Medical Marijuana: Is That Cannabis Dragon Really Magical?

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Loveland, Ohio

Opening Prayer

Taking a Poll

- How many are from states that have passed laws to legalize MMJ?
- How many are from states that have not passed laws to legalize MMJ?

Industry News

- By 2016, 2.4 million people were registered as medical cannabis patients
- This industry will grow to $9 billion by 2017

Objectives

- Discuss the history of medical marijuana use and the legal landscape in Ohio
- Review cannabinoid receptor pharmacology
- Identify & manage evidence-based indications, side effects, interactions associated with the use of medical marijuana
- Discuss the role of the physician, nurse, pharmacist in patient education and monitoring of medical marijuana use

Genesis 1:29

Then God said, "I give you every seed-bearing plant on the face of the whole earth and every tree that has fruit with seed in it. They will be yours for food." - NIV

Found in the Garden of Eden
June 2017

Cannabis History

- Earliest documented use 2700 BC in China (e.g., gout, malaria, constipation, menstrual disorders, absentmindedness).
- Western medicine adopted use of cannabis as an analgesic in 19th Century (William O’Shaughnessy MD in 1839). 1854 listed in U.S. Pharmacopoeia.

Prior to WWI, pharmaceutical supplies of cannabis imported from India per USP requirements. From 1915-1927, some states banned cannabis. 1930’s Parke Davis, Eli Lilly manufacture, and Lloyd Brothers Cincinnati pharmacists dispense cannabis extracts for medicine.

- 1937 Marijuana Tax Act created criminal fine for recreational use/possession but affirmed right of physicians and pharmacists to prescribe and dispense medical marijuana. AMA opposed. Led to decline in MJ scripts. Fed’s 1st attempt to regulate MJ. By 1942, MJ removed from the U.S. Pharmacopoeia.

Cannabis Regulation

- THC discovered in 1964
- U.S. Congress passed Controlled Substances Act in 1970 in response to soaring recreational drug use – Schedule I - federally, not considered legitimate for medical use along with Heroin, LSD, Ecstasy, Methaqualone, Peyote category
- Amount of marijuana that a person may possess for medical use varies widely from state to state

Medical Marijuana

- California was the first to legalize in 1996 for AIDS wasting and cancer pain under Compassionate Use Act (Prop 215)
- Ohio June 8, 2016 HB523 signed into law by Governor John Kasich – includes 20 indications & employer protection (25th state). In Ohio, Schedule II (regulated as ‘high potential for abuse’ like heroin).
- Arkansas, Florida, North Dakota in November 2016 legalized medical use; Montana voted on whether to ease restrictions on existing medical marijuana law. Still not legal in Kentucky.
- 22 states have approved MJ use for seizure control including Ohio

Federal Legislation

- July 28, 2014 HR 5226 Bill (Charlotte’s Web Medical Hemp Act) introduced by Scott Perry (R-PA), Paul Broun (R-GA), Steve Cohen (D-TN), Dana Rohrabacher (R-CA) - to amend the definition of marijuana and exclude medical marijuana from controlled substance list. Bill died in committee.
- March 2015 US Senate passed Compassionate Access, Research Expansion, and Respect States (CARERS) Act of 2015 (S 683) to transfer medical marijuana from Schedule I to Schedule II of CSA. Ensures states with legal MMJ will have their patients’ access to drug respected by federal officials.
- December 14, 2016 DEA issued final ruling that classified all cannabis extracts as Schedule 1 drugs including hemp.


- States with medical cannabis laws had a 24.8% lower mean annual opioid overdose mortality rate compared with states without medical cannabis laws. Will this be true in Ohio?

Graph: Chart of graphic showing opioid overdose mortality rates.
Ohio Medical Marijuana Control Program

September 8, 2016 – HB 523 bill signed on June 8, 2016 became effective

September 8, 2017 – rules and regulations must be completed

September, 2018 – Ohio Department of Commerce and State of Ohio Board of Pharmacy are required by law to ensure Ohio’s Medical Marijuana Control Program is fully operational no later than September, 2018 (cultivating, processing, testing, dispensing, physicians, patient and caregivers)

MMJ Ohio Advisory Committee
www.medicalmarijuana.ohio.gov

Ohio Sub. H.B. 523 Summary – Medical Marijuana Control Program

• Requires Ohio Department of Commerce and State Board of Pharmacy to administer MMCP
• Establishes MMJ Advisory Committee who will make recommendations to Department of Commerce, Board of Pharmacy, State Medical Board
• Permits patients, on recommendation of physicians, to use MMJ to treat qualifying medical conditions
• Patients must apply to Board of Pharmacy for registration
• Authorizes Department of Commerce to issue licenses to MMJ cultivators, processors, and testing labs
• Authorizes Medical Board to issue certificates to physicians seeking to recommend treatment with MMJ
• Prohibits cultivation of MMJ for personal, family, or household use
• 90-day supply – max 7.5 oz (three THC % tiers). THC plant < 35%, THC extract < 70%

Ohio HB 523

• Provides that the use or possession of medical marijuana by a registered patient in accordance with the bill’s provisions cannot be used as a reason for disqualifying the patient from medical care or from including the patient on a transplant waiting list.
• Requires that the Board of Pharmacy establish a program to assist patients who are veterans or indigent in obtaining medical marijuana.
• Specifies that it does not permit the use, possession, or administration of medical marijuana on federal land located in Ohio.

Ohio Law 2016 Allows:

<table>
<thead>
<tr>
<th>AIDS/HIV</th>
<th>Multiple Sclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS</td>
<td>Pain (chronic &amp; severe or intractable)</td>
</tr>
<tr>
<td>Alzheimer's</td>
<td>Parkinson’s Disease</td>
</tr>
<tr>
<td>Cancer</td>
<td>PTSD (weak evidence)</td>
</tr>
<tr>
<td>Crohn’s Disease</td>
<td>Sickle Cell Anemia</td>
</tr>
<tr>
<td>Chronic Traumatic Encephalopathy (CTE)</td>
<td>Spinal Cord Disease/Injury</td>
</tr>
<tr>
<td>Epilepsy or another Seizure Disorder</td>
<td>Tourette’s Syndrome</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>Traumatic Brain Injury (TBI)</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>Idiopathic Cysts</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Any other disease or condition added by state medical board under section 4731.302 of Revised Code</td>
</tr>
<tr>
<td>Inflammatory Bowel Disease</td>
<td></td>
</tr>
</tbody>
</table>

17 States Allow Marijuana CBD Oil

<table>
<thead>
<tr>
<th>Alabama</th>
<th>South Carolina</th>
</tr>
</thead>
<tbody>
<tr>
<td>Florida</td>
<td>Tennessee</td>
</tr>
<tr>
<td>Georgia</td>
<td>Texas</td>
</tr>
<tr>
<td>Iowa</td>
<td>Utah</td>
</tr>
<tr>
<td>Kentucky</td>
<td>Virginia</td>
</tr>
<tr>
<td>Mississippi</td>
<td>Wisconsin</td>
</tr>
<tr>
<td>North Carolina</td>
<td>Wyoming</td>
</tr>
<tr>
<td>Oklahoma</td>
<td>Idaho (approved, vetoed)</td>
</tr>
<tr>
<td>Ohio</td>
<td>New York (investigating in clinical trials now)</td>
</tr>
</tbody>
</table>
Cannabis Patch by Cannabis Science in California

November, 2016

Indication – Fibromyalgia, diabetic nerve pain

Anti-inflammatory/analgesic

Active – CBD and B-carophyllene (sesquiterpene)

B-carophyllene is also found in rosemary, black pepper, oregano, cloves!

May be a selective agonist at CB2 receptors

Ohio HB 523 – Permissible Forms

- Oils
- Tinctures
- Plant Material
- Edibles
- Patches

- “Any other form approved by the Board of Pharmacy”
- Suppository and spray under debate…….
Table 2-2: Cannabinoid-Based Medications

<table>
<thead>
<tr>
<th>Substance</th>
<th>Route of Administration</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabidiol (CBD)</td>
<td>Oral capsule</td>
<td>Cannabinoid extracted from Cannabis multiple active cannabinoids</td>
</tr>
<tr>
<td>Epidiolex® (FDA Fast Track)</td>
<td>Oral capsule</td>
<td>Concentrated CBD from Cannabis Oil</td>
</tr>
<tr>
<td>Tigabinol (Oralmist®)</td>
<td>Transnasal spray</td>
<td>THC and CBD from Cannabis plant inactive cannabinoids</td>
</tr>
<tr>
<td>THC/CBD</td>
<td>Oral capsule</td>
<td>Combination of cannabinoids</td>
</tr>
<tr>
<td>Ajulemic acid (Alj)</td>
<td>Synthetic non-psychoactive cannabinoid</td>
<td></td>
</tr>
<tr>
<td>Dronabinol (Marinol®)</td>
<td>Synthetic THC analogue</td>
<td></td>
</tr>
<tr>
<td>Nabilone (Cesamet®)</td>
<td>Synthetic cannabinoid-THC analogue</td>
<td></td>
</tr>
</tbody>
</table>

Argument Against Dronabinol (Marinol) Capsules
- Approved in 1986 (chemotherapy-induced N&V), expanded indication in 1992 (treatment of anorexia associated with weight loss in AIDS wasting)
- C-III, synthetic THC, very sedating, psychoactive
- Not an appropriate substitute for natural cannabis
- No studies comparing cannabis plant cannabinoids to first-line prescription drugs for CINV

Cannabis ADME Process
- Absorption: varies via different routes: smoking (not Ohio approved), vaping, oral ingestion, IV, ophthalmic, transdermal, SL, rectal
- Distribution: 90-95% protein bound (in lipoproteins of brain, heart, lung, liver, testes); 10% in RBC’s
- Metabolism: hepatic (allylic oxidation, epoxidation, decarboxylation, conjugation). THC oxidized by CYP2C9, CYP2C19, CYP3A4 to produce 11-hydroxy-THC and inactive 11-nor-9-carboxy THC (THC-COOH). Other metabolic paths via CYP2C8 and CYP3A2. Oral-first pass hepatic metabolism to 11-OH-THC.
- Elimination: 20-45% of THC is eliminated in urine and 65% - 80% in feces

THC Onset Peak Duration

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Oral</th>
<th>Inhaled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>60 minutes-1 hour</td>
<td>3-6 hours</td>
</tr>
<tr>
<td>Time to peak blood [1]</td>
<td>2 hours</td>
<td>2-30 minutes</td>
</tr>
<tr>
<td>Maximal duration</td>
<td>2-6 hours</td>
<td>Dose dependent: 20-60 minutes</td>
</tr>
<tr>
<td>Variables</td>
<td>Dose/concentration, pattern of use, bioavailability</td>
<td>Dose, pattern of use</td>
</tr>
</tbody>
</table>


THC Bioavailability

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Bioavailability</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>10-20%</td>
<td>From package insert to treatment, while 90-95% of the oral dose is absorbed, only 10-20% of the dose reaches systemic circulation due to high first pass metabolism and high lipid solubility.</td>
</tr>
<tr>
<td>Oral</td>
<td>6-8%</td>
<td>Chocolate cookie prepared with 20 mg THC. Reported range is 3-8%.</td>
</tr>
<tr>
<td>Oral via smoking</td>
<td>10-40%</td>
<td>No pharmacokinetic or clinical studies in human.</td>
</tr>
<tr>
<td>Oral via vaporization</td>
<td>10-40%</td>
<td>Unknown in clinical settings.</td>
</tr>
</tbody>
</table>

Ohio State Medical Marijuana Program 2017 Reference
Dose Calculation - Colorado

- A typical marijuana joint contains 0.5 grams of marijuana
- THC content ranges from 12% - 23% in the joint
- A typical joint contains 60 mg -115 mg THC
- The standard serving size for a marijuana edible is 10 mg

Δ-9-THC Detection

- **Serum** – Active THC (positive at 20 ng/mL)
- **Urine** – Inactive THC-COOH-glucuronide (positive at 50 ng/mL). Answers, “has this person used cannabis over the last days or weeks?”

Levels of THC or metabolites correlate with efficacy or toxicity

Detected in the Urine

<table>
<thead>
<tr>
<th>THC-COOH-Glucuronide</th>
<th>Single Use</th>
<th>Moderate Use [4x/Week]</th>
<th>Daily Use</th>
<th>Long-Term Heavy Smoker</th>
<th>THC - T 1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 Days</td>
<td>5 – 7 Days</td>
<td>10 – 15 Days</td>
<td>&gt; 30 Days</td>
<td>2-7 Days</td>
</tr>
</tbody>
</table>

Endocannabinoid System

- Endogenous cannabinoids, cannabinoid receptors, and enzymes that synthesize and degrade endocannabinoid ligands (anandamide & 2-AG)
- Effects of cannabinoids are mediated by two G protein-coupled receptors, CB1 and CB2 (discovered 1980’s)
- Retrograde signaling, partial agonism, inverse agonism, and functional selectivity determine the cellular response to specific cannabinoid receptor ligands (endocannabinoids, plant cannabinoids, synthetic cannabinoids)

Cannabinoid Receptors – Retrograde Signaling

- Anandamide and 2-AG (arachidonoylglycerol) are synthesized and released from post synaptic neuron terminals, travel backwards across the synaptic cleft to presynaptic neurons, and bind CB1 receptors on pre synaptic terminals = retrograde signaling
- This inhibits release from excitatory and inhibitory synapses of serotonin, glutamate, acetylcholine, GABA, norepi, dopamine, and cholecystokinin

Partial Agonism

<table>
<thead>
<tr>
<th></th>
<th>Efficacy toward CB1</th>
<th>Efficacy toward CB2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anandamide</td>
<td>Full agonist</td>
<td>0</td>
</tr>
<tr>
<td>2-Arachidonoylglycerol</td>
<td>Full agonist</td>
<td>0</td>
</tr>
<tr>
<td>Δ-9-Tetrahydrocannabinol</td>
<td>Partial agonist</td>
<td>Partial agonist</td>
</tr>
<tr>
<td>CBD</td>
<td>Very weak agonist/antagonist (blocks reuptake of anandamide)</td>
<td>Very weak agonist/antagonist</td>
</tr>
<tr>
<td>JWH-018</td>
<td>Full agonist</td>
<td>Full agonist</td>
</tr>
</tbody>
</table>
Inverse Agonism

- Receptors exist in equilibrium between active and inactive states.
- Some receptors are in an active state, even in the absence of an agonist, when there is a low level of signaling mediated by the receptor (basal signaling).
- Agonists will shift more of the receptors to the active state, increasing signaling.
- G proteins preferentially bind to inactive receptors.

Functional Selectivity

- Cannabinoid receptors are located throughout the body but have differing effects based on location.
- Cannabinoids bind reversibly and stereoselectively to the cannabinoid receptors.

Herbal MJ Alternatives

- Synthetic cannabinoids (JWH-018, JWH-073 in K2 or Spice incense) which cannot be detected in urine drug screen for THC and THCA metabolites.
- Products sold in gas stations, convenience stores, internet.
- Urine/blood screens specific for JWH-018 metabolites.

Compare Chemical Structures for JWH-018 and THC - Herbal Marijuana Alternatives

- K2 or Spice belong to a group of blends that contain a mixture of inert plant matter plus chemical grade synthetic cannabinoids sprayed on it.
- Symptoms similar to marijuana PLUS sympathomimetic SXS: agitation, anxiety, HR, tremors, seizures.
- Agonists at CB1 and CB2 receptors.
- May be NDMA glutamatergic antagonists.

Cannabinoid CB1 Receptors

- Mostly in brain (cerebellum, cerebral cortex, basal ganglia), spine, GI tract, liver, pancreas, skeletal muscle combined with GABAergic & dopaminergic & serotonergic receptors; to affect appetite, pain sensation, memory, mood.
- In the hippocampus and amygdala, areas associated with partial seizures.
- In liver, activation of CB1 receptor increases de novo lipogenesis (expression of cannabinoid receptors in normal liver tissue is low).
- Tolerance and down regulation of CB1 receptors occur with repeated marijuana exposure.

<table>
<thead>
<tr>
<th>Synthetic Cannabinoids Family</th>
<th>Principal Compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzoylindole</td>
<td>AM-694, AM-2233, RCS-4, RCS-8</td>
</tr>
<tr>
<td>Phenylacetylindole</td>
<td>JWH-167, JWH-250, JWH-316</td>
</tr>
<tr>
<td>Indazolecarboxamide</td>
<td>AM-PINACA, AM-DPNAC, 5F-APINACA, 5F-DPNACA, 5F-APINACA, 5F-DPNACA, 5F-APINACA, 5F-DPNACA</td>
</tr>
<tr>
<td>Cyanoindole/1</td>
<td>DP-56, 5F-CP-47, 56, 57, 58, 5F-CP-47</td>
</tr>
<tr>
<td>Naphthylpropylindole</td>
<td>JWH-176</td>
</tr>
<tr>
<td>Naphthylpropylacetone</td>
<td>JWH-180, JWH-087, JWH-078</td>
</tr>
<tr>
<td>Naphthylpropylamine</td>
<td>JWH-176, JWH-201</td>
</tr>
<tr>
<td>Methylketone molecule</td>
<td>5F-APINACA, 5F-DPNACA</td>
</tr>
<tr>
<td>Alkaloid molecule</td>
<td>JWH-018</td>
</tr>
<tr>
<td>Tetrabenzoylethropanolactone</td>
<td>IR-55, SR-111</td>
</tr>
<tr>
<td>Analogous molecular model</td>
<td>IR-55, SR-111</td>
</tr>
<tr>
<td>Semisynthetic model</td>
<td>IR-55, SR-111</td>
</tr>
<tr>
<td>Semisynthetic model</td>
<td>IR-55, SR-111</td>
</tr>
<tr>
<td>Synthetic molecule</td>
<td>IR-55, SR-111</td>
</tr>
<tr>
<td>Synthetic molecule</td>
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</tr>
<tr>
<td>Synthetic molecule</td>
<td>IR-55, SR-111</td>
</tr>
</tbody>
</table>
CB2 Receptors

- Activation causes inhibition of proinflammatory cytokine production, cytokine, and chemokine release, and blockade of neutrophil and macrophage migration (anti-inflammatory)
- In peripheral immune system T-cells, B cells, spleen, macrophages (immunosuppression), kidneys, lungs
- In peripheral nerve terminals with a role in anti-nociception

Main Phytocannabinoids

- Psychoactive: THC (Δ9-THC, Δ8-THC, Δ11-hydroxy-THC) [active metabolite]. Binds to CB1 & CB2 receptors as a partial agonist.
- Not Psychoactive: THCV (tetrahydrocannabivarin) – analogue of THC
- Synthesized in glandular trichomes of leaves and flowers; first appear in their acidic forms (THCA, CBDA), then decarboxylate to neutral counterparts (THC, CBD) due to oxidation, heat, light

Cannabidiol Pharmacology

- Low affinity for CB1 and CB2 receptors (compared to THC-partial agonist for both)
- Agonist at serotonin (5-HT1A) receptors (pain, migraines, anxiolytic & adapts to stress)
- Agonist at Transient Receptor Potential Vanilloid Type 1 (TRPV1) receptor (anti-nociception)
- Enhances adenosine receptor signaling by inhibiting adenosine inactivation (pain, inflammation, BP modification)
- Anti-inflammatory via CB2 receptors (different from COX-2 system)
- Anti-fibrotic – pulmonary (Zurier. FASEB J 2016)
- Neuroprotective via CB1 receptors (epilepsy, multiple sclerosis)

CBD/SHT1A Receptor Pharmacology

- MOA of CBD is not fully understood
- Anxiolytic and antipsychotic MOA mediated by endocannabinoid system or by activation of SHT1A receptors
- Low affinity for cannabinoid receptors, but blocks the reuptake of anandamide
- SHT1A receptors are located pre-synaptically in raphé nuclei of brain stem and post-synaptically in hippocampus and hypothalamus – areas related to stress and anxiety
- Unclear whether anxiolytic effects from SHT1A agonists are due to activation of pre- or the post-synaptic receptors
- Depending on where post-synaptic receptors are, activation -> anxiolytic or anxiogenic

CANNABIS

Side effects

Common Adverse Effects

- Anxiety
- Dry mouth
- Sedation
- Dizziness
- Reddened eyes
- Altered sense of time
- Inverse effect on the sense of smell
- Increased heart rate
- Dry eyes
- Inverse effect on vision
- Increased appetite
- Impaired coordination
- Impaired memory
- Increased thirst
- Increased pupil size
- Increased sensitivity to light
- Increased appetite

DOH

2017 CPFI Annual Meeting
Aditi Kalla MD, Cardiology Fellow at Einstein Medical Center in Philly

Study involved 1000 hospitals

Researchers found that MJ use was associated with a significantly increased risk for stroke (26% increase), heart failure (10% increase), CAD, and sudden cardiac death

Cardiac muscle cells have cannabis receptors relevant to contractility
Cannabinoid Hyperemesis Syndrome (CHS)

- Paradoxical, diagnosis of exclusion, due to chronic long-term use
- Does it accumulate over time due to large Vd?
- THC may activate CB1 receptors in entropic nervous system and reduce gastric motility, increasing risk of N&V
- THC may activate CB1 receptors in hypothalamus to induce emesis by impairing thermoregulation, leading to the potential relief through hot bathing
- Cyclic; relieved by anti-emetics
- Relieved by compulsive bathing in hot water and abstinence
- In Colorado, rates of CHS have doubled since 2009 when cannabis was legalized there
CANNABIS LD-50

- Lethal dose at which 50% of population is killed in a given time period
- At present it is estimated that marijuana's LD-50 is 1:20,000 – 1:40,000. Active dose is far below lethal dose (Gable 2006)
- In order to induce death a marijuana smoker would have to consume 20,000 – 40,000 times as much marijuana as is continued in one marijuana cigarette
- NIDA-supplied marijuana cigarettes weight 0.9 grams
- A smoker would have to consume nearly 1,500 pounds of marijuana within about 15 minutes to induce a lethal response

Marijuana Use Disorder

Physiologic withdrawal, psychological dependence

Chronic low doses not associated with significant physical withdrawal on abrupt discontinuation

Chronic users exhibit compulsive drug-seeking behaviors characteristic of dependence

Gateway drug?

Diagnostic Criteria for Substance Use Disorder

1. Use of substance in larger amounts or for longer durations than intended
2. Personal desire to cut down or stop use of substance but unable to do so
3. Excessive time spent in the acquisition, use, or recovery of substance
4. Craving substance in question
5. Failure to honor personal commitments because of use
6. Ongoing use of substance despite problems in relationships
7. Discontinuing important activities because of use of substance
8. Continued use of substance despite known harm or danger
9. Continued use of substance despite worsening physical or psychological problems
10. Increased tolerance to substance
11. Experiencing withdrawal symptoms without ongoing use of substance

Gateway drug?

Common Terminology Used in Assessment of Substance Use

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addiction</td>
<td>A physiological disease characterized by impairment, cravings, withdrawal symptoms, and negative social, professional and spiritual consequences as well as inability to abstain from continued use of the substance</td>
<td>Addiction has been replaced by substance use disorder in DSM-V</td>
</tr>
<tr>
<td>Aberrant Drug-Taking Behavior</td>
<td>Departure from strict adherence to prescription instructions or indication for use</td>
<td></td>
</tr>
<tr>
<td>Misuse</td>
<td>Departure from adherence to prescribed instructions while maintaining therapeutic intent (taking more than prescribed for what the drug was prescribed for)</td>
<td></td>
</tr>
<tr>
<td>Abuse</td>
<td>Departure from adherence to prescribed instructions and use for nontherapeutic intent (taking more than prescribed for euphoria vs. pain control)</td>
<td>Previously used interchangeably with substance dependence in a diagnostic term and is being phased out</td>
</tr>
<tr>
<td>Tolerance</td>
<td>Decreased responsiveness to substance requiring higher doses or amounts to produce the same effect achieved during initiation</td>
<td></td>
</tr>
<tr>
<td>Withdrawal</td>
<td>Cluster of SXs experienced upon cessation or inability to reduce a substance characterized by stress, anxiety, depression, etc.</td>
<td></td>
</tr>
</tbody>
</table>

FDA FOI FAERS Marijuana Analysis 2011-2016

- Search terms: marijuana, Cannabis sativa seed, seed extract, seed oil, Cannabis indica flowering top and whole plant
- Limitations: doses used were largely unknown; FAERS contains observational data from real world use of marijuana and related products and does not include data from well designed, controlled RCTs
- Results: Potential for serious cardiac, respiratory, CNS effects from marijuana abuse, misuse, overdose have been reported
Cincinnati Poison Control Center THC TESS Report Analysis 2010-2016

- Search terms: THC, marijuana, Cannabis sativa, THC homologs (Spice, K2, JWH-018, JWH-073 AB-Fubinaca)
- Scope: Southwest and northeast Ohio regions
- Limitations: Doses were largely unknown; large % involved intentional overdose or abuse; not possible to determine if other drugs were being concurrently abused/misused
- Results: 2330 reports involving children, teens, adults; 1242 reports involving K2, Spice, THC homologs; 7 deaths; Main body systems involved – neurological, cardiovascular (drowsiness, irritability, confusion, hallucinations, tachycardia, hypertension)

CANNABIS

Summary
- Cannabis is generally well tolerated, and serious adverse effects, including increased risk of cardicardiac events, are rare.
- Adverse changes in cognitive function, especially executive function, may occur, especially with high dose or frequent use.
- Cannabis should be avoided by adolescents, pregnant women, and nursing mothers.
- Cannabis should be avoided in those at risk of psychosis.
- Many studies show driving impairment, but an exact lower safe limit than alcohol
- Drug interactions are a concern.
- Cannabis enhances CYP1A2 effects when combined with vitamin B6 and acetaminophen (Yamaori et al 2012).
- THC inhibits CYP3A4 and CYP2D6, and may increase warfarin metabolized by these isoenzymes (Cullen JH Pharmacol Therapeut 2013).

Drug Interactions

Cytochrome P450 Enzymes
- THC is a CYP2A6 inducer.
  - Therapeutically, THC decreases serum concentrations of clonidine, aliskiren, irinotecan, paxil, and ticlopidine.
  - Anaban (terbinafine), allopurinol, and dexamethasone may increase THC levels.
- CBD is a potent inhibitor of CYP1A2 and CYP2D6.
  - As CYP1A2 metabolizes about a quarter of all drugs, CBD may increase serum concentrations of medications which are metabolized by CYP3A4, CYP2C9, CYP2C19, CYP2D6, or CYP2E1.
  - Rifampin, dexamethasone, and amitriptyline (which inhibit CYP3A4, CYP2C9, and CYP2C19) may increase THC levels.

Case

62 yo male stage IV B-cell lymphoma
Overnight admission to oncology service
PMHx: COPD, atrial fibrillation, viral hepatitis C, chronic low back pain, B-cell lymphoma
CC: severe back pain, lethargy
Meds PTA:
- Amiodarone 200 mg daily
- Oxydron 400 mg TID
- Entecavir (Baraclude) 0.5 mg daily
- Fentanyl Patch 50 mcg TD q72h
- Metoprolol succinate ER 50 mg daily
- Olanzapine ODT (Zyprexa) 5 mg BID

Interactions/Medication Issues?
- Oxycodone 5 mg q6h PRN severe pain
- Naproxen 500 mg BID PRN arthritis pain
- Medical Marijuana (THC:CBD 20:1)
  - 10 mg vaped PRN breakthrough cancer pain

Plan?

5976600702014

- 28 randomized clinical trials reviewed
- Per authors: use of MJ for chronic pain, neuropathic pain, and spasticity due to multiple sclerosis is supported by high quality research.
- Six trials that included 325 patients examined chronic pain, 6 trials that included 396 patients investigated neuropathic pain, and 12 trials that included 1600 patients focused on MS.
- Several of these trials had positive results, indicating that MJ or oral cannabinoids may be efficacious for these indications.

Intractable Cancer Pain

- RCT, 5 week trial in 360 patients found that adjunctive use of low (1-4 sprays/day) and medium (60-10 sprays/day) doses of nabiximols (Sativex, THC & CBD extract) was significantly more effective than placebo in relieving intractable cancer pain and comparable to placebo in adverse effects.
- There are no well designed studies on the effectiveness of cannabis for this indication.
- The Medical Letter August 1, 2016

Multiple Sclerosis

- Several studies found that cannabinoids are effective in treating some MS symptoms.
- American Academy of Neurology recommends use of an oral cannabis extract containing a mix of THC and CBD (Cannador 2:1, Germany) or (THC) dronabinol (Marinol) for treatment of spasticity and pain and nabiximols (Sativex) (THC & CBD extract) for treatment of pain, spasticity, and urinary dysfunction.
- The Medical Letter August 1, 2016

Epilepsy

- Open label, 12 week study in patients 1-30 years with severe childhood-onset treatment-resistant epilepsy, addition of Epidiolex (investigational purified cannabis extract with 99% CBD) reduced median monthly frequency of seizures by 38%.
- Randomized clinical trials of Epidiolex are in progress in US (2-50 mg/kg/day).
- Data not adequate to recommend use of cannabinoids for treatment of patients with more common types of epilepsy.
- The Medical Letter August 1, 2016
Migraine Studies

- Reduced frequency of migraines with medical marijuana use: THC Anti-inflammatory MOA by inhibiting prostaglandin E2 synthesis (20x potency of ASA, 2x potency of HC) (Rhyne. Pharmacotherapy 2016;36(6):595-596)
- CBD interacts with serotonergic system to inhibit serotonin reuptake. Reduced use of opioids for migraines with medical marijuana. (Bradford. Health Aff 2016;33(7):1230-1236)

Summary of Randomized Controlled Trials Examining Marijuana's Effect on Various Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>RCTs</th>
<th>Patients</th>
<th>Findings</th>
<th>Lead Author</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy-induced nausea</td>
<td>3</td>
<td>43</td>
<td>Smoked cannabis has a modest anti-nausea effect greater than placebo but less effective than ondansetron</td>
<td>Chang 1979, Chang 1981, Levitt 1984</td>
<td>1979-1984</td>
</tr>
<tr>
<td>Capsaicin-induced pain</td>
<td>1</td>
<td>15</td>
<td>Half of the patients experienced a 30% reduction in pain ratings</td>
<td>Wallace 2007</td>
<td>2007</td>
</tr>
<tr>
<td>Spasticity from multiple sclerosis</td>
<td>2</td>
<td>43</td>
<td>Reduced scores for pain (50%) and spasticity (30%) were observed using high potency cannabis cigarettes</td>
<td>Greenberg 1994</td>
<td>1994</td>
</tr>
<tr>
<td>Intraocular pressure</td>
<td>1</td>
<td>18</td>
<td>Smoked cannabis (1mg THC) caused a significant reduction in intraocular pressure</td>
<td>Merritt 1990</td>
<td>1990</td>
</tr>
</tbody>
</table>

Ohio

Process of Obtaining Medical Marijuana Recommendation

- Doctors must be certified to recommend medical marijuana by the Medical Board.
- Patients then visit a doctor who is certified and can be “recommending” medical marijuana if the patient has been diagnosed with a qualifying medical condition and there is a bona fide physician-patient relationship that has been established through all of the following:
  - A written or personal physical examination
  - A review of the patient’s medical history by the physician
  - The expectation that providing and receiving care serve an appropriate basis
- An application must be submitted to the Board of Pharmacy on behalf of the patient by the physician to become a registered medical marijuana patient.
- Patients must then be able to obtain medical marijuana from a dispensary that has been licensed and is regulated by the Board of Pharmacy.

Patient Education

- Ohio certified patients register with state to receive a medical marijuana ID card that they bring to a dispensary for products (some states allow home grown)
- Patient will be dispensed MJ in unmarked outer wrap
- Patients should not to share any of their cannabis with others
- Take care with driving under the influence
- May be some paranoia and disorientation in novice users

Patient Counseling Tips

- Go slow (2-5 mg THC to start)! No consistency in dosing
- Patients of all ages should not drive for 6 hours after taking 35 mg THC or less, and longer if they take more
- Cannabinoids are very sensitive to light and heat, so patients should store their cannabis in the refrigerator or freezer
Ohio Dispensary Clinical Directors

Each dispensary will have to hire a clinical director who is either a licensed pharmacist, or one of the following licensed professionals authorized to prescribe drugs: a clinical nurse specialist or certified nurse practitioner, a physician, or physician assistant.

The clinical director will be responsible for implementing a variety of employee trainings and overseeing the dispensary’s operations.

The key dispensary employee is different from the clinical director.

May 1, 2017 update – rescinded this requirement (too expensive!)

Dispensaries & Product Labeling

- Dispensaries requiring pharmacists on staff - CT, MN, NY (Maryland has a PharmD Clinical Director but is not required to have a pharmacist)
- Dispensary certified for a maximum allowable amount set by the state

Dispensed MMJ labels have strict requirements

Pharmacy Practice News May 2017

- ASHP policy opposes procurement, storage, preparation, distribution of medical marijuana by licensed pharmacies or health care facilities for purposes other than research
- Information about medical marijuana for use during patient counseling and a systematic method for obtaining patient medical histories that ensures the confidentiality of patient health data (HIPAA)

2014 - 2015 APhA Policy Committee Report Recommendations

Support
- Resolution of federal and state conflicts, e.g., legal status
- Establish IUP monograph
- Regulatory change to increase research on safety and efficacy
- HCP education
- Pharmacists to collect and document information in patient profile about patient use & provide counseling
- Clinical judgment of pharmacists to decide whether to furnish medical cannabis

Oppose
- Pharmacist participation in furnishing cannabis until scientific data support legitimate medical use and delivery mechanisms and federal, state laws permit pharmacists to furnish them
- Furnishing medical cannabis unless performed by licensed HCPs whose scope of practice includes dispensing of Rx meds and who comply with state/local laws
- Pharmacist involvement in furnishing cannabis for recreational use
Nursing Issues

- Accidental pediatric ingestion of edibles
- Marijuana is highly protein bound so crosses the placenta, found in breast milk. Triaging mothers-to-be?
- Novice users may experience increase in heart rate and decrease in blood pressure after initial consumption. Monitoring?

Physician Roles & Responsibilities

- Medication reconciliation process/Epic documentation (social history vs medication history?)
- Closer clinical monitoring of cardiac and neuro patients
- Monitoring for potential drug/marijuana interactions
- Research protocol, clinical trial, IND application (Ohio physicians exempted from certificate to recommend requirement)
- Annual submission to Ohio Medical Board a report that describes the MD’s observations regarding effectiveness of MMJ in treating his/her patients
- Request & review Ohio OARRS report covering at least 12 months preceding the date of the report
- Patient education

Mind Body Spirit

- Heartache for healthcare professionals as medical marijuana programs are implemented across the country (Mind)
- Patient’s physical heart – monitoring cannabis CV side effects & interactions (Body)
- Compassionate heart (Spirit)

Associations/Resources

- American Herbal Products Association Cannabis Committee
- Foundation of Cannabis United Standards Creations Committee
- National Association of Specialty Pharmacy Task Force on Medical Marijuana 2014 – established National Association of Cannabis Based Medicine (NACBM) to help pharmacists obtain required coaching to make the most of cannabis as a therapy in the retail channel
- Cannabis Training Institute – online certification resource or cannabis businesses, entrepreneurs, clinicians, policymakers, and certification & CEUs for pharmacists that will be recognized by ACPE
- American Association of Colleges of Pharmacy Medical Cannabis Toolkit (goo.gl/2zyyF5x)

Summary of Position Statements by Medical Organizations on Medical Marijuana (Cannabis)

<table>
<thead>
<tr>
<th>Organization</th>
<th>Approval of Smoked?</th>
<th>Support of More Research?</th>
<th>Comments</th>
<th>Lead Authors &amp; Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institute of Medicine</td>
<td>Yes, conditionally</td>
<td>Yes</td>
<td>Calls for more safety data on inhaled cannabis, rigorous development of safe and reliable delivery systems</td>
<td>J. Joy 1999</td>
</tr>
<tr>
<td>American College of Physicians</td>
<td>No</td>
<td>Yes</td>
<td>Endorses use of non-smoked THC with physician’s approval. Calls for review to reclassify CSA Class I status. Recommends clinical exemp are for prescribing physicians.</td>
<td>ACP 2008</td>
</tr>
<tr>
<td>American Medical Association</td>
<td>No</td>
<td>Yes</td>
<td>Calls for special CSA schedule to encourage cannabis research</td>
<td>CSAMH</td>
</tr>
<tr>
<td>American Society of Addiction Medicine</td>
<td>No</td>
<td>Yes, conditionally</td>
<td>Calls for applying established research standards to cannabis; discourage clinicians prescribing all research confirms safety and efficacy</td>
<td>Barlowe 2014</td>
</tr>
</tbody>
</table>

The current pattern of physician-authorized medical MJ use in the U.S. is far from the standard established for medicine

Inconsistencies in how medical conditions are qualified for medical marijuana use within each state

Inconsistencies in evaluating research, variable product composition/dose (dose conversion from product to product)

Ohio’s reciprocity with Michigan for MMJ possession?

How will hospitals handle admission medication reconciliation?

Chad D. Kollas MD FACP Medical Director Palliative and Supportive Care MD Anderson Cancer Center Orlando FL

2017 CPFI Annual Meeting
Closing on a High Note

Thank you

Dabbing
- Flash vaporizing butane hash oil based concentrate
- More intoxicating than smoking or vaping
Green City Hemp is a full-spectrum extract infused in MCT oil. It is a product for current hemp/CBD users seeking an all-natural complement to their routine.

- All Natural
- Non-Psychoactive
- No Preservatives
- 100% USA Grown & Extracted
- Lab Tested for Quality & Potency
- Just 5 Calories per Serving
- 250 total cannabinoids —<em>min./mg.</em>
- 500 total cannabinoids —<em>mg./mg.</em>
- 750 total cannabinoids —<em>mg./mg.</em>

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