

# The Impact of Cannabis Use on Mental Health

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# Today's Webinar

- Cannabis, which used to be known as a gateway drug to other substances, has become legalized in many U.S. states as well as the District of Columbia.
- People in states where recreational cannabis use is legal use it 20% more frequently than jurisdictions that did not legalize it.
- What impact has this increase in legal access and use had on mental health?
- We thank the SAMHSA CE-MHTTC for its partnership on the BPA Health Equity Webinar series.
- Content has both Central East region and national relevance.
- Our featured speaker is Benjamin Roy, MD

# History of Cannabis

- Cultivation of cannabis present in China and Japan (10,000 BCE)
- Burned cannabis present in Romanian burial mounds (3,500 BCE)
- The Hindu Atharva Veda (2000 BCE) describes Cannabis as an entheogen and aphrodisiac that is a gift from the gods to give people pleasure and happiness
  - Bhang: crushed leaves, seeds, edible in food and drinks (Thandai and Lassi) used by ancient armies and continues at Holi, a spring festival celebrating good over evil
  - Ganga: smoked (Rastafarians) resin and cannabis flower of female plants
  - Charas: highest quality
- Marco Polo described a cult of assassins dependent on cannabis in *Livre des Merveilles du Monde* or *Devisement du Monde* 1300

# History of Cannabis (cont.d)

- Garcia de Ota wrote of bhang in *Conversations on the simples, drugs and materia medica of India* (1563)
- John Huygen van Linschoten travelogue *Discours of Voyages into Ye East & West Indies* (1592)
- John Wolfe - *Discours of voyages into ye Easte & West Indies* (1598)
- Obsession with hashish piqued after Napoleon occupied Egypt and French soldiers were introduced to cannabis (1798)

# History of Cannabis (cont.d)

- *Confessions of an English Opium Eater. Being an Extract from the Life of a Scholar* (1821) by Thomas De Quincey was lionized as "that most wondrous, most inspired Dreamer" who introduced "a realm in which all the range of average thought found its conditions surpassed, if not violated." (Fitz Hugh Ludlow)
- William Brooke O'Shaughnessy patents *Squire's Extract* in 1842, a commercial tincture of hemp for medicinal purposes but used also as a sexual stimulant or date-rape drug
- British Colonial Raj demonized cannabis, claiming it promoting violence, i.e., resistance to British rule, particularly among the Thugs, propagandized as a cult of assassins that used Hashish to steel themselves – a fiction to outlaw the drug and garner judicial supremacy and justify oppression
- Club des Hashischins (Club of Assassins) in Paris 1844-1849
  - Victor Hugo, Alexandre Dumas, Jacques-Joseph Moreau, Theophile Gautier, Gerard de Nerval, Charles Baudelaire and Honore de Balzac
- The intelligentsia justify their use of drugs as exploration of the expanse of consciousness and spiritual enlightenment. They were psychonauts, heroes who broke the chains of unenlightened normal conscious experience

# European Hashish Literature

- Charles Baudelaire - *The Poem of Hashish* 1821 (published 1850)
- Theophile Gautier - *Club des Hashischins* (1846)
- Dr. Jacques-Joseph Moreau - *Hashish and Mental Illness - Psychological Studies* (1846)
- Charles Baudelaire – *On Wine and Hashish* (1851)
- Gerard de Nerval - *Aurelia* (1855) – committed suicide and subject of Carl Jung study
- Fitz Hugh Ludlow - *The Hashish Eater. Being passages from the life of a Pythagorean* (1857)
- Charles Baudelaire - *Les Fleurs du Mal (Flowers of Evil)* (1857)
- Charles Baudelaire - *Artificial Paradise* (1860)
- Ernest Bosc De Veze – *Theoretical & Practical Treaty of Hashish* (1895)
- Walter Benjamin - *Main Features of My First Impression of Hashish* (1927)

# European Royalty and Hashish

- Queen Maria I of Portugal
- Queen Victoria
  - 1. Hashish for menstrual pain
  - 2. Chloroform during delivery
  - 3. Vin Mariani (cocaine wine)

# Epidemiology of Recreational Cannabis

- Recreational marijuana is legal in 23 states and the District of Columbia and available to 134.4 million people
  - 52% of Americans have tried recreational cannabis
  - **3.9% of 8th graders** have used marijuana
  - **35% of 12th graders** have smoked or vaped marijuana
- Age
  - **18-29 years: 26%**; 30-49 years: 15%; 50-64: 10%; > 64 years: 3%
- Race
  - Whites: 56%; African Americans: 44%
- Geographic region
  - West: 56%; Midwest: 52%; South: 51%; Northeast: 48%



# Epidemiology of Cannabidiol (CBD)

- Hemp-derived CBD is legal in all 50 states
- Marijuana-derived CBD is legal in only 9 states (AK, CO, IL, ME, MI, NH, NV, OR, WA)
  - 14% of Americans have tried CBD; 16.7% of 4,348 surveyed used  $\Delta$ -8 THC
  - Vaping was the most common method of use (41%)
- Age
  - 18-29 years: 20%; 30-49 years: 16%; 50-64: 11%; > 64 years: 8%
- Race
  - Whites: 56%; African Americans: 44%
- Geographic region
  - West: 21%; South: 11%; Midwest: 11%; Northeast: 48%

# Cannabis Industry Marketing Research 2023

- \$30 Billion industry
- **16 million cannabis addicts**
- Cannabis demand unaffected by inflation: 73% spent more money
- Demand for **cheaper price and higher THC%**
- **Cannabis and CBD use are exceeding tobacco and alcohol use, sales of which are decreasing**
- Cannabis products: Pre-rolls (+12%); Beverages (+10%); Edibles (+10%); Vapes (+5%)

# Cannabis Industry Marketing Research 2023 (cont.d)

- **Time from medical marijuana to recreational use legalization shortening**
- **Recreational consumption outpacing medical use**
- **Recreational market to exceed \$100 billion by 2030**
- **COVID-19 Pandemic increased CBD use 45%**
- **Reasons for CBD use**
  - **Anxiety 49%**
  - **Pain 40%**

# Endogenous Cannabinoid Pharmacology

- Endocannabinoids (endogenous)
  - 2-Arachidonoylglycerol (full agonist)
  - Anandamide (Sanskrit word meaning “*Supreme Joy*”)
  - N-Homo- $\gamma$ -linolenylethanolamine
  - N-Docosatetraenoylethanolamine
  - N-Arachidonoyl dopamine
  - Virodhamine (O-arachidonoyl ethanolamine; O-AEA)
  - Endocannabinoids cross lipid membranes but are not water soluble so must be transported through cytoplasm by endocannabinoid transporters (eCBTs)
    - Heat shock proteins (Hsp70s)
    - Fatty acid binding proteins 1,3,5, and 7

# Phytocannabinoid Pharmacology

- Cannabis sativa
  - Of 480 chemicals 113 are cannabinoids and 120 terpenes
  - $\Delta$ -9 Tetrahydrocannabinol,  $\Delta$ 9-THC
  - **$\Delta$ 9-Tetrahydrocannabiphorol ( $\Delta$ 9-THCP)**
  - **$\Delta$ 8-Tetrahydrocannabiphorol ( $\Delta$ 8-THCP)**
- Hemp
  - Cannabidiol (CBD)
  - $\Delta$ 8-THC

# CB1 G-Coupled Membrane Receptor

- Isolated from porcine brain
- Inhibits N-, P-, and Q-type calcium channels
- Activates inwardly rectifying potassium channels
- CB1 increases nitric oxide synthase (NOS) activity, increases NO production, enhances anandamide transporter activity
- Central and peripheral nervous system
- Endogenous ligands: 2-arachidonoylglycerol and anandamide
- THC has high affinity for CB1 receptor
- Rimonabant (Acomplia) anti-obesity CB1 inverse agonist caused depression and suicidality in > 30%

# CB2 G-Coupled Membrane Receptor

- Isolated from human promyelocytic leukemia cell line HL60
- Distribution: immune system > CNS
- Signaling pathways:
  - Gi/o-dependent inhibition of adenylyl cyclase, stimulation of mitogen-activated protein kinase
  - Phosphoinositide 3-kinase pathways
  - Activation of de novo ceramide production or cyclooxygenase-2 (COX-2) induction
- Inhibits NOS, NO release, and reduces anandamide transporter activity
- CBD has low to negligible affinity for CB2 receptor
- Ajulemic acid synthetic analog of THC-11-oic acid, a metabolite of THC binds CB2
- Energy homeostasis
  - Reduces GI motility
  - Increases lipogenesis
  - Steatosis in the liver
  - Increases lipogenesis and inflammation and reduces lipolysis, in the white adipose tissue (WAT)
  - Impairs insulin sensitivity

# Non-Cannabinoid Receptors

- Orphan G Protein Coupled Receptor (GPR55)
  - G-protein-coupled receptor ( $G_{\alpha 12/13}$  and  $G_q$  proteins)
  - L-alpha-lysophosphatidylinositol is an endogenous agonist
  - Palmitoylethanolamide is an agonist
  - Induces  $Ca^{2+}$  release
  - Lennox Gastaut Syndrome (autosomal dominant seizure disease)
- Peroxisome Proliferator-Activated Receptors (PPARs)
  - Ajulemic acid - synthetic analog of THC-11-oic acid, a metabolite of tetrahydrocannabinol (THC) is a selective agonist for the PPAR- $\gamma$
- Transient Receptor Potential channel subfamily V member 1 (TRPV1) voltage gated potassium and sodium ion channels



Molecule	Binding	Affinity	pKi (nM)	Functional	Activity	GTP $\gamma$ S EC <sub>50</sub> nM (E <sub>max</sub> %)
	<b>CB1</b>	<b>CB2</b>	<b>GPR55</b>	<b>CB1</b>	<b>CB2</b>	<b>GPR55</b>
Anandamide ( <i>N</i> -arachidonylethanolamine (AEA))	61	279		31.6 (66)	27.6 (58)	18 (73)
<b>2-Arachidonoylglycerol (2-AG)</b>	<b>3</b>	145		519 (92)	618 (87)	3 (99)
Virodhamine ( <i>O</i> -arachidonoyl ethanolamine; <i>O</i> -AEA)	1740	agonist		2920 (75)	381 (91)	12 (160)
<b><math>\Delta</math>-9 Tetrahydrocannabinol (<math>\Delta</math>-9 THC)</b>	<b>40</b>	<b>36</b>		6 (61)	0.4 (67)	8.1 (92)
<b><math>\Delta</math>-8 Tetrahydrocannabinol</b>	<b>44</b>	<b>12.2</b>		5820	524	
<b>(-)-11-hydroxy-<math>\Delta</math>8 -THC-dimethylheptyl (HU 210) (synthetic)</b>	<b>0.06</b>	<b>0.17</b>				
<b><math>\Delta</math>9-Tetrahydrocannabiphorol (THCP)</b>	<b>1.2</b>	<b>6.2</b>				
<b><math>\Delta</math>8-Tetrahydrocannabiphorol</b>	<b>22</b>					
THC- <i>O</i> -acetate (synthetic)						
<b>Arachidonyl-2'-chloroethylamide (ACEA)</b>	<b>1.4</b>	3100				
<b>Cannabidiol</b>	151	4,582	350	> 30,000	> 30,000	Antagonist
<b>L-alpha-lysophosphatidylinositol (LPI)</b>					1.25 $\mu$ M (118.7)	1 $\mu$ M

Affinity measures binding to the receptor- High Affinity: < 10 nM; Intermediate Affinity: 10-100 nM

EC<sub>50</sub> (half maximal effective concentration) is the concentration required to obtain 50% of the maximum biological response

# How Sweet Is It?



- \* **Diameters 84.1 mm,**
- \* **Volume 217.8 cm<sup>3</sup>**
- \* **Mass 215.4 g**
- \* **Bulk density 0.44 g/cm<sup>3</sup>**
- \* **Fruit density 1.03 g/cm<sup>3</sup>**
- \* **Porosity 44.64%**
- \* **Sphericity 0.948**
- \* **Static angle of friction on galvanized, glass and plywood surfaces is 20.2**
- \* **Orange mass was determined through a polynomial function of third degree involving the average diameter of the orange. The function was evaluated with a determination coefficient of 0.991.**

# Cannabis Species

- There are three species of cannabis: sativa, indica, and ruderalis. Marijuana differs by ratio of Sativa:Indica
- Cannabis sativa (%THC defines “sweetness”)
  - a. Destroyer: 100:0 Sativa: Indica; 20% THC
  - b. Kwazulu: 100:0 Sativa: Indica; 20% THC
  - c. Kilimanjaro: 100:0 Sativa: Indica; 20% THC
  - Thai: 100:0 Sativa: Indica; 22% THC
- Cannabis indica
  - Afghan Kush: 0:100 Sativa: Indica 18%
  - Purple Kush: 0:100 Sativa: Indica; 15.5% THC
  - Hindu Kush: 0:100 Sativa: Indica 15%
  - Northern Lights: 0:100 Sativa: Indica; 16% THC
- Cannabis ruderalis

# Synthetic Cannabinoids

- Ajulemic acid - analog of THC-11-oic acid, a metabolite of tetrahydrocannabinol (THC)
- Spice/K2/Mojo (sprayed on plant material sold in convenience stores)
  - Cannabicyclohexanol (Pfizer)
  - HU-210 (Hebrew University of Jerusalem)
  - JWH-018 (John W Huffmand of Clemson University)
  - JWH-073
  - ADB-CHMINACA (MAB-CHMINACA):
- Cloud 9/Relax/Crown
  - AB-FUBINACA
  - AB-PINACA: 1.5 x THC
- Blaze; Skunk; No More Mr. Nice Guy

# FDA Approved Medical Cannabinoids

- Dronabinol (Marinol and Syndros)
  - Nausea of cancer chemotherapy
  - HIV/AIDS cachexia
- Nabilone (Cesamet)
  - Nausea of cancer chemotherapy
- Cannabidiol solution (Epidiolex)
  - Lennox-Gastaut syndrome (autosomal dominant seizure disease)
  - Dravet syndrome (autosomal dominant myoclonic seizure disease)
  - Tuberous Sclerosis Complex (autosomal dominant tubers in CNS)
- Nabiximols (Sativex) under review – oromucosal spray 2.7 mg THC and 2.5 mg CBD
  - Multiple Sclerosis spasticity

# Commissioned Cannabis Reports

- British Indian Hemp Drugs Commission Report (1894) found no physical or mental sequelae during ordinary use
- La Guardia Report by the New York Academy of Medicine, *The Marihuana Problem in the City of New York* (1944) marijuana was not a gateway drug and did not induce violence, insanity or sex crimes and its distribution was primarily in Harlem where the majority of marijuana smokers were Blacks and Latinos
- Marijuana and Health (1982) – Institute of Medicine
- Commission on Narcotic Drugs in Force as of 5 March 1990 - internationally cannabis is a Schedule I drug
- Marijuana and Medicine: Assessing the Science Base (1999) – Institute of Medicine
- The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research (2017) - Health and Medicine Division, National Academies of Sciences, Engineering, and Medicine doi: 10.17226/24625

# Conclusive or Substantial Evidence

- Effective for chronic pain in adults (cannabis)
- Effective antiemetics for chemotherapy-induced nausea and vomiting (oral cannabinoids)
- Improves multiple sclerosis spasticity by patient reports
- Statistical association with increased risk of motor vehicle crashes
- Statistical association with lower birth weight of the offspring
- Statistical association with the development of schizophrenia or other psychoses, with the highest risk among the most frequent users
- Being male and smoking cigarettes are risk factors for the progression of cannabis use to problem cannabis use
- Initiating cannabis use at an earlier age is a risk factor for the development of problem cannabis use
- Stimulant treatment of attention deficit hyperactivity disorder (ADHD) during adolescence is *not* a risk factor for the development of problem cannabis use

# Moderate evidence for:

- Improved short-term sleep outcomes in obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis (cannabinoids, primarily nabiximols)
- No statistical association with incidence of lung cancer (cannabis smoking)
- No statistical association with Incidence of head and neck cancers
- **Increased risk of overdose injuries, including respiratory distress, among pediatric populations in U.S. states where cannabis is legal**
- Impairment in the cognitive domains of learning, memory, and attention (acute cannabis use)
  - Better cognitive performance among individuals with psychotic disorders and a history of cannabis use
  - **Increased symptoms of mania and hypomania** in individuals diagnosed with bipolar disorders (regular cannabis use)
  - **Statistical association with**
    - a small increased risk for the development of depressive disorders
    - an increased incidence of suicidal ideation and suicide attempts with a higher incidence among heavier users
    - an increased incidence of suicide completion
    - an increased incidence of social anxiety disorder (regular cannabis use)



# Moderate evidence

- Anxiety, personality disorders, and bipolar disorders are *not* risk factors for the development of problem cannabis use
- **Major depressive disorder is a risk factor for the development of problem cannabis use**
- Adolescent ADHD is *not* a risk factor for the development of problem cannabis use
- Being male is a risk factor for the development of problem cannabis use
- Exposure to the combined use of abused drugs is a risk factor for the development of problem cannabis use
- Neither alcohol nor nicotine dependence alone are risk factors for the progression from cannabis use to problem cannabis use
- **Risk factors for the development of cannabis addiction during adolescence are:**
  - frequent cannabis use
  - oppositional behaviors
  - a younger age of first alcohol use
  - nicotine use
  - parental substance use
  - poor school performance
  - antisocial behaviors
  - childhood sexual abuse

# Moderate evidence (cont.d)

- **Statistical association**
  - **between chronic cannabis use and a history of psychiatric treatment**
  - **between a problem with cannabis use and increased severity of posttraumatic stress disorder symptoms**
  - **with the development of substance dependence and/or a substance abuse disorder including alcohol, tobacco, and illicit drugs**
  - **between a persistence of problem cannabis use and a history of psychiatric treatment**
  - **between a problem with cannabis use and increased severity of posttraumatic stress disorder symptoms**

# Limited Evidence that Cannabis or Cannabinoids

- Increase appetite and decrease weight loss associated with HIV/AIDS
- Improve clinician-measured multiple sclerosis spasticity symptoms (oral cannabinoids)
- Improve Tourette syndrome
- Improve social anxiety disorders
- Improve posttraumatic stress disorder
- Are effective for improving symptoms associated with dementia
- Are effective for Improving intraocular pressure associated with glaucoma
- Are effective for reduction of depressive symptoms in individuals with chronic pain or multiple sclerosis
- Increase risk for non-seminoma-type testicular germ cell tumors (current, frequent, or chronic cannabis smoking)
- Triggers acute myocardial infarction (cannabis smoking)
- Induce ischemic stroke or subarachnoid hemorrhage
- Decrease risk of metabolic syndrome and diabetes
- Increase risk of prediabetes

# Limited Evidence of *NO* Statistical Association

- **Worsening of negative symptoms of schizophrenia (e.g., blunted affect) among individuals with psychotic disorders**
- An increased risk of acute myocardial infarction
- The progression of liver fibrosis or hepatic disease in hepatitis C (HCV) (daily cannabis use)
- Pregnancy complications for the mother
- Admission of the infant to the neonatal intensive care unit (NICU)
- **Impaired academic achievement and education outcomes**
- Increased rates of unemployment and/or low income
- Impaired social functioning or engagement in developmentally appropriate social roles

# Limited Evidence of a Statistical Association

- **An increase in positive symptoms of schizophrenia (e.g., hallucinations) among individuals with psychotic disorders**
- The likelihood of developing bipolar disorder, particularly among regular or daily users
- The development of any type of anxiety disorder, except social anxiety disorder
- Increased symptoms of anxiety (near daily cannabis use)
- Increased severity of posttraumatic stress disorder symptoms among individuals with posttraumatic stress disorder
- Childhood anxiety and childhood depression are risk factors for the development of problem cannabis use
- The initiation of tobacco use
- Changes in the rates and use patterns of other licit and illicit substances

## No or Insufficient Evidence to Support or Refute an Association

- Cancers, including glioma
- Cancer-associated anorexia cachexia syndrome and anorexia nervosa
- Symptoms of irritable bowel syndrome (dronabinol)
- Epilepsy
- Spasticity in patients with paralysis due to spinal cord injury
- Symptoms associated with amyotrophic lateral sclerosis
- Chorea and certain neuropsychiatric symptoms associated with Huntington's disease
- Motor system symptoms associated with Parkinson's disease or the levodopa-induced dyskinesia (cannabinoids)
- Dystonia (nabilone and dronabinol)
- Achieving abstinence in the use of addictive substances (cannabinoids)
- **Mental health outcomes in individuals with schizophrenia or schizophreniform psychosis**

## No or Insufficient Evidence to Support or Refute an Association (cont.d)

- Incidence of esophageal cancer (cannabis smoking)
- Incidence of prostate cancer, cervical cancer, malignant gliomas, non-Hodgkin lymphoma, penile cancer, anal cancer
- Kaposi's sarcoma, or bladder cancer
- Subsequent risk of developing acute myeloid leukemia/acute non-lymphoblastic leukemia, acute lymphoblastic leukemia, rhabdomyosarcoma, astrocytoma, or neuroblastoma in offspring (parental cannabis use)
- Other adverse immune cell responses in healthy individuals (cannabis smoking)
- Adverse effects on immune status in individuals with HIV (cannabis or dronabinol use)
- Increased incidence of oral human papilloma virus (HPV) (regular cannabis use)
- All-cause mortality (self-reported cannabis use)
- Occupational accidents or injuries (general, nonmedical cannabis use)
- Death due to cannabis overdose
- Later outcomes in the offspring (e.g., sudden infant death syndrome, cognition/academic achievement, and later substance use)
- **Changes in the course or symptoms of depressive disorders**
- **The development of posttraumatic stress disorder**

# Some Research Disagrees

- Daily cannabis users are 34% more likely to be diagnosed with coronary artery disease
- THC causes tachycardia and atrial fibrillation within 1 hour of exposure
- THC increases the risk of myocardial infarction, stroke, and heart failure



# e-Cigarette or Vaping Use-Associated Lung Injury (EVALI)

- Emergency room visits for cough, chest pain, shortness of breath, abdominal pain, nausea, vomiting, diarrhea, chills, or weight loss peaked August-September 2019. February 2020: More than **2,800 patients with 68 deaths**
- Median age 21 with **15% less than 18 years old**
- $O_2\% \leq 88\%$ ; tachycardia (63%), tachypnea (43%), and fever (33%)
- Differential diagnosis
  - Influenza
  - Community-Acquired Pneumonia (*Streptococcus pneumoniae*; *Legionella*)
  - COVID-19
  - Acute Eosinophilic Pneumonia
- Pathology
  - **Diffuse bilateral bronchiolocentric “ground glass” pneumonia**
  - Acute fibrinous pneumonitis
  - Diffuse alveolar damage
  - Bronchiolitis obliterans (“popcorn lung”) – diacetyl flavoring in vaping cartridges also causes bronchiolitis obliterans
- Vitamin E acetate - illegal diluent in counterfeit THC containing cartridges detected in bronchoalveolar lavage fluid

# Cannabis Screening

- Urine drug screens for marijuana is radioimmunoassay that uses antibodies that bind to the metabolite 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid.
- UDS is a colorimetric test, i.e., the test changes color when the concentration of the metabolite is above a threshold value, e.g., 50 ng/ml - the test does not measure the concentration of the metabolite
- Gas chromatography-mass spectrometry (GC-MS) test, which uses a threshold of 15 ng/mL
- A single use of marijuana is typically detectable for 3 to 7 days, moderate use can be detected for 5 to 7 days, daily use for 10 to 15 days
- Positive results for THC carboxylase have been reported up to 10 days after weekly use and up to 30 days after heavy daily use, making the timeline of exposure different and the severity of intoxication difficult to correlate

# False Negative Urine Cannabis Screening

- Over-the-Counter Yellowroot Cannabis Antagonists
  - Yellowroot species
    - Xanthorhiza simplicissima (**Yellowroot**)
    - Hydrastis canadensis (**Goldenseal**)
  - Biochemistry: isoquinoline alkaloids
    - Hydrastine - structurally related to bicuculline is a potent inhibitor of GABA A receptor
    - Berberine
    - Hydrastinine
    - Berberastine
  - Biotransformation
    - Inhibition of cytochrome P450 CYP2D6, CYP3A4 and CYP3A5
  - Toxicity
    - Teratogenic - brain damage
- Visine Eye Drops
  - Tetrahydrozoline
  - Benzalkonium Chloride
  - Boric Acid

# False Positive Urine Cannabis Screening

- Dronabinol, (Marinol) a synthetic cannabinoid 30% to 45%
- Efavirenz (Sustiva)
- Proton Pump Inhibitors
- Hemp seed oil
- NSAIDs (0.02%), dose-dependent > 1.2 grams
- Baby wash products in infants
- Gas chromatography has significantly less false positives

# Cannabis Toxicology and Overdose

- Doses > 7.5 mg/m<sup>2</sup> inhaled in adults and oral doses from 5 to 300 mg in pediatrics can produce hypotension, panic, anxiety, myoclonic jerking/hyperkinesia, delirium, respiratory depression, ataxia, depersonalization, fear of dying, irrational panic, and paranoid ideas
- Inhaled doses of 2 to 3 mg of THC and ingested doses of 5 to 20 mg THC can cause impairment of attention, memory, executive functioning, and short-term memory
- Conjunctivitis is a consistent physical exam finding
- In children, lethargy and hyperkinesia can be signs of life-threatening toxicity
- Adults present with hyperemesis, behavioral problems, impaired judgment, chronic cough, bronchospasm
- The risk of heart attack is generally five times higher right after smoking weed

# Laced Cannabis

- “Loveboat” in the ‘70s and ‘80s: Formaldehyde or Ethylene Glycol (Antifreeze)
- "Loud": Gasoline?
- Fentanyl
- Xylazine "Tranq"
  - Overdose deaths: Philadelphia: 26%, Maryland: 19%, Connecticut: 10%

# Child (Pet) Cannabis Poisoning (Edibles)

- **Colorful sugar-coated candies, e.g., gummies, worms, cookies, chocolate candy bars, etc.**
  - Secondary exposure by inhalation of smoke
- **From 2017 to 2023 child overdoses of edible cannabis increased from 207 to 3054 cases, a 1375% increase**
- Age under 6
- Child cannabis poisoning accounts for 41% of all poisonings
- 98% of poisonings occurred in the home
- 22% required hospitalization
- **Altered Mental Status**
  - Obtundation - mild to moderate decreased alertness evident as loss of interest in the environment and slower than normal reactivity to stimulation
  - Stupor - unresponsiveness with little or no spontaneous movement requiring vigorous and repeated stimulation to arouse
  - Coma - unarousable, sustained unconsciousness for at least 1 hour

# CBD Poisoning

- Only 30% of CBD products from 31 companies were accurately labeled for CBD and THC content; while 40% had higher concentrations, the remainder lower or negligible concentrations (Bonn 2017).
- Anecdotal observations of the use of CBD as a folk medicine for child ailments, e.g., colds, aches and pains, etc.
- 42% of CBD users replaced over-the-counter pharmaceuticals to treat: anxiety (67%), insomnia (60%), joint pain and inflammation (52%), depression (43%), headaches (38%), and chronic pain (30%).
- CBD creams and ointments present problems for children who have greater surface area to volume ratio than adults leading to greater absorption into the circulation and higher plasma concentrations
- Case Reports CBD Poisoning (Herbst 2020; Bass 2020)
  - Respiratory depression with impaired O<sub>2</sub>%
  - Respiratory acidosis
  - Bradycardia
  - Obtundation
  - Vomiting
  - Creatine kinase elevation
  - Lactic acidosis



# Synthetic Marijuana Poisoning

- Masquerades as CBD
- 4-cyano CUMYL-BUTINACA (4-CCB)
  - EC<sub>50</sub> values of 0.58 nM and 6.12 nM for CB<sub>1</sub> and CB<sub>2</sub> receptors, respectively
  - Cyanide byproduct of metabolism
  - Hyperthermia
  - Rhabdomyolysis
  - Seizures
  - Renal failure

# Legal History of Marijuana

- Cannabis became "marihuana" after 1910 attached to Mexicans immigrating to the US to escape the Mexican Revolution. Mexicans were denigrated as vagrants smoking "locoweed" trafficking the drug. Others included "Negroes, prostitutes, pimps, and a criminal class of whites"
- Opium and Coca Leaves Trade Restrictions Act (Harrison Narcotics Tax Act) of 1914 did not class cannabis
- Rodrigues Dória, a Brazilian psychiatrist, "the pernicious and degenerative vice" of "savage" Blacks (1915)
- Reefer Madness (1936) - film attributes loose morals, crime, and orgies high on marijuana to Black music (streaming on YouTube)
- Marihuana Tax Act of 1937 - Harry J Anslinger, head of the Federal Bureau of Narcotics
- Army Board of Inquiry finds no disadvantages to cannabis use in the Panama Canal Zone

# Legal History of Marijuana (cont.d)

- Single Convention on Narcotic Drugs (1961)
- *Leary v. United States* 1969: Supreme Court of the United States declares Marijuana Act violates the Fifth Amendment against self-incrimination
- *Controlled Substances Act* (1970) Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970 classified THC and CBD as Schedule I drugs.
- Shafer Report: *Marihuana: a signal of misunderstanding; first report* (1972) - United States. Commission on Marihuana and Drug Abuse
  - marijuana is not a gateway drug and does not induce violence, insanity or sex crimes, which contradicted Richard Nixon's explicit directive to conclude the contrary
- Oregon becomes the first state to decriminalize cannabis - 1973
- Colorado and Washington legalize recreational marijuana - 2012
- The Medical Marijuana and Cannabidiol Research Expansion Act (2022)

# Cannabis Legal History

- Agricultural Act of 2018 (2018 Farm Bill)
  - President Donald Trump's 2018 farm bill defined hemp as containing less than 0.3% THC and explicitly legalized "hemp and hemp-derived products," removing them from Schedule I and regulation by the Controlled Substance Act of 1970
  - Marijuana-derived CBD remains a controlled substance regulated by the Food and Drug Administration (FDA) and Drug Enforcement Administration (DEA), despite there is no difference in the CBD molecule derived from either variant
- High Intensity Drug Trafficking Areas (HIDTA) program}
- Amateur and Professional Athletes
  - $\Delta$ -9 Tetrahydrocannabinol is listed as a prohibited substance by the World Anti-Doping Agency (WADA).
  - WADA permits the use of CBD. Unfortunately, studies of over-the-counter and internet CBD oil products have found up to 30% show  $\Delta$ -9 THC contamination content as high as 2.5 mg that will test positive for cannabis use

# Alcohol (Marijuana?) Outlet Density

- **Alcohol outlet density directly correlates with alcoholism in adults and proximity to schools with teenage alcohol abuse. Can one expect the same for marijuana?**
- **Although African American and Hispanics report lower use, alcohol outlet density is highest in Black and Hispanic redlined districts (Lee JP et al. SSM Popul Health 2020; doi:10.1016/j.ssmph.2020.10069). Can one expect the same for marijuana?**
- **New York City is the most densely populated city in US, 27,747.9/sq mile. Brownsville, Brooklyn, 91.8% Black, has the highest concentration of public housing in the country, with 30 liquor stores within reach**
  - **1<sup>st</sup> in elementary school absenteeism 40/100,000 (20 or more school days) [NYC COMMUNITY HEALTH PROFILES 2015]**
  - **2<sup>nd</sup> in pre-term births 13.3/100,000**
  - **8<sup>th</sup> teen pregnancies 38.5/100,000 (ages 15-19)**
  - **2<sup>nd</sup> in incarceration rate at 348/100,000**
  - **1<sup>st</sup> in violent assaults 180/100,000**
  - **4<sup>th</sup> in alcohol-related hospitalizations 2,285/100,000**
  - **4<sup>th</sup> in drug-related hospitalizations 2,682/100,000**
  - **4<sup>th</sup> in HIV incidence 66/100,000**

# Teen Casual Marijuana Use Outcomes

Sultan RS et al. JAMA Network Open. 2023;6(5):e2311294.

- Arrest (adjusted odds ratio, 4.15)
- Aggression (2.16)
- Fighting (2.04)
- Suicidal ideation (2.08)
- Truancy (1.90)
- Major depression (1.86)
- Difficulty concentrating (1.81)
- Low grade point average (1.80)
- Slower thoughts (1.76)

# African American Teen Suicides Before COVID-19

- African American teen suicide up 47% for males and 59% for females
- Marijuana use odds ratio for **suicidal ideation 1.50** (95% CI, 1.11-2.03) and for **suicide attempts 3.46** (95% CI, 1.53-7.84) (Gobbi G et al. JAMA Psychiatry 2019;76(4):426-434)
- Early onset marijuana use reported suicidal ideation 3 times the rate of non-users (Floyd LJ. J. Ethnicity in Substance Abuse 2023; 2:1-15)
- Marijuana legalization associated with increased rate of suicide among 14-16 year old youth (Hammond CJ et al. J Child Adol Psych 2023)
- Cannabis users 6.9 times more likely to attempt suicide (Hinckley JD et al. JAACP OPEN 2023; 1(1):24-35)
- Among 626 completed suicides of 15-17 year-old Black youths 29.2% tested positive for marijuana, compared to 5.6% of 5-11 year old children (Sheftal AH et al. J Child Adol Psych 2022; 61(5):662-675)

# Coming Marijuana Outlet Density

- **U.S. Department of Health and Human Services recommends to DEA marijuana be rescheduled from a Schedule I to a Schedule III controlled substance - 8/29/2023**
- 2023 Cosponsored bill HB1080 in the Pennsylvania Senate and House proposes **converting state alcohol outlets to marijuana outlets** (Senator Marty Flynn and Representative David M. Delloso)
- Expunge marijuana possession convictions
- Justification: consumer safety, social justice, economic equity, substance abuse prevention and revenue
- State auditor estimated PA marijuana market at \$1.66 billion. Industry experts estimate the market at \$4 billion
- Pennsylvania Independent Fiscal Office estimated tax revenues between \$500 and \$700 million (current \$41.8 million)
- Philadelphia's poorest neighborhoods less than 10% white have more than 3 outlets per sq mile whereas neighborhoods with <16% of residents below the Federal poverty level and >57% white have less than 2 outlets per sq mile (Drexel University Urban Health Collaborative)



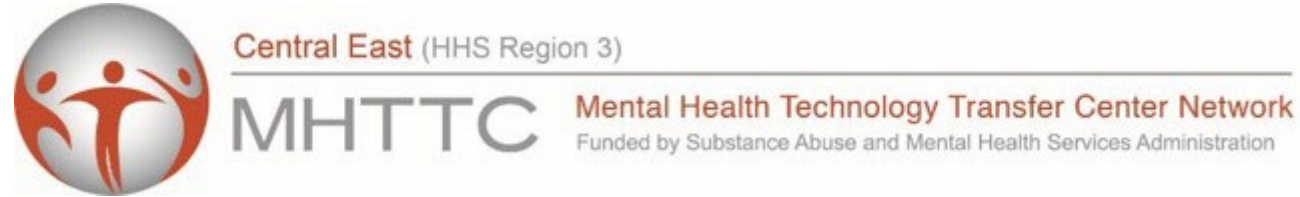
# Questions



# Appreciation



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