn et al., 2011)

• Allosteric modulators of cannabinoid receptors in development – alter response to endogenous ligands (Baillie et al., 2013; Morales et al., 2016)- CBD may do this (LaPrairie et al., 2015)
Harm Considerations
But its "natural" and can't be addictive...

...Or Can It?
C’s of Addiction

• Chronic nature of illness
• Control [loss of]
• Consequences [use despite]
• Compulsive  [nature of use]
• Cravings
Addiction Potential of Marijuana

• According to SAMHSA, 39.2% of people who use marijuana daily are dependent on it, as opposed to 13.5% of those who use it less than daily

• “There is no question marijuana can be addictive; that argument is over. The most important thing right now is to understand the vulnerability of young, developing brains to these increased concentrations of cannabis”

  -Dr. Nora Volkow, NIDA Director, Los Angeles Times, 4/26/04
Cannabis Use and Addictions

• Hill (2017): cannabis use associated with development of multiple substance use disorders, including alcohol and nicotine use disorders

• Most cannabis users do NOT go on to use other drugs

• However, early cannabis users more likely than peers to use other drugs and develop SUDs

• Cannabis use precedes other drugs, except tobacco and nicotine

• Access

• Common vulnerabilities

• Alterations in reward system
Pregnancy

• Marijuana use rates in pregnancy 2-5%
• 15-28% in young, urban, socioeconomically disadvantaged women
• 34-60% of marijuana users continue use during pregnancy (ACOG, 2017)
• Highly lipophilic; crosses placenta
• Many confounds in studies:
  • Pregnant cannabis users more underweight, lower levels of education, lower income, less likely to use folic acid supplementation, more likely to experience intimate partner abuse
  • Use of other substances, including tobacco and alcohol
Pregnancy

• Endocannabinoids play a key role in fetal brain development
• In animal studies, cannabinoid exposure may disrupt normal brain development (Compolongo et al. 2011)
• Cannabis exposure sensitizes fetus to effects of alcohol (Hansen et al., 2008)
• Impaired cognition and increased sensitivity to drugs of abuse (Szutorisz et al., 2014), including marijuana
• Deficits in behavior and cognition, including visual memory, language, attention, and problem solving in childhood and adolescence
• Effects on school performance unclear- worse in low SES, unchanged in middle to high SES
Pregnancy

- No increase in anatomical birth defects - association with anencephaly complicated by folic acid supplementation rates
- No association with perinatal mortality
- Association with stillbirth complicated by tobacco use
- Marijuana use > weekly associated with higher likelihood of low birth weight
- Not associated with preterm birth after controlling for tobacco use
- Lactation: little data
- ACOG: Avoid use; encourage cessation
Adolescence

• Dose related increase in adverse outcomes: academic achievement, income, life satisfaction, other SUDs

• Loss of IQ points- significant and possibly permanent in cannabis users who started as adolescents and developed cannabis use disorder (Meier et al., 2012)- but causality is in question

• Many confounding variables
Psychosis

• Numerous studies suggest that the use of cannabis increases the risk for schizophrenia, worsens symptoms, and is associated with poorer prognosis

• Data also suggest that those people with genetic vulnerability to psychosis, those with previous psychotic episodes, or those with **cannabis use in early adolescence**, particularly prone to development of schizophrenia

• Cannabis dependence = 1.5-2x increased risk of psychotic illness

• A significant risk factor, but no causality

• THC may be psychotogenic, while CBD has antipsychotic properties
Harms Shown in Clinical Trials

• Nugent et al., 2017 Review:
  • Higher overall short term AEs
  • MVA OR 1.35- small but consistent; no increase in fatal MVAs in a recent study
  • Moderate-strength evidence that light to moderate cannabis smoking does not adversely affect lung function over about 20 years.
  • A possible deleterious effect on lung function over time
  • Low-strength evidence that light to moderate cannabis use is not associated with lung cancer or head and neck cancer diagnoses independent of tobacco use
  • Insufficient evidence whether cannabis use is associated with cardiovascular events over the long term
  • Small, short-term deleterious effects on cognition in active users, but long-term effects in past users are uncertain
Bringing it All Together!
Qualifying Conditions

• ☐ Amyotrophic Lateral Sclerosis (ALS)
• ☐ Cancer (please specify type)
  ☐ Crohn’s Disease
  ☐ Epilepsy
• ☐ Glaucoma
• ☐ Hepatitis C Infection currently receiving antiviral treatment (proof of current anti-viral treatment required)
• ☐ HIV/AIDS
• ☐ Huntington’s Disease
• ☐ Hospice Care
• ☐ Inclusion Body Myositis
• ☐ Inflammatory autoimmune-mediated arthritis
Conditions Continued

- Intractable Nausea/Vomiting
- Multiple Sclerosis
- Damage to the nervous tissue of the spinal cord, with (proof of objective neurological indication of intractable spasticity required)
- Painful Peripheral Neuropathy
- Parkinson’s disease
- Post-Traumatic Stress Disorder
- Severe Chronic Pain
- Severe Anorexia/Cachexia
- Spasmodic Torticollis (Cervical Dystonia)
- Ulcerative Colitis
Potential Patients

• Must sign release of information
• Must have NM ID to prove residency
• Must have a qualifying diagnosis
• Must have symptoms treatable with medical cannabis
• Must have benefits that outweigh risks
• Prescriber must have office and license in NM, patient must be seen in person
Prescribers

- Medical Doctor (MD) including Psychiatrists
- Physician Assistant (PA)
- Osteopathic Physician (DO)
- Osteopathic Physician Assistant (OA)
- Naturopathic Physician (ND)
- Advanced Registered Nurse Practitioner (ARNP)
- Note: Must have DEA or controlled prescribing authority depending on state
Best Practices [Hill, JAMA 2015]

• MUST carry out a comprehensive assessment that includes a risk-benefit discussion
• If necessary, collaborate care with other providers
• start with the patient expressing how they think medical marijuana will be helpful to treat their medical condition
• Prior treatments
• Possible contra-indications [psychosis, SUDs]
• Have a discussion of current state of knowledge
• Discuss legal status [state and federal]
Making the Choice

• Decision shared with provider and patient
• Is not a means of “natural remedy”, should be utilized where and when other first line treatments have failed
• Avoid if planning pregnancy, stop if pregnancy occurs during therapy
• Regular follow up to monitor effectiveness, side effects, problems, and general condition
• Monitor PMP, UDS screens
Harm Reduction

• No sharing of medicine
• Keep away from children (especially edibles which can be packaged to represent candies)
• Keep track of strains, dosing, intervals
• Stick with same strains that work (but can be different location to location)
• No driving or operating heavy machinery
• Vaporizing or edible formulations may reduce some risks of smoking
• Monitor for abuse (of cannabis and other drugs)
Which am I Supposed to Use?
Gram
~1-2 joints worth

Eighth (1/8)
~3.5 grams

Quarter (1/4)
~7 grams

Half (1/2)
~14 grams

1 Ounce
~28 grams
**types of infused edibles**
- tea
- infused drinks
- hard candy
- baked goods
- savory snacks
- tinctures

**onset & duration**
- allow up to **15-90 minutes** for most edibles to take effect

**caution**
- **Read the label**
  - Understand how much THC your edibles contain and take the correct serving size. What looks like 1 portion may be more than 10!
- **Keep out of reach**
  - Children love sweets but may be unaware that your medicine is only for adults. Make sure to keep edibles under lock and key.
- **Contains THC!**
- **Label homemaes**
  - If you make edibles at home, be sure to properly label them. This will prevent accidental ingestion by friends, family, and roommates.
- **Don’t drive**
  - Make sure you are in a safe and friendly environment to prevent a bad experience. Always have a designated driver on hand.

**Remember... start low, go slow!**
- 10mg is typically considered a good starting point
Very Similar Appearance
Clever Advertising
What is a dose?
The Feds, The Feds

• 2013: DOJ advised US attorneys not to pursue actions against physicians in states that allow medical marijuana.
• Remember this could change with current administration
Will I be sued, or lose my license?

• Remember, you are licensed by the medical board and must practice medicine with care, your license is a privilege – not a right

• Think of prescribing MMJ similar to prescribing opiate medications and take similar precautions when doing so, for example checking the PMP, requesting records from other providers, assessing for previous history of substance abuse
Cases of Legal Issues

• Here are a few media reports from different states of involvement of state medical boards taking action against certain physicians prescribing medical cannabis
Colorado

• Medical license suspension of four Colorado doctors recommending medical marijuana
• The state constitution says medical marijuana patients may grow six cannabis plants but also allows doctors to recommend higher plant counts for patients if it is “medically necessary.”
• State Health Department policy is to refer doctors to the Medical Board for investigation if doctors recommend an increased plant count for more than 30 percent of their medical marijuana patients.
• The suspension orders for the four doctors put special emphasis on whether the recommendations were issued to patients diagnosed with cancer. Without a cancer diagnosis, the Medical Board alleges a recommendation for more than 75 plants, “falls below generally accepted standards of medical practice and lacks medical necessity.”
California

• One physician charged with failure to perform appropriate exams, coordinate care with other practitioners, and obtain medical records received 5 years' probation.

• Another doctor was sanctioned because he said he saw 60-70 patients on Fridays and charged $150-$250 per patient. The diagnoses were actually made by a physician's assistant. The Medical Board of California charged him with gross negligence, incompetence, and creation of false medical records. He received a 45-day suspension of his license and 5 years' probation.
New York

• The state's Compassionate Care Act, imposes a new felony for doctors who issue certifications if they have reasonable grounds to know that the patient has no medical need or isn't using medical marijuana to treat a qualifying medical condition.
From the Lawyers

• "I would recommend that doctors use a specific written disclosure form, to be signed by the patient, noting that the possible addictive properties of marijuana and smoking were discussed... The form should note that the marijuana is given in reliance on the patient's statement of their condition, the need for pain relief, their diagnosis, and the patient's waiver of any risks associated with the drug's use. It would certainly help in a lawsuit, but it would also help in the event of a visit from the law enforcement folks."
Other legal suggestions

• Although no malpractice suits have yet been filed, there are still potential liability risks that are similar to those for other drugs. "The physician could be liable for failing to discuss the risks of the drug, such as driving under the influence or suicidal thoughts...Liability could arise from drug/drug interactions. The drug may not be appropriate for the patient's condition, and patients may have reactions to the drug.”

• An informed consent discussion should include information about side effects, the possibility of addiction, short- and long-term cognitive effects, psychiatric conditions ranging from anxiety and depression to psychosis, obstructive lung disease, lung cancer, motor vehicle accidents, and reproductive risks.
Thank You!!!!