

Marijuana: A Tale of Two Patients

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Disclosures

- I have no financial disclosures.
- I am solely and exclusively presenting in my capacity as an individual and not representing or attempting to speak on behalf of OSU or the OSU-CHS

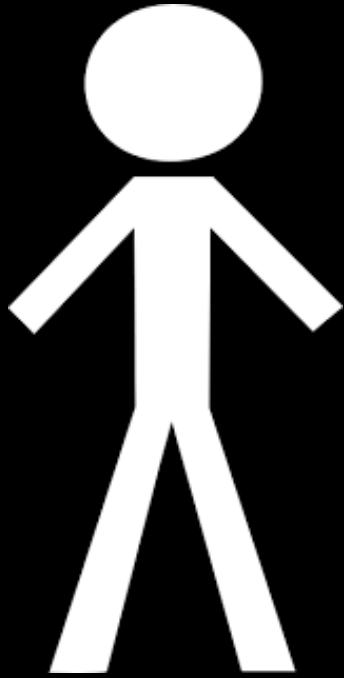
Objectives

- Learn about the complex components of the **Cannabis** plant
- Review the **research** on how marijuana affects the individual
- Define the **risks and benefits** of marijuana use
- Understand the intersection of marijuana and **current laws**
- Clarify next steps if someone **needs help**

“It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity, it was the season of Light, it was the season of Darkness, it was the spring of hope, it was the winter of despair, we had everything before us, we had nothing before us, we were all going direct to Heaven, we were all going direct the other way—in short, the period was so far like the present period, that some of its noisiest authorities insisted on its being received, for good or for evil, in the superlative degree of comparison only.”

-Dickens, A Tale of Two Cities

A Tale of Two Patients



Cannabis – a complex plant

- Over 400 chemical entities

THC

Delta-9-tetrahydrocannabinol

MOA: partial CB1R agonist

Psychoactive component

CBD

Cannabidiol

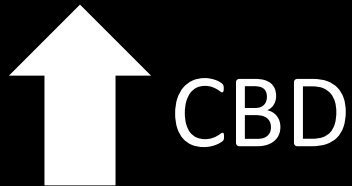
MOA: Unknown

Not Psychoactive

Cannabis – a complex plant



INDICA



CBD



SATIVA

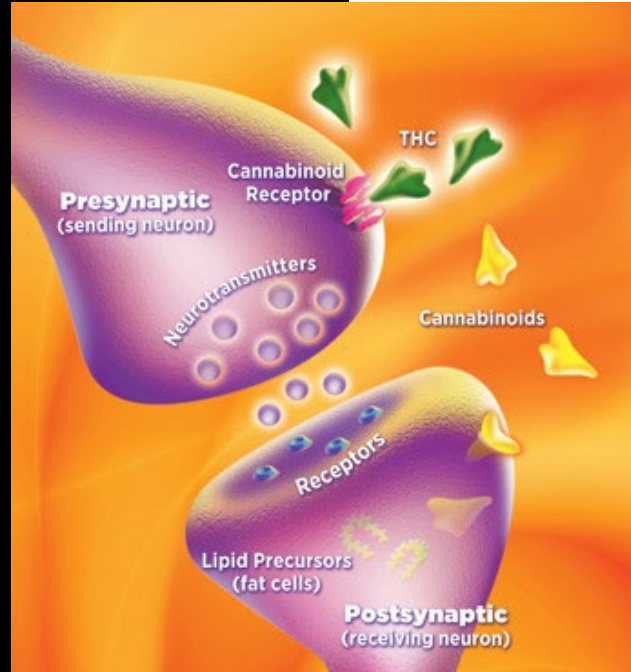


THC

Endocannabinoid System

AEA

Anandamide



2-AG

2-Arachidonylglycerol

Release from postsynaptic sites to work on presynaptic CB1 receptors to maintain homeostasis and prevent excessive neuronal activity

The are rapidly removed from the extracellular space

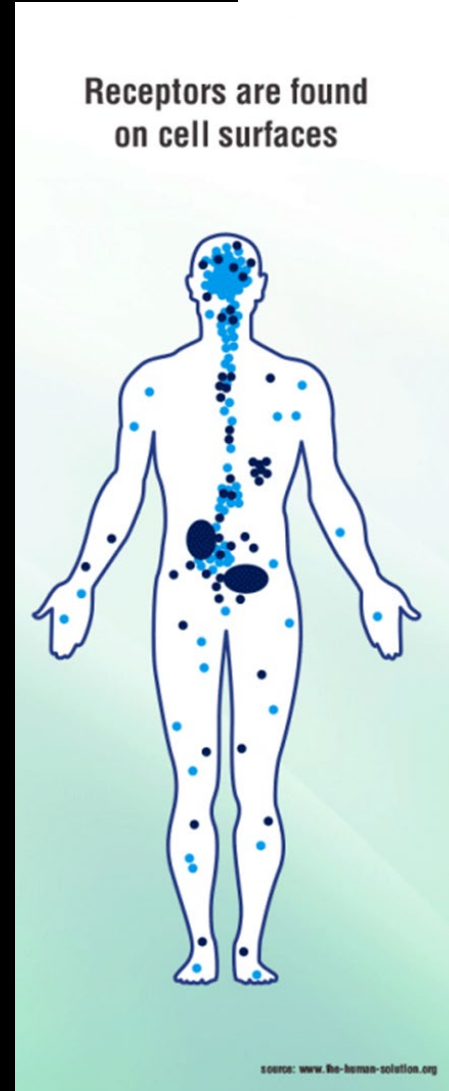
CB1 Receptors

- Mainly in the brain
- Also PNS, liver, thyroid, uterus, bones and testicular tissue, placenta

Activation results in changes in multiple neurotransmitter systems

CB2 Receptors

- Mostly expressed in immune cells, spleen, GI system
- Some brain and PNS, placenta



CB-like receptors.....

Data from the National Survey of Drug Use and Health 2016

- 24 million Americans ages 12 and older were current users of marijuana
- Past month users of marijuana corresponds to 8.9% of the U.S. population
- 1.6 million (6.5%) of adolescents ages 12 to 17 were current users of marijuana
- 7.2 million (20.8%) of young adults ages 18 to 25 were current users of marijuana
- 15.2 million (7.2%) of adults 26 years of age and older were current users of marijuana

Current formulations

- Oral preparations – with FDA indications
 - synthetic THC (dronabinol, Marinol[®])
 - Appetite stimulant for HIV/AIDS
 - Anti-emetic for chemotherapy induced nausea and vomiting
 - synthetic analog of THC (nabilone, Cesamet[®])
 - Chemotherapy induced nausea and vomiting
- Nabiximol's (Sativex) – mouth spray approved in UK with standardized THC/CBD dosing
- Other Routes of Administration: smoking, vaporizing, baked goods, tea, resins/oils, sub-lingual, suppository

Not your Momma's Marijuana

- Advances in cultivation techniques and grower knowledge have produced vastly **more potent** marijuana
- THC concentration has increased from 0.5% in 1970 to 10.6% in 2010
- CBD concentration has **fallen**
- The variable chemistry makes it challenging to study
- Much of the research on cannabis studied lower potency MJ and therefore may **not be as applicable**

BECAUSE MARIJUANA IS ILLEGAL, I WON'T SEE MY MOMMY FOR 12 YEARS...



Georgia
Cultivating Compassion By Georgia

BECAUSE MARIJUANA IS ILLEGAL, I WILL LIVE A LIFE OF PAIN...



BECAUSE MARIJUANA IS ILLEGAL, I WILL WATCH MY BROTHER DIE...



BECAUSE MARIJUANA IS ILLEGAL PEOPLE ALL OVER THE WORLD ARE SUFFERING



PLANT THE SEED OF CANNABIS EDUCATION TODAY!

SEED: MADE BY GOD

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Intoxication

- Mild euphoria
- Perceptual alterations
 - Time distortion
 - Intensification of ordinary experiences
- Infectious laughter
- Talkativeness
- Motor skills impairment
- Conjunctival injection
- Slurred Speech

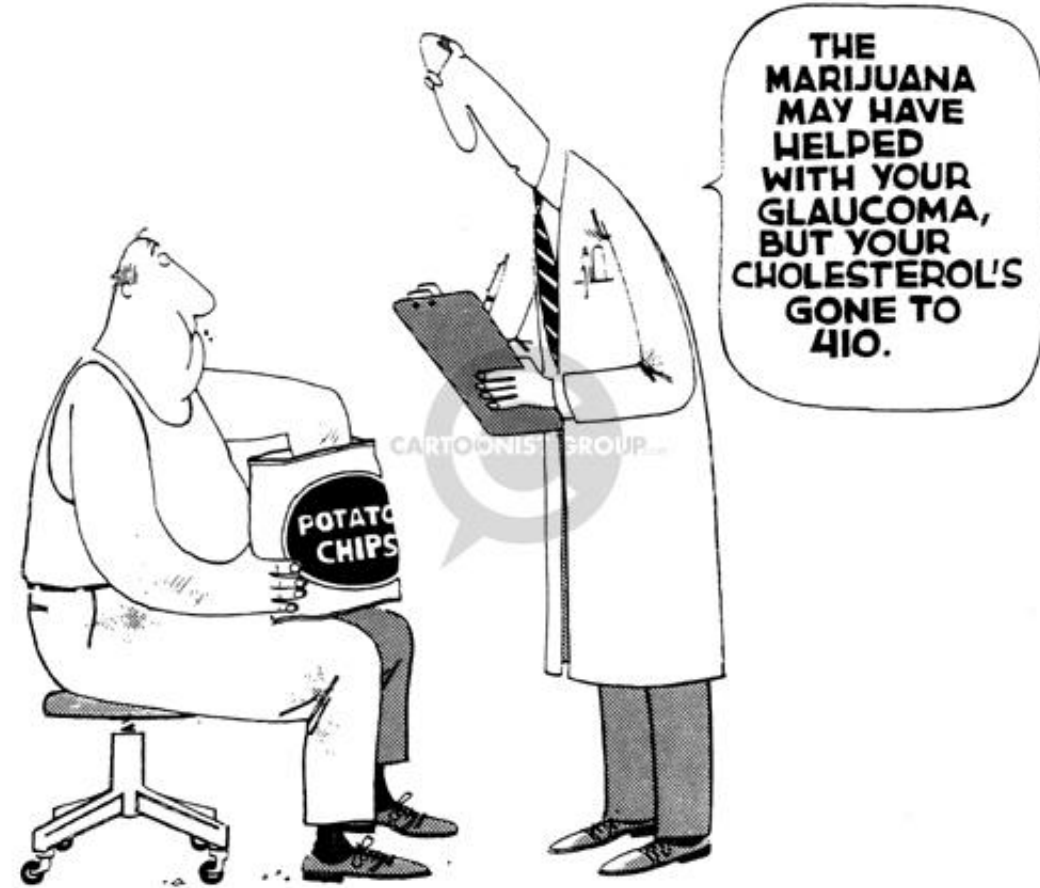


Lungs

- Inhaled marijuana causes respiratory irritation
- Users are at increased risk of both acute and chronic bronchitis
- Pound for pound, the quantity of tar inhaled through smoking MJ is **greater** than from smoking tobacco
- Cannabis smoke has shown to cause metaplastic changes in respiratory epithelium and may increase risk of **lung cancer** and head and neck cancer – but more research is needed

Cardiovascular

- CBD can cause bradycardia and hypotension
- THC can cause tachycardia and hypertension → increase workload
- Mittleman, et al (2001) studied 3882 patients who had heart attacks showed that in the hour after smoking MJ users were 4.8-fold more likely than non-users to have **heart attacks**



GI

- Both are strong **antiemetics**
 - Chemotherapy-induced nausea and vomiting
- THC > CBD slowed GI motility
- THC stimulates appetite
 - AIDS associated anorexia
- THC might have negative metabolic effects
- Some small studies show improvement in symptoms of Crohn's, but effects do not last and sample size is small
- **Cannabinoid hyperemesis** is a clinical syndrome characterized by repeated vomiting and associated learned compulsive hot water bathing behavior

Ophthalmologic

- THC > CBD reducing intraocular pressure
- The **American Academy of Ophthalmologists** does not recommend treating glaucoma with MM because the effect is short-lasting and MM causes cognitive impairment when compared to other standardized treatments
- MM can also lead to decreased blood pressure which lowers blood flow to the optic nerve and may increase risk of blindness

Cancer

- Cannabis **smoke** produces **mutations** in cells in the test tube and in live animals and hence is a potential cause of cancer, especially aerodigestive tract cancers
- New Case Studies report increased risk of **testicular cancer** (nonseminoma) among cannabis users

Cancer

- A laboratory study of CBD in human glioma cells showed that when given along with **chemotherapy**, CBD may make chemotherapy more effective and increase cancer cell death without harming normal cells
- Studies in mice and rats have shown that cannabinoids may inhibit tumor growth by causing cell death, blocking cell growth, and blocking the development of blood vessels needed by tumors to grow. Laboratory and animal studies have shown that cannabinoids may be able to kill cancer cells **while protecting normal cells.**
- Animal/Laboratory research: Breast cancer, colon cancer, hepatocellular cancer, non-small cell lung cancer
- “At this time, there is not enough evidence to recommend that patients inhale or ingest *Cannabis* as a treatment for cancer-related symptoms or side effects of cancer therapy” (cancer.gov)

Reproductive and Peri-natal effects

- **Animal studies:** MJ/THC have shown to effect secretion of reproductive gonadotrophic hormones, sperm production and capacitation, ovulation, fertilization, early embryonic development, implantation, placental functions, fetal growth, number of pregnancies carried to term, lactation, suckling behavior by newborns and growth of malignant breast and prostate cells
- Compounds in smoked marijuana **cross** the placenta and pass into **breast milk**
- Low birth weight, developmental delay, behavioral problems, stillbirth
- ACOG encourages **MJ cessation** during pregnancy and breastfeeding

Pain

- Several small studies have demonstrated **analgesic** effects of THC and CBD
 - can improve central and peripheral neuropathic pain
 - pain associated with rheumatoid arthritis and fibromyalgia
- In an RCT of 39 patients w/ complex regional pain syndrome, thalamic pain, spinal cord injury, peripheral neuropathy, radiculopathy or nerve injury, a **30% pain reduction** was found in
 - 26% of those in the placebo group
 - 57% in the low-dose group (1.29% THC)
 - 61% in high-dose group (3.53% THC)

Pain

- Likely safer than opioids – hard to overdose on, less addictive
- Alternative to NSAIDs which bring their own complications
- a trial employing an experimental model of neuropathic pain (intradermal injection of capsaicin) in healthy volunteers suggested that there may be a **“therapeutic window”** or optimal dose for smoked cannabis: low dose cigarettes (2% THC) had no analgesic effect, high dose (8%) was associated with reports of significant pain increase, and medium dose cannabis cigarettes (4% THC) provided significant analgesia

Pain

- Some benefit in **headache** syndromes
- A recent randomized trial suggests **highly-structured** approaches may result in successful analgesia and restoration of function without aberrant opioid use in “high risk” patients prescribed opioids for chronic pain
- Campbell et al. 2018 showed “**no evidence** that cannabis use reduced pain severity or interference or exerted an opioid-sparing effect” in a 4 year prospective cohort study.

CNS Effects

- Both THC, but more so CBD, have **anticonvulsant** effects
- THC>CBD muscle relaxant
- According to the American Academy of Neurology, medical marijuana may be considered an alternative treatment for **MS-related spasticity**
 - Compared to placebo, patients who received MM had significant adverse effects, primarily cognitive impairment
- Also the AAN state cannabis extracts are probably **ineffective** for levodopa induced dyskinesia in patients with Parkinson's disease but may improve sleep and pain in these patients.
- Behavioral disturbances associated with dementia?
- High doses lead to sedation and ataxia

Cognition

- Short-term Effects
 - THC causes problems with short-term memory, sensory perception, sense of time, attention span, problem solving, verbal fluency, psychomotor control
- Long-term Effects
 - Growing research to suggest subtle effects **may persist** after discontinuation
 - Functional imaging studies have shown less activity in brain regions in memory and attention in chronic marijuana users than in non-users, even **after 28 days** of abstinence
 - Long-term marijuana users have been shown to have **reduced volumes** of the hippocampus and amygdala

Driving

- Driving while under the influence of marijuana **doubles or triples** the risk of a crash:
 - Increases lane weaving, impairs critical-tracking tasks, reaction time and divided attention
- Although users can develop tolerance, they still can manifest impairment when there is a need to adaptively respond to sudden unexpected emergencies
- The combination of **alcohol and marijuana** produces levels of impairment greater than their independent sum

Addiction

- THC has been shown to stimulate mesolimbic **dopamine** release
- **Adolescent** initiators are **2 to 4 times** more likely to exhibit dependence within two years of their first use, up to 17%
- Withdrawal syndrome: anorexia, irritability, anxiety, depression, anger, restlessness and sleep disruption – especially the first 10 days

Addiction

- Tolerance may develop as quickly as 2-12 days of repeated use
- Intoxication alone is not deadly
- Harm and risk reduction vs. **Gateway drug**
- Nine percent of first-time cannabis users gets hooked



Addiction

- Cannabis Use Disorder

DSM-V Criteria for a Substance Use Disorder	
<p>The <i>Diagnostic and Statistical Manual 5</i> defines a <i>substance use disorder</i> as the presence of at least 2 of 11 criteria, which are clustered in four groups:</p>	
<p><i>Impaired Control</i></p> <ol style="list-style-type: none">1. Taking more or for longer than intended2. Unsuccessful efforts to stop or cut down use3. Spending a great deal of time obtaining, using, or recovering from use4. Craving for substance	<p><i>Risky Use</i></p> <ol style="list-style-type: none">1. Recurrent use in hazardous situations2. Continued use despite physical or psychological problems that are caused or exacerbated by substance use
<p><i>Social Impairment</i></p> <ol style="list-style-type: none">1. Failure to fulfill major obligations due to use2. Continued use despite problems caused or exacerbated by use3. Important activities given up or reduced because of substance use	<p><i>Pharmacologic Dependence</i></p> <ol style="list-style-type: none">1. Tolerance to effects of the substance2. Withdrawal symptoms when not using or using less

Mental Illness

- Pot-psychosis link
 - THC contributes to the **development and expression** of psychotic illness, especially in vulnerable populations
 - Appears dose-dependent based on systematic review by Zammit et. Al.
 - Once a psychotic disorder has developed, THC may make it **worse**
 - Earlier onset of symptoms, more severe and persistent psychotic symptoms, higher relapse rates and a worse prognosis due to poor treatment adherence
 - Brain volume loss significantly greater in schizophrenics who use MJ
 - Hall et. al document that cannabis use **doubles** the risk of developing psychosis from 7 in 1,000 to 14 in 1,000.
 - However, high **CBD** cannabis has been associated with fewer psychotic experiences

Intoxication Delirium

- Occurs at higher doses of THC
- Perhaps even at low doses in susceptible individuals
- Produces **visual and auditory hallucinations**, delusional ideas, thought disorders in normal users



A Word about Psychosis

What's the big deal?

1. Loss of connectivity to reality can be emotionally terrifying
2. Psychosis can stimulate **unsafe** behavior
3. Mounting evidence that psychosis itself is **harmful** to the brain

Mental Illness

- Depression & Anxiety
 - THC: **Anxiogenic**
 - CBD: Multiple studies have shown **anxiolytic** effects
 - Study of hair samples of daily users, those with higher THC levels were associated with **increased depression and anxiety** as well as poorer memory
 - “Paradoxical reaction” – dejection, dysphoria, depressed mood
 - Marijuana **Amotivational** Syndrome
 - **Withdrawal** also causes mood issues, which may be improved with MJ, thus making it appear it treats mood problems

Mental Illness

- PTSD
 - Some promising research that cannabinoids may facilitate the extinction of **aversive memories**
 - Small studies in veterans report **improved PTSD symptoms and sleep**

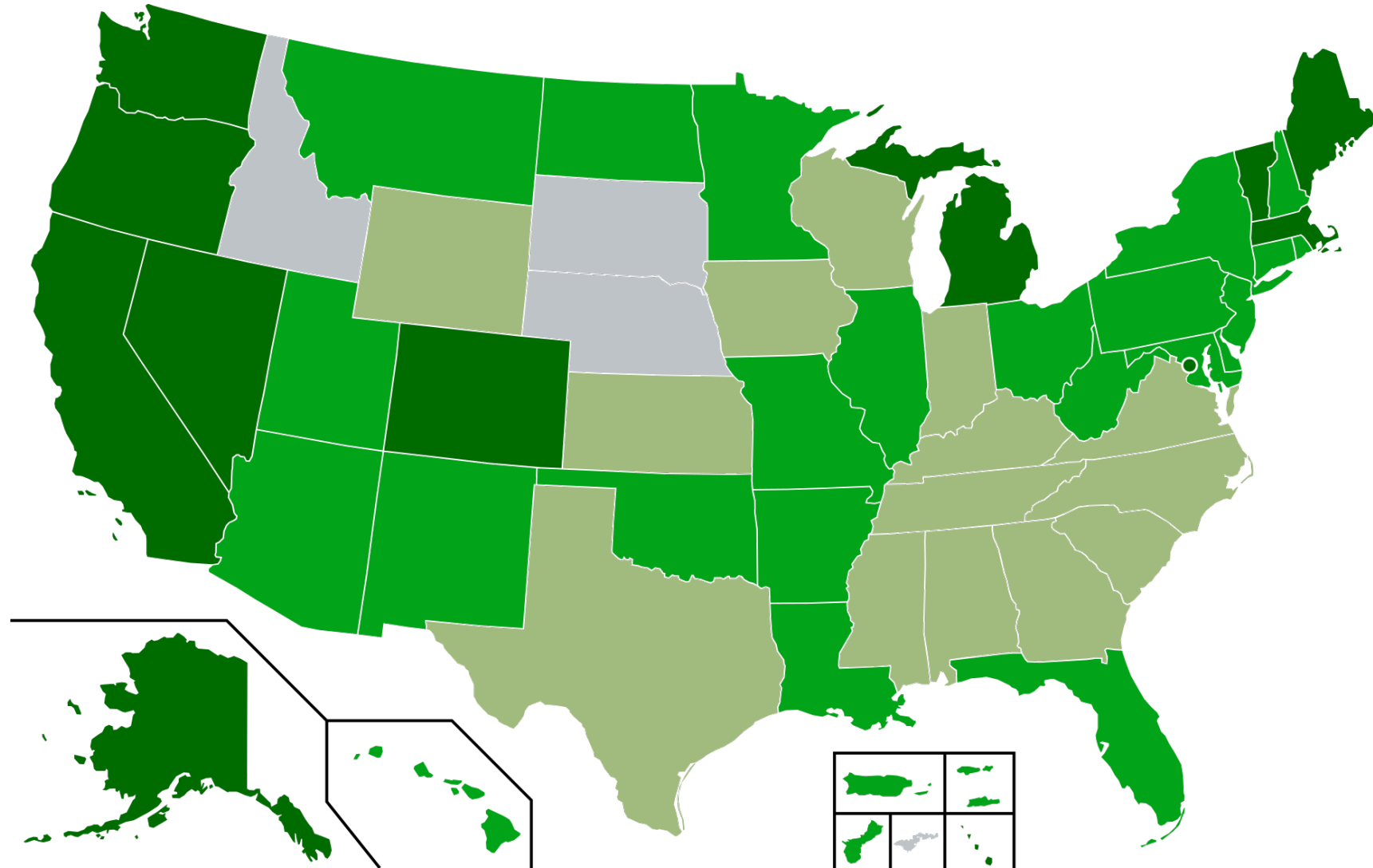
Adolescent use

- **Sensitive Window** of Development
 - Neurobiological circuits are pruned and reinforced
 - Sensitive to rewards and limited inhibitory structures
 - Increased risk for psychosis
- First use of cannabis typically begins in the mid- to late teenage years
- Heaviest use typically occurs in the early 20s

Adolescent use

- Associated with low academic achievement and increased rates of school drop-out
- Fergusson et al performed a longitudinal study of over 1,000 New Zealanders from birth to age 25 years of age
 - Elevated marijuana use between ages 14 and 21 was associated with lower likelihood of getting a bachelor's degree, lower income, higher unemployment and welfare dependence, lower levels of relationship and life satisfaction
 - These correlates **survived adjustments** for covariates, including socioeconomic status, maltreatment and comorbid mental disorders
- Disruptions in cognitive function may persist longer and **may not be recoverable**, especially as a result of adolescent use

Legal Issues



Legal Issues

- In states where **medical marijuana** is legal, you can receive a medical card from a physician which authorizes you to buy marijuana from specific dispensaries
- MM States generally have lists of qualifying conditions
- Dispensaries not subject to governmental standardization, and its constituents and potency are consequently unknown

Legal Issues in Oklahoma

- Oklahoma State Question 788 passed and emergency rules in place
 - 18 years or older may possess a marijuana license
 - Same regulations as Smoking Tobacco in Public
 - No limit on THC content.
 - Smokable MJ allowed.
 - No list of qualifying conditions
- Next legislative session will determine final guidelines
- The possession and use of marijuana is still **prohibited** under federal law

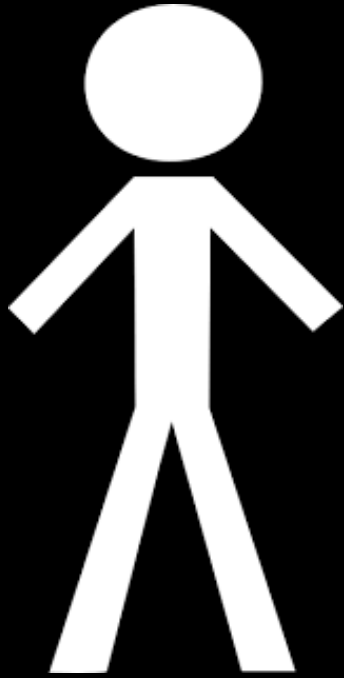
DEA Scheduling

- “**Schedule I drugs**, substances, or chemicals are defined as drugs with no currently accepted medical use and a high potential for abuse.
 - LSD, heroin and MDMA
- Schedule II drugs, substances, or chemicals are defined as drugs with a high potential for abuse, with use potentially leading to severe psychological or physical dependence. These drugs are also considered dangerous.” (DEA.gov)
 - Combination products with less than 15 milligrams of hydrocodone per dosage unit, cocaine, methamphetamine, methadone, hydromorphone (Dilaudid), meperidine (Demerol), oxycodone (OxyContin), fentanyl, Dexedrine, Adderall, and Ritalin
- Marijuana is Schedule 1
 - This makes access to the drug for scientific study more difficult

Treatment

- Cannabis Intoxication
 - Psychotic? → Safety. COPES (744-4800), 911
 - Reassurance and support
- Cannabis Dependence
 - Psychosocial Treatment
 - Cognitive Behavioral Therapy
 - Treat comorbid addictions
 - Treat comorbid psychiatric conditions
- **Where?**
 - SAMHSA (Substance Abuse and Mental Health Services Administration) Website
 - 211 – Eastern Oklahoma Services
 - Call Insurance Company

A Tale of Two Patients



Summary

- Cannabis contains an **extensive number** of pharmacological and biochemical compounds, of which only a minority are understood, so many potential therapeutic uses remain undiscovered.
- Changes in potency of marijuana, variance of components, delivery systems make applicable marijuana **research limited**
- **Schedule I** appears to be inconsistent with growing evidence of potential medicinal purposes of cannabis
- Public health burden of cannabis is probably modest compared to that of alcohol, tobacco, and illicit drugs ... but studies are limited.
- There is currently **narrow empirical basis for efficacy** compared to standard treatments.

RESEARCH

Summary

- CBD products have been legal in Oklahoma.
- MM is now legal in **Oklahoma** and under emergency rules until the Spring.
- MJ is not a good option for **vulnerable populations**, such as adolescents and those with mental illness or risk factors for mental illness.
- Like standard treatments, there are **risk and benefits** and patients should undergo informed consent
- Treatment is available for those who become dependent on marijuana

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