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

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
Marijuana Industry Colorado

♦ Adult use concentrate prices fell from $41.43 to $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
Pharmacology

- Over 100 identified cannabinoids
  - $\Delta^9$ – tetrahydrocannabinol (THC)
  - Cannabidiol (CBN)
  - Cannabidiol (CBD)

- Cannabinoid receptors (CB)
  - CB1 – CNS, tissue
  - CB2 – Immune cells

More than 460 active chemicals
# Mechanism of Action

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

<table>
<thead>
<tr>
<th>Action</th>
<th>Effect</th>
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<tbody>
<tr>
<td>↑ Blood flow to right frontal brain</td>
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<tr>
<td>↓ IOP (carbonic anhydrase inhibitor sympathetic)</td>
<td></td>
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<tr>
<td>↓ Acetylcholine</td>
<td></td>
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<tr>
<td>↓ GABA &amp; Glutamate</td>
<td></td>
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<tr>
<td>Tri-cyclic ring</td>
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<tr>
<td>↓ Emetic center of medulla oblongata</td>
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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 $t_{1/2} = 2 - 6$ hours
- Plasma $t_{1/2} = 1 - 4$ days
- $t_{1/2} =$ biphasic (30 minutes/30 hours)
  - Redistribution to adipose = terminal $t_{1/2}$
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
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.
Most patients obtain cannabis products from recreational dispensaries.

Typically staff does not have clinical background.

Recommendations:
- 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
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

![Graph showing the number of traffic deaths related to marijuana when a driver tested positive for marijuana from 2006 to 2017.](image)

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

- 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

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

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.
<table>
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<th>Row</th>
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<th>Status</th>
<th>Study Title</th>
<th>Conditions</th>
<th>Interventions</th>
<th>Locations</th>
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</table>
| 1   |       | Completed   | Comparing the Effects of Smoked and Oral Marijuana in Individuals With HIV/AIDS | HIV Infections              | Drug: dronabinol             | New York State Psychiatric Institute  
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  
Other: Adolescent Only Health Promotion                                     | Rhode Island Hospital  
Providence, Rhode Island, United States                                       |
| 3   |       | Recruiting  | MEMO-Medical Marijuana and Opioids Study                                    | Opioid Use                  |                               | Montefiore Health System  
Bronx, New York, United States  
Vireo Health  
White Plains, New York, United States                                          |
| 4   |       | Recruiting  | Outcomes Mandate National Integration With Cannabis as Medicine              | Chronic Pain                | Drug: Cannabis, Medical       | OMNI Medical Services  
Boca Raton, Florida, United States  
OMNI Medical Services  
Bradenton, Florida, United States  
OMNI Medical Services  
Fort Lauderdale, Florida, United States                                        |
| 5   |       | Recruiting  | Pharmacokinetic (PK) and Pharmacodynamics (PD) Study                        | ALS                         | Other: Registry               | Children's Hospital of                                                                 |
|     |       |             |                                                                             |                             |                               |                                                                           |

Showing: 1-10 of 44 studies 10 studies per page
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?
References


♦ Thompson, A.E., Medical Marijuana JAMA. 2015;313(24).

♦ Epidiolex (Cannabidiol) [package insert]. Carlsbad, CA: Greenwich Biosciences, Inc; June 2018

♦ Marinol (Droabinol) [package insert]. North Chicago, IL: AbbVie Inc.; August 2017

♦ Syndros (Droabinol) [package insert. Chandler, AZ: Insys Therapeutics, Inc.; July 2016


References

References


