Medical Marijuana – A Brief Overview of the Program in Ohio and Pharmacology of Cannabinoids

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Objectives

- Describe a broad overview of the Medical Marijuana Control Program in Ohio
- Discuss the pharmacology of cannabinoids

Background

- Federal Controlled Substance Act:
  - “Marihuana” means all parts of a plant of the genus cannabis, whether growing or not; the seed of a plant of that type; the resin extracted from a part of a plant of that type; and every compound, manufacture, salt, derivative, mixture, or preparation of a plant of that type or of its seeds or resin.

Who is Responsible?

Department of Commerce
- Cultivators
- Processors
- Testing laboratories

State Board of Pharmacy
- Dispensaries
- Patients/Caregivers
- New forms and methods of medical marijuana

Medical Board
- Certified physicians
- New qualifying conditions

Ohio Medical Marijuana Control Program. http://medicalmarijuana.ohio.gov/
Medical Marijuana Process Flow Chart

Dispensaries

- Must have proof of registration and recommendation prior to dispensing
- Must submit data to Ohio Automated Rx Reporting System (OARRS)
- No healthcare professional required to dispense
  - Policy must exist for education of patients
  - Employee must have documented training
    - Must maintain 16 CE hours/2 year licensing period

House Bill 523-Approved Forms

Certificate to Recommend (CTR) Eligibility

- Active, unrestricted license
- OARRS registration
- DEA registration
- No prior action on license from DEA or any licensing entity for inappropriate prescribing
- 2 hours of approved CME
- No defined conflict of interest
  - Ownership/investment in or compensation agreement with a medical marijuana entity/applicant

http://medicalmarijuana.ohio.gov/
Qualifying Medical Conditions

Infection - HIV/AIDS, Hep C
Inflammatory Bowel Disease - Crohn’s, Ulcerative Colitis
Neurologic Conditions - Seizure/Epilepsy, Tourette’s
Neurodegenerative - Alzheimer’s, ALS, MS, Parkinson’s
CNS Trauma - Traumatic Brain Injury/Encephalopathy, Spinal Cord Injury
Psychiatric - PTSD
Chronic Pain, Fibromyalgia, Sickle Cell Anemia
Other - Glaucoma, Cancer

Pharmacology of Cannabinoids

Types of Cannabinoids

- Endocannabinoids
- Phytocannabinoids
  - Δ-9 tetrahydrocannabinol (THC)
  - Cannabidiol (CBD)
  - Cannabinol (CBN)
- Synthetic
  - Pharmaceutical
  - Illicit

Ohio Medical Marijuana Control Program. http://medicalmarijuana.ohio.gov/
**Importance of Constituents**

- THC trends over time
  - 1980s ~4%
  - 2012 average concentration from police confiscation ~15%
  - 2015 ~20% with potencies up to 30%
- Percentage of constituents and ratios play a role in therapeutic applications, adverse effects, etc.
- Entourage effect

1) “Marijuana far more potent than it used to be, tests find” article. CBS News Web site. Published 3/23/2015.  

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**Primary Clinical Implications of THC and CBD**

- THC
  - Psychoactive
    - emotional and cognitive changes, analgesia, hypothermia and appetite stimulation
- CBD
  - Non-psychotropic
    - Modulation of behavioral effects

**Pharmacokinetics**

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Smoked/Vaporized</th>
<th>Oral Ingestion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Seconds – minutes</td>
<td>30 – 120 minutes</td>
</tr>
<tr>
<td>Peak</td>
<td>6 – 10 minutes</td>
<td>4 – 6 hours</td>
</tr>
<tr>
<td>Distribution</td>
<td>Highly lipophilic, accumulates in fatty tissues and reaches peak concentrations in 4-5 days. Tissue ( t_{1/2} ) = ~7 days with complete elimination taking up to 30 days</td>
<td></td>
</tr>
<tr>
<td>Metabolism</td>
<td>Phase 1 &amp; 2 in liver</td>
<td></td>
</tr>
<tr>
<td>11-OH-THC metabolite (active)</td>
<td>Lower concentrations</td>
<td>Higher concentrations</td>
</tr>
<tr>
<td>Elimination ( t_{1/2} ) (chronic use)</td>
<td>THC = 4.1 days</td>
<td>11-OH-THC = 12.6 days</td>
</tr>
</tbody>
</table>

Adapted from Chemistry & biodiversity. 2007;4(8):1770-1804

**Drug/Drug Interactions**

- Metabolism
  - THC and CBN
    - CYP 3A4 & 2C9
  - CBD
    - CYP 3A4 & 2C19
- Synergy with CNS depressants
- Opioids: Cross tolerance and mutual potentiation

Res Social Adm Pharm. 2015 Sep 16. pii: S1551-7411(15)00170-9
Cannabinoids Used With Opioids

Observational Findings of Interest

- Medicare opioid prescriptions
- Self-reported reduction in opioid use
- Synergy for analgesia
- Cannabinoids demonstrate analgesia sans opioids


Substance Abuse Considerations

- Rx opioids + cannabis =
  - ↑ Cannabis Use Disorder?
  - Problematic Opioid Use Behaviors?
  - ↓ tolerance and dependence?
  - ↓ discriminative stimulus and reinforcing effects of opioids?


Bachhuber et al, 2014

- States with medical cannabis laws had 24.8% lower mean annual opioid overdose mortality rate
- Lower rates of overdose mortality strengthened over time

Summary

- Medical Marijuana dispenses on OARRS
- Be aware of drug – drug interactions
- Constituents matter
- Cannabis + opioids

Medical Marijuana

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The Ohio State University College of Medicine Chair,
Pharmacy & Therapeutics Executive Committee
The Ohio State University Wexner Medical Center

Problem

- Internet search almost any disease along with the word “marijuana” and you will find support for using marijuana to treat the disease.
- 29 U.S. States, Washington D.C., Puerto Rico and Guam have “legalized” marijuana, including Michigan, Pennsylvania and Ohio.
  - 9 States for recreational use in adults
- What do medical providers need to know?

Take Home Points

- 1) Medical marijuana is ancient and many people feel that marijuana is benign.
- 2) There is evidence supporting use of medical marijuana in a few specific clinical conditions.
- 3) However, clinical research of marijuana is extremely limited.
- 4) There are known dangers of marijuana, and, as clinicians it is our duty to educate patients about these dangers.
Outline

- Background
  - Biology
  - History
- Attitudes
- Therapeutics
- Dangers

Biology - Plant

- Cannabis
  - ~500 chemical compounds – e.g. terpenes, flavonoids have been isolated from the Cannabis plant.
  - >100 different cannabinoids
  - Delta-9-tetrahydrocannabinol (THC) is the primary psychoactive cannabinoid.
  - Cannabidiol (CBD) is the cannabinoid in Epidiolex.
  - Hemp and Marijuana are both cannabis and they can cross fertilize.
  - Hemp has no more than trace THC.
  - Marijuana has significant amounts of THC concentrated in the flower-female buds.
  - Cannabis can occur as separate male and female plants and as a plant with both male and female parts.

Biology - Animal

- Two identified receptors
  - CB1, CB2
    - On separate genes on different chromosomes
    - G-proteins
    - Inhibitory effect on neurotransmitter release and uptake
  - CB1
    - Central Nervous System - primarily
    - Lower concentration throughout the body
  - CB2
    - Microglia
    - Macrophages
    - Spleen

History to 1900

- ~5000 years ago – Medicinal use of marijuana is described in Chinese and Indian texts
- ~2000 year ago – The psychotropic effects of marijuana are described in Chinese medical texts
- Middle-ages – Hemp and marijuana are widely disseminated for “industrial” and medical use
- 1800’s - In the U.S. Cannabis is a more economically important crop than tobacco
- 1850 – Marijuana is widely use and is added to U.S. Pharmacopeia
History since 1900 (U.S.)

- 1906 - Pure Food and Drug Act
- 1914 - Harrison Act - Marijuana is criminalized
- 1930s - AMA opposes marijuana use
- 1936 - Refer Madness – movie “trailer”
- 1937 - Marijuana Tax Act - $100/ounce, $1/ounce if for medical use
- 1970 - Controlled Substance Act – Schedule 1
- 1980s-'90s - Cannabinoid receptors, endogenous
- 1996 - 1st Medical Marijuana bill - California

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Attitudes towards Marijuana

- On-line survey of 16,280 adults
- United States
- 2017
- 55% (9003) responded

Attitudes towards Marijuana

- Benefits
  - 81% believe marijuana has at least 1 benefit
  - 66% Pain Management
  - 48% Epilepsy, Multiple Sclerosis
  - 47% Anxiety, Stress, Depression
  - 29% agree that smoking marijuana prevents health problems
Attitudes towards Marijuana

- Risks
  - 91% believe marijuana has at least 1 risk
    - 52% Legal
    - 50% Addiction
    - 42% Impaired Memory


Attitudes towards Marijuana

- Beliefs that marijuana is benign
  - 18% believe second-hand marijuana smoke is safe for adults
  - 7.6% believe second-hand marijuana smoke is safe for children
  - 7.3% believe marijuana is safe during pregnancy
  - 22% believe marijuana is not addictive


Attitudes towards Marijuana

- Beliefs that marijuana is benign
  - Survey of >20,000 children in grades 6 through 12
  - 9% of middle-school and high-school students in the U.S. report having used electronic cigarettes to vaporize cannabis.
  - 25% reported ever using e-cigarettes
    - 31% of these reported ever vaping cannabis
      - 23% of middle-school e-cigarette users
      - 33% of high-school e-cigarette users


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Effects of Medical Marijuana

• Increased
  – Euphoria
  – Appetite
  – Sedation
  – Psychosis (unmasking?)

• Decreased
  – Pain
  – Nausea
  – Spasticity
  – Memory/Cognition
  – Locomotor function


The Health Effects of Cannabis and Cannabinoids 2017
National Academies of Sciences, Engineering, and Medicine (NASEM)

• Conclusive or substantial evidence for improving
  – Chronic pain in adults
  – Nausea
    • Chemotherapy-induced Nausea/Vomiting
  – Patient-reported spasticity in Multiple Sclerosis

• Moderate evidence for improving
  – Short term sleep in sleep apnea, fibromyalgia, multiple sclerosis, and chronic pain


• Limited evidence for improving
  – Anorexia and weight loss in HIV/AIDS
  – Not as effective as megestrol acetate (Megace)
  – Objective spasticity in Multiple Sclerosis
  – Social Anxiety (public speaking test)
  – Post-Traumatic Stress
  – Tourette syndrome
  – Traumatic Brain Injury or Hemorrhage

• Limited evidence for NOT improving
  – Dementia
  – Glaucoma
  – Depression associated with chronic pain or MS

The Health Effects of Cannabis and Cannabinoids 2017
National Academies of Sciences, Engineering, and Medicine (NASEM)

• Insufficient evidence for
  – Cancer
  – Cancer-associated anorexia-cachexia
  – Irritable Bowel
  – Epilepsy
  – Spasticity not due to Multiple Sclerosis (MS)
  – Amyotrophic Lateral Sclerosis (ALS)
  – Huntington Disease – chorea, neuropsychiatric
  – Parkinson Disease or levodopa dyskinesia
  – Dystonia
  – Drug addiction
  – Schizophreniform psychosis

• Infectious
  – HIV/AIDS, Hepatitis C
    • Possibly for associated anorexia/cachexia, but NOT for the underlying disease.

• Inflammatory Bowel Disease
  – Crohn Disease, Ulcerative Colitis
    • Possibly for associated pain or anxiety, but NOT for the underlying disease.

• Seizure/Epilepsy
  • Not supported by current evidence.

• Tourette Syndrome
  • Supported by limited evidence.

• Neurodegenerative
  – Alzheimer Dementia
    • Evidence against improving or slowing progression.
  – Amyotrophic Lateral Sclerosis (ALS)
    • Not supported by current evidence.
  – Multiple Sclerosis (MS)
    • Reduced spasticity supported by current evidence.

• Parkinson Disease
  • Not supported by current evidence.

• Central Nervous System Trauma
  – Traumatic Brain Injury/Encephalopathy, Spinal Cord Injury
    • Supported by limited evidence.

• Psychiatric
  – Post-Traumatic Stress Disorder (PTSD)
    • Supported by limited evidence.

• Chronic Pain
  – Fibromyalgia, Sickle Cell Anemia
    • Supported for treatment of chronic pain.

• Cancer
  • Not supported by current evidence.

• Chemotherapy-associated nausea/vomiting
  • Supported by current evidence.

• Glaucoma
  • Evidence against benefit.
Conditions for which cannabinoids work, and don’t

- Yes, supported by current evidence
  - Pain
  - Nausea
  - Anxiety
  - Insomnia
  - Spasticity in Multiple Sclerosis
  - Seizures in Lennox-Gastaut/Dravet

- No, not supported by current evidence
  - Dementia
  - Depression
  - Glaucoma
  - Cancer

FDA-Approved Cannabinoids (Schedule II)

- Dronabinol (Marinol, Syndros)
  - anorexia associated with weight loss in patients with Acquired Immune Deficiency Syndrome (AIDS)
  - nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments

- Nabilone (Cesamet)
  - nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments

- Cannabidiol (Epidiolex)
  - seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older

Nabiximols

- Trade name - Sativex
- A 1:1 THC:CBC extract of Cannabis
- Oral spray
- approved as a botanical drug in the United Kingdom in 2010 to alleviate neuropathic pain, spasticity, overactive bladder, and other symptoms of multiple sclerosis

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### Adverse Effects of Medical Marijuana

- **Central Nervous System**
  - Sedation, dizziness, numbness, cognitive impairment, slowed reaction time, sensory disturbances
  - Dysphoria, anxiety, nightmares, psychosis
- **Cardiovascular**
  - Hypotension, hypertension, tachycardia, palpitations
- **Gastrointestinal**
  - Dry mouth, nausea, hyperemesis
- **Long term**
  - Immunosuppression, decreased fertility


### Acute Toxicity / Overdose

- **Psychosis**
- **CNS Depression**
  - Sedation
  - Confusion
  - Psychomotor retardation
- **Cardiovascular**
  - Hypotension
  - Hypertension
  - Tachycardia

*Consult Pharm. 2017 Jun 1;32(6):341-351*

### Neurodevelopment

- **Human studies - associations**
  - Slower cognitive processing
  - Poorer learning/memory
  - Psychiatric disorders
- **Animal studies – rats**
  - Poorer learning/memory
  - Abnormal social interactions
  - Addictive behavior

*Future Neurol. 2011 Jul 1; 6(4): 459–480*

### Acute Toxicity / Overdose

- **More common with edible formulations**
  - Educate, encourage to minimize risk to children

*Consult Pharm. 2017 Jun 1;32(6):341-351*
Driving Impairment

- Independent risk factor for motor vehicle accidents
- Associated with increased fatality in motor vehicle accidents
- Avoid driving
  - Inhalation – 4 hours
  - Oral ingestion – 6 hours
  - Euphoria experienced – 8 hours

Cannabis Use Disorder

- 10 – 30 % of users develop
- DSM-5 Diagnostic Criteria - at least two in the prior 12 months
  - Increasing use over time
  - Inability to control consumption
  - Use with negative impacts on social, professional or educational life
  - Craving
  - Withdrawal syndrome, e.g. hyperemesis

Cannabis Withdrawal Syndrome

- Symptoms
  - Anxiety
  - Depression
  - Sleep disturbance
  - Irritability
  - Anorexia and weight loss

Proposed Contraindications and Cautions

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<td>Age under 25</td>
<td>Concurrent active mood or anxiety disorder</td>
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<tr>
<td>Personal or family history of psychosis and/or schizophrenia</td>
<td>Use of tobacco</td>
</tr>
<tr>
<td>Current or past history of cannabis use disorder</td>
<td>Heavy user of alcohol, opioids, and/or benzodiazepines</td>
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<tr>
<td>Active substance use disorder</td>
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<tr>
<td>Significant cardiovascular or respiratory disease</td>
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<td>Pregnancy or breast feeding</td>
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