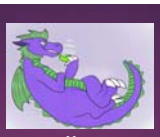
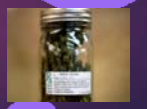


Medical Marijuana: Is That *Cannabis* Dragon Really Magical?

Cathy Rosenbaum PharmD MBA RPh CHC
Founder & CEO, Rx Integrative Solutions
Loveland, Ohio



1

Opening Prayer

2

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?

3

Industry News

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

4

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

5

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***?

6

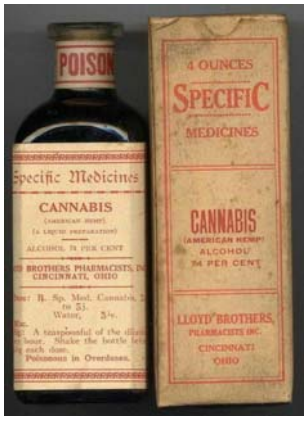
Cannabis History

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

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. Pharmacopeia**

7



8

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

9

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** cannabis.

10

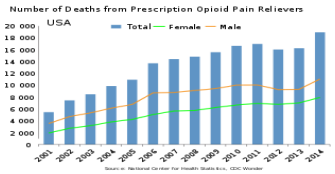
Medical Marijuana

- **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**

11

Bachhuber. Medical cannabis laws and opioid analgesic overdose mortality in the US 1999-2010. JAMA Intern Med 2014;174(10):1668-1673.

- 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?***



12

Ohio Medical Marijuana Control Program

13

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

14

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%

15

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.

16

Ohio Law 2016 Allows:

AIDS/HIV	**Multiple Sclerosis**
ALS	**Pain (chronic & severe or intractable)**
Alzheimer's	Parkinson's Disease
Cancer	PSTD (weak evidence)
Crohn's Disease	Sickle Cell Anemia
Chronic Traumatic Encephalopathy (CTE)	Spinal Cord Disease/Injury
Epilepsy or another Seizure Disorder	Tourette's Syndrome
Fibromyalgia	Traumatic Brain Injury (TBI)
Glaucoma	Ulcerative Colitis
Hepatitis C	**Any other disease or condition** added by state medical board under section 4731.302 of Revised Code
Inflammatory Bowel Disease	

17

17 States Allow Marijuana CBD Oil

Alabama	South Carolina
Florida	Tennessee
Georgia	Texas
Iowa	Utah
Kentucky	Virginia
Mississippi	Wisconsin
North Carolina	Wyoming
Oklahoma	Idaho (approved, vetoed)
Ohio	New York (investigating in clinical trials now)

18

Introduction to Cannabis

- ***Cannabis indica*** and ***Cannabis sativa*** are the best-known species.
- A product's chemical profile is more important than the strain of plant from which it originated.
- Products should be characterized by analytical chemistry - percentages of cannabinoids and terpenoids.

19

Compounds in Cannabis

- Cannabis, like all herbs, is a polypharmaceutical substance.
- 108 cannabinoids have been isolated (Hanuš 2008).
- The cannabis-derived cannabinoids of most therapeutic interest are THC and cannabidiol (CBD).
  - Minor cannabinoids include cannabigerol, cannabichromene, and tetrahydrocannabivarin (a short-chain C19 homolog of THC).
- Terpenoids are common, often aromatic, organic compounds found in many plants. Terpenoids found in cannabis include β-caryophyllene, myrcene, limonene, and pinene.
- As many as 420 other constituents occur in the plant (Turner et al 1980).

- phytoestrogens, flavonoids

20

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

21

Common Modes of Administration and Formulations

Inhalation by smoking or vaporization	Oral	Oro-mucosal or sublingual	Topical or Rectal
(herbal cannabis, resin, concentrates)	(prescription cannabinoids, edibles, tinctures)	(lollipops, lozenges, nabiximols)	(herbal cannabis, resin, concentrates)

22

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……

23

Edibles

24

Images of a marijuana vaporizer

25

TABLE 2-2 Cannabinoid-Based Medications

CANNABINOID-BASED MEDICATIONS

	Substance	Route of Administration	Description
Natural product Derived Compounds	Cannabidiol (CBD)	Oral capsule Oromucosal	Cannabinoid extracted from *Cannabis* t
	Cannabis	Multiple	Multiple active cannabinoids
	Cannador	Oral capsule	THC and CBD from *Cannabis* extract
	Epidiolex® (FDA Fast Track)	Oil	Concentrated CBD from *Cannabis* extract
	Nabiximol (Sativex®) (FDA Fast Track)	Oromucosalspray	THC and CBD extract from two *Cannabis* plant varieties
	Tetrahydrocannabinol (THC)	Oral capsule Smoked Oromucosal	Active cannabinoid of *Cannabis* plant
	THC/CBD	Oral capsule	Combination of cannabinoids
Synthetic Compounds	Ajulemic acid (AjA) (FDA PHASE II Active)	Oral capsule	Synthetic nonpsychoactive cannabinoid
	Dronabinol (Marinol®; Syndros®) (FDA approved)	Oral capsule	Synthetic THC
	Nabilone (Cesamet®) (FDA approved)	Oral capsule	Synthetic cannabinoid- THC analogue

26

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**

27

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 **active metabolite 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-Δ-9-THC.
- ***Elimination***: 20-45% of THC is eliminated in urine and 65% - 80% in feces

28

THC Onset Peak Duration

Parameter	Oral	Inhaled
Onset	30 minutes- 1 hour	Seconds/minutes (9-23 minutes for 11-OH-THC)
Time to peak blood [ ]	2 hours	2 – 30 minutes
Maximal duration	2-6 hours	Dose dependent; 20 - 60 minutes
Variables	Dose/concentration, pattern of use, bioavailability	Dose, pattern of use

Clin Pharmacol Ther 2015;97(6):575-586

29

THC Bioavailability

Route of Admin	Bioavailability	Comments
Oral	10-20%	From package insert for Marinol: 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**
Oral	6%	Chocolate cookie prepared with 20 mg THC Reported range 2-56%
Inhalation via smoking	10-40%	No pharmacokinetic or clinical studies in humans
Inhalation via vaporization	10-40%	
Transdermal	Unknown	

Ohio State Medical Marijuana Program 2017 Reference

30

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

31

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

32

Detected in the Urine

THC-COOH-Glucuronide	
Single Use	3 Days
Moderate Use (4x/Week)	5 – 7 Days
Daily Use	10 – 15 Days
Long-Term Heavy Smoker	> 30 Days
THC - T 1/2	2-7 Days

33

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)

34

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**

35

Partial Agonism

	Efficacy toward CB1	Efficacy toward CB2
Anandamide	Full agonist	?
2-Arachidonylglycerol (2-AG)	Full agonist	?
Δ-9-Tetrahydrocannabinol	**Partial agonist**	**Partial agonist**
CBD	**Very weak agonist/ antagonist? (blocks reuptake of anandamide)**	**Very weak agonist/antagonist?**
JWH-018	Full agonist	Full agonist

36

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

37

Functional Selectivity

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

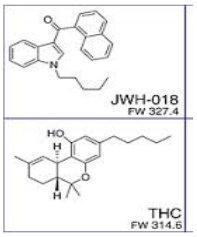
38

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 THC metabolites
- Products sold in gas stations, convenience stores, internet
- Urine/blood screens specific for **JWH-018 metabolites**

39

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

40

Solimini, et al. Hepatotoxicity associated with synthetic cannabinoids use. Eur Rev Med Pharmacol Sci 2017;21 (1 Suppl):1-6. (Table 1)

Synthetic Cannabinoids Family	Principal Compounds
Benzoylindole	AM-694, AM-2233, AM-679, RCS-4, RCS-8
Naphthoylindole	JWH-018, JWH-022, JWH-073, JWH-081, JWH-122, JWH-210, AM-2201, AM-2232, MAM-2201
Phenylacetylindole	JWH-167, JWH-250, JWH-316
Indazolecarboxamide	ADB-PINCACA, ADB-FUBINACA, AB-FUBINACA, AB-PINACA, 5F-APINACA, AKB48 (APINACA), MAB-CHMINACA
Cyclohexylphenyl	CP-55, 940, CP-47, 497, 497-C8 homologue
Naphthylmethylindole	JWH-175
Naphthylpyrrole	JWH-145, JWH-307, JWH-370
Naphthylmethylindene	JWH-176, JWH-220
Aminoalkylindole	WIN-55, 212-2
Adamantoylindoles	AB-001
Tetramethylcyclopropylketone indole	UR-144, XLR-11
Quinolinyl ester indole	5F-PB-22, PB-22
Ibenzopyran	HU-210, JWH-133

41

Cannabinoid CB1 Receptors

- Mostly in **brain (cerebellum, cerebral cortex, basal ganglia)**, spine, GI tract, liver, pancreas, skeletal muscle combined with **GABAergic & dopaminergic & serotoninergic 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

42

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**

43

Main Phytocannabinoids

- ***Psychoactive***: **THC** (Δ-9-THC, Δ-8-THC, 11-hydroxy-THC [active metabolite]). Binds to CB1 & CB2 receptors as a partial agonist.
- ***Not Psychoactive***: **THCV** (tetrahydrocannabivarin) – analogue of THC
- ***Not Psychoactive***: **CBD** (cannabidiol), **CBN** (cannabinot) – degradation product of THC, **CBC** (cannabichromene) – sedative and analgesic, **CBG** (cannabigerol) – precursor of other cannabinoids
- ***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

44

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 I (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)

45

CBD/5HT1A Receptor Pharmacology

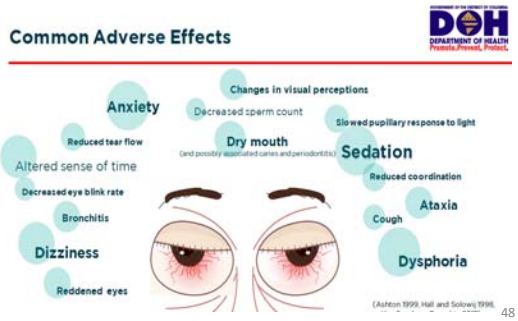
-MOA of CBD is not fully understood
-Anxiolytic and antipsychotic MOA mediated by endocannabinoid system or by activation of 5HT1A receptors
-Low affinity for cannabinoid receptors, but blocks the reuptake of anandamide
-5HT1A receptors are located pre-synaptically in raphe nuclei of brain stem and post-synaptically in hippocampus and hypothalamus – areas related to stress and anxiety
-Unclear whether anxiolytic effects from 5HT1A agonists are due to activation of pre- or the –post synaptic receptors
-Depending on where post-synaptic receptors are, activation -> anxiolytic or anxiogenic

46

CANNABIS

47

CANNABIS



48

CANNABIS

Respiratory Effects
Vaporization

- A survey of 6,883 cannabis users found that vaporizing, compared with smoking, causes fewer respiratory symptoms (coughing, wheezing, shortness of breath, mucus production) (Earlywine and Barnwell 2007).
- Analysis of vapor from a vaporizer recovered 89.1% THC and 9.5% smoke toxins; in contrast, cannabis smoke from a pipe recovered 10.8% THC and about 87% smoke toxins (Chemic Laboratories 2003).
- Vaporization, compared to smoking, generates less carbon monoxide (Abrams et al 2007).

49

CANNABIS

Respiratory Effects
Smoked Cannabis

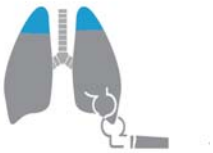
- Smoked cannabis is clearly associated with symptoms of bronchitis, which resolve after cessation of use (Tashkin 2013, Tashkin 2014).
- At least 200 compounds occur in cannabis smoke (Sparacino et al 1990): these include carbon monoxide, acetaldehyde, ammonia, nitrosamines, and polycyclic aromatic hydrocarbons ("tars").
- Combining tobacco and cannabis appears to have synergistic adverse effects, increasing respiratory symptoms over tobacco use alone (MacLeod et al 2015, Bloom et al 1987).

50

Cannabis

Respiratory Effects
Lung Cancer

- Cannabis does not appear to increase lung cancer risk.
- A pooled meta-analysis of 6 case-control studies in the US, Canada, UK, and New Zealand that included data on 2,159 lung cancer cases and 2,985 controls found **"little evidence for an increased risk of lung cancer among habitual or long-term cannabis smokers, although the possibility of potential adverse effects for heavy consumption cannot be excluded"** (Zhang et al 2015).



51

CANNABIS

Cardiovascular Effects

- THC can cause tachycardia; chronic users may develop bradycardia.
- Cannabis can cause changes in blood pressure.
  - High doses can cause orthostatic hypotension and syncope (Handbook on Cannabis 2015).
  - Cannabis can cause an acute increase in blood pressure (Frost et al 2013).
- Cannabis can increase the risk of angina (Frost et al 2013).
- Rarely marijuana can trigger an acute myocardial infarction (Mittleman et al 2001).
- In patients who have had a myocardial infarction, an 18-year follow up study showed no conclusive evidence that smoking marijuana increased mortality (Frost et al 2013).
- Case reports have associated cannabis use with acute coronary syndrome, arrhythmias, sudden cardiac death, cardiomyopathy, transient ischemic attack, stroke (Thomas et al 2014, Jouanjus 2014).

52

American College of Cardiology 66th Annual Scientific Session March, 2017

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

53

CANNABIS

Neuropsychiatric Effects
Cognitive Function

- Long-term cannabis users exhibit deficits in prospective memory and executive function (Montgomery 2012).
- In depressed and non-depressed regular marijuana users, there was an inverse association between marijuana use and verbal learning function.
  - The effect was not moderated by depression (Roebke 2014).

Adolescent marijuana users demonstrated significantly smaller medial orbitofrontal and inferior parietal volumes (regions of the brain associated with higher order cognition); smaller medial orbitofrontal volumes were associated with poorer complex attention.

(Price et al 2015)

54

CANNABIS

Psychiatric Effects
Psychosis/Schizophrenia

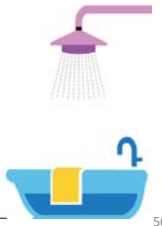
- Whether or not cannabis can cause psychosis is debated.
- Studies suggest that people at risk for schizophrenia run a higher risk of psychosis outcomes after cannabis use (Morrison et al 2015).
- A study of cannabis use in 1237 people with schizophrenia, who had ever used cannabis, found no additive effect of cannabis use on cognitive dysfunction (Power 2015).
- Smoking cannabis with a significant proportion of CBD may produce fewer psychotic symptoms (Morgan and Curran 2008, Schubart et al 2011).
- It has been suggested that cannabis has antipsychotic effects, but a Cochrane systematic review of cannabis and schizophrenia noted that studies were limited, and that "currently evidence is insufficient to show cannabidiol has an antipsychotic effect" (McLoughlin 2014).

55

CANNABIS

Cannabinoid Hyperemesis Syndrome

- Chronic cannabis use may be associated with Cannabinoid Hyperemesis Syndrome (also called Cyclic Vomiting Syndrome).
- It is characterized by episodes of nausea and vomiting, abdominal pain, and sometimes polydipsia.
- Obsessive hot-water bathing may be observed, as it alleviates symptoms.
- The syndrome can lead to weight loss or acute renal failure from dehydration.
- The etiology of CHS is thought to be activation of CB_1 receptors that can reduce gastric emptying.



(Galli et al 2011, Woods et al 2014, Beech et al 2015, Iacopetti and Packer 2014, Yap and Luther 2012, Habboushe and Sedor 2014)

56

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 enteric 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; unrelieved 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

57

CANNABIS

Reproductive Effects
Lactation and Fertility

Cannabis use during lactation is not recommended.

- THC and its metabolites are excreted in breast milk.
- Infants exposed to marijuana during lactation had lower scores on the Psychomotor Developmental Index compared to non-exposed infants (effects could not be separated from prenatal exposure).

Fertility effects in men

- Some studies indicate that chronic use of marijuana may decrease plasma testosterone and decreases sperm count, concentration, and motility.

(Reprotox.org, Metz and Stickreth 2015)

58

CANNABIS

Reproductive Effects
Exposure During Pregnancy

Cannabis use during pregnancy is not recommended.

- Heavy use of cannabis during pregnancy may cause adverse effects on early neurodevelopment, including subtle cognitive impairment and decrements in executive functioning later in life.
- Cannabis use has not been shown to increase the risk of congenital anomalies.
- Some but not all studies have shown a decrease in fetal growth.
- There is a possible increased risk of preterm birth.

(Fried et al 2003, Goldschmidt et al 2012)

59

CANNABIS

Clinical Aspects
Contraindications

- **Absolute contraindications**
  - Acute psychosis and other unstable psychiatric conditions
- **Relative contraindications**
  - Severe cardiovascular, immunological, liver, or kidney disease, especially in acute illness
  - Cannabis may exacerbate arrhythmia or a history of arrhythmias

(Handbook on Cannabis 2015)

60

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**

61

CANNABIS

Psychiatric Effects

Dependence

- Cannabis dependence may occur: the estimated global prevalence is 0.23% in males and 0.14% in females (Degenhardt et al 2013).
- Prevalence peaks in the 20-24 years age group, and decreases steadily with age.
- In a survey of 6,917 marijuana users, 15% met the criteria for a marijuana use disorder. People who met the criteria for marijuana use disorder also were correlated with weekly marijuana use, early marijuana use, other substance use disorders, substance abuse treatment, and serious psychological distress (Wu et al 2012).
- Marijuana usage goes up in states that pass medical marijuana laws. However, the dependence rate among marijuana users does not differ between states with or without medical marijuana laws (Cerda et al 2012).

62

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?

63

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

< 2 SXS (no disorder), 2-3 SXS (mild disorder) 4-5 SXS (moderate disorder) >6 SXS (severe disorder) Pharmacy Today April 2017

64

Common Terminology Used in Assessment of Substance Use

Term	Definition	Comments
Addiction	A neurobiologic disease characterized by impairment, cravings, withdrawal syndrome, and negative social, professional and spiritual sequelae as well as inability to abstain from continued used of the substance	Addiction has been replaced by substance use disorder in DSM-V
Aberrant Drug-Taking Behavior	Departure from strict adherence to prescription instructions or indication for use	
Misuse	Departure from adherence to prescribed instructions while maintaining therapeutic intent (taking more than Rx'ed for what the drug was prescribed for)	
Abuse	Departure from adherence to prescribed instructions and use for nontherapeutic intent (taking more than prescribed for euphoria vs pain control)	Previously used interchangeably with substance dependence as a diagnostic term and is being phased out
Tolerance	Decreased responsiveness to substance requiring higher doses or amounts to produce the same effect achieved during initial dose	
Withdrawal	Cluster of SXS experienced upon cessation or inability to reduce a substance characterized by stress, anxiety, depression, NV	SXS may be experienced by person possessing no signs of substance misuse or substance use disorder if drug is abruptly DC'd

65

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

66

Cincinnati Poison Control Center THC TESS Report Analysis 2010-2014

- 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 concomitantly abused/misused
- Results: 2330 reports involving children, teens, adults ad 1242 reports involving K2, Spice, THC homologs. 7 deaths. Main body systems involved – **neurological, cardiovascular** (drowsiness, irritability, confusion, hallucinations, tachycardia, hypertension)

67

CANNABIS

Summary

- Cannabis is generally well-tolerated, and serious adverse effects, including increased risk of cardiovascular events, are rare.
- Adverse changes in cognitive function, especially executive function, may occur, especially with fetal or adolescent exposure.
- 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 on a much lower scale than alcohol.
- Drug interactions are a concern.
  - Cannabis enhances CNS depressant effects when combined with alcohol, barbiturates and benzodiazepines, but probably not opioids
  - THC induces CYP1A2, and can reduce levels of drugs metabolized by CYP1A2.
  - CBD inhibits CYP3A4 and CYP2D6, and can increase levels of drugs metabolized by these isoenzymes. CPY3A4 metabolizes about a quarter of all drugs.

68

CANNABIS

Drug Interactions
Cytochrome P450 Enzymes

- THC and CBD are metabolized by CYP3A4 and CYP2C9 (Yamaori et al 2012, Watanabe et al 2007).
  - CYP3A4 inhibitors slightly increase THC levels.
  - CYP3A4 inducers slightly decrease THC and CBD levels.
- CBD, but not THC, is metabolized by CYP2C19 (Stout and Cimino 2014).

69

CANNABIS

Drug Interactions
Cytochrome P450 Enzymes

- **THC is a CYP1A2 inducer.**
  - Theoretically, THC can decrease serum concentrations of clozapine, duloxetine, naproxen, cyclobenzaprine, olanzapine, haloperidol, and chlorpromazine (Flockhart 2007, Watanabe et al 2007).
- **CBD is a potent inhibitor of CYP3A4 and CYP2D6.**
  - As **CYP3A4** metabolizes about a quarter of all drugs, CBD may increase serum concentrations of macrolides, calcium channel blockers, benzodiazepines, cyclosporine, sildenafil (and other PDE5 inhibitors), antihistamines, haloperidol, antiretrovirals, and some statins (atorvastatin and simvastatin, but not pravastatin or rosuvastatin).
  - **CYP2D6** metabolizes many antidepressants, so CBD may increase serum concentrations of SSRIs, tricyclic antidepressants, antipsychotics, beta blockers and opioids (including codeine and oxycodone).

70

Cannabis/Drug Interactions

- May interact with warfarin (THC and CBD increase warfarin levels (Yamaori et al 2012)
- Alcohol may increased THC levels (Hartman 2015)

71

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
Acyclovir 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
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

Interactions/Medication Issues?

Plan?

72

Hill. Medical marijuana for treatment of chronic pain and other medical and psychiatric problems. A clinical review. JAMA 2015;313:2474.

- 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

73

The Effectiveness of Cannabinoids in the Management of Chronic Nonmalignant Neuropathic Pain: A Systematic Review. *J Oral & Facial Pain Headache 2015 (Boychuk)*

- 13 studies rated
- Cannabinoids provide effective **non-inferior** analgesic in chronic neuropathic pain conditions refractory to other treatments
- Very few side effects
- Further high quality studies needed to assess impact of treatment duration(1-6 weeks) as well as best form (smoking versus Sativex-nabixmols: THC:CBD oromucosal spray)

74

Intractable Cancer Pain

- RCT, 5 week trial in 360 patients found that adjunctive use of low (1-4 sprays/day) and medium (6010 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

75

Whiting. Cannabinoids for medical use: A systematic review and meta-analysis. JAMA 2015;313:2456

- Of 79 trials reviewed, 4 were judged at low risk of bias
- Most trials showed symptom improvement associated with cannabinoids but these associations did not reach statistical significance in all trials
- Compared with placebo, cannabinoids were associated with a greater average number of patient showing a complete **N&V** response in 3 trials (47% vs 20%, OR, 3.82 [95% CI, 1.55-9.42].
- Reduction in **pain** in 8 trials (37% vs 31%, OR, 1.41 [95% CI, 0.99-2.00]
- Average reduction in Ashworth **spasticity** scale in 5 trials (Weighted Mean Difference -0.12 95% [CI, -0.24 to 0.01])
- Increased risk of short term AEs with cannabinoid (dizziness, dry mouth, N &V, fatigue, somnolence, euphoria, drowsiness, confusion, loss of balance, hallucination).

76

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

77

Epilepsy

- Open label, 12 week study in patients 1-30 years with severe childhood-onset treatment-resistant epilepsy, addition of **Epidiolex** (investigational purfieid cannabis extract with 99% CBD) reduced median monthly frequency of seizures by 36%.
- 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

78

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(5):505-510)
- Endocannabinoid dysfunction, serotonin level reduction, and migraines (Rossi. Euro J Clin Pharm 2008;64(1):1-8)
- CBD interacts with serotonergic system to inhibit serotonin reuptake. Reduced use of opioids for migraines with medical marijuana. (Bradford. Health Aff 2016;35(7):1230-1236)

79

.....By Chad D. Kollas MD FACP

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

Symptom	RCTs	Patients	Findings	Lead Author Year
Chemotherapy-induced nausea	3	43	Smoked cannabis has a modest anti-nausea effect greater than placebo but less effective than ondansetron	Chang 1979 Chang 1981 Levitt 1984
HIV-related anorexia	3	97	Smoked cannabis and oral THC produced comparable but small increases in caloric intake and weight; viral load was unaffected	Abrams 2003 Haney 2005 Haney 2007
HIV-related neuropathic pain	2	89	Half of the patients experienced a 30% reduction in pain ratings	Wilsey 2008 Ellis 2009
Capsaicin-induced pain	1	15	Half of the patients experienced a 30% reduction in pain ratings	Wallace 2007
Spasticity from multiple sclerosis	2	40	Reduced scores for pain (50%) and spasticity (30%) were observed using high potency cannabis cigarettes	Greenberg 1994
Intraocular pressure	1	18	Smoked cannabis (one 2% THC cannabis cigarette) caused a significant reduction in intraocular pressure	Merritt 1990

80

81

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 "recommended" 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:
  - *An in-person physical examination;*
  - *A review of the patients medical history by the physician; and*
  - *An expectation of providing and receiving care on an ongoing basis.*
- An application then may be submitted to the Board of Pharmacy on behalf of the patient by the physician to become a registered medical marijuana patient.
- Patients would then be able to obtain medical marijuana from a dispensary that has be licensed and is regulated by the Board of Pharmacy.
- *Marijuana cannot be "prescribed" or distributed through a pharmacy due to the fact that it is still illegal under federal law.*

82

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

83

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

84

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!)

85

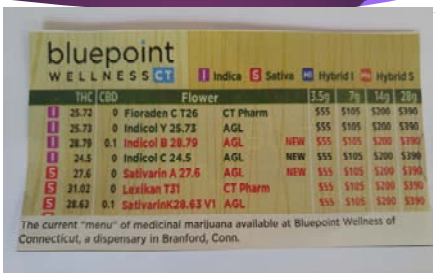
Dispensaries & Product Labeling

- 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

86

Pharmacy Practice News May 2017



The current "menu" of medicinal marijuana available at Bluepoint Wellness of Connecticut, a dispensary in Branford, Conn.

87

Pharmacy Practice News May 2017

88

American Society of Health-System Pharmacists

- 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)

89

2014 - 2015 APhA Policy Committee Report Recommendations

Support

- Resolution of federal and state conflicts r.e. legal status
- Establish USP 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

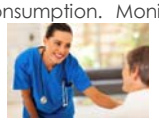
Oppose

- 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/federal laws
- Pharmacist involvement in furnishing cannabis for recreational use

90

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?



91

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

92

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

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

Organization	Approval of Smoked?	Support of More Research?	Comments	Lead Authors & Year
Institute of Medicine	Yes, conditionally	Yes	Calls for more safety data on smoked cannabis. Urges development of safe and reliable delivery systems	Joy 1999
American College of Physicians	No	Yes	Encourages use of non smoked THC with proven benefit. Calls for review to reclassify CSA Class I status. Recommends clinical exemption for prescribing physicians.	ACP 2008
American Medical Association	No	Yes	Calls for special CSA schedule to encourage cannabis research	CSAPH
American Society of Addiction Medicine	No	Yes, conditionally	Calls for applying established research standards to cannabis. Discourages cannabis prescribing until research confirms safety and efficacy	Barthwell 2919

93

TODAY'S ISSUES

- 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**?

94

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/ZqyFSx)

95

Mind Body Spirit

- **Heart**ache 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)

96

Closing on a High Note

97

98

99

100

Dabbing

- Flash vaporizing butane hash oil based concentrate
- More intoxicating than smoking or vaping

101

102


Queen City Hemp is a full spectrum
extract suspended in MCT oil. It is
product for current hemp/CBD user
seeking an all-natural alternative to h
products
All Natural
Non Psychoactive
No Preservatives
100% USA Grown & Extracted He
Lab Tested for Quality & Potency
Just 5 Calories per Serving
250 total cannabinoids- ~4mg/ser
500 total cannabinoids- ~8mg/ser
750 total cannabinoids- ~12mg/se
A Product of QC Infusion
QCInfusion.com
Born
QUEEN CITY HEMP
MCT Oil +250
QUEEN CITY HEMP
MCT Oil +500
QUEEN CITY HEMP
MCT Oil +750
103