# Medical Marijuana for People Living with HIV

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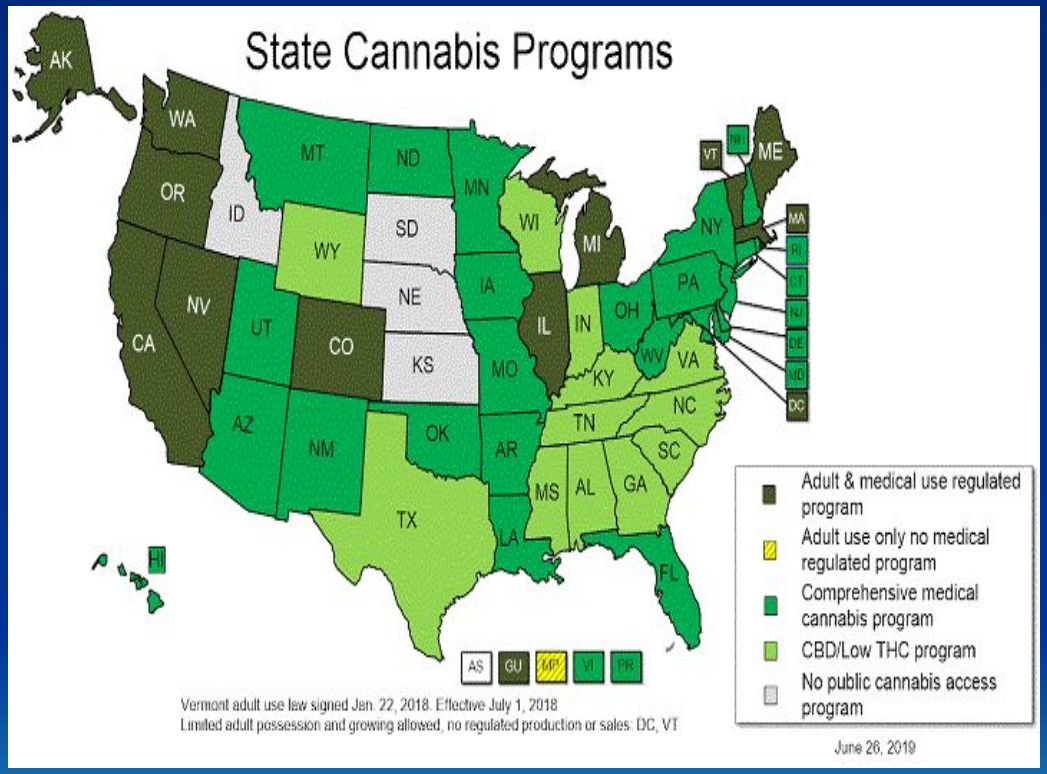
# Learning Objectives

- Review the laws and history of cannabinoids
- Describe the complexity of pharmacokinetic parameters of marijuana and how they may affect patient care
- Identify possible drug-drug interactions, side effects or adverse drug reactions with medical marijuana in healthcare

# Marijuana Law

- Medical + recreational use is approved in **14** states
  - **34** states including District of Columbia, Guam, Puerto Rico and US Virgin Islands have medical marijuana laws
  - **12** states allow low THC, high CBD products for medical reasons in limited situations
  - Mariana Islands are the only territory to have recreational use only, no medical use laws




http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx

# A Brief History of Medicinal Marijuana

- Controlled Substance Act
- Scheduling
  - FDA
  - DHHS – Federal registry
  - NIDA
  - DEA
- Colorado
  - November 2000 Amendment 20
  - 2010 the Colorado Legislature passed HB-1284
  - November 2012 Amendment 64

# Medical Marijuana in Healthcare

- China 2737 B.C
- No official US standards for herbals
- No German Commission E monograph
- US Pharmacopeia 1850 – 1942
- 1937 Marijuana Tax Act
- Merck Index until 1950
- Dronabinol Orphan Drug status 1985
- No federally recognized use of marijuana

# Dosage Forms

- Flowered Plant Dried (oral or inhaled)
- Hashish – Pure Resin
- Oil Hashish (5-10 times more potent)
- Capsule Marinol® , Nabilone®
- Buccal Spray Sativex®
- Solution Epidiolex® (purified CBD)
- Solution Syndros® (Dronabinol)




# New Drugs approved by FDA

- Epidiolex (purified CBD) - (Schedule V) approved for add-on therapy for treatment of seizures related to Lennox-Gastaut and Dravet Syndrome. (2018)

- Marinol and Syndros (Dronabinol) – (Schedule III) approved for treatment of Loss of appetite in AIDS patients and Chemotherapy induced Nausea and Vomiting.



# Edible Marijuana Products

- Regulatory standards for marijuana edibles vary by state
- Growing scrutiny of all dosage forms following reports of deaths and other adverse reactions linked to edible marijuana products
- In Colorado, current standards for marijuana edibles state that each cannot contain more than 100 mg of THC
- CDPHE mandating tests for content and other screening, including contamination



# THE DIFFERENT TYPES OF CANNABIS

# CONCENTRATES






# Question 1

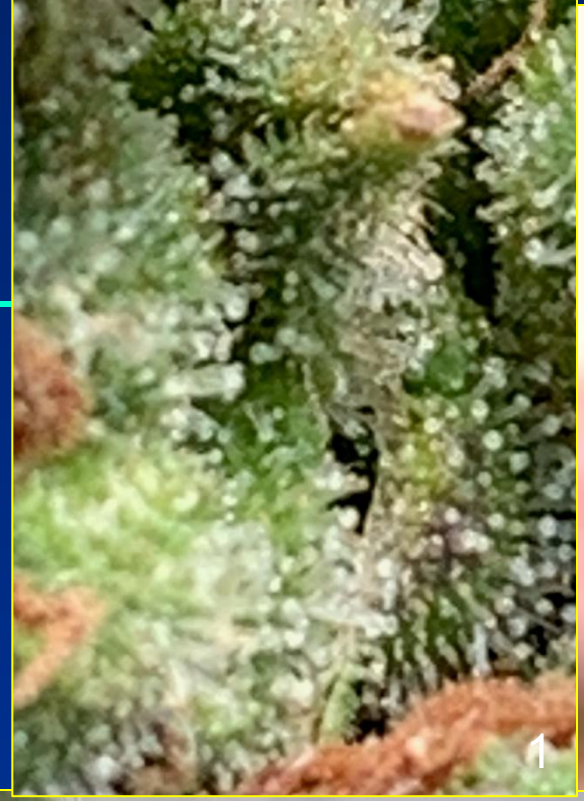
- Which agencies collaborate to determine the Scheduling “class” of marijuana?
  - a. DHHS
  - b. NIDA
  - c. DEA
  - d. FDA
  - e. All of the above

# Medicinal Indications in the US

- Alzheimer's
- Amyotrophic lateral sclerosis
- Anorexia/ Appetite stimulant
- Antiemetic
- Autism Spectrum
- Anxiety
- Cancer
- Cerebral Palsy
- Crohn's Disease/ UC
- Cystic Fibrosis
- Diabetes
- Epilepsy
- Fibromyalgia
- Glaucoma
- Hepatitis C
- HIV/ AIDS
- Hospice
- Huntington's
- Lupus
- Migraine
- Multiple sclerosis spasticity
- Myasthenia Gravis
- Nausea/ Vomiting
- Nerve damage spasticity
- Pain
- Parkinson's Disease
- Psoriatic Arthritis & RA
- PTSD
- Tourette's Syndrome
- Schizophrenia
- Seizures
- Sickle Cell Disease
- AND MORE…..

# Question 2

- Which of the following is a medicinal use of marijuana?
  - a. Appetite Suppressant
  - b. Depression
  - c. Immune Booster
  - d. Congestive Heart Failure
  - e. None of the above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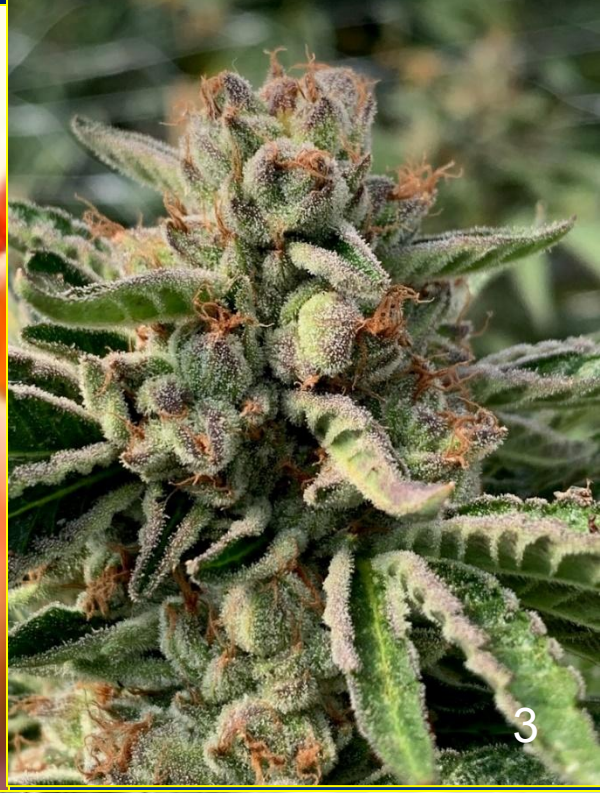
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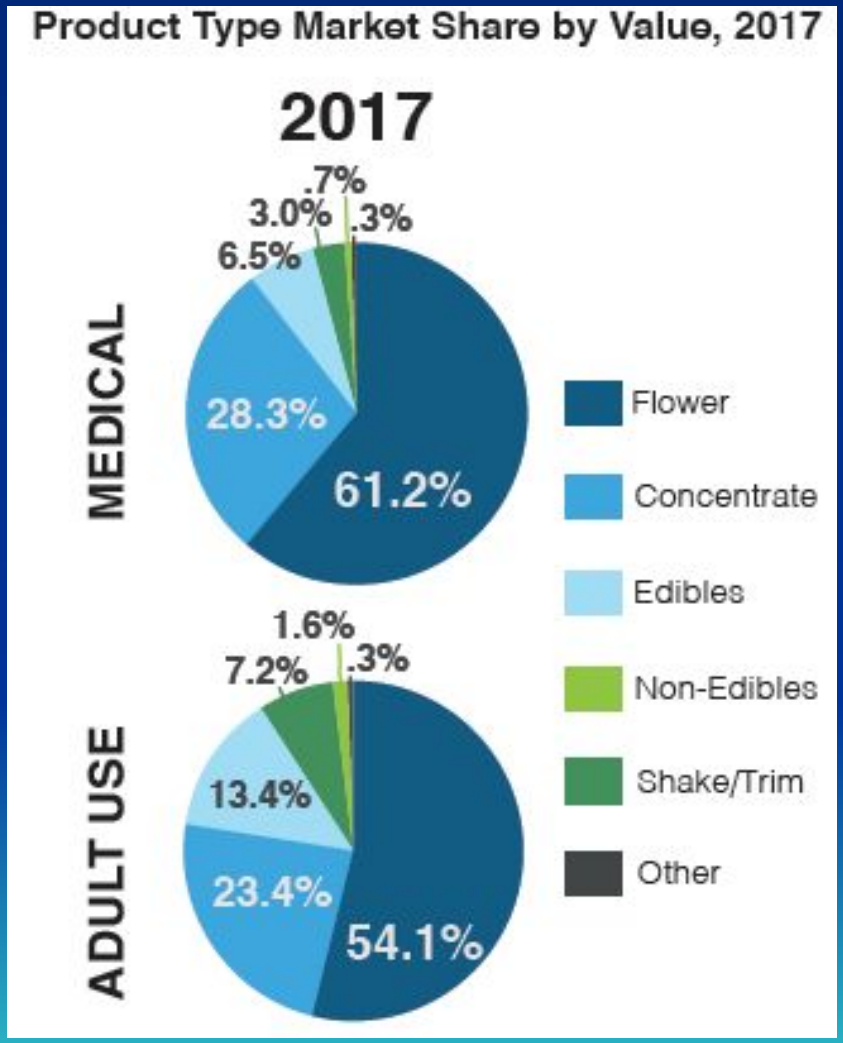
# Marijuana Industry Colorado

- Adult use concentrate prices fell from $41.43 $21.57/gm
- Average THC content was 19.6% state wide compared to 17.4% (2016)
- June 2017
  - 491 Retail dispensaries
  - 392 Starbucks
  - 208 McDonald's




Marijuana Policy Group, Market Size and Demand for Marijuana in Colorado 2017 Market update

# Pharmacology

- Over 100 identified cannabinoids
  - $\Delta^9$ – tetrahydrocannabinol (THC)
  - Cannabaniol (CBN)
  - Cannabidiol (CBD)
- Cannabinoid receptors (CB)
  - CB1 – CNS, tissue
  - CB2 – Immune cells

More than 460 active chemicals

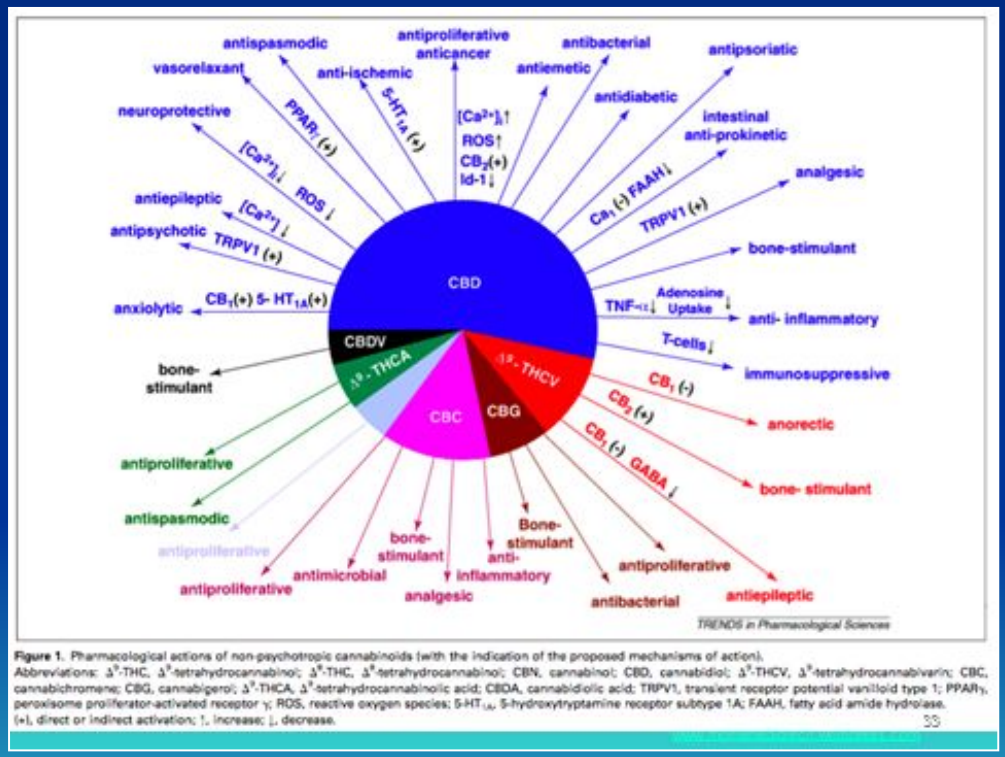
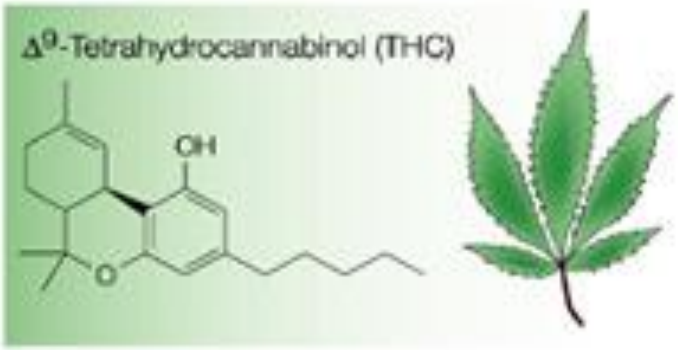



Figure 1. Pharmacological actions of non-psychotropic cannabinoids (with the indication of the proposed mechanisms of action).
Abbreviations: $\Delta^9$-THC, $\Delta^8$-tetrahydrocannabinol; $\Delta^9$-THC, $\Delta^9$-tetrahydrocannabinol; CBN, cannabinol; CBD, cannabidiol; $\Delta^9$-THCV, $\Delta^9$-tetrahydrocannabivarin; CBC, cannabichromene; CBG, cannabigerol; $\Delta^9$-THCA, $\Delta^9$-tetrahydrocannabinolic acid; CBDA, cannabidiolic acid; TRPV1, transient receptor potential vanilloid type 1; PPARγ, peroxisome proliferator-activated receptor γ; ROS, reactive oxygen species; 5-$HT_{1A}$, 5-hydroxytryptamine receptor subtype 1A; FAAH, fatty acid amide hydrolase. (+), direct or indirect activation; ↑, increase; ↓, decrease.

**Plant-derived cannabinoid**

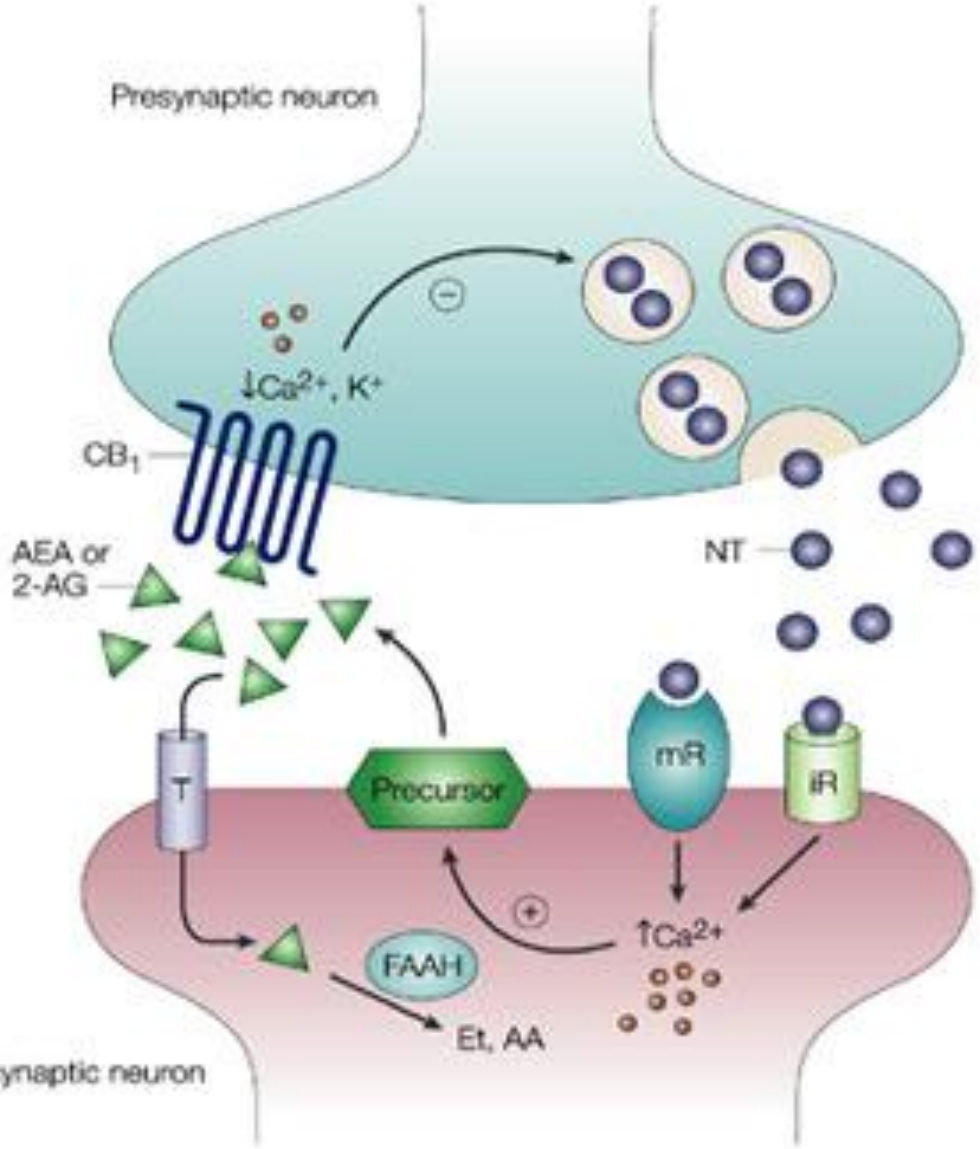
$\Delta^9$-Tetrahydrocannabinol (THC)




**Endogenous cannabinoids**

Anandamide (AEA)


2-Arachidonoylglycerol (2-AG)

# Mechanism of Action

- Inhibit prostaglandin
- Cytostatic
- Stimulation of parasympathetic nervous system
- B-Adrenergic
- Muscarinic

- ↑ Blood flow to right frontal brain
- ↓ IOP (carbonic anhydrase inhibitor sympathetic)
- ↓Acetylcholine
- ↓ GABA & Glutamate
- Tri-cyclic ring
- ↓ Emetic center of medulla oblongata

# Absorption

## Oral

- Onset: 30 – 60 minutes
- Peak: 30 – 120 minutes
- DOA: 6-8 Hours
  (24 hours appetite)
- Bioavailability: 20%
- 1st pass metabolism
- Food increases absorption

## Smoked

- Onset: 6 – 12 minutes
- Peak: 30 – 120 minutes
- DOA: 2 – 4 hours
- Bioavailability: 10 – 23%
- THC: 10 – 35%
- Food increases absorption

# Distribution

- Highly protein bound (97 – 99%)
- Lipophillic
- Liver
- Adipose (fat)
  - heart, liver, salivary glands, brain, kidneys, adrenals, bile
- Not in blood, brain or testes
- Vd = 2.55 – 6.4 liters/kg (500 liters)
- Steady State = Vd x 100

# Metabolism

- Liver (CYP450, CYP3A4, CYP2C, CYP2D6, CYP 1A2)
  - Hydroxylation
  - Oxidized (more polar)
- Active Metabolite 11-hydroxy-delta-9-tetrahydrocannabinol (THC-OH)
  - Dec. with severe liver damage
- UDP – Glucuronosyltransferase (UGT)
  - Conjugation, Glucuronidation

# Excretion

- Kidney (35% acid metabolites)
- Breast milk 60ng/mL
- Feces (65%)
- Elimination t ½ = 2 – 6 hours
- Plasma t ½ = 1 – 4 days
- t ½ = biphasic (30 minutes/30 hours)
  - Redistribution to adipose = terminal t ½

# Toxicology

- Lethal dose
  - Oral is unknown
    - 300mg = inc. sleeping
    - Coma, stupor in children
  - Injection = 30mg/kg dronabinol
- Non-linear THC levels to Intoxication
  - Tachycardia, palpitations, a. fib, orthostatic hypotension
- Activated charcoal, support

- Rarely serious, spontaneous rebound
- Tolerance
- Withdrawal
- Abuse (high potential): less than morphine, cocaine, barbiturates or amphetamine
- Dependence: psychological, physical?

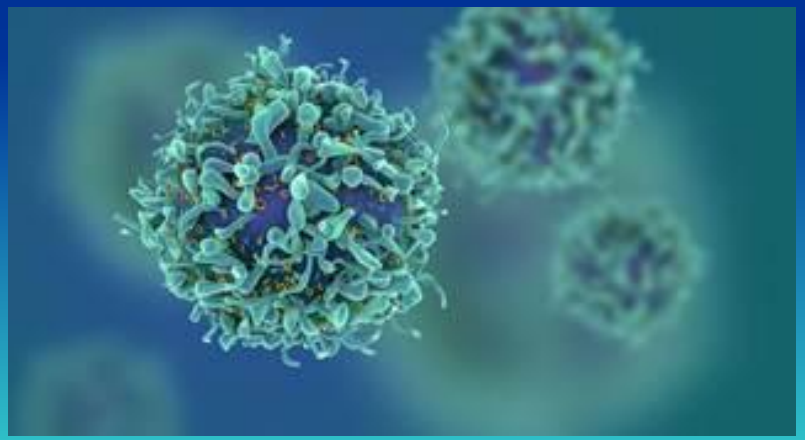
# Mechanism of Interaction

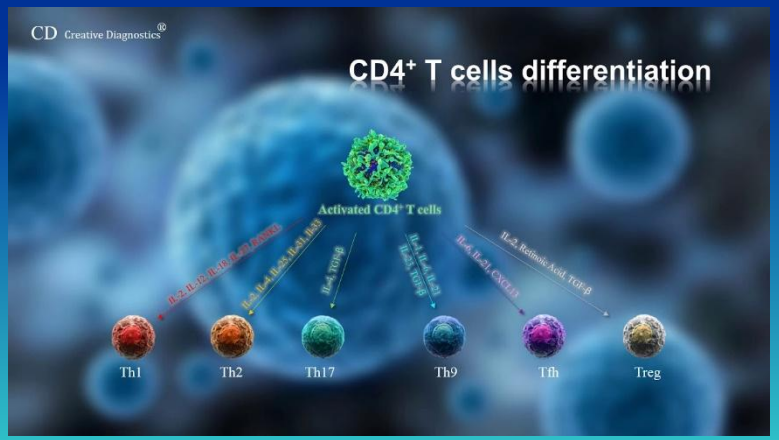
- Cytochrome P450 Isozyme (CYP)
  - CYP2C, CYP3A
  - Smoke = induces CYP1A2 (theophylline)

- ↑ B-adrenergic
- ↑ ↓ ADME, Clearance

# HIV-related Interactions

- Inhibits increase of CD4 T-cells
- Indinavir or nelfinavir
  - Smoked cannabis had no effect on drug levels
- ↓ Conc. of Protease inhibitors & NNRTI's
  - For ex: Darunavir, atazanavir, etc.





# Potential Drug-Drug Interactions

- ↑ Barbiturates
- Anticholinergics
- Sympathomimetics
- Neuroleptics
- Naltrexone
- ↑ Lithium
- ↑ Benzodiazepine
- ↑ Warfarin (↑ INR) ↑ Lithium
- ↑ Cocaine
- Cyclophosphamide ↓
- Disulfiram, ↑ THC
- ↓ Doxorubicin
- ↑ Opiate
- Ethanol → ↑ THC
- SSRIs additive HT3 effect
- ↓ Sildenafil
- ↓ Theophylline conc.
- TCA: ↑ Ach side effects
- Steroids ↓ Immune system
- CNS depressants ↑ additive or synergistic

# ADRs / Side Effects

- Allergy
- Altered Mental State
- Blurred Vision
- Syncope
- Dizziness
- Xerostomia
- Euphoria
- Gastro-Intestinal
- Gynecomastia
- Hallucinations
- Hepatic enzyme changes
- Hyperthermia
- Hypertension
- Memory loss
- Mood changes
- Nausea
- Prediabetes
- Rash
- Sexual dysfunction
- Sperm defects
- Urinary Retention

# ADRs / Side Effects

- Respiratory
  - Aspergillus
  - Asthma
  - Byssinosis (Obstructive disease)
  - Dyspnea
  - Tar
  - Hematemesis
  - Smoke
  - Carcinogenic
- Cardiovasular
  - Myopathy
  - Tachycardia
  - Bradycardia
  - Hypotension
  - Hypertension
  - Palpitations
  - Vasodilation
  - MI

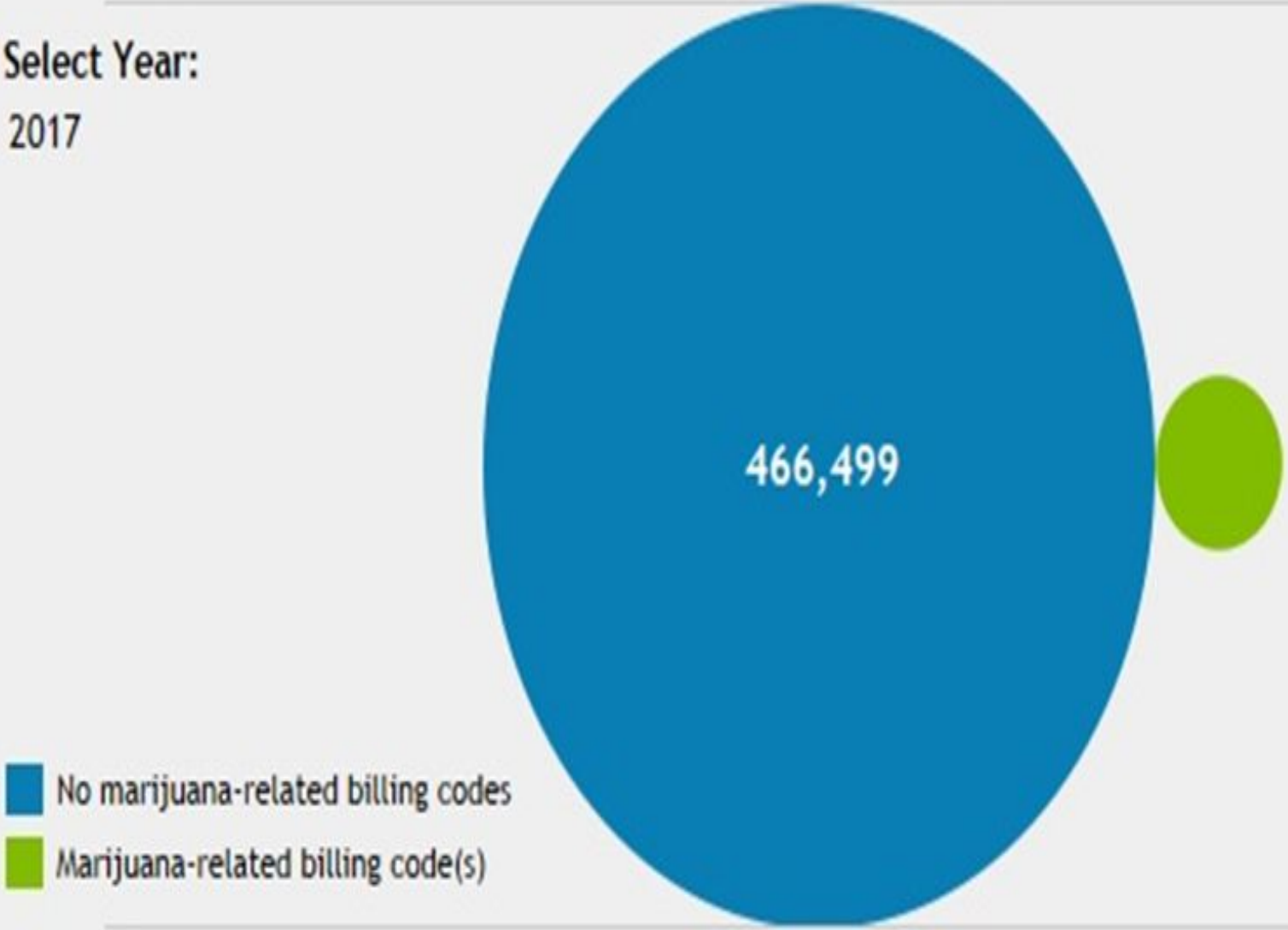
# Hospitalizations Related to Marijuana*


*Hospitalization Visits with Possible Marijuana Exposures, Diagnoses, or Billing Codes

**Only 9 months of comparable 2015 data, see ICD definition on page 36

SOURCE: Colorado Hospital Association, Hospital Discharge Dataset. Statistics prepared by the Health Statistics and Evaluation Branch, Colorado Department of Public Health and Environment

**Figure 1:** In 2017, there were **16,614 hospitalizations** with marijuana-related* billing codes compared to **466,499 hospitalizations** without marijuana-related billing codes.



# Question 4

- Which of the following is a side effect of marijuana?
- a. Dry mouth
- b. Euphoria
- c. Mood changes
- d. Hallucination
- e. All of the above

# Potential Drug-Disease Interactions

- Pregnancy (FDA Pregnancy “C”)
- Alcohol withdrawal
- Cocaine use
- Depression
- Geriatric
- Cardiovascular
- Seizures
- Immune system

# Counseling Points

- Medications
- OTC/Herbals
- Allergies
- Aspergillus
- Breastfeeding
- Pregnant
- Liver disease
- Mental Illness

- Seizure disorder
- Disease states
- Substance abuse
- High blood pressure
- Cardiovascular disease
- Regularly in contact with physician

# Cannabis and the Elderly

- Marijuana use has increased in the elderly, especially 65yrs and older.
- Among geriatrics patients:
  - 32% reported having used Marijuana in the past
  - 16% of whom have used since legalization
  - 44% used Marijuana for common conditions such as: chronic pain, depression, anxiety, and insomnia.

Reynolds et al. 2018 Journal of The American Geriatrics Society

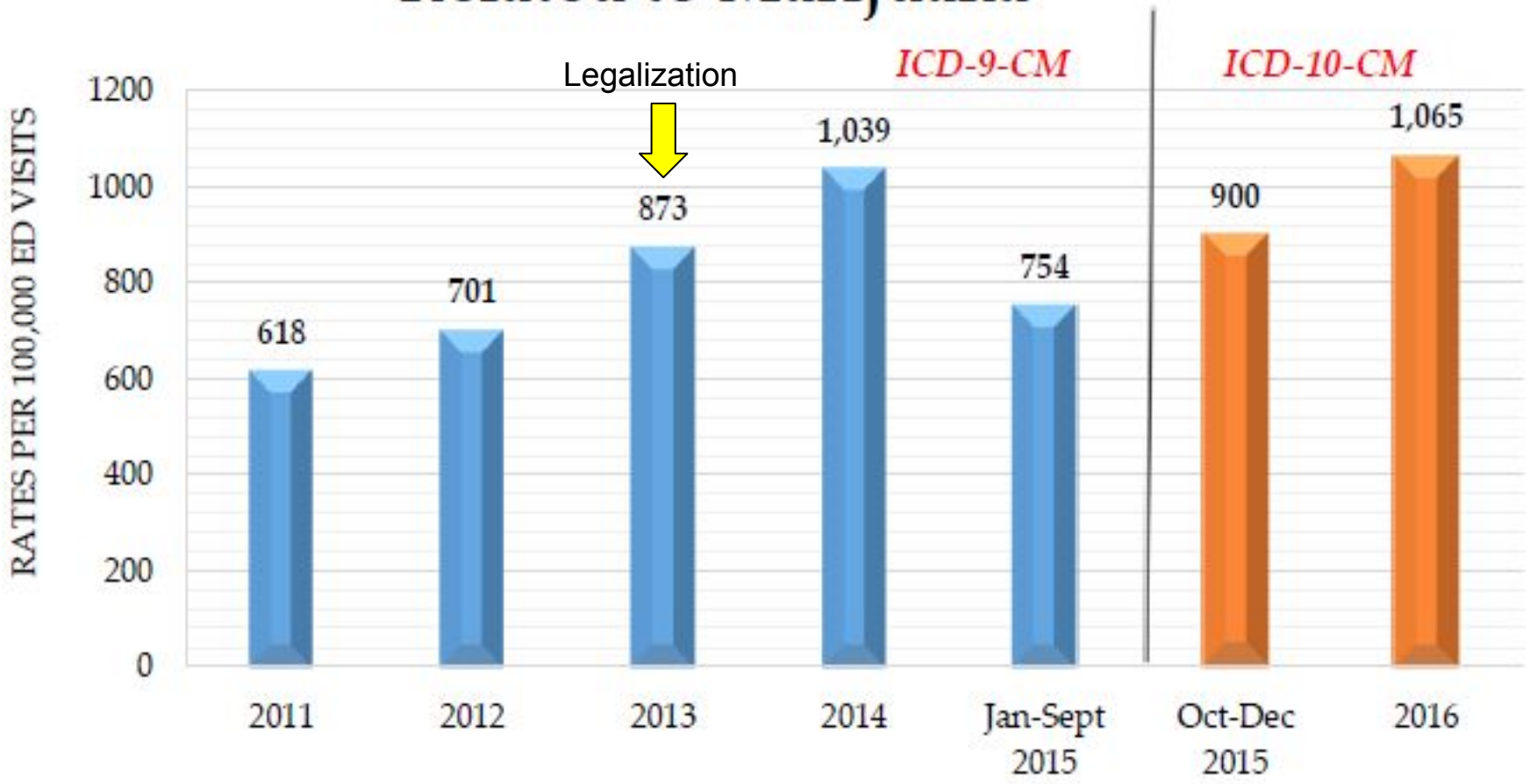
# Dispensaries

- Most patients obtain cannabis products from recreational dispensaries
- Typically staff does not have clinical background

<u>Recommendations:</u>

- Higher CBD and Lower THC
- Smoked cannabis is not recommended
- Edibles may be preferred
- Start low and go slow

# Emergency Department Rates Related to Marijuana*




*Rates of Emergency Department (ED) Visits with Possible Marijuana Exposures, Diagnoses, or Billing Codes per 100,000 HD visits by Year in Colorado

SOURCE: Marijuana Health Monitoring and Research Program, Colorado Department of Public Health and Environment

GRANTS

Drug-Free Communities
- Information for Current Grantees
- Information for Applicants
- Mentoring Program
- DFC Me
- Contacts

High Intensity Drug Trafficking Areas
- Initiatives
- Points of Contact
- New County Designation Process

Find Grantees Near You

# High Intensity Drug Trafficking Areas (HIDTA) Program

The High Intensity Drug Trafficking Areas (HIDTA) program, created by Congress with the Anti-Drug Abuse Act of 1988, provides assistance to Federal, state, local, and tribal law enforcement agencies operating in areas determined to be critical drug-trafficking regions of the United States.

The purpose of the program is to reduce drug trafficking and production in the United States by:

- Facilitating cooperation among Federal, state, local, and tribal law enforcement agencies to share information and implement coordinated enforcement activities;
- Enhancing law enforcement intelligence sharing among Federal, state, local, and tribal law enforcement agencies;
- Providing reliable law enforcement intelligence to law enforcement agencies needed to design effective enforcement strategies and operations; and
- Supporting coordinated law enforcement strategies which maximize use of available resources to reduce the supply of illegal drugs in designated areas and in the United States as a whole.

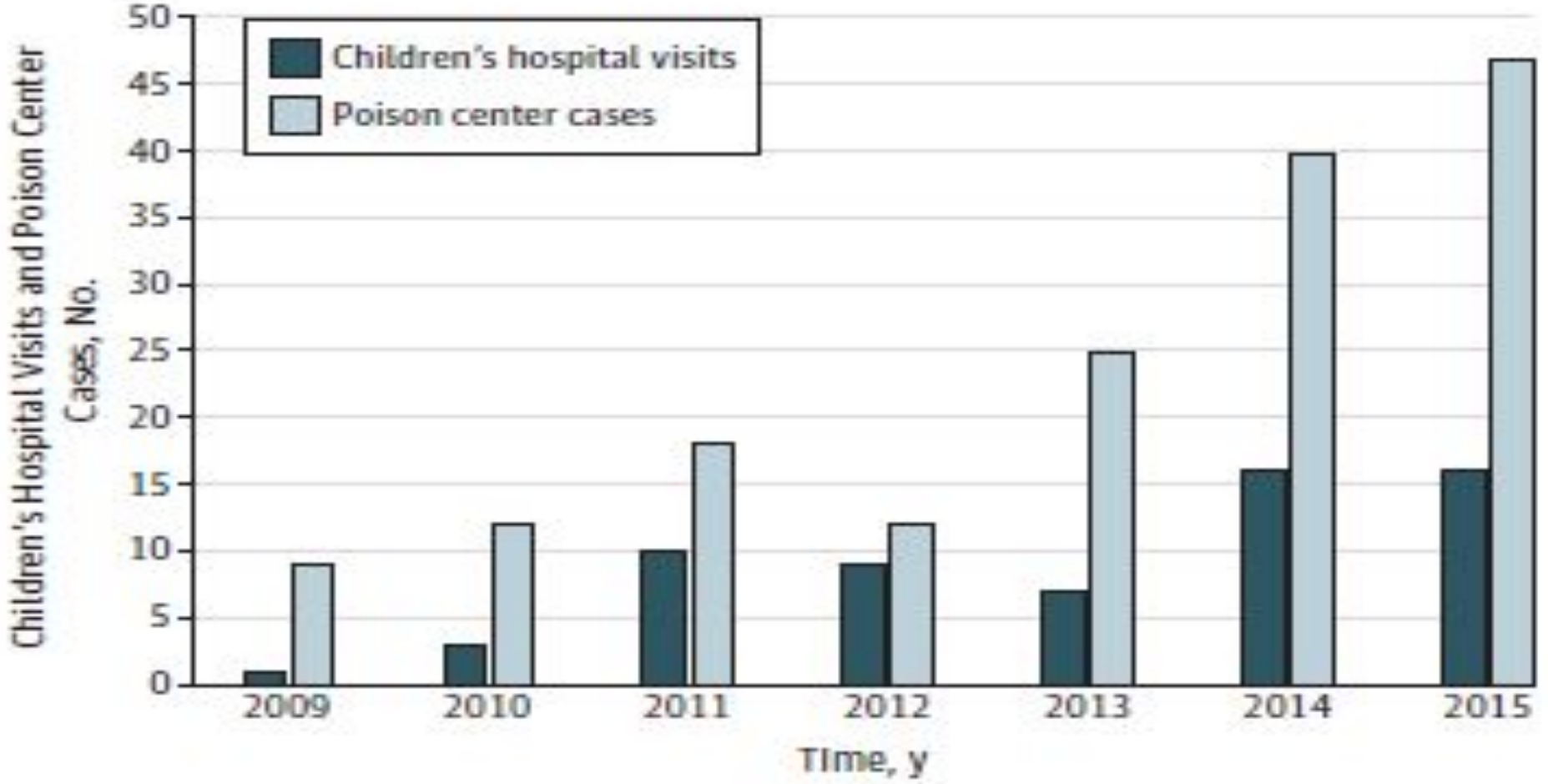
# Traffic Deaths Related to Marijuana when a Driver Tested Positive for Marijuana


SOURCE: National Highway Traffic Safety Administration, Fatality Analysis Reporting System (FARS), 2006-2011 and Colorado Department of Transportation 2012-2017


# Pediatric Issues


- Between 2005 and 2009, Children's Hospital Colorado (CHC) ED saw no cases of accidental marijuana ingestions
- In 2013 alone, CHC saw 8 patients with marijuana ingestions
- This number increased to 14 children in 2014
- Colorado House Bill 1366 (May 2014): marijuana products must be recognizable even when they are out of their package

## Figure 1. State Pediatric Marijuana Exposures




Annual children's hospital visits and regional poison center cases for unintentional marijuana exposures in children 9 years or younger in Colorado between 2009 and 2015. Children's hospital visits include emergency department visits, urgent care visits, and inpatient hospital admissions.

# THC in Breast Milk

- THC is found in the breast milk of mothers smoking marijuana
- THC peak = 1 hour after smoking
- Estimated infant dose = 2.5% of the maternal dose


Baker T et al. (2018) Obstet Gynecol

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

# Adverse Health Effects of Marijuana Use

Nora D. Volkow, M.D., Ruben D. Baler, Ph.D., Wilson M. Compton, M.D., and Susan R.B. Weiss, Ph.D.

# Psychiatric Issues

- From *NEJM* - June 5, 2014
  - Adults who smoked marijuana regularly during adolescence have impaired neural connectivity
  - Regular use is linked with an increased risk of anxiety, depression, and psychoses
  - Exposure to marijuana may decrease dopamine activity in the brain's reward system = gateway drug

# Other Adverse Effects

- From *NEJM* - June 5, 2014
- Effects of long-term marijuana use on risk of lung cancer unclear
  - Risk may be lower than that associated with tobacco use
- Increased risk of MVA
- Potential age-related cognitive decline and memory impairment

# Appetite

- May increase appetite
- ↑ Ghrelin and Leptin; ↓ PYY levels
- Dronabinol -> anorexia associated weight loss in patients with AIDS

PK Riggs et al. 2012, *Brain Research*

# Nausea and Vomiting

- Conflicting data
- Studies found no significant difference in nausea and vomiting individually and combined
- However, dronabinol is FDA approved for adjunctive therapy for chemotherapy induced nausea and vomiting

Smith LA et al. Cochrane Database of Systematic Reviews 2015

# Neuropathic Pain

- Smoking cannabis significantly
  - Reduced neuropathic pain intensity in HIV associated distal sensory polyneuropathy (DSPN)
  - Reduced daily pain by 34% vs 17% with placebo (p=0.03).

R Ellis et al. 2009, Neuropsychopharmacology
DI Abrams et al. 2007, Neurology


# The Efficacy Debate

- From *JAMA* – June 18, 2014 JAMA
  - Some evidence for use in chemotherapy-induced vomiting, cachexia in HIV/AIDs patients, spasticity, and neuropathic pain
  - Evidence for PTSD, glaucoma, Crohn's disease, and Alzheimer disease is largely testimonial
  - Need for the same evidence-based review as other medications prescribed by physicians

# Potential Role of Cannabinoids in HIV

- Even with long-term ART therapy, HIV+ individuals have a higher risk of comorbidities
  - ASCVD
  - CKD
  - Hepatitis B and C
  - Cancer
  - Neurologic disease
- Comorbidities are linked to chronic inflammation
  - Cannabis has potential anti-inflammatory effects, but the relationship between HIV-induced inflammation and cannabis is not clearly defined

# Heavy Cannabis Use Associated with Reduction in Activated and Inflammatory Immune Cell Frequencies in HIV

- Objective: Cannabis impact on inflammation and immune activation in HIV+ ART use patients

- 3 groups:
  - Heavy cannabis users (n = 14)
  - Moderate cannabis users (n = 40)
  - Non-cannabis users (n = 128)

- Conclusions: Cannabis use had a significant reduction of systemic inflammation and immune activation in HIV+ ART patients

Manuzak JA, et al. . Clin Infect Dis. 2018

# High-intensity Cannabis Use and HIV Clinical Outcomes

- Design: Retrospective observational
- Objective: In HIV+ patients does illicit drug use correlate to viral load, engaged in ART care
- Groups: total n=874; 62% on ART care, 32% undetectable
  - HIV+ & daily cannabis use (n=215)
  - HIV+ & not daily cannabis use (n=659)
- Results: No significant impact of daily cannabis use on ART care or non detectable viral load

Lake S, et al. Int J Drug Policy. 2017.

# Cannabis Use for Chronic Pain in HIV

- Design: Secondary data analysis
- Objective: understand patterns of use of cigarettes, alcohol, and illicit drugs (including cannabis, heroin, and cocaine) in HIV-infected people who are prescribed opioid analgesics

- Results:
  - In patients with HIV and chronic pain, cannabis use was significantly associated with lower odds of prescribed opioid analgesic use
  - People prescribed opioids were significantly older and were significantly more likely to report 100% adherence to ART

Sohler NL, et al. Subst Use Misuse. 2018

# Marijuana Use Impacts Midlife Cardiovascular Events in HIV-Infected Men

- Design: Prospective study
- Objective: Long-term marijuana effects on HIV disease progression and comorbidities
- Results: (n=558)
  - Long-term heavy marijuana use showed insignificant associations for viral load, CD4 counts, AIDS, cancer, or death.
  - Heavy marijuana use is a risk factor for CV disease in HIV+ men aged 40-60, regardless of tobacco smoking and traditional risk factors.

Lorenz DR, et al. Clin Infect Dis. 2017

# ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Showing: 1-10 of **44** studies 10 studies per page

Show/Hide Columns

| Row | Saved | Status | Study Title | Conditions | Interventions | Locations |
|---|---|---|---|---|---|---|
| 1 | ☐ | Completed | Comparing the Effects of Smoked and Oral **Marijuana** in Individuals With **HIV/AIDS** | • **HIV** Infections | • Drug: dronabinol | • New York State Psychiatric Institute<br>New York, New York, United States |
| 2 | ☐ | Completed | Project RAP: Family-based **HIV** Prevention in the Juvenile Drug Court | • **HIV/AIDS** | • Behavioral: Family-Based HIV prevention<br>• Other: Adolescent Only Health Promotion | • Rhode Island Hospital<br>Providence, Rhode Island, United States |
| 3 | ☐ | Recruiting | MEMO-Medical **Marijuana** and Opioids Study | • Opioid Use<br>• **Marijuana**<br>• Chronic Pain<br>• **HIV/AIDS** | | • Montefiore Health System<br>Bronx, New York, United States<br>• Vireo Health<br>White Plains, New York, United States |
| 4 | ☐ | Recruiting | Outcomes Mandate National Integration With **Cannabis** as Medicine | • Chronic Pain<br>• Chronic Pain Syndrome<br>• Chronic Pain Due to Injury<br>• (and 24 more...) | • Drug: **Cannabis**, Medical | • OMNI Medical Services<br>Boca Raton, Florida, United States<br>• OMNI Medical Services<br>Bradenton, Florida, United States<br>• OMNI Medical Services<br>Fort Lauderdale, Florida, United States<br>• (and 14 more...) |
| 5 | ☐ | Recruiting | Pharmacokinetic (PK) and Pharmacodynamics (PD) Study | • ALS | • Other: Registry | • Children's Hospital of |

# Upcoming Clinical Trials

- Effect of Cannabis and Endocannabinoids on HIV Neuropathic Pain
  - Sponsor: University of California, San Diego
  - Est. Completion: December 2020
- Acute Effects of Cannabis on Cognition and Mobility in Older HIV-infected and HIV-Un-infected Women
  - Sponsor: Albert Einstein College of Medicine/National Institute on Aging (NIA)
  - Est. Completion: December 2019
- Consequences of Marijuana Use in HIV-infected Youth
  - Sponsor: Duke University/University of North Carolina, Chapel Hill
  - Est. Completion: March 2021

# Patient Case

- TM is a 54 y/o white male who was diagnosed with HIV in 1996. He states he has been smoking marijuana for the past 6 years to alleviate his loss of appetite, weight loss and nausea he gets from taking such a large pill burden. TM is asking for your professional opinion on his choice to self medicate with marijuana.

# Thank You!

Question?

Comments?

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