

Lobby Poll

What percentage of Americans have used marijuana in the past year?

- 5.2%
- 10.7%
- 15.9%
- 21.4%



Pacific Southwest (HHS Region 9)

PTTC

Prevention Technology Transfer Center Network

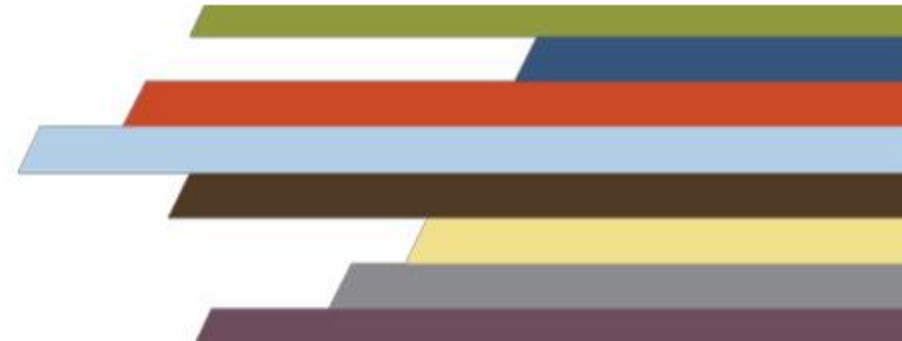
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Case Studies in Marijuana

From Pharmacology to the Emergency Department

Roneet Lev, MD, FACEP



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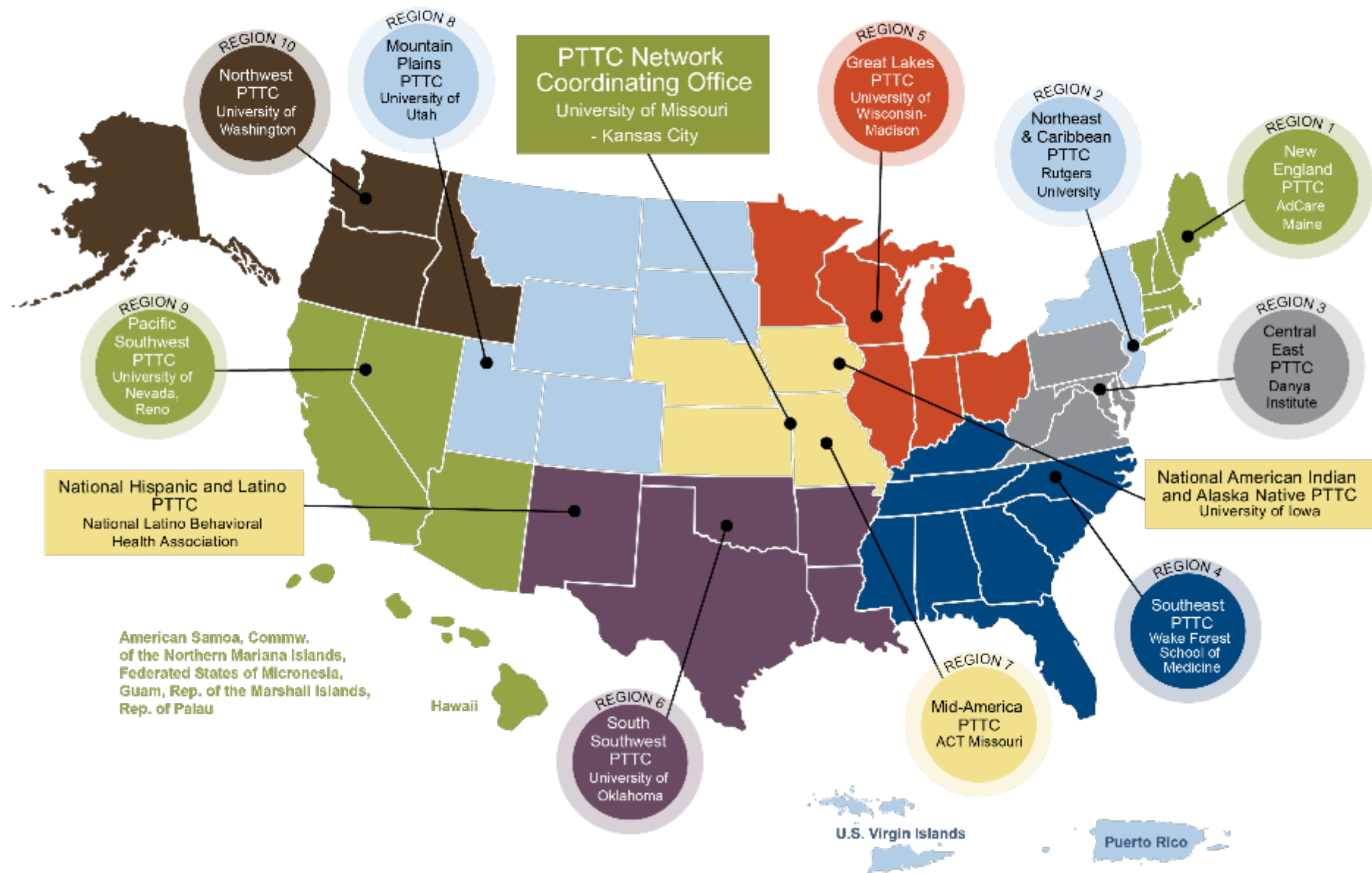
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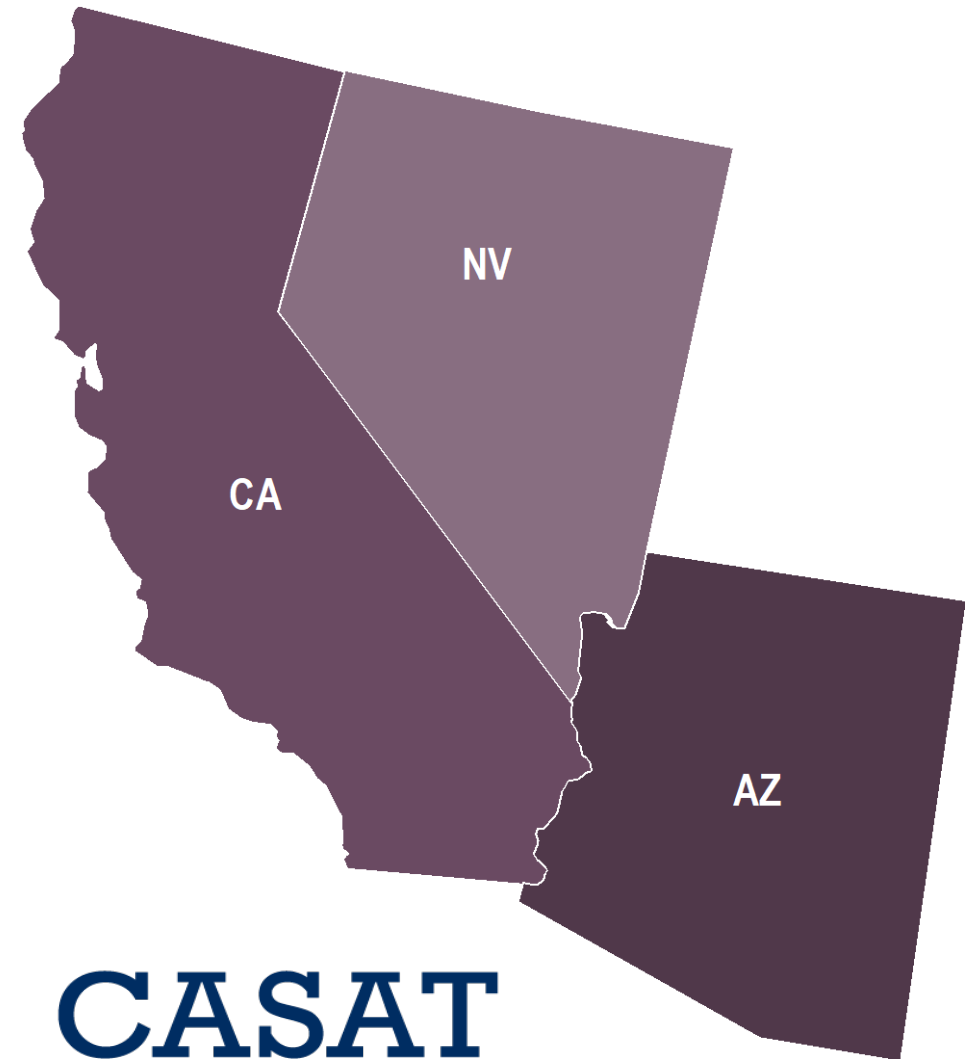
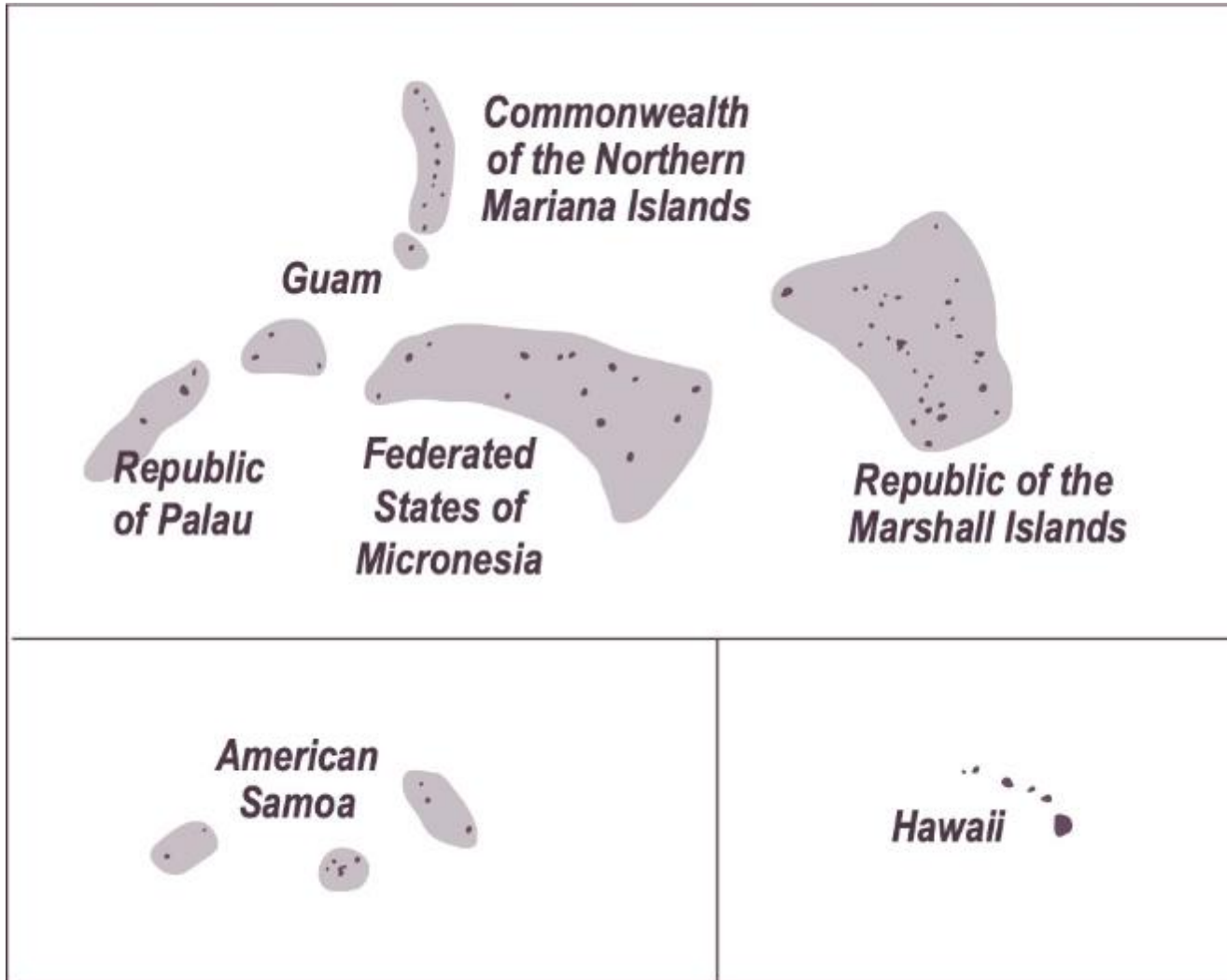
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Pacific Southwest



Mark Your Calendars!

**Substance Use Prevention in Native Communities:
Initiating and Sustaining Meaningful Connections Across Cultures**

September 23, 2020*

Why Health Equity Matters in Prevention – Part I

September 10, 2020

Part II

October 14, 2020

*all times 3:00 PM Pacific

Presenter



Roneet Lev, MD, FACEP, was the first Chief Medical Officer of the White House Office of National Drug Control Policy, ONDCP. She is a nationally acclaimed medical expert and speaker who continues to treat patients in the emergency department. As a mother of four, she relates to families who struggle. Dr. Lev is dually board certified in emergency and addiction medicine, bringing over 25 years of experience treating the frontline cases of addiction. She came to the White House as chief of the emergency department at Scripps Mercy Hospital in San Diego.



Case Studies in Marijuana from pharmacology to the emergency department

Roneet Lev, MD

Emergency and Addiction Physician

Scripps Mercy Hospital San Diego

Former White House Chief Medical Officer ONDCP

Marijuana Case Studies



Case Studies in Marijuana

1

What is Marijuana?

2

Pharmacology of Marijuana

3

Medical consequences of Marijuana

4

Cases from the Front Lines



Quiz

Which statement is false?

- a. Medical marijuana is safer than black market marijuana because it comes from a pure source
- b. 30% of marijuana users have a substance use disorder
- c. People have died from using marijuana
- d. Marijuana use in people under age 27 is associated with 4-7 x increase risk in addiction
- e. Marijuana use is associated with increase chance of bleeding (elevated PT/INR)
- f. 4.7% of pregnant women have used marijuana in past month



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Name this plant -

- "Natural
- Activates many neurochemicals
- Causes drug interactions with several medications
- Reduces anxiety and schizophrenia effects
- No one dies of one puff



Big Tobacco Lessons



... and possibly she may—for the amazing strides of medical science have added years to life expectancy

“I’m going to grow a hundred years old!”

• It’s a fact—a warm, wonderful fact—that this five-year-old child, or your own child, has a life expectancy almost a whole decade longer than was her mother’s, and a good 18 to 20 years longer than that of her grandmother. Not only the expectation of a longer life, but of a life by far healthier. Thank your doctor and thousands like him... tending ceaselessly... that you and yours may enjoy a longer, better life.



According to a recent Nationwide survey:

More Doctors smoke Camels than any other cigarette!

NOT ONE but three outstanding independent research organizations conducted this survey. And they asked not just a few thousand, but 113,597, doctors from coast to coast to name the cigarette they themselves preferred to smoke.

Answers came in by the thousands... from general physicians, diagnosticians, surgeons, nose and throat specialists too. The most-named brand was Camel.

If you are not now smoking Camels, try them. Let your “T-Zone” tell you (see right).

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CAMELS Costlier Tobaccos

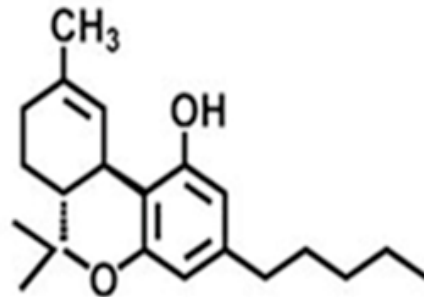
THE “T-ZONE” TEST WILL TELL YOU

The “T-Zone”—T for taste and T for throat—is your own proving ground for any cigarette. Only your taste and throat can decide which cigarette tastes best to you... how it affects your throat.

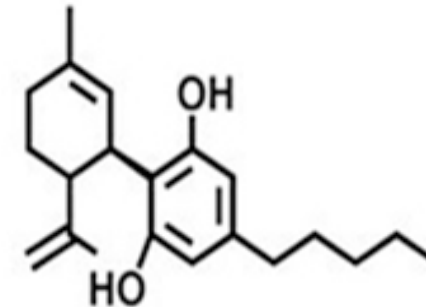
- **1920** German scientists link tobacco and cancer
- **1931** Hoffman, Cancer and Tobacco Habits
- **1950s** Many publications
- **1964** Surgeon General warning based on 7,000 articles
- **1980** Tobacco Law suits
- **1990** Ban on Flights

What is Marijuana?

- Plant: Cannabis sativa/indica with **over 420** known compounds
 - 60 active cannabinoids
 - Only **female** plants grow flowers
 - **Flowers/ Buds** have highest THC content
- THC: Delta -9-Tetrahydrocannabinol, psychoactive substance
- CBD: Cannabidiol – blocks psychoactive effect



Δ^9 -tetrahydrocannabinol
(THC)



Cannabidiol
(CBD)

What is “Synthetic” Marijuana?

- Human made chemical produced in a lab
 - Sprayed on plant, liquid in vaping devices
- Cannabinoids
- Illegal
- Spice/ K2 / Herbal or Liquid Incense
- Does not show up on drug tests
- Much greater psychoaffective effects
- Binds 100 – 800 x more to CB 1 receptor compared to THC
- You don't know what you are smoking



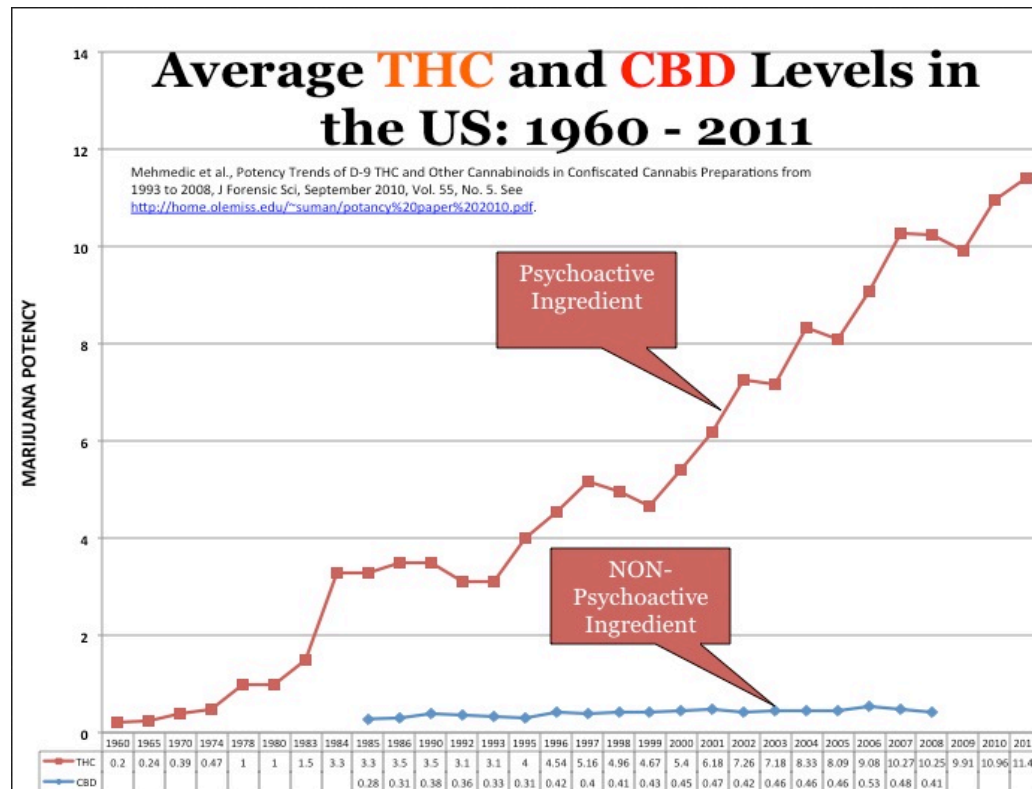
What is “Medical” Marijuana?

- “Medical” is **political** definition not a scientific definition
- **No different** in plant quality
- Not held to international medicinal standards of prescribing
- “Medical” users
 - Less than 3% of California users have cancer, HIV, seizures
 - Average age 32



Marijuana Potency

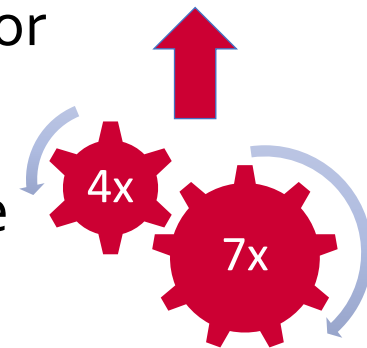
- THC Potency has been genetically increased over the years
- Hemp = can include 0.3% dry weight THC



	THC Content
1983	3.3%
2007	9.6%
Some plants	33%

Marijuana Statistics

- Youth age 12 – 18 who use marijuana are **4 – 7 times** more likely than adults to develop a cannabis use disorder
- **43.5 million** American age 12 or older used marijuana, **15.9%** of population
- **2.7 million** people age 12 and older meet criteria for marijuana use disorder
- **9 – 50%** of those who use marijuana develop some degrees of use disorder
 - 9% adults
 - 17% youth
 - 25-50% chronic users
- **4.7%** of Pregnancy Women Used Cannabis in past month



THC available by prescription

- Dronabinol (Marinol)
- Nabilone (Cesamet)
 - THC medications
 - Schedule III and II
 - 2.5 – 10 mg/ 0.25 – 1 mg
 - Treat nausea caused by chemotherapy and boost appetite in patients with AIDS wasting syndrome
- Nabiximols (Sativex)
 - approved in UK and Canada
 - 2.5 mg THC and 2.5 mg CBD / 0.1 cc
 - for multiple sclerosis



THC in pot shops

- **Varied state regulations**
 - CA: no regulation on smoked products
 - Edibles: no packaging attractive to children
 - Dose 10 mg per serving, 100mg per package
- **Product Diversity**
 - smoke, vape, edible, suppositories, drinks, wax, creams
- **Wax products – up to 99% THC**
- **Impurities including pesticides**



Truth in Labeling

75 products, 45 brands
17% accurate labeling
23% under label/ 60% over
label THC levels
THC = 0 – 6.4 mg/ml
JAMA study

CBD available by prescription

- The only FDA regulated CBD product is Epidiolex
- Indication: Dravet Syndrome or Lennox-Gastaut syndrome
- FDA studies show clinical side effects and adverse reactions

-----INDICATIONS AND USAGE-----
EPIDIOLEX is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older (1)

- WARNINGS AND PRECAUTIONS-----
- Hepatocellular Injury: EPIDIOLEX can cause transaminase elevations. Concomitant use of valproate and higher doses of EPIDIOLEX increase the risk of transaminase elevations. See Full Prescribing Information for serum transaminase and bilirubin monitoring recommendations. (5.1)

-----ADVERSE REACTIONS-----
The most common adverse reactions (10% or more for EPIDIOLEX and greater than placebo) are: somnolence; decreased appetite; diarrhea; transaminase elevations; fatigue, malaise, and asthenia; rash; insomnia, sleep disorder, and poor quality sleep; and infections. (6.1).



Warning:

- Liver damage
- Suicide
- Somnolence
- Sleep Disorder
- Infections

CBD in Pot Shops

- CBD = cannabidiol, in marijuana plant, hemp
- CBD products are Not Regulated
- Common Side Effects – liver damage, suicide
- Medication Interactions (pain, psychiatric, anti-histamines, blood thinners)
- Impurities including pesticides

Truth in Labeling

84 products

31% correct labeling

THC = 0 – 6.4 mg/ml

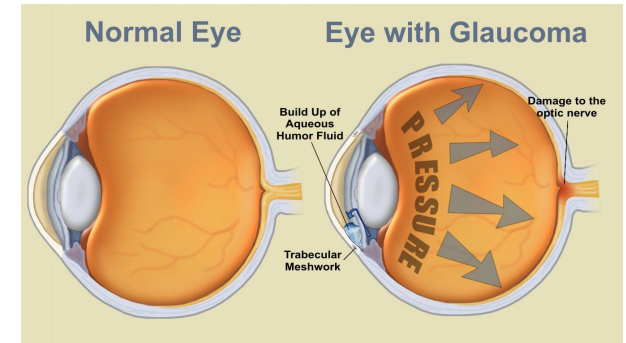
JAMA study



USP Seal = Dietary
Supplement
Standard Verified

Medical Society Position Statements

- **American Academy of Ophthalmology**
- **American Glaucoma Society**
 - Marijuana **not** recommend for glaucoma
- **American Epilepsy Society**
 - No recommendation of THC for seizure
 - Epidiolex for specific seizures
 - Caution in buying CBD from dispensaries
- **American Academy of Neurology**
 - Does not support legalization or prescription of “medical” marijuana for neurological disorders
- **American Society of Addiction Medicine**
 - Oppose legalization of marijuana
- **American Academy of Pediatrics**
 - Oppose marijuana use ages 0 – 21
 - Oppose “medical marijuana”
- **American College of Obstetrics and Gynecology**
 - Discourage marijuana use preconception, pregnancy, lactation



Marijuana for Pain



- Marijuana use does not reduce opioid use for people in chronic pain
- Marijuana users increase opioid use without obtaining more pain relief
- Concurrent marijuana and opioid use interferes with treatment of opioid use disorder
- Studies that show marijuana is helpful for pain use low dose THC, low number of patients and do not balance the risks

- Larkin PJ, Madras BK. Opioids, overdoses, and cannabis: is marijuana an effective response to the opioid abuse epidemic? *The Georgetown Journal of Law and Public Policy*.
- Nugent SM. Et al. Patterns and correlates of medical cannabis use of pain among patients prescribed long term opioid therapy. *Gen Hosp Psychiatry* 2018.
- Lee DC, et al. Systemic review of outcome domains and measures used in psychological and pharmacological treatment trials for cannabis use disorder. *Drug Alcohol Depend*. 2018.
- Shover LE, et al. Association between medical cannabis laws and opioid overdose mortality has reversed over time. *Proc Nat Acad Sci*. 2019.

Marijuana Research

Things to ask:

- How many people in study?
- What was dose of THC / CBD used?
- Who sponsored?

Opioid Epidemic
based on NEJM
Letter to the Editor
and study of 38
patients



Surgeon General Advisory on Marijuana and the Developing Brain - Adolescents



- No amount of marijuana use in adolescence is safe
- 9.2 million youth 12 – 25 reported marijuana use in past month (NSDUH 2019)
- Brain continues to develop up mid 20s
 - Changes in front lobe
 - Reduced school performance
 - Reduced life satisfaction
 - Impaired Driving
 - Psychosis, Schizophrenia
 - 130% greater likelihood of misusing opioids



Surgeon General Advisory on Marijuana and the Developing Brain - Pregnancy

- Pregnant woman should not use marijuana
- No one should smoke marijuana or tobacco around a baby
- Women who are breast feeding should not use marijuana
- Marijuana use in past month among pregnant women doubled from 3.4% to 7% between 2002 and 2017
- Marijuana use may make it hard for a mother to properly care for baby
 - Association with low birth weight and stillbirth
 - May disrupt fetal brain development
 - May cause preterm labor

CDC/FDA Investigation on Electronic/ Vaping Associated Lung Injury - EVALI

- 2807 cases, 68 fatalities, associated with EVALI (peak Sept 2019)
- Vitamin E acetate association
- Youth and young adults should not use e-cigarette products
- Pregnant women should not use e-cigarette products
- Anyone who uses an e-cigarette should not buy them off the street and should not modify or add any substances to these products
- Do not return to smoking cigarettes

For every **1** adult who quits cigarettes using e-cigarettes, **80** adolescents who never smoked will eventually become daily smokers through e-cigarette use



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Cases from the Front Lines

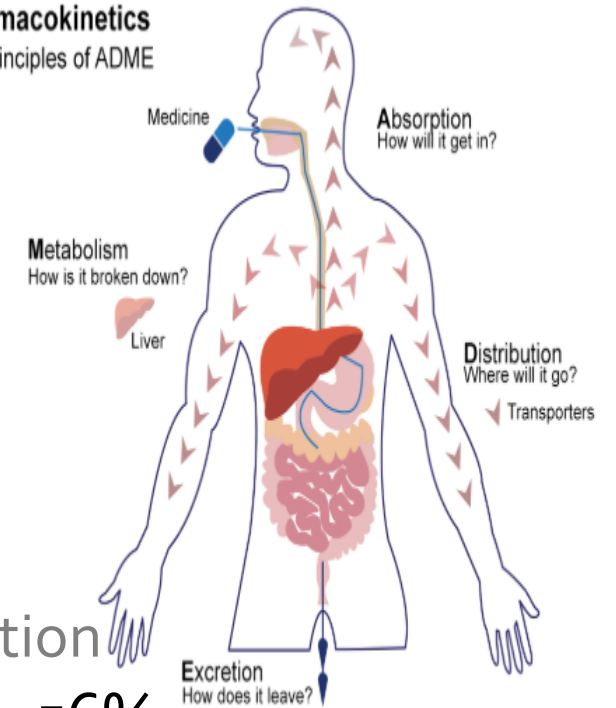


THC Pharmacokinetics

- **Absorption** – how drug gets in the body
 - Inhaled – peak concentration in 22 min
 - Oral/ Sublingual – 1-2 hrs – 8 hrs
 - Rectal/ Vaginal – 15 min
 - Transcutaneous – 2 hours
 - Intravenous – immediate
- **Bioavailability** - how much is degraded before action
 - Inhaled – drugs destroyed by pyrolysis – 2 – 56% available
 - Oral – drug destroyed in stomach first-pass effect: 10-20%
 - Rectal – 2x as much as oral
 - Transcutaneous – no degradation, 10% available
 - Intravenous – 100% available

Pharmacokinetics

The principles of ADME



www.medicosite.com

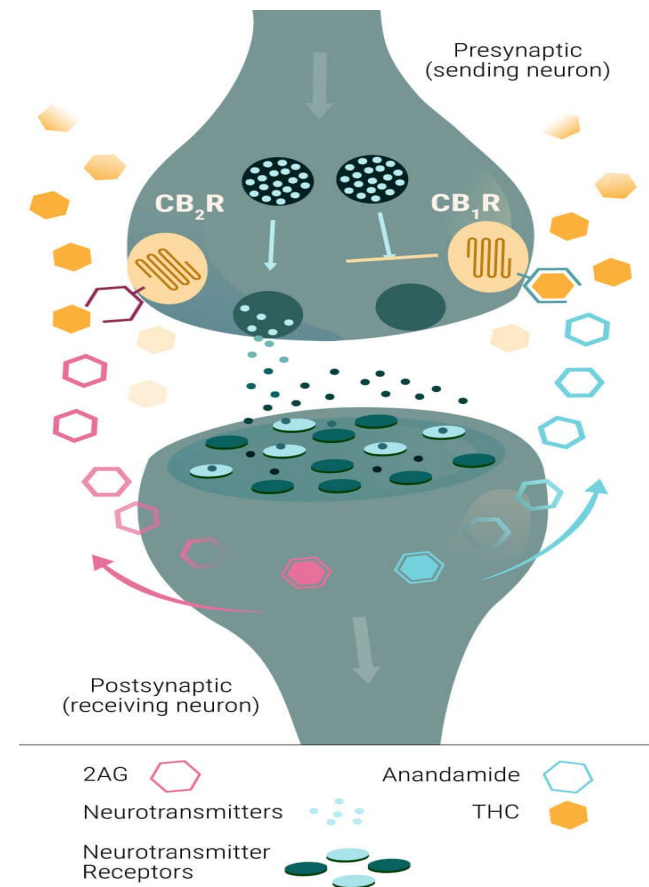
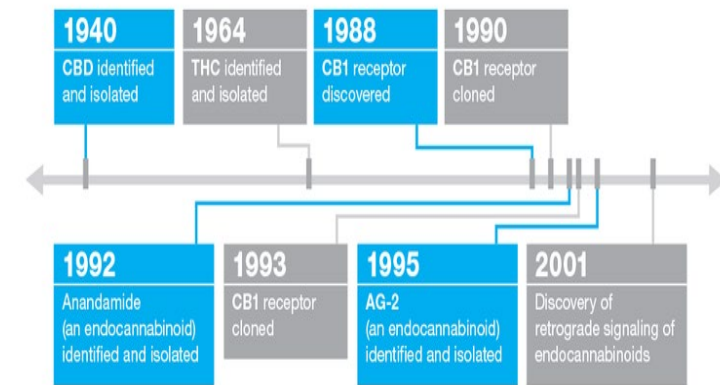
THC Pharmacokinetics

- **Metabolism** – how is drug broken down
 - Liver metabolism with CYP450 complexities
 - Marijuana + Coumadin = Toxic level of INR
 - Marijuana + Anti-depressants, SSRI = extend THC effects
 - More than 100 metabolites
 - Active Metabolites
 - 11-OH-THC - psychoactive
 - Inactive Metabolites
 - THC-COOH
- **Distribution** – where drug go
 - Lipophilic – brain, heart, lung, liver, muscle
 - Half – Life
 - Infrequent users – 1.3 days
 - Frequent users – 3 – 13 days
 - - able to store and recirculate THC (unlike opioids or alcohol)
 - Placenta/ Breast Milk
- **Excretion** – how does it leave body
 - Urine 20 % - THC-COOH
 - Feces 65% – 11-OH-THC



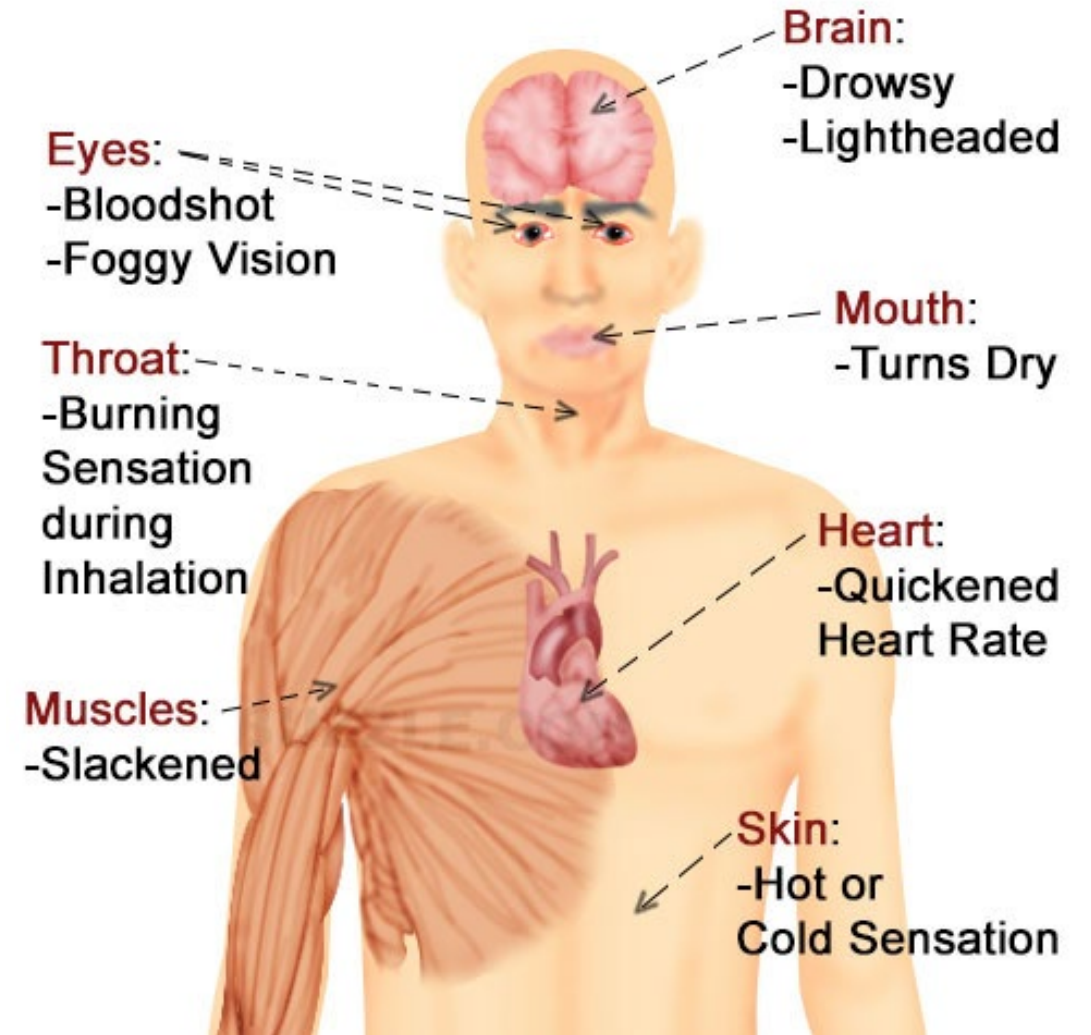
Endocannabinoid System

- Two Main Receptors – G proteins (the lock)
 - CB₁** – brain and spinal cord (1990)
 - CB₂** – immune system, blood and spleen (1993)
- Endogenous (naturally produced) (the keys)
 - Anandamide (AEA)**
 - partial agonist to **CB₁**
 - Endocannabinoid 2-arachidonoylglycerol (**2-AG**)
 - full agonist **CB₁** and **CB₂**
- Marijuana
 - THC** – partial agonist **CB₁**, similar structure to **Anandamide**
 - CBD** – weak antagonist to endocannabinoid receptors
- Anandamide action (rodent studies)
 - “runner’s high”, impair memory, fertility



Marijuana Activity on the Body

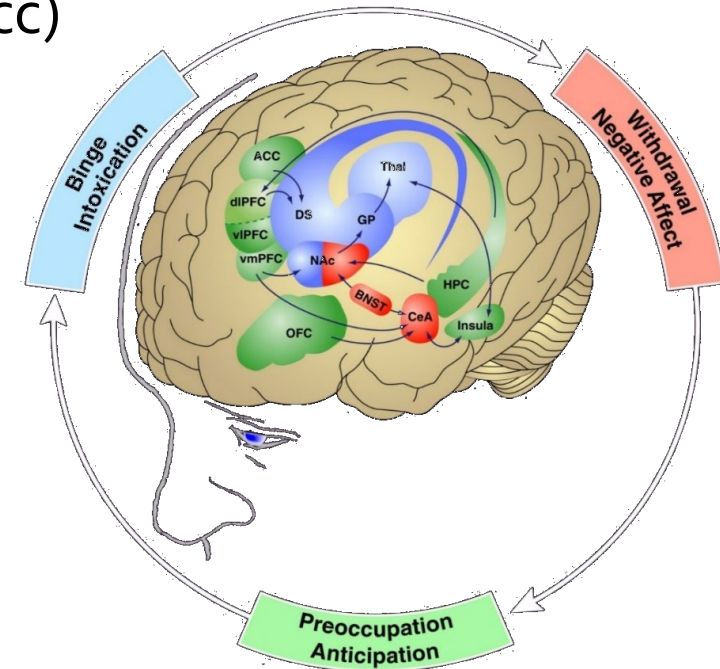
- Hippocampus – Memory
- Cerebellum- balance, posture, coordination, reaction time
- Stimulant symptoms: fast heart rate, chest pain
- Neuropsychiatric symptoms
- Immune and Gastrointestinal effects



Implication in Reward Cycle of Addiction

■ Three Stage Cycle of Addiction

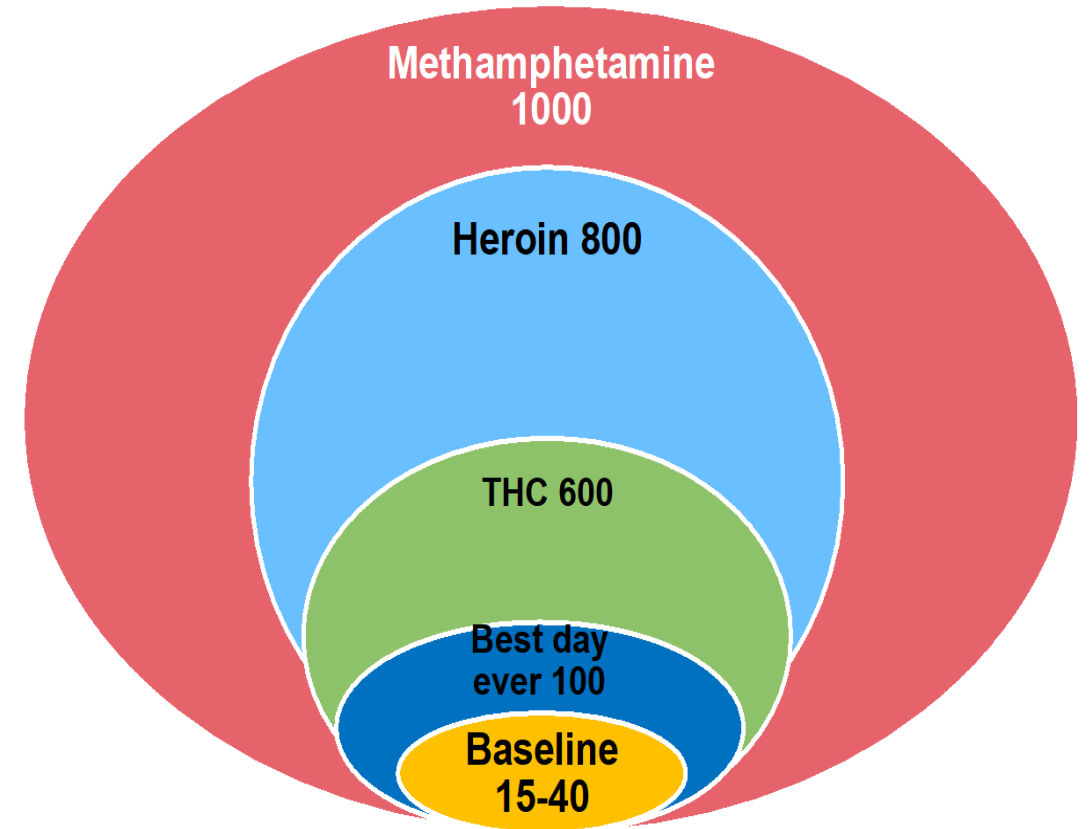
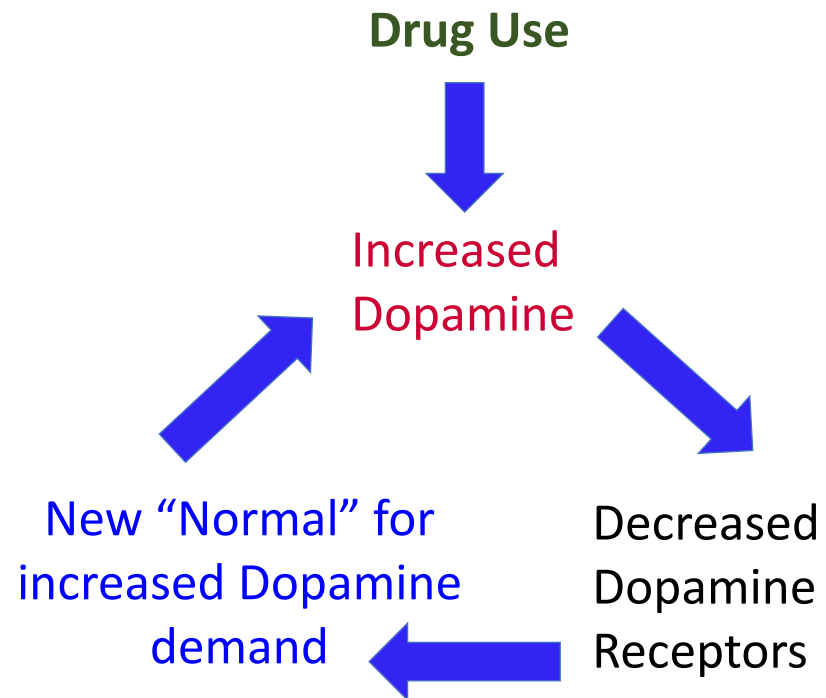
1. Binge/Intoxication Stage
 - Basal Ganglion/ Ventral Trigeminal Area (VTA)
 - Dopamine - goes to nucleus accumbens (NAcc)
2. Withdrawal/ Negative Affect Stage
 - Amygdala
 - Corticotrophin Releasing Factor, Dynorphin, Norepinephrine, Vasopressin
3. Preoccupation/Anticipation Stage
 - Frontal Cortex
 - Glutaminergic



Koob GF, Volkow ND. *Neuropsychopharmacol Rev*, 2010, 35:217-238; George O, Koob GF. *Proc Natl Acad Sci USA*, 2013, 110:4165-4166.

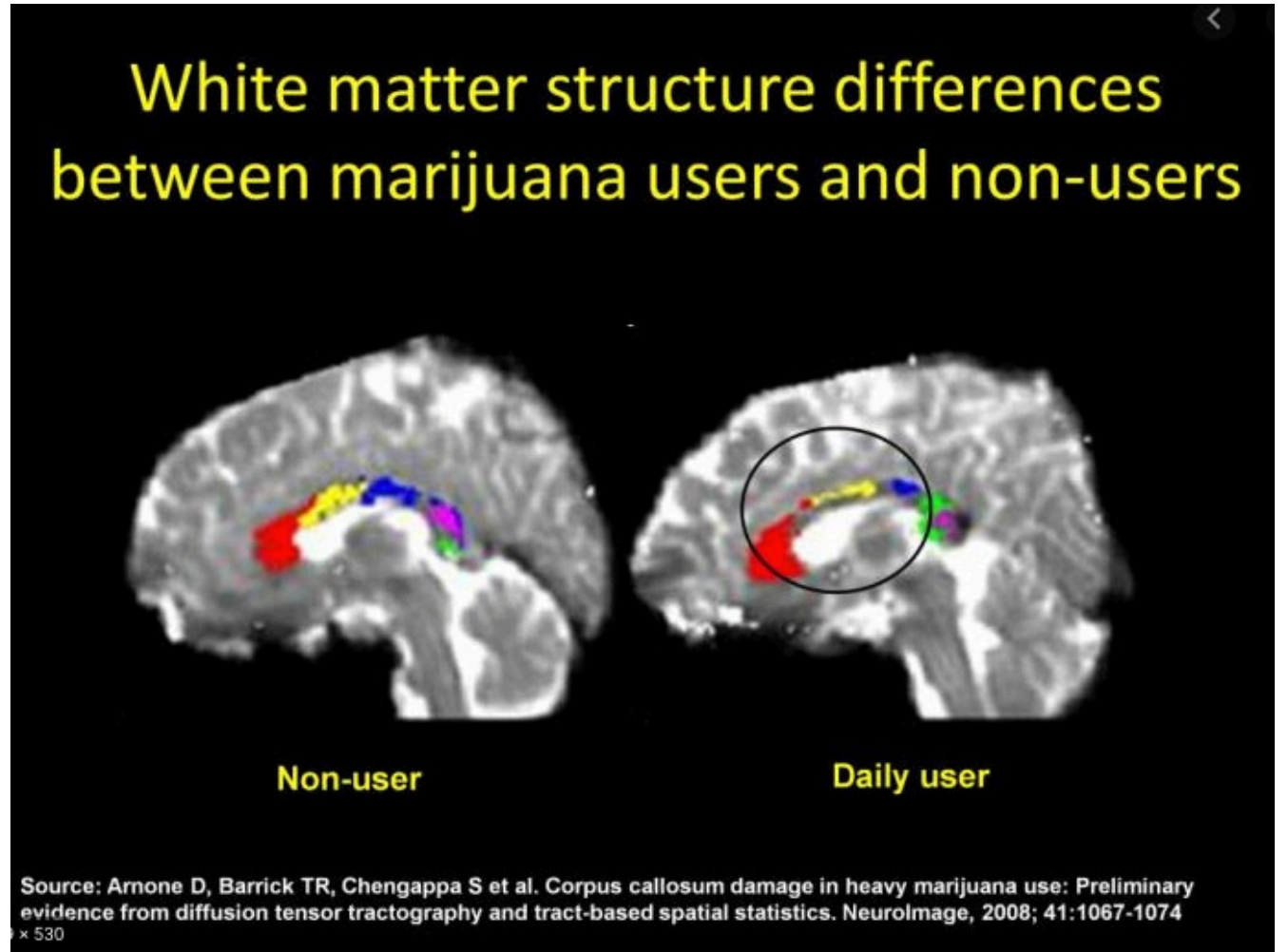
Dopamine set point is altered

- Marijuana hijacks user's dopamine level



Neuroimaging

- Neuroimaging changes depends on
 - Age of onset
 - Frequency of use
 - Dosage

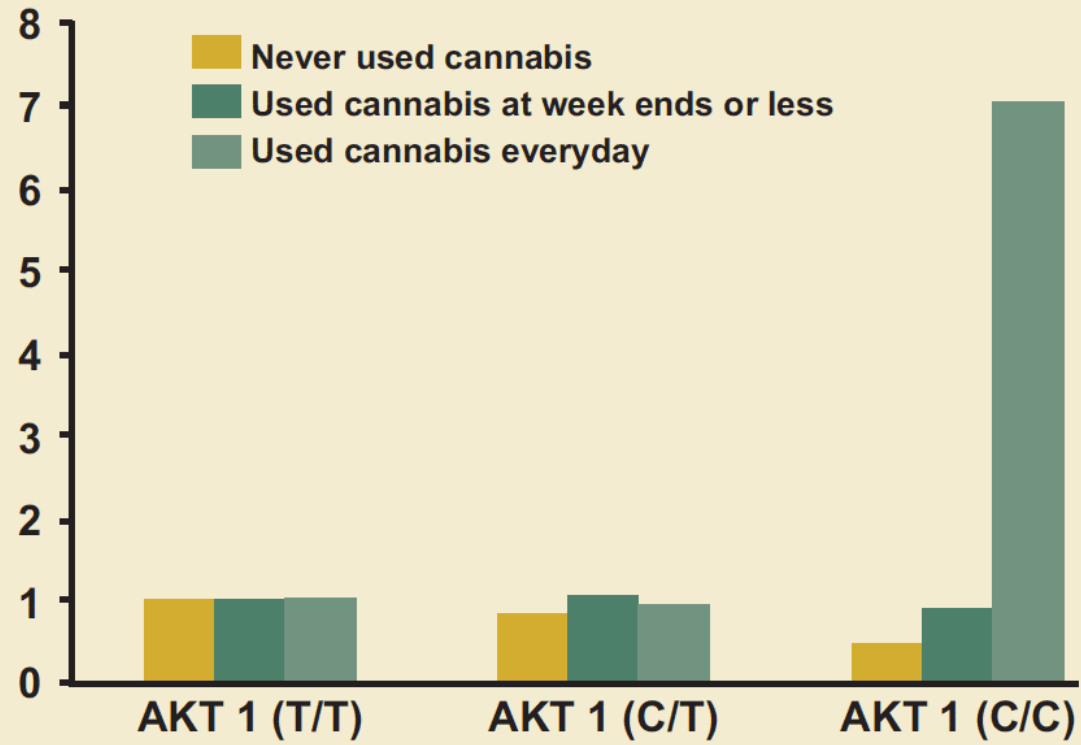


Marijuana Psychosis Genetics

- 7 x increase risk of psychosis if have AKT₁(C/C) gene



AKT1 Gene Variations and Psychosis



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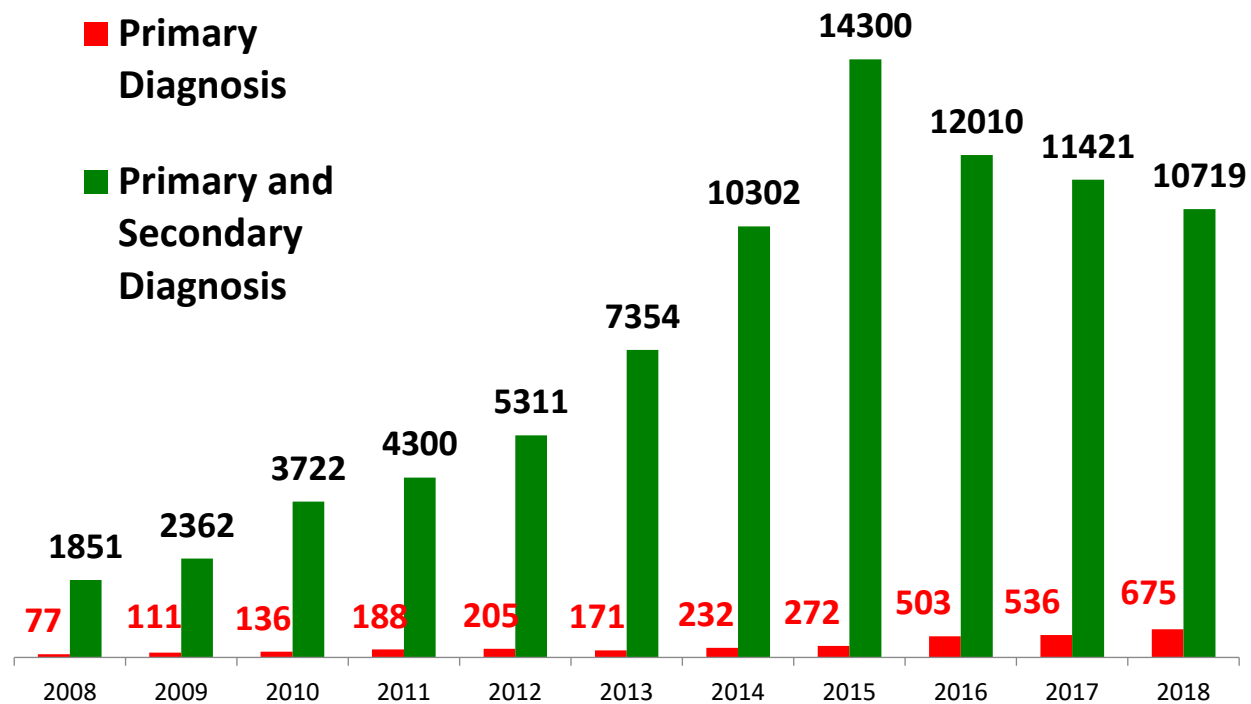
Cases from the Front Lines



Emergency Department Visits

776% increase in THC primary diagnosis in past 10 years

Emergency Department Discharges for Cannabis related
Diagnosis in San Diego County, 2006-2018



Marijuana Death Diaries

- 1 year old “undetermined”
- 15 year old “undetermined”
- 19 year old lost control of vehicle, struck tree (32 Drivers)
- 21 year old jump off bridge in suicide – “suicide” (76 suicides)
- 34 year old fall while hiking – “accident”
- 55 year motorcycle driver struck embankment, (9 MCA)
- 23 year old with pneumonia – “natural”
- 50 year old struck by car (pedestrians) – “accident”
- 69 year old with heart disease – “natural”
- 24 year old with seizure – “natural”
- 38 year old electrocuted – “accident”
- 54 year old with hypertension – “natural”
- 34 year old stabbed to death – “homicide” (23 homicides)
- 52 year old with COPD/emphysema ‘ “natural”
- 33 year old sudden cardiac death, history of diabetes, “natural”
- 42 year old riding bicycle, hit a car, “accident”
- 47 year old with diabetic ketoacidosis, “natural”
- 22 year old skateboard into car, “accident”
- 61 year old hemopericardium, “natural”

55% of all drug deaths
had THC in system



Marijuana Drug Interactions


Cannabis - THC

- 377 drugs interact with cannabis
- 24 Major reactions
- 353 moderate reactions


Cannabidiol - CBD

- 529 drugs interact with cannabis
- 9 Major reactions
- 519 moderate reactions

Do not take
with Marijuana




Do not take
with CBD



 TAKE WITH
FOOD


NOON

 CAUTION
THIS DRUG ALONE OR WITH
ALCOHOL MAY IMPAIR YOUR
ABILITY TO DRIVE

 MAY CAUSE
DISCOLORATION
OF URINE OR FECES

 FOR ORAL USE
ONLY

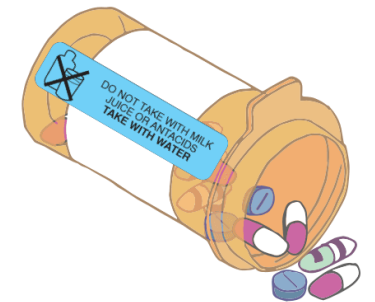
CAUTION: Federal Law PROHIBITS
the transfer of this drug to any
person other than the patient for
whom it was prescribed.

 CAUTION: DO NOT TAKE WITH
ALCOHOL, TRANQUILIZERS
OR SEDATIVE-HYPNOTICS.

 KEEP OUT OF REACH OF
CHILDREN. This type of
container was requested
by Doctor or Patient.

 SHAKE WELL

 DO NOT TAKE ASPIRIN
WITHOUT THE
CONSENT OF YOUR PHYSICIAN



Marijuana Adverse Effects

- **Motor Vehicle Collisions:** 2x risk of MVC, most common illicit drug identified in impaired drivers
- **Pain/Opioids:** marijuana users are more likely to have associated misuse of prescription drugs
- **Neurocognitive Effects:** marijuana is associated with impaired memory, lower intelligence, decreased processing speed, altered judgment, poor educational outcome, increase likelihood of dropping out of school
- **Amotivational Syndrome:** characterized by detachment, blunted emotion drives
- **Depression and Suicidality**
- **Psychosis and Schizophrenia**
- **Violence**
- **Cardiovascular Health:** heart rate, heart attack, blood pressure, stroke, irregular heart rate
- **Pulmonary Health:** 2 x increase risk of lung cancer
- **Cancer:** associated with testicular cancer
- **Neonatal Exposure:** 2.3 x increase risk of stillbirths
- **Contamination:** 20 out of 20 “medical” dispensaries were contaminated



FUNGI and BACTERIA

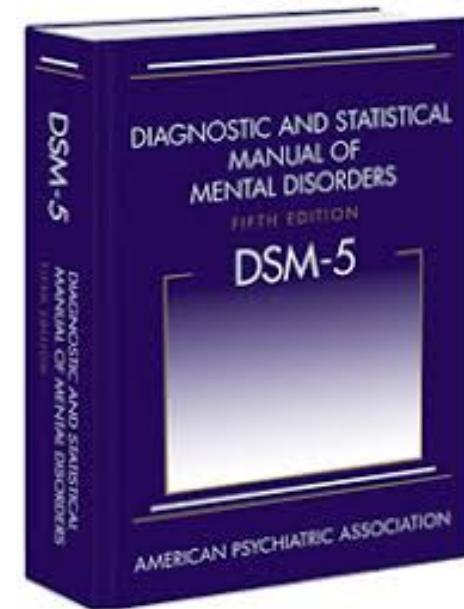
- Cryptococcus
- Mucor
- Aspergillus Fungi
- Escherichia Coli
- Klebsiella pneumonia
- Acinetobacter baumannii bacteria

Cannabis Use Disorder

DSM V Diagnostic Criteria: Substance Use Disorder

SEVERITY: 2-3: mild 4-5: moderate 6 or more: severe

1. Taking the substance in larger amounts or for longer than you meant to.
 2. Wanting to cut down or stop using the substance but not managing to do so.
 3. Spending a lot of time getting, using, or recovering from use of the substance
 4. Cravings and urges to use the substance
 5. Not managing to do what you should at home, work, or school because of substance use
 6. Continuing to use, even when it causes problems in relationships
 7. Giving up important social, occupational, or recreational activities because of substance use
 8. Using substances again and again, even when it puts you in danger
 9. Continuing to use, even if you have a physical or psychological problem that could have been caused or made worse by the substance
 - *10. Needing more of the substance to get the effect you want (tolerance)
 - *11. Development of withdrawal symptoms, which can be relieved by taking more of the substance
- *Criteria not met if taking prescribed drugs under supervision



Cannabis Withdrawal

- 50-90% of heavy users report withdrawal
- 44% of frequent users reported 2 or more withdrawal symptoms upon cessation
- 34% reported 3 or more symptoms
- Onset: 1-2 days of abstinence, peaks at 2-6 days, resolve 7-14 days, sleep disturbance, irritability, and physical tension may persist for weeks.
 - Fatigue (31%)
 - Yawning (27%)
 - Hypersomnia (26%)
 - Psychomotor retardation (25%)
 - Anxiety (19%)
 - Depression (16%)
 - Anorexia, weight loss, anger, irritability, strange dreams, chills, tremor, diaphoresis, stomach pain



Marijuana Black Box Warning

- If Marijuana was a Medicine it would require a FDA Black Box Warning
- Marijuana + Opioids = Higher risk association than Opioids + Benzodiazepines



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Cases from the Front Lines



Marijuana Poisoning

- Add Marijuana Poisoning to your Diagnosis
- Daily Marijuana Poisoning in Emergency Visits

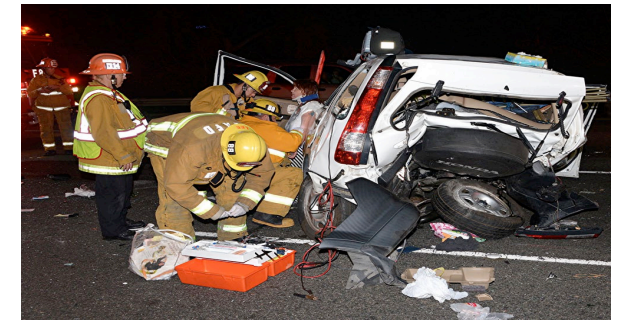
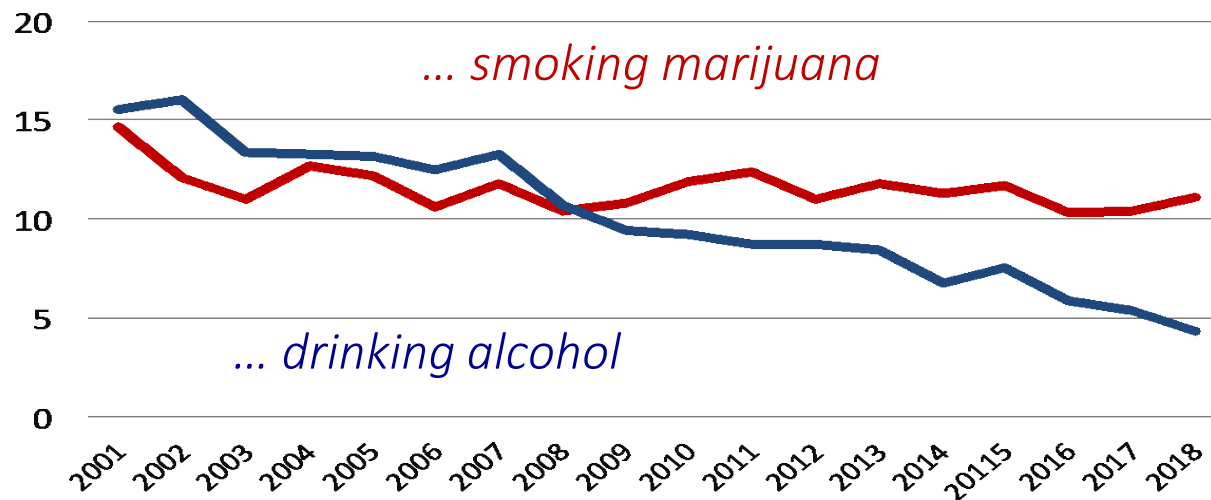


- Psychosis
- Suicidal ideation
- Scromiting
- Excited Delirium
- Seizures
- Cardiovascular Collapse
- Pneumothorax
- Motor Vehicle Collisions
- Stroke like symptoms
- Anxiety
- Tachycardia
- Amotivational Syndrome
- Over sedation – can't wake up
- Chest Pain and Palpitations
- Excessive Bleeding
- Allergic Reaction

Drugged Driving

- 2 x risk of Motor Vehicle Collision
- Since 2009, more high school seniors reports driving after smoking marijuana than driving after drinking alcohol

During the LAST TWO WEEKS, have you driven a car, truck, or motorcycle after ...



- 36 year old **Hyun Choi** convicted vehicular manslaughter while high on marijuana, March 2016.
- 22 year old **Jennifer Gasper** died by driver going 82 mph through red light and high on marijuana

Psychosis

Distracted

Hearing voices

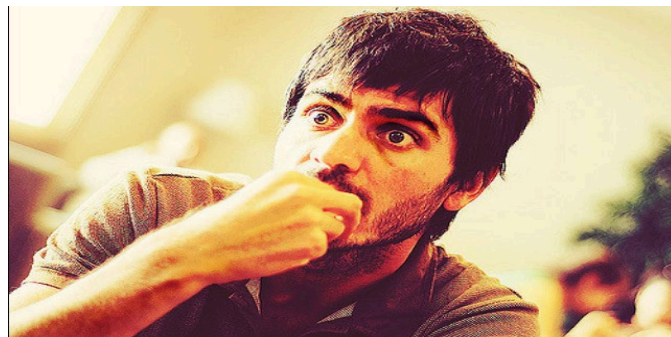
Visual hallucinations

Paranoid Delusions

Nonsensical speech

Bizarre behavior

31 year old man presented to the emergency department because he believed **people are following her**. The voices in his head are laughing at her making her feel **depressed** and **anxious**. His psychiatrist told her she should use medical marijuana to help her relax. He required **admission to the behavioral health unit** because of severe impairment.



“There is substantial evidence of a statistical association between cannabis use and the development of schizophrenia or other psychoses, with the highest risk among the most frequent users.” - National Academies of Sciences, Engineering and Medicine. The Health Effects of Cannabis and Cannabinoids. 2017

Excited Delirium



26 year old man brought in by paramedics and law enforcement **kicking, screaming, spitting**, flailing in a **violent** outburst. He was home alone tearing up his apartment when neighbors were concerned. After chemical sedation and 8 hours in the emergency department his toxicology test was positive **just for THC**. He was a nice young man and admitted to using a single marijuana gummy bear.

Scromiting



- A daily diagnosis in most emergency departments
- “Audible Diagnosis
- Scromiting – Screaming and Vomiting, also known as Cannabis Hyperemesis Syndrome
- Patients are screaming for pain medications



<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5851514/> Hyperemesis Syndrome: Public Health Implications and a Novel Model Treatment Guideline

Stroke?



38 year old business man traveling cross county for a convention awoke with slurred speech and inability to grip in one hand. He was worked up for **possible stroke**. CT scan and angiogram were negative. After several thousand dollar \$\$\$ of medical tests, he remembered the “Hangover Remedy” gummy bears he ate while having munchies in his hotel room.



Grandpa can't sleep



88 year old man on vacation with family

History of

- Diabetes
- High Blood Pressure
- Cirrhosis
- Insomnia

Given marijuana by grandson to help sleep.

Admitted to hospital with **altered mental status** because he could not wake up.

M&M

- Most people use multiple drugs:
Meth & Marijuana; Methadone & Marijuana;
- Fentanyl found in inhaled marijuana products



Marijuana Dashboard

- **FATALITIES**
 - Marijuana Alone
 - With other drugs
 - With prescriptions
 - Motor vehicle fatalities
 - Cardiovascular fatalities
 - Suicides
 - Homicides
- **MATERNAL-CHILD HEALTH**
 - Pregnant women using marijuana
 - Newborns testing positive for marijuana
 - Pediatric Admissions
- **EMERGENCY DEPARTMENT VISITS**
- **MENTAL HEALTH**
 - Psychiatric admission testing positive for marijuana
 - Marijuana exacerbating psychosis



Let's not be fooled by Big Tobacco Again

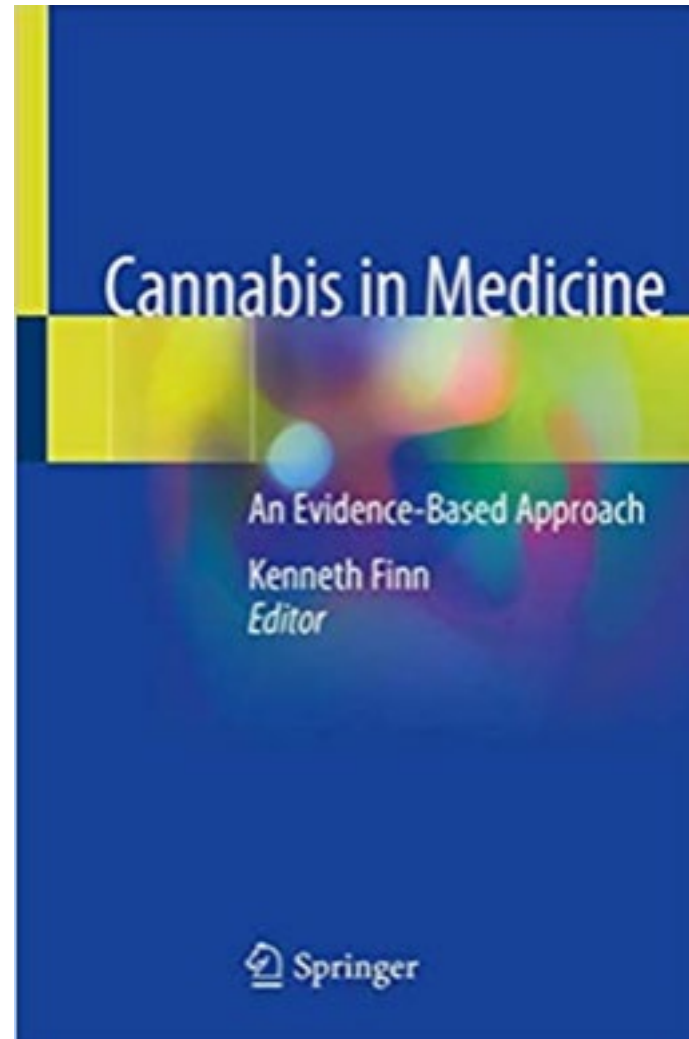
Are We Sure?



Marijuana Case Studies



Reference



Quiz

Which statement is false?

- a. ~~Medical marijuana is safer than black market marijuana because it comes from a pure source~~
- b. 30% of marijuana users have a substance use disorder
- c. People have died from using marijuana
- d. Marijuana use in people under age 27 is associated with 4-7 x increase risk in addiction
- e. Marijuana use is associated with increase chance of bleeding (elevated PT/INR)
- f. 4.7% of pregnant women have used marijuana in past month



Marijuana Case Studies



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