Cannabis (Medical Marijuana) Therapeutics & Policy:

July 11, 2020 -- IRETA webinar series presentation

A Substantive Discussion of a Substance Worth Discussing

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Financial Disclosures:

We have no disclosures or conflicts of interest relevant to the cannabis Industry.

Cannabis has Disclosures Too

Cannabis: not FDA approved for any condition

Cannabis is currently DEA Schedule 1 (illegal)
- No currently accepted medical use AND
- High potential for abuse

Investigational
- IND applications - 3 US agencies: National Institute of Drug Abuse (NIDA), DEA, FDA
- Approved research - cannabis product- NIDA - Univ. of Mississippi

OBJECTIVES:

- Learn about the endocannabinoid system, cannabis pharmacology, & patient management & risk management considerations, including potential adverse events and addiction.
- Describe the changing policy landscape of medical cannabis regulations under U.S. federal and state laws & how healthcare professionals & facilities have responded.
- Explain how cannabis legalization is theorized to impact the drug overdose crisis & the challenges & controversies in public health research in this regard.

US Government: Grows Cannabis, Supplies it to Patients and even has Patented it

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US Government Owns Patent

"Cannabinoids are found to have particular application as neuroprotectants, for example limiting neurological damage following ischemic insults, such as stroke and trauma, or in the treatment of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and HIV dementia"

What Should Medical Cannabis Be:

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- Cannabis Sativa
- Good Manufacturing Practices applied to grow and processing
- Cannabinoid and Terpenes
- 3rd Party Assay
- Labeled with Expiration
  - Mold / Yeast
- Contaminants below acceptable levels
  - Pesticides
  - Heavy Metals
  - Residual Solvents

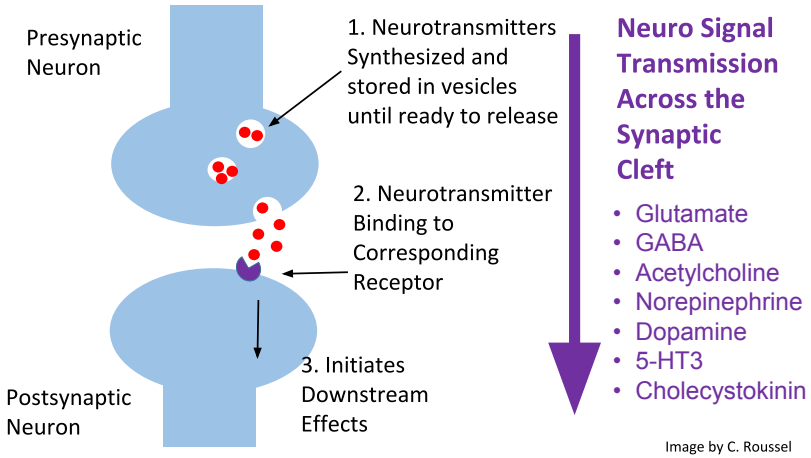
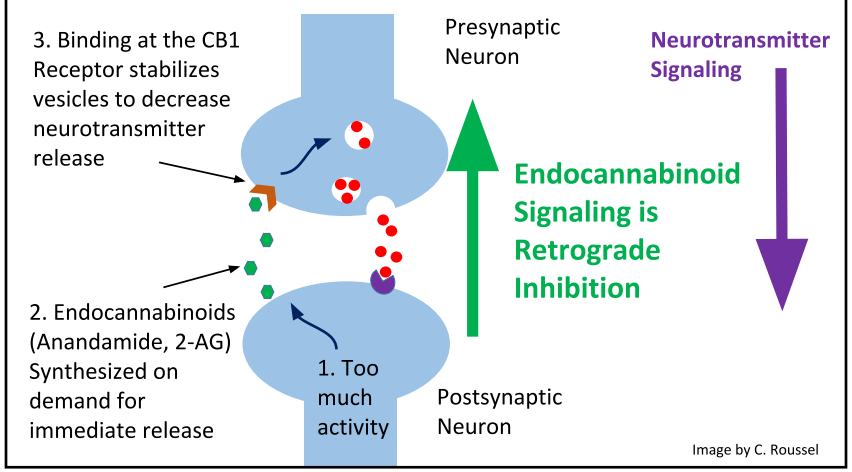


Image by C. Roussel



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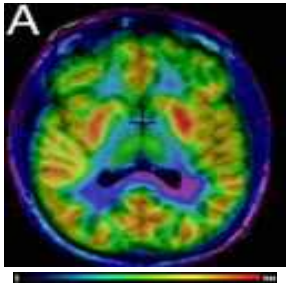
CB1 Receptors



Human brain after injection of radio tracer to show the regional distribution of CB1R

CB1 – Primarily in Brain

- NOT significant in brainstem (so won't affect breathing)

Other Locations

- Fat cells
- Endocrine and Exocrine Glands
- Liver
- Heart, Smooth Muscle in Blood Vessels

Cannabinoid Pharmacology in CNS

- Parasympathetic (Rest and Digest)
- Anti-Nociceptive (anti-pain)
- Neuroprotection
- Neuroplasticity

Originall publication: Burns, et al. [^{18}F]MK-9470, a positron emission tomography (PET) tracer for *in vivo* human PET brain imaging of the cannabinoid-1 receptor. PNAS June 5, 2007 vol. 104 no. 23. Pg. 9800–9805 © [2007] All rights reserved. Reprinted with permission."
Shohami E and Horowitz M (ed). Cannabinoids in Health and Disease. Themed special issue, Journal of Basic and Clinical Physiology and Pharmacology 2016; 27(3).

CB2 Receptors

- Signally ↓ release of activators and sensitizers

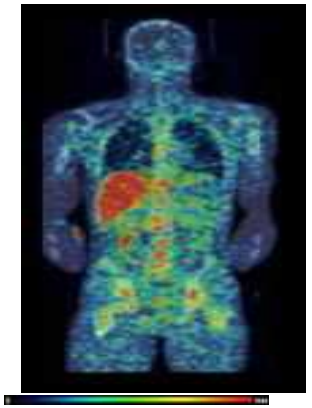
Modulation of Immune System:

- White Blood cells
  - Monocytes and Macrophages
  - B-cells and T-cells

Liver, Spleen, Tonsils

Central & Enteric Nervous System

Endocrine and Exocrine Glands



"Originally publication: **Ahmad R., et al. 2016** Whole-body bio-distribution and radiation dosimetry of the cannabinoid type 2 receptor ligand [11C]-NE40 in healthy subjects. Mol Imaging Biol. 2013 Aug;15(4):384-90© [2013]All rights reserved. Reprinted with permission."

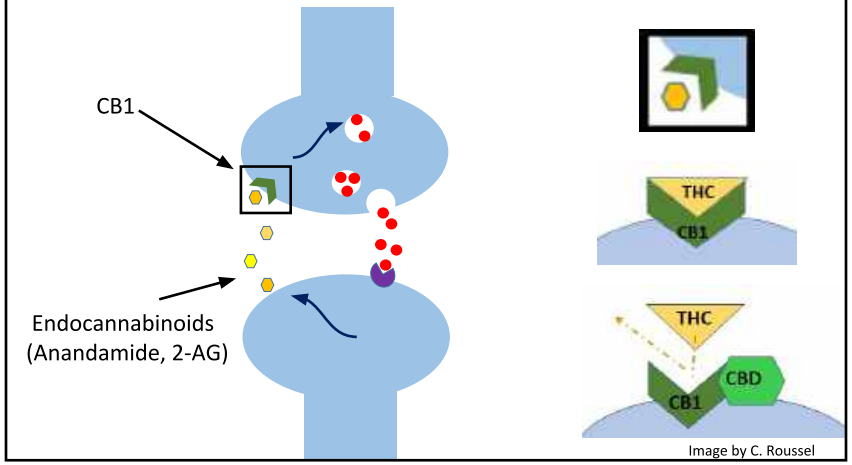
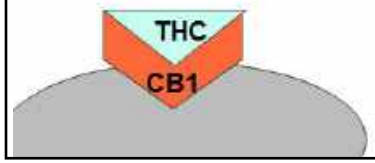
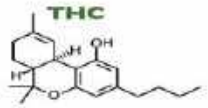


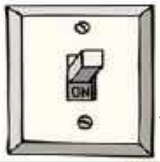
Image by C. Roussel

TETRAHYDROCANNABINOL (THC)

- Partial Agonist of CB1 and CB2
- Euphoria
- Analgesia (primary Pain relief molecule)
- Muscle Relaxant
- Anti-emetic / appetite stimulant
- Sleep





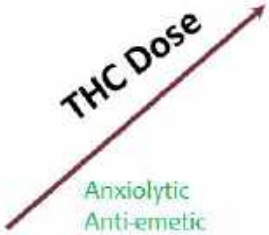


TETRAHYDROCANNABINOL (THC)

Psychoactivity vs Psychotoxicity
- Impaired cognition
- Difficulty concentrating
- Memory Impairment

Dry mucous membranes
Dizziness
Weakness , increase risk of falls

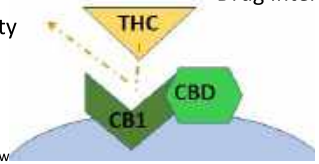
Anxiogenic / Paranoia
Cannabis Induced Psychosis
Hyperemesis syndrome



Cannabidiol (CBD)

- Decrease negative effects of THC (anxiety, memory impairment, psychoactivity)
- Enhances natural endocannabinoid activity
- Agonist at 5-HT (anti-nausea)
- Agonist at TRPV1
- Potent Immune Modulator = Strong Anti-Inflammatory Activity
- Anti-seizure
- Neuroprotective

ADVERSE EFFECTS
- Diarrhea
- Headache
- Suppress Appetite
- Stimulating (trouble sleeping) …..Somnolence
- Drug Interactions



World Health Organization: Cannabidiol Critical Review

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Adverse Effects of Short Term Use
Dizziness, Increased Risk of Falls
Impaired motor coordination
Rapid Heart Rate, changes in heart use of Oxygen
Altered judgement
Anxiety and Paranoia with high doses (bi-phasic response)
Impaired short term memory

Adverse Effects in Long Term Use
Use Disorder (1 in 10 chronic (daily) RECREATIONAL users)
Chronic Bronchitis
Hyperemesis Syndrome (overuse)

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Drug Interactions: Cannabis Effects on Other Drugs

Potentiate the Effects of Other CNS Depressants
- Alcohol, Opioids, Benzos, Muscle Relaxers

Cardiac Effects
- Amphetamines (Potentiate), ejection fraction

CYP Interactions 2C19, 2C9, 3A4
- Cancer
- HIV
- Anti-Seizure

Oral Chemotherapy Food and Drug Interactions: A Comprehensive Review of the Literature *Segal EM 2013*

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Relative contraindications: CV Disease

Population analysis increased risk of MI with inhaled illegal product … likely a function of the THC

- 4.8-fold higher risk of MI
  - 124 / 3882 patient cohort
- 2.5-fold increased risk of death (weekly use)
  - 54/1913 adults follow-up for h/o MI
- Increased CVD in cannabis users
  - 316,397 of > 20 million
- Cannabis not associated w/ ↑ CVD
  - 4286 with h/o cannabis use

Pacher, et al. Nature Reviews Cardiology, 2017; Kattoor, Marijuana and Coronary Heart Disease, ACC Expert Analysis Online, 2016

Absolute Contraindications: Uncontrolled Psychosis

Cannabis Induced Psychosis (CIP): DSM-5

- Diagnosis of exclusion
- Mood lability & paranoid, 24 hrs - 7 days
- Symptoms precipitated by increased THC potency or use
- Symptoms persist beyond typical intoxication

- Proposed mechanism: Δ9-THC ↑ dopaminergic signal
- Systematic Review: Higher risk psychosis symptoms w/ marijuana
- Case Report in recreational use

Khan, et al., Cannabis-Induced Bipolar Disorder with Psychotic Feature:Psychiatry 2009
Grewal, et al., Cannabis-Induced Psychosis: A Review. Psychiatric Times 2017
Moore, et al., Cannabis use & risk of psychotic or affective mental health outcomes:systematic review. Lancet 2007

Cannabis Use During Pregnancy

American Academy of Obstetrics – Recommends Against Cannabis Use During Pregnancy

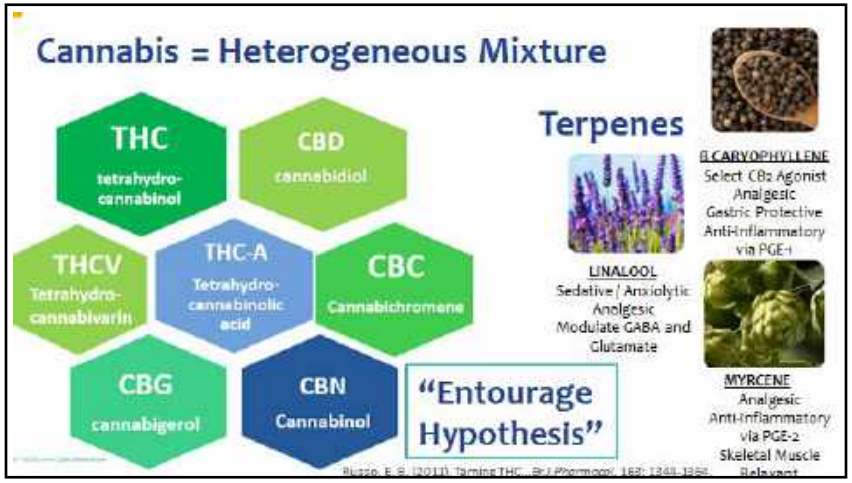
Chronic use evidence:

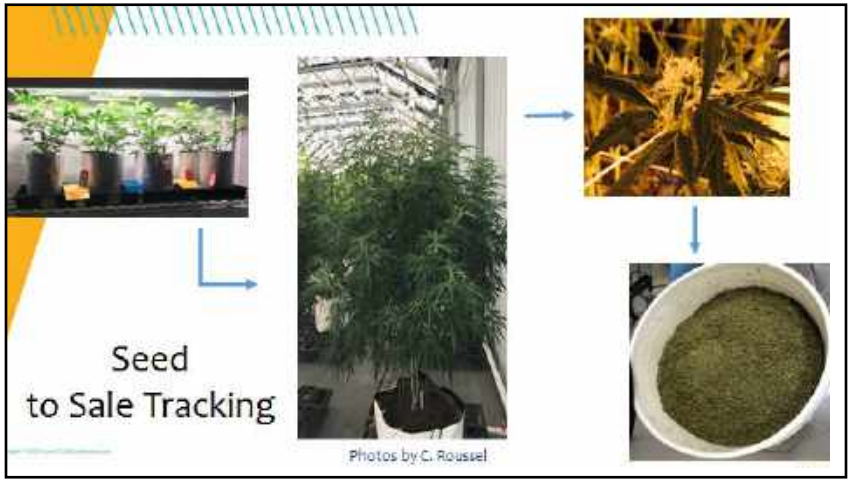
- Substantial: statistical association w/ **Low Birth Weight**
- Limited: **Increased Admission to the NICU**
- *confounders:* mother's income + education, alcohol/cigarettes

Insufficient Evidence to support or Refute Adverse Developmental Outcomes

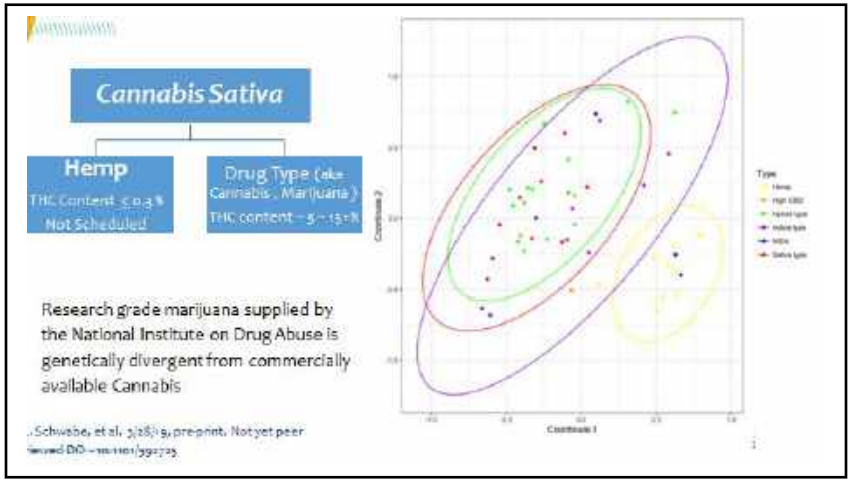
- ↑ Hyperactivity, Inattention, Impulsivity
- Conflicting changes on IQ
  - some reporting no change
- confounder: income + education, alcohol/ cigarettes
- Study Heterogeneity, magnitude of use

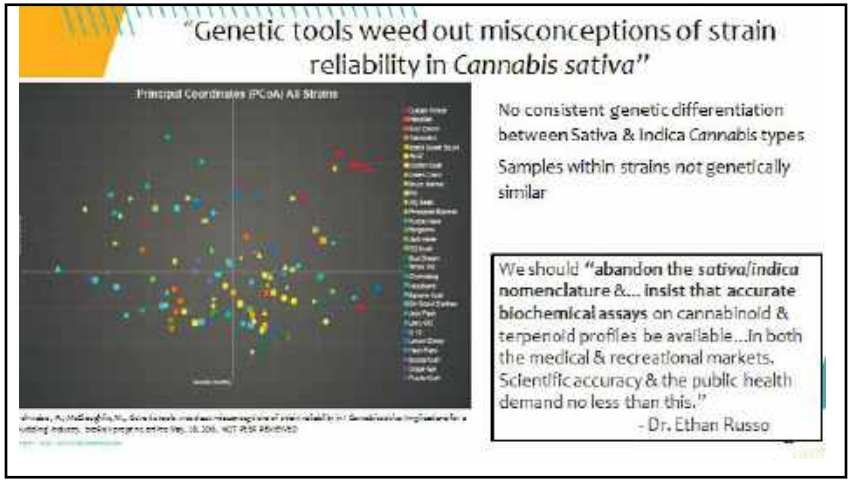
NASEM 2017, Cannabis Handbook 2014




Seed
to Sale Tracking
Photos by C. Roussel


Extraction
Photos by C. Roussel


Cannabis Sativa
Hemp
THC Content < 0.3 %
Not Scheduled
Drug Type (aka Cannabis , Marijuana)
THC content ~ 5 – 15+ %
Research grade marijuana supplied by the National Institute on Drug Abuse is genetically divergent from commercially available Cannabis
Coordinate 1
Coordinate 2
Type


"Genetic tools weed out misconceptions of strain reliability in Cannabis sativa"
Principal Coordinates (PCoA) All Strains
No consistent genetic differentiation between Sativa & Indica Cannabis types
Samples within strains not genetically similar
We should "abandon the sativa/indica nomenclature &... insist that accurate biochemical assays on cannabinoid & terpenoid profiles be available...In both the medical & recreational markets. Scientific accuracy & the public health demand no less than this."
- Dr. Ethan Russo

THC:CBD Chemotypes or Preparations

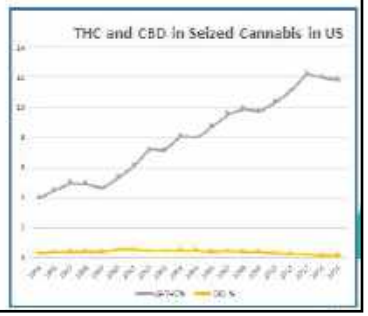
Hmm?
- THC:CBD or
- CBD:THC

Psychoactivity

THC-predominant
Ex. 50:1, 19:1, 4:1

Balanced = Intermediate
1:1, 1:4

CBD-dominant
Ex. CBD only, 1 : >20



Resource: Health Canada

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National Academies of Sciences, Engineering, & Medicine (NASEM) 2017 Report: *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence & Recommendations for Research*

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National Academy of Science 2017

***Beneficial* Associations - Substantial Findings:**

- Chronic pain in adults
- Chemo Induced Nausea and Vomiting (CINV)
- MS spasticity & improved sleep
- Short-term sleep outcomes associated w/ obstructive sleep apnea syndrome, fibromyalgia & chronic pain

***Harmful* Associations - Substantial Findings:**

- Worsening of respiratory symptoms & chronic bronchitis
- Increased risk of motor vehicle crashes
- Chronic Cannabis use in pregnancy = Low Birth Weight
- Frequent user & development of schizophrenia

NASEM, 2017

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NASEM Report: Evidence of Therapeutic Effectiveness

Limited evidence of effectiveness- Improving

- Appetite & decreasing weight loss assoc. w/ HIV/AIDS
- *Clinician-measured* MS spasticity symptoms
- Symptoms of Tourette syndrome
- Anxiety symptoms (assessed by public speaking test, in individuals w/ social anxiety disorders
- symptoms of posttraumatic stress disorder

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Physicians Cannot Prescribe Medical Marijuana:

- May NOT order a patient to consume/obtain a Schedule 1 Controlled Substance
- May NOT Order a pharmacist to dispense of a Schedule 1 Controlled Substance
- May NOT Specify specific amount to consume (dose)

Physicians CAN Recommend Medical Marijuana:

- Can Discuss treatment options (inc. cannabis or cannabis products)
- Can Discuss pros & cons of treatment w/ medical cannabis.
- Can Recommend that a patient consider the use of medical cannabis for symptoms

The court held that what it regarded as physicians' "legitimate need to discuss with and to recommend to their patients all medically acceptable forms of treatment" outweighs the government's "legitimate interest in suppressing and controlling the flow of dangerous drugs and controlled substances within the United States."

https://www.justice.gov/osg/brief/walters-v-conant-petition

Addiction and Cannabis

Cannabis Use Disorder

1 in 10 daily users may meet criteria

Withdrawal syndrome well established

Cannabis as Use Disorder Treatment

May decrease craving

May moderate withdrawal severity

May increase retention in care

Evidence is around alcohol and opioid use disorders

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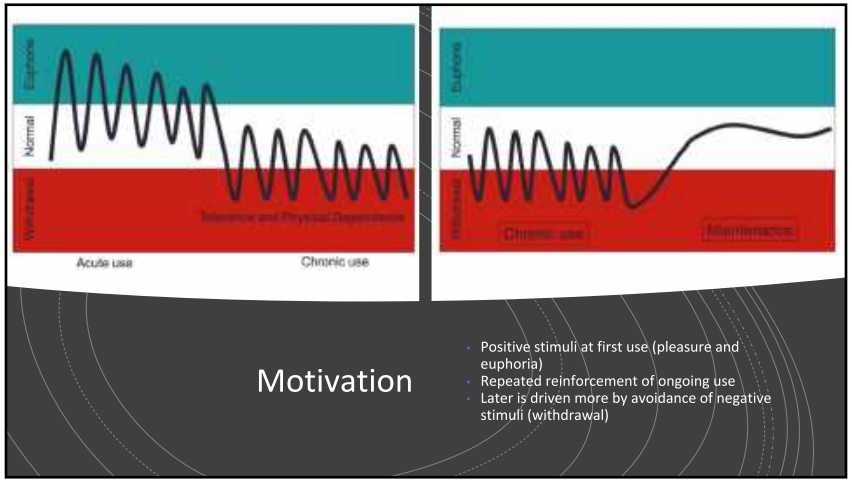
Use vs Use Disorder

Dependence

Addiction



Motivation

- Positive stimuli at first use (pleasure and euphoria)
- Repeated reinforcement of ongoing use
- Later is driven more by avoidance of negative stimuli (withdrawal)

Brain-behavior links and pharmacology

- Phase 1 – first use
  - Use -> positive response
  - Use
    - Effective absorption
    - Effective dose
    - Clear effect +/- Rapid effect
  - Positive response
    - Biologic
    - Psychologic
    - Social

Phase 1 physiology

1. Mu agonism in VTA (ventral tegmental area)
2. Less GABA tone to NA (nucleus accumbens) and mesolimbic system
3. Enhanced dopamine release (less GABA inhibition)
4. Dopamine release curve is faster and steeper
5. Activation of both D1 (low affinity) and D2 (high affinity)
6. Increased salience of the temporally correlated memory

Sum it up – phase 1

- Salience
  - Can be increased by chronic stress
  - Increased if effect is faster and stronger the onset of substance's effect



Testing substances for addictive potential

1. Photo credit: Jinrikisha Amufabalo
2. Addiction: The View from Rat Park (2010) Bruce K Alexander (2019).

Environmental & Genetic Factors for Addiction

Risk Factors

- Aggressive behavior in childhood
- Lack of parental supervision
- Poor social skills
- Drug experimentation
- Availability of drugs at school
- Community poverty

Protective Factors

- Good self-control
- Parental monitoring & support
- Positive relationships
- Academic competence
- School anti-drug policies
- Neighborhood pride

NIDA. (2018, July 20). Drugs, Brains, and Behavior: The Science of Addiction

Clinical correlation

- If chronic stress begets addictive potential then decrease stress related to drug access
- Licit market may reduce possible harms (and thus stress)
  - From unregulated market
  - From law enforcement related consequences

Potency vs Risk


1

3

2

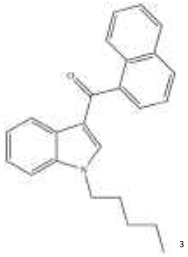

4

1. The Last Supper by Leonardo da Vinci 2. Beer Street and Gin Lane by William Hogarth 1751 3. Gold signet ring, Knossos. 1500 BC 4. Drugabuse.gov – image by Bruce Taylor/NHSP Forensic Lab

Potency vs Risk

1

2



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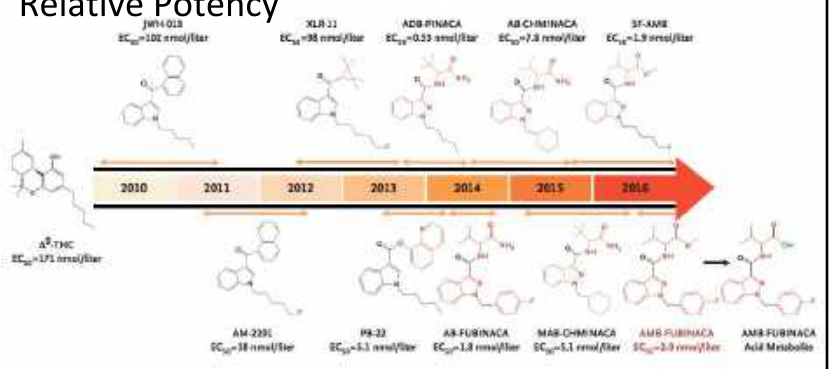
JW-018

1. Kantharos. Attica, ca. 780 BC. 2. Evan Amos 3. Wikimedia Commons – CNorman55

Relative Potency



NEJM 2017.

Temporal Correlation

Close

Delayed

Clinical correlation

- Pharmacology of the form and means of administration may impact use disorder risk
- Higher risk with higher potency
  - Can ingest higher functional doses more rapidly – intentionally or not
- Higher risk with more rapid onset of action
  - More salient memories with rapid onset
- Would expect less use disorder risk with use of lower potency, slower onset products

More stimuli ignored

Random Stimuli

- Behavior that is randomly reinforced will become increasingly erratic

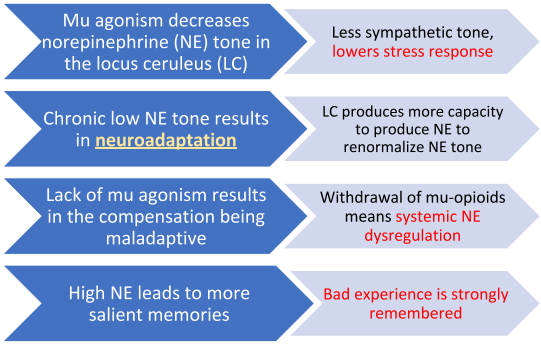
Phase 2 - summary

- Repeated intermittent stimuli with regular outcomes enhance learned behavior & eventually automate it
- A constant stable stimulus is ignored
- Random outcomes begets random behavior

Clinical correlation

- Consistent access to a consistent quality with consistent steady use may lead to decreased risk of use disorder
- Differences between regulated (medical) & unregulated (illicit) markets

Phase 3 – negative reinforcement



Phase 3 - summary

- The chronic use of opioids leads to neuroadaptation
- Withdrawal is an overcompensation of adrenalin
- Withdrawal is a negative reinforcement to continue to use

Clinical correlation

- Removing withdrawal symptoms with regular access to a drug may remove repeated negative reinforcement of withdrawal

Metasummary

- Consistent **access** to a consistent **quality** with consistent steady **use**
- may lead to decreased risk of use disorder
  - Less salience of positive reinforcement
  - Less occurrence of negative reinforcement
  - Less random stimuli
- Pharmacology of form & means of administration may impact use disorder risk
  - Higher risk with higher potency, rapid onset of action
  - Less risk with lower potency, slower absorption
- Limit stress of process
  - Differences between regulated (medical) & unregulated (illicit) markets

Use disorder risk and cannabis?

- Legalization is not the same as regulation nor standardization
- From an addiction risk perspective the risk would be least with:
  - Reliable, low-stress, consistent access to standardized products
  - Use of lower potency, slower onset of action products

Cannabis Use Disorder (CUDIT-SF)

How often in the past 6 months:

1. Did you find you were unable to stop using cannabis once you had started?
2. Have you devoted a great deal of your time to getting, using or recovering from cannabis?
3. Have you had a problem with memory or conversation after using cannabis?

Never(0) Less than monthly (1) Monthly (2) Weekly (3) Daily (4)

CUD present with ≥ 2

Bonn-Miller M. et al., Cannabis Cannabinoid Res. 2016 Dec 1;1(1):252-261.

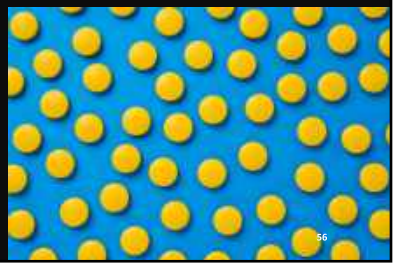
Cannabis and substance use / use disorders

- Population Level Impacts
  - Opioids – medical and non-medical use
  - Alcohol consumption
- Observational Cannabis use & Substance Use Disorder Outcomes
- Animal Models

Medical Cannabis Access & Opioid Use

Medical Marijuana Laws
- Chronic opioid prescriptions (↓5.88%)[1]
- Hospitalizations due to use disorder (↓23%) [2]
- Hospitalizations due to opioid overdose (↓18%) [2]

Observational / Retrospective
- Cannabis Use correlates with successful taper of chronic opioid therapy[3]
- Medical Certification Correlates with cessation of opioid requirement in chronic pain[4]



1. Wen, et al. JAMA Int med 2018
2. Shi, *Drug Alcohol Depend*. 2017
3. Darnall et al. JAMA Int Med, 2018.
4. Vigil, et al. PLoS ONE 2017.

Medical Access/Legalization of Cannabis Impacts on Alcohol

- 11% decrease in traffic fatalities[1]
- 10.6% decrease in alcohol consumption[2]
- May increase binge alcohol use in heavy users[3]

1. Anderson DM, Hansen B, Rees DI. Medical marijuana laws, traffic fatalities, and alcohol consumption. Journal of Law and Economics. 2013;56:333–369
2. Guttmannova K, Lee CM, Kilmer JR, et al. Impacts of Changing Marijuana Policies on Alcohol Use in the United States. *Alcohol Clin Exp Res*. 2016;40(1):33-46. doi:10.1111/acer.12942
3. Wen H, Hockenberry JM, Cummings JR. The effect of medical marijuana laws on adolescent and adult use of marijuana, alcohol, and other substances. *J Health Econ*. 2015;42:64-80. doi:10.1016/j.jhealeco.2015.03.007

Cross-addiction

Cross-addiction : history of addiction to one drug increases risk of developing addiction to another

If you have a use disorder which is treated to remission, the odds of developing another is lower OR = 0.66

Blanco C, Okuda M, Wang S, Liu S, Olfson M. Testing the Drug Substitution Switching-Addictions Hypothesis: A Prospective Study in a Nationally Representative Sample. JAMA Psychiatry. 2014;71(11):1246–1253. doi:10.1001/jamapsychiatry.2014.1206

Data viewpoints - Observational

- Opioid use disorder outcomes
  - Conflicting data from multiple studies across all forms of MAT [1-4]
- Alcohol Use Disorder Outcomes
  - Cannabis use increase alcohol consumption if AUD +/- CUD[5]
  - Decreased if CUD alone[5]
- No studies recommended or provided cannabis

1. Zielinski L, Bhatt M, Sanger N, et al. Association between cannabis use and methadone maintenance treatment outcomes: an investigation into sex differences. *Biol Sex Differ*. 2017;8:8. Published 2017 Mar 30. doi:10.1186/s13293-017-0130-1
2. Socias, M. E., Wood, E., Lake, S., Hayashi, K., Fairbairn, N., Hayashi, K., ... & Milloy, M. J. (2018). High-intensity cannabis use is associated with retention in opioid agonist treatment: a longitudinal analysis. *Addiction*, *113*(12), 2250-2258.
3. Bagra, I., Krishnan, V., Rao, R., & Qureshi, K. (2018). Does Cannabis use influence opioid outcomes and quality of life among buprenorphine maintained patients? A cross-sectional, comparative study. *Journal of addiction medicine*, *12*(4), 312-316.
4. Raby WN, Carpenter KM, Rothenberg JL, et al. Intermittent marijuana use is associated with improved retention in naltrexone treatment for opiate-dependence. *Am J Addict*. 2009;18(4):303–308. doi:10.1080/10550490902927785
5. Metrik J, Gunn RL, Jackson KM, Sokolovsky A, Borsari B. Daily Patterns of Marijuana and Alcohol Co-Use Among Individuals with Alcohol and Cannabis Use Disorders. Alcohol Clin Exp Res. 2018;42(6):1096-1104. doi:10.1111/acer.13639

Cannabinoids and Opioid Use – Animal Models

- Animal Models
  - Mouse genetics modulate the ability for THC to change opioid addiction propensity[1]
  - Mice without μ, δ, or κ opioid receptors
    - lose THC antinociceptive and reward effects
    - still have THC tolerance and withdrawal[2]
  - THC and CBD decreasing opioid withdrawal in mice[3], but neither in rats[4]

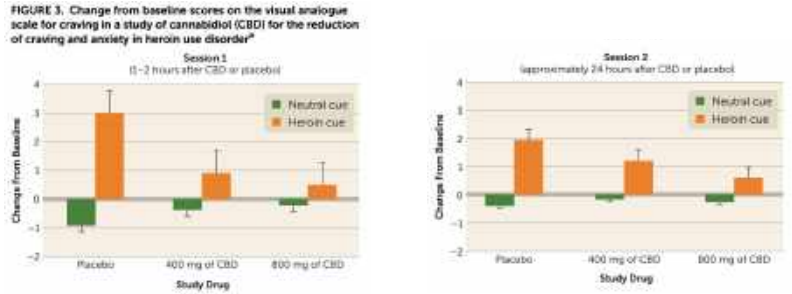
No randomized controlled trials in humans with medical cannabis and opioid use disorder

Cannabis and Alcohol Use – Animal Models

- Adding CBD to Naltrexone, but not CBD alone decreases alcohol consumption in habituated mice[1]
- CBD alone does decrease level of resumption of alcohol use in mice who are in recovery[2]
- No human trials published yet, but at least 2 are in process: NCT03252756; NCT03248167

1. Viudez-Martínez A, García-Gutiérrez MS, Fraguas-Sánchez AI, Torres-Suárez AI, Manzanares J. Effects of cannabidiol plus naltrexone on motivation and ethanol consumption [published correction appears in Br J Pharmacol. 2019 Jan;176(2):334]. *Br J Pharmacol*. 2018;175(16):3369-3378. doi:10.1111/bph.14380
2. Viudez-Martínez A, García-Gutiérrez MS, Navarrón CM, et al. Cannabidiol reduces ethanol consumption, motivation and relapse in mice. Addict Biol. 2018;23(1):154-164. doi:10.1111/adb.12495

Phase II RCT - CBD for Heroin Use Disorder



Citation: Hurd, Y. L., Spriggs, S., Alishayev, J., Winkel, G., Gurgov, K., Kudrich, C., … Salsitz, E. (2019). Cannabidiol for the Reduction of Cue-Induced Craving and Anxiety in Drug-Abstinent Individuals With Heroin Use Disorder: A Double-Blind Randomized Placebo-Controlled Trial. American Journal of Psychiatry, appi.ajp.2019.1. doi:10.1176/appi.ajp.2019.18101191

The Changing Regulatory & Policy Landscape

Key U.S. Drug Control Policies timeline

1906- The Pure Food & Drug Act

1914- Harrison Narcotic Act Regulated/ taxed Opium, Coca (not cannabis_

1920-1933 - Alcohol Prohibition

1922- Jones Miller Act -Narcotics Control Board

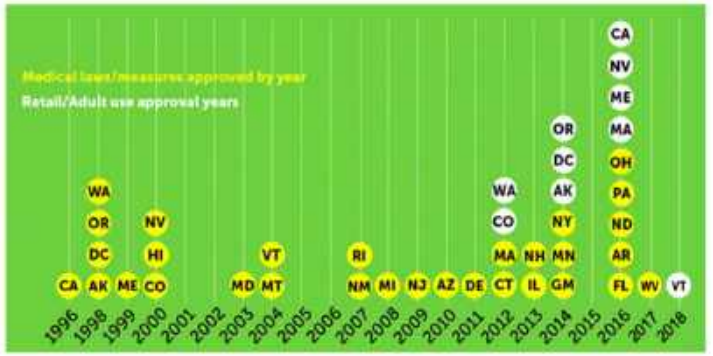
1930 Federal Bureau of Narcotics Harry Anslinger, Commissioner 1930-1962

1937 - Marijuana Tax Act

U.S. Drug Control timeline

- 1969 – Marihuana Tax Act found unconstitutional
- **1970 - Controlled Substance Act**
- 1977- 1993 Federal Compassionate IND (n=13) U. Miss gov't grown cannabis
- 1996-2020: States legalize medical cannabis & retail/ adult use cannabis
- **2018: "Farm bill"** - removes agricultural hemp from CSA
- **2019-20:** DEA evaluating new licensing for research grow
- SAMHSA warns re: no federal $ for medical cannabis tx
- CBD enforcement - violations of FD&C Act

STATE MARIJUANA POLICIES TIMELINE



Graph: National Conference of State Legislatures, 2018

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Limitations to Federal Action

Attorney General Statements

Ogden 2009: Feds won't "focus federal resources" … i.e. prosecute individuals/ caregivers) w/serious illnesses **if using MM per state law**

Sessions Jan. 2017: Return to "1980" = Federal Prosecutors decide

- AG Crime Priorities: seriousness, deterrent effect, cumulative impact
- Previous guidance (i.e Cole memo) *"is unnecessary & is rescinded"*

U.S. Congress: uses appropriations to restrict DOJ

➔ Amendment / riders on yearly appropriations bills

➔ Prohibits DOJ from using federal funds to interfere w/state **medical** cannabis laws

justice.gov/opa/pr/justice-department-issues-memo-marijuana-enforcement

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Agricultural Hemp and the "2018 Farm Bill"

- Allows legal cultivation of Hemp (growers registered w/state & Department of Agriculture)
- Hemp removed from Controlled Substance Act
- Allows interstate commerce - legally grown hemp/ hemp products
- **Does not supersede Food, Drug & Cosmetic Act**
- Does not prohibit ability to promulgate Federal regulations & guidelines re: production of hemp

www.congress.gov/115/bills/hr2/BILLS-115hr2enr.pdf

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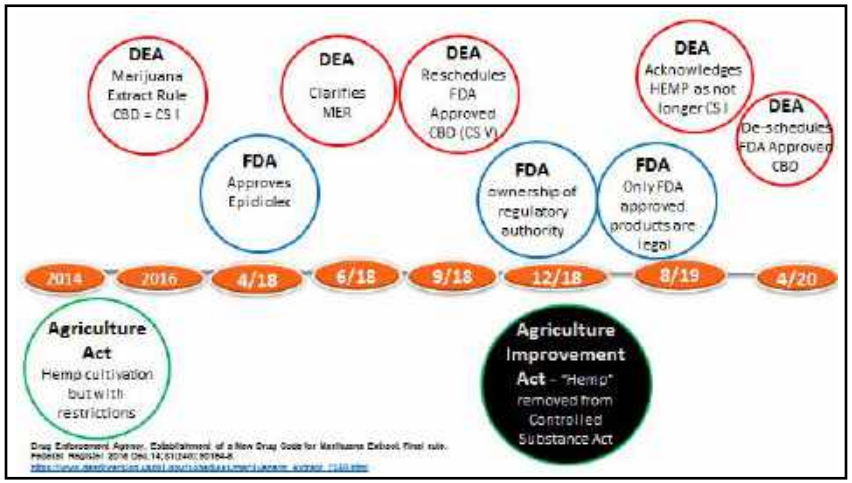


Cannabidiol: Food, Drug & Cosmetics Act has authority

Unlawful to:

- introduce food w/ added CBD or THC into interstate commerce
- market CBD or THC products as, or in, dietary supplements, (whether or not hemp-derived)

Both CBD & THC = active ingredients in FDA-approved drugs

Labeling Accuracy of Cannabidiol on the Internet

- Using +/- 10% for label accuracy of CBD content (n=84)
  - 43% over label
  - 26% under label
  - 31% on label
- 18 / 84 samples (22%) had detectable THC
- THC contamination detected as high as 6.43 mg/mL

Certificate of Analysis Please

Bonn-Miller, Loflin, Thomas, et al. Labeling Accuracy of Cannabidiol Extracts Sold Online. *JAMA* 2017.

Healthcare Facility Considerations

- Cannabis is not an FDA approved Drug
- Physicians cannot Prescribe Cannabis
- The facility cannot provide it

Policy Options

- Do not allow any Products
- Allow Products
- Allow with restrictions & strict criteria

The attending physician should decide whether or not to interrupt therapy previously initiated as an outpatient based on clinical considerations.

Necessary Procedural / Legal Criteria

What form of medical marijuana is the patient taking?	If Inhalation, patient **CANNOT** continue
Does patient have valid State Medical Marijuana ID card <u>from the state the hospital is in?</u>	If no card, patient **CANNOT** continue
Is the MM product(s) from state licensed dispensary & labeled for what it contains?	• Must be from state dispensary (or considered illegal drugs.) • Original packaging • If these 2 criteria are not met, the patient **CANNOT** Continue

Clinical Considerations for health care facility:
continuation of MMJ therapy previously initiated as an outside of that facility?

Presenting w/any side effects from medical marijuana therapy? (ie. dizziness, fall, cognitive impairment)	Would <u>NOT</u> recommend continuing MMJ
Does the patient appear Intoxicated	Would <u>NOT</u> allow the patient to continue
Myocardial Infarction, Tachycardia, A-Fib or hypotension?	Relative contraindication & should NOT be continued inpatient. (population cohort studies link inhaled cannabis to increase risk of MI)
Is the patient displaying symptoms of mania or uncontrolled behavioral health conditions?	NOT recommended MMJ can contribute/ precipitate exacerbations of their condition

If physician allows previously initiated therapy to continue:

- "Patient Owns" controlled substance process
- Facility **<u>cannot</u>** provide or replenish supply
- Verification & identification of product
- Ensure that it is obtained from a legal state dispensary
- Limit allowable dosage forms
- In-facility chain of custody vs. patient responsible for product
- Patient / caregiver solely responsible to safeguard & administer
- Documentation of self or caregiver administration

Documentation of Patient Responsibilities

Provide copy of policy and staff fully explains obligations upon admission

- Understand and agree that patient or my caregiver are solely responsible to:
- Maintain, safeguard and administer the medical marijuana.

Keep product in their possession or the possession of their Caregiver

Will Your facility allow Self-administration or Just Caregiver Administration??
Is the Patient Competent to Self Administer and Safeguard?
How do you assess competency?

Cannabis Labeling Concerns

Consistent Ratio

Dose per unit

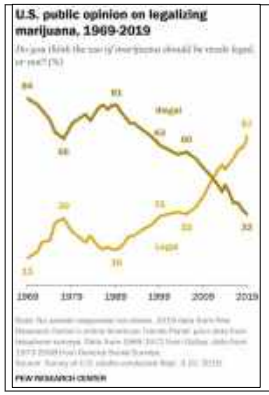
Concentration

Volume for appropriate dose

Communication….

How to Identify the Product and Determine the Dose?
Vs. Allow the Patient Use However Much they Want

- Which Dispensary is the Product From
- Product Patient is using
- Cannabinoid Content Listed
  - Amount of THC and CBD
- Dose Patient Reports Taking?
  - 1 drop or 1 dropperful



U.S. Public Opinion

91% support legalization for therapeutic &/or adult use

- Supporters cite health benefits, risks ~ other drugs
- Opponents cite risks to health & society

- Coincides with state actions to increase access

Nov. 2019, Pew Research

Cannabis Impairment and Driving?

- Marijuana slows reaction time, ability to make decisions.

Can impair coordination, distort perception, difficulty in problem-solving.

Risk of impaired driving associated with marijuana **in combination with alcohol** appears to be greater than that for either by itself.

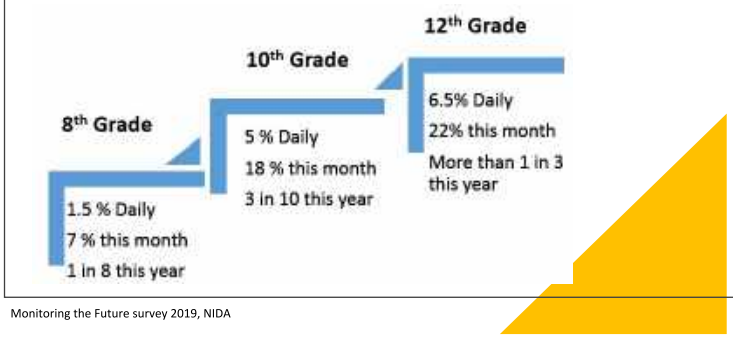
- NHTSA study -large case-control study, National Highway Traffic Safety Administration

No significant increased crash risk attributable to cannabis *after controlling for drivers' age, gender, race, presence of alcohol*

- Sampling issues: toxicology data
- No reliable measure of impairment

CDC, 2019; NIDA 2019

Key Policy concerns: Adolescent Cannabis Use



Monitoring the Future survey 2019, NIDA

Percent of Students Reporting Daily Use of Marijuana, by Grade

*Significant increase compared to the 2018 MTF Survey.

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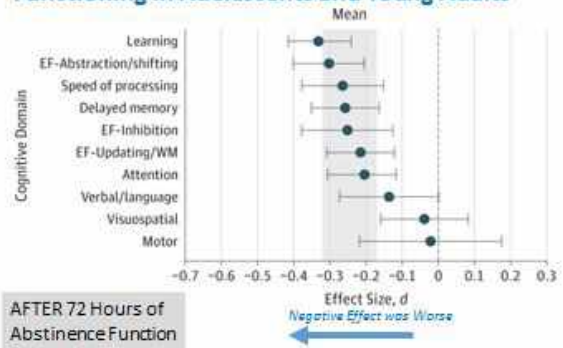
Association of Cannabis With Cognitive Functioning in Adolescents and Young Adults



AFTER 72 Hours of Abstinence Function Returns to Normal

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Adolescent Use & Cognitive Function: long term data

Adolescent-onset cannabis users / continued using ~ daily through early adulthood
- Declines in IQ
- Worse performance: verbal memory, working memory, perceptual reasoning --by late 30s
- New Zealand (Meier et al., *PNAS*, 2012)

Studies question impact of confounders (Jackson et al., 2016; Mokrysz et al., 2016; Meier et al., 2017)
- All found no specific effect of cannabis on decline in cognitive functioning or IQ
- Better accounted for by familial factors or confounders

Abstinence after frequent use -- minimal evidence of cognitive deficits
- Even in adolescents or with longer (~10 year) follow-up
- Fried et al. (2005), Tait et al. (2011), Pope et al. (2001)

But Scientists are not sure yet !! -> More Studies Needed
- Many confounds ->Definitely factors that increase or decrease risk

Cannabis legalization will [positively *or* negatively] impact the opioid crisis.

- increased use = "gateway theory" to opioids?
- impact on overdose deaths?
- potential for opioid substitution?

Population level study challenges

Must control for individual level + state level covariates

Outcome measures? Can you control for:

- medical use (RX) + benzo RX *and* frequent non-medical use
- OUD (addiction), DUI, overdose
- state demographics
- opioid legislation AND cannabis legalization

Gateway Theory to opioids?

CDC: *The majority of people who use marijuana do not go on to use other, 'harder' substances"*

But- "*more research needed.*"

--Marijuana & Public Health on cdc.gov/marijuan/faqs (2018)

Debunked: *"Simply stated, people who have used other drugs are more likely to have also used marijuana.*

Not the other way around."

-- Debunking the "Gateway" Myth on drugpolicy.org (2017)

Rand, 2017 Powell, Pacula, Jacobson

Journal of Health Economics


Journal of Health Economics

Do medical marijuana laws reduce addictions and deaths related to pain killers?

David Powell, Rosalie Liccardo Pacula, Mireille Jacobson

Complex! Shift from RX opioid to heroin /mortality

"...medical marijuana, by itself, will not be the solution to the nation's opioid crisis today." - Dr Rosalie Pacula

Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the U.S., 1999–2010

Bachuber, Saloner, Cunnigham, Barry, JAMA Internal Med, Oct. 2014

Time-series analysis, MM laws + 50 state death certificates

Medical cannabis laws *associated* w/ ↓ rates of opioid analgesic overdose mortality

- 24.8% lower annual rate
- generally strengthened in the years after passage
- in 2010, an est. 1729 fewer deaths

BUT: indirect evidence, needs rigorous evaluation.

Significance decreased when controlling for state linear time trends.

How do policies vary among states?

State marijuana laws & opioid overdose mortality

Chihuri & Lee, ***Injury Epidemiology***, Sept. 2019

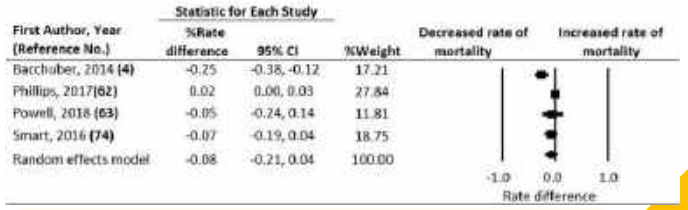

Fig. 2 Forest Plot, Summary Percent Rate Differences (RD) & 95% Confidence Intervals (CI) of Opioid-related Mortality Associated with Medical Marijuana Laws in the U.S. The Diamond Indicates the Summary Percent RD. Horizontal Bars Indicate the 95% CI. Heterogeneity: Q statistic: 24.080, df = 4, P = 0.000, I2 = 83.389

https://www-ncbi-nlm-nih-gov.db.usciences.edu/pmc/articles/PMC6717967/

Opioid Prescribing assoc. w/MM laws?

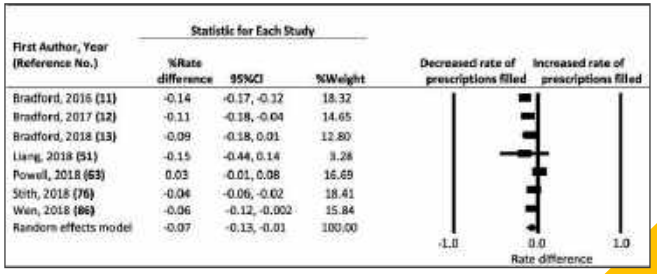

Fig. 3 Forest Plot, Summary % Rate Differences (RD) U 95% Confidence Intervals (CI) of Opioid RXs Filled Assoc. w/MM Laws in U.S. The Diamond Indicates the Summary Percent RD. Horizontal Bars Indicate the 95% CI. Heterogeneity: Q statistic: 70.276, df = 6, P = 0.000, I2 = 91.462

Chihuri & Lee, ***Injury Epidemiology***, Sept. 2019

Ineffective drug policies

Supply-side controls: can ↑ drug prices, which can ↓ drug initiation /use - but changes are difficult to maintain over time.

Wide-scale arrests/ incarceration -- "War on Drugs"

Ineffective for drug use prevention:

- Knowledge & awareness education: illicit drugs, tobacco, alcohol
- "Just say no"
- DARE school-based prevention programs
- Mass media campaigns for cannabis prevention (to date)

Strang et al, Drug Policy & the Public Good, Lancet 2012

The Lancet- JHU Commission: Carefully researched public health, evidence-based approach to drug policy (April 2016)

- Decriminalize, non-violent drug use. Eliminate police violence/ carceral harms
- Strengthen non-criminal sanctions/ social alternatives / harm reduction
- Prioritize effective treatment for SUDs & infectious diseases
- Remove policies harming women & families
- Move to regulated drug markets/ Improve UN drug policy & controls

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)00619-X/fulltext

USciences | Substance Use Disorders Institute

Upcoming Trainings

Medical Cannabis Certification Courses

Webinar Courses:

Thursday, June 25, 2020, Online
5:15-9:30 pm: 4-hour Certification Course
More Information and registration.

usciences.edu/MedicalCannabisEducation

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Question & Answer? Contact info:

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