LOST IN THE WEEDS: MAKING SENSE OF MEDICAL MARIJUANA

OHIO SOCIETY OF ADDICTION MEDICINE

Annual Meeting – October 11, 2019

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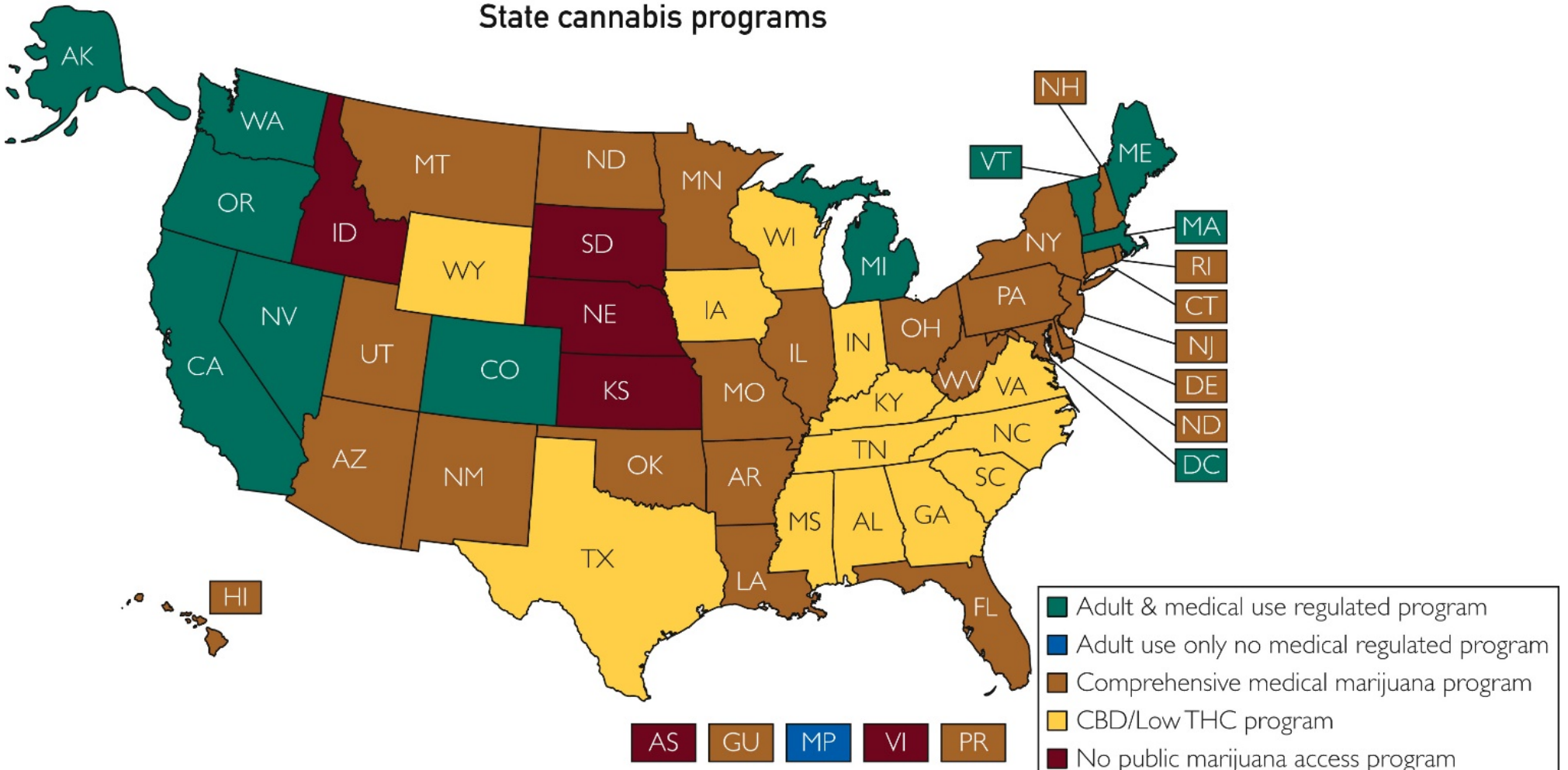
Overview

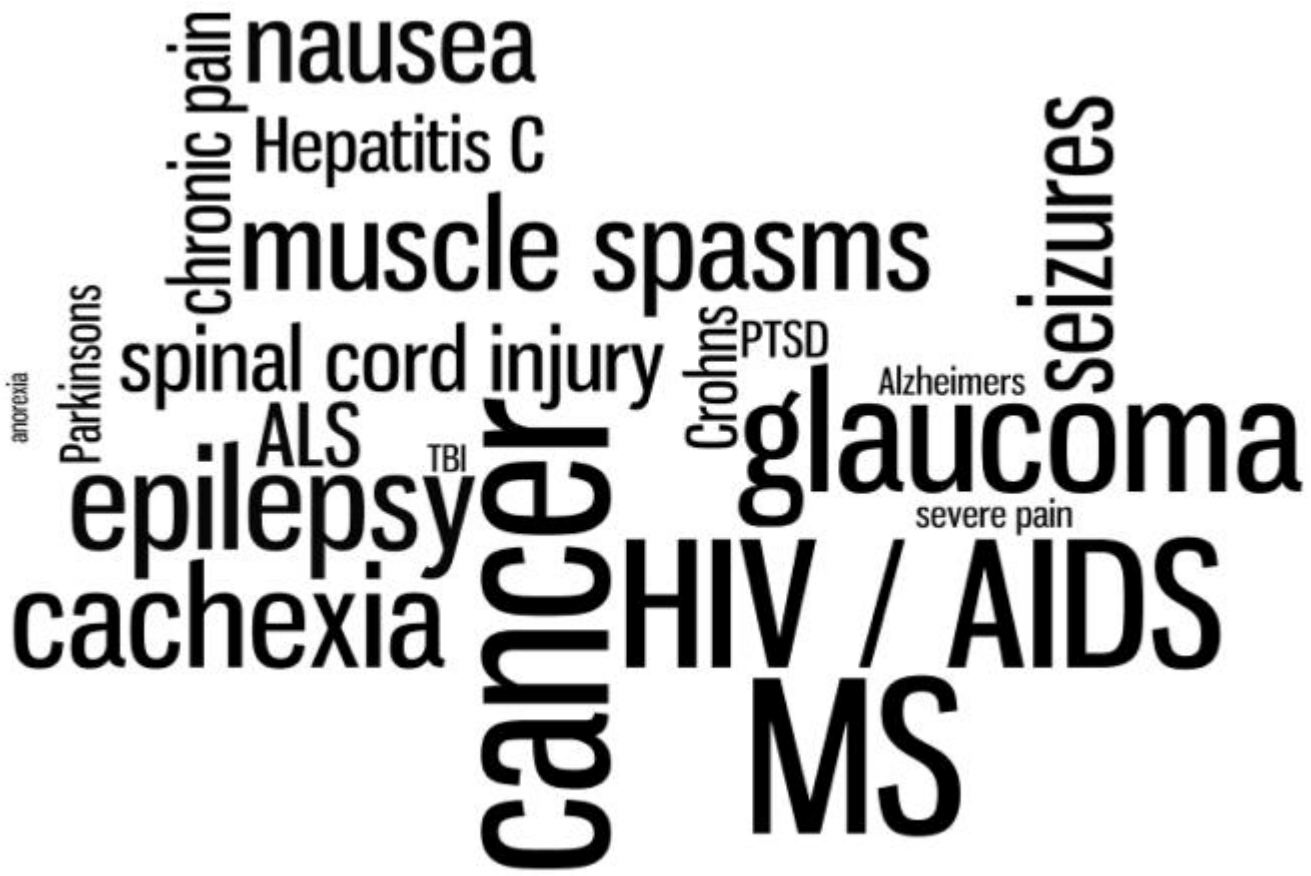
- Is it a medicine?
- Who is using it?
- What is it?
- What are the risks?
- What is the evidence?

Medicine?

- China-2700 B.C.
  - Constipation, Malaria, Gout, forgetfulness, "female disorders"
- India- 2000 B.C.
  - Euphoric properties, reduces fever, improves sleep, ↑ appetite, relieves headaches, cures venereal disease
- 30 of 50 states have legalized medical marijuana
- Most used illicit substance in the world
- Natural
- No violence, No overdose



Mayo Clinic Proceedings 2019 94, 1840-1851DOI: (10.1016/j.mayocp.2019.01.003)



Variability in Medical Marijuana Laws in the United States.Bestrashniy, J. Psychol Addict Behav. 2015 Sep; 29(3): 639–642

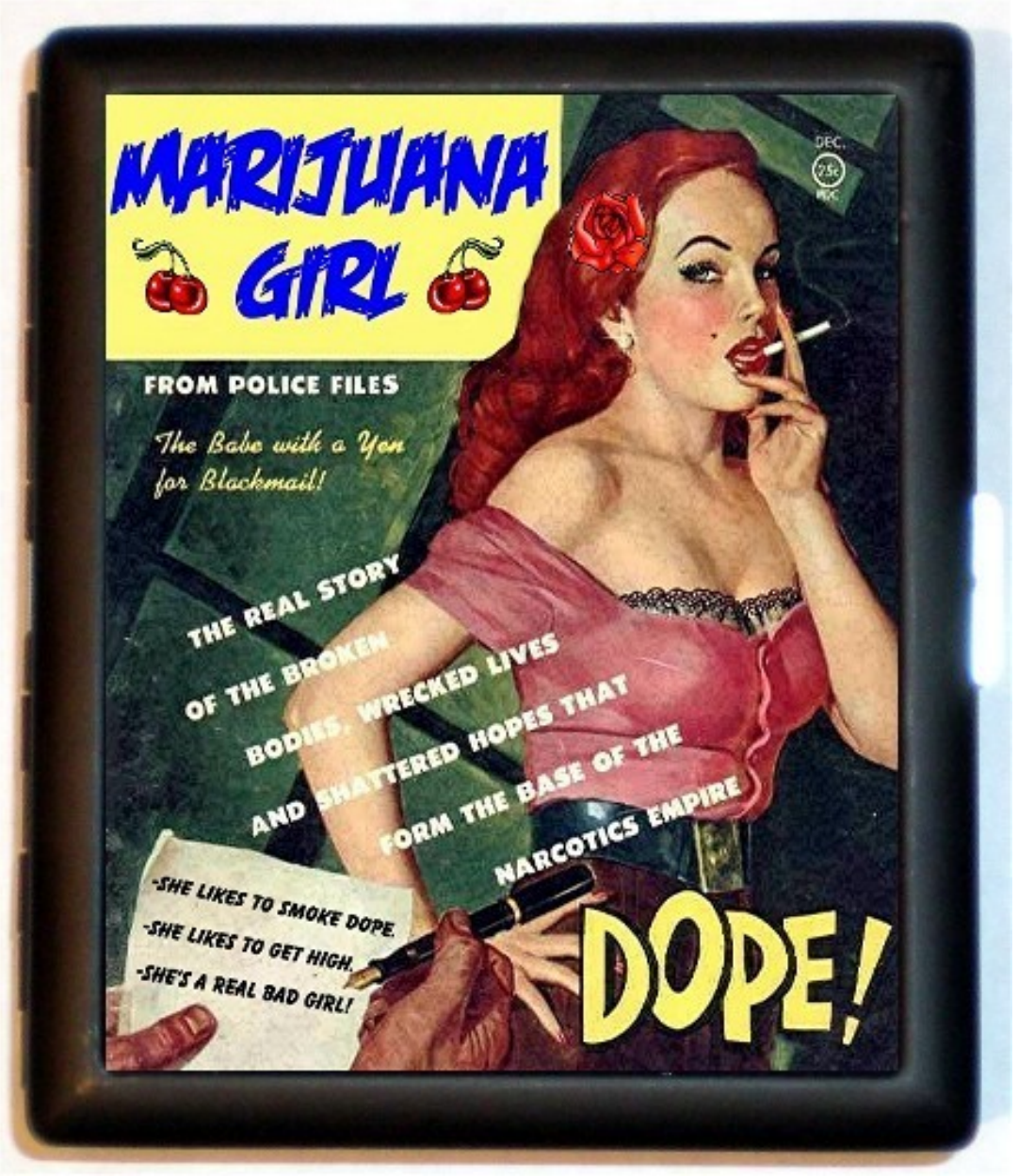
Medicine?

- Marijuana is NOT an FDA approved drug
- Marijuana is a Schedule I substance
- Active ingredients are cannabinoids
- Synthetic cannabinoids: **Dronabinol** and **Nabilone** are FDA approved
  - Nausea/vomiting due to chemo
  - Appetite and weight loss in HIV/AIDS and Cancer
- Doctors **can't** write a Rx for marijuana
  - Prescription, supply or sale is illegal by federal law
  - Liability for certifying use? Malpractice coverage?

Medications

- UK, Canada and several European countries have approved:
  - Nabiximols (**Sativex**)- mouth spray w/ THC and CBD
    - Indicated for MS
- **Epidiolex**
  - CBD-based liquid to treat childhood epilepsy
  - FDA advisory committee approved on 4/20/18 (Final Approval June 2018)

Who's Using?


MARIJUANA GIRL
DEC.
25c
FROM POLICE FILES
The Babe with a Yen for Blackmail!
THE REAL STORY OF THE BROKEN BODIES, WRECKED LIVES AND SHATTERED HOPES THAT FORM THE BASE OF THE NARCOTICS EMPIRE
-SHE LIKES TO SMOKE DOPE.
-SHE LIKES TO GET HIGH.
-SHE'S A REAL BAD GIRL!
DOPE!

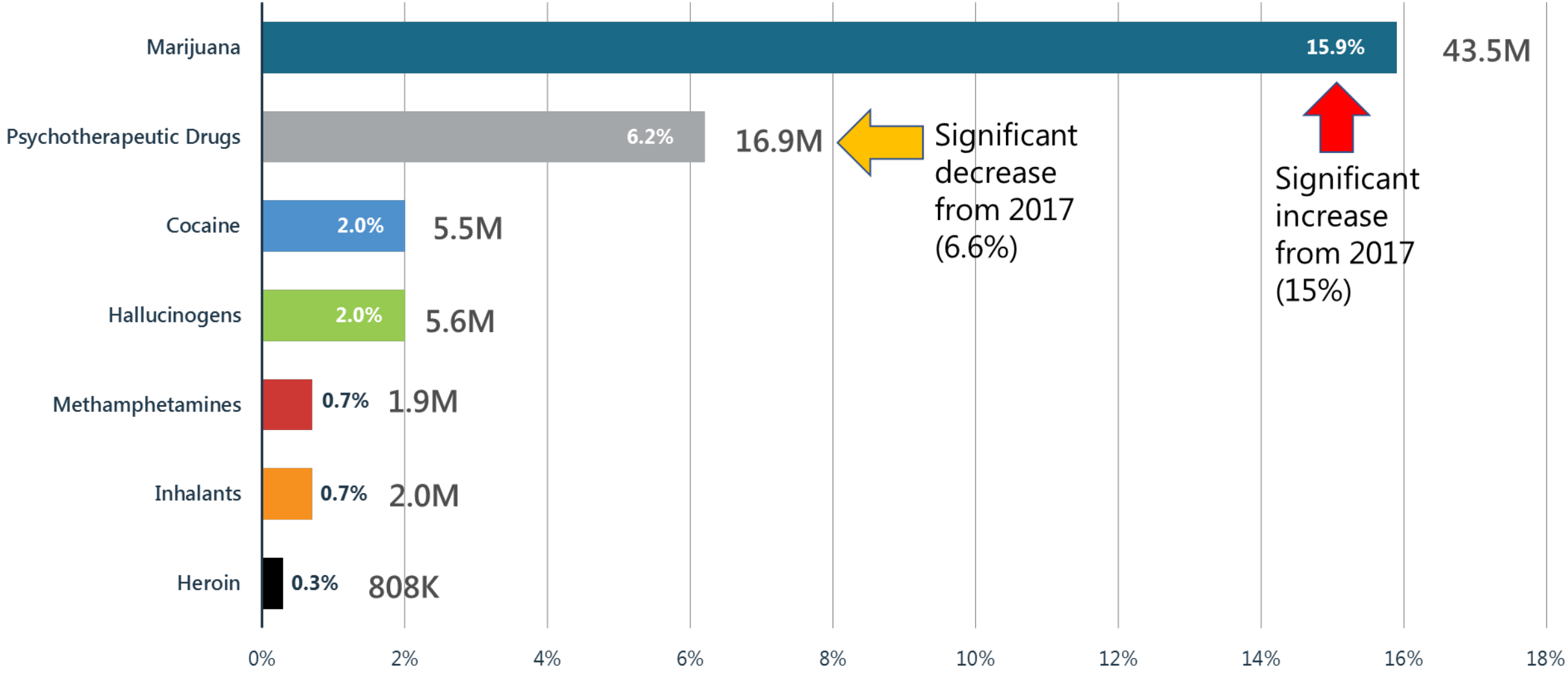
Epidemiology

- National Survey of Drug Use and Health (NSDUH)
  ~70,000 respondents ≥12 y/o annually
  - 43.5 million users in 2018
  - 4.4 million had CUD
- Almost 50% of Americans report ever using MJ
  - 10% of ever-users become daily users
  - 20-30% become weekly users

https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHDetailedTabs2018R2/NSDUHDetTabsSect1pe2018.htm. Accessed Online 9/21/19

WD Hall. Cannabis use and dependence: public health and public policy, Cambridge University Press, Cambridge, UK (2003)

Illicit Drug Use: Marijuana Most Used Drug



PAST YEAR, 2018 NSDUH, 12+

SAMHSA
Substance Abuse and Mental Health Services Administration

NESARC 2001-2002 vs. 2012-2014

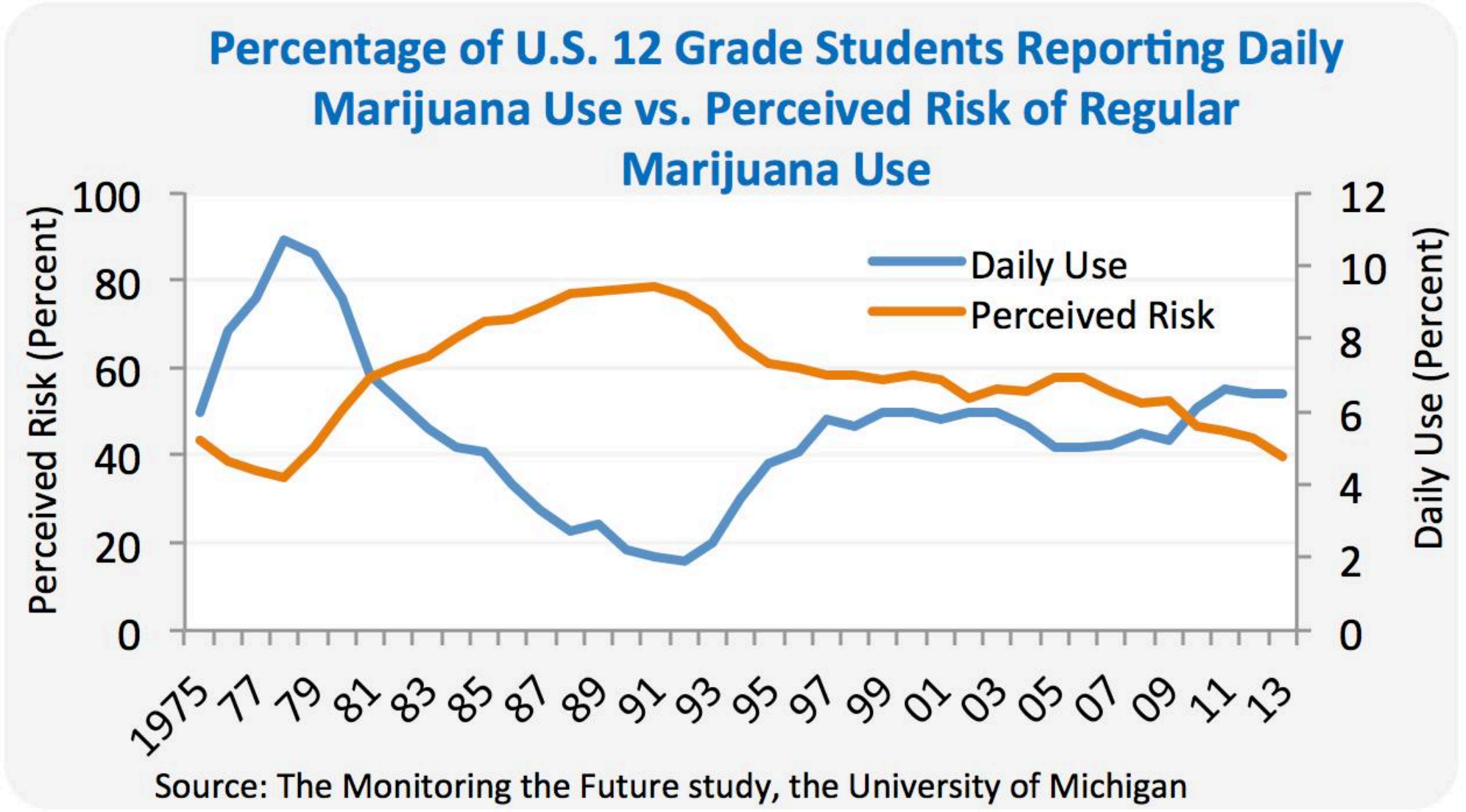
~79,000 respondents

- Use in past year:
  - 4.1 → 9.5%
- Cannabis Use Disorder:
  - 1.5 → 2.9%
- 30% of users in past year met criteria for CUD
- Young adults at highest risk (18-29y)
  - Use: 10.5 → 21.2%
  - CUD: 4.4 → 7.5%
- Black pop. had greatest increase
  - Use: 4.7 → 12.7%
  - CUD: 1.8 → 4.6%

"Based on the results of our surveys, marijuana use in the United States has risen rapidly over the past decade, with about 3 in 10 people who use marijuana meeting the criteria for addiction. Given these increases, it is important that the scientific community convey information to the public about the potential harms"

- George Koob, director of NIAAA

https://www.nih.gov/news-events/news-releases/prevalence-marijuana-use-among-us-adults-doubles-over-past-decade. Published online Oct 21, 2015

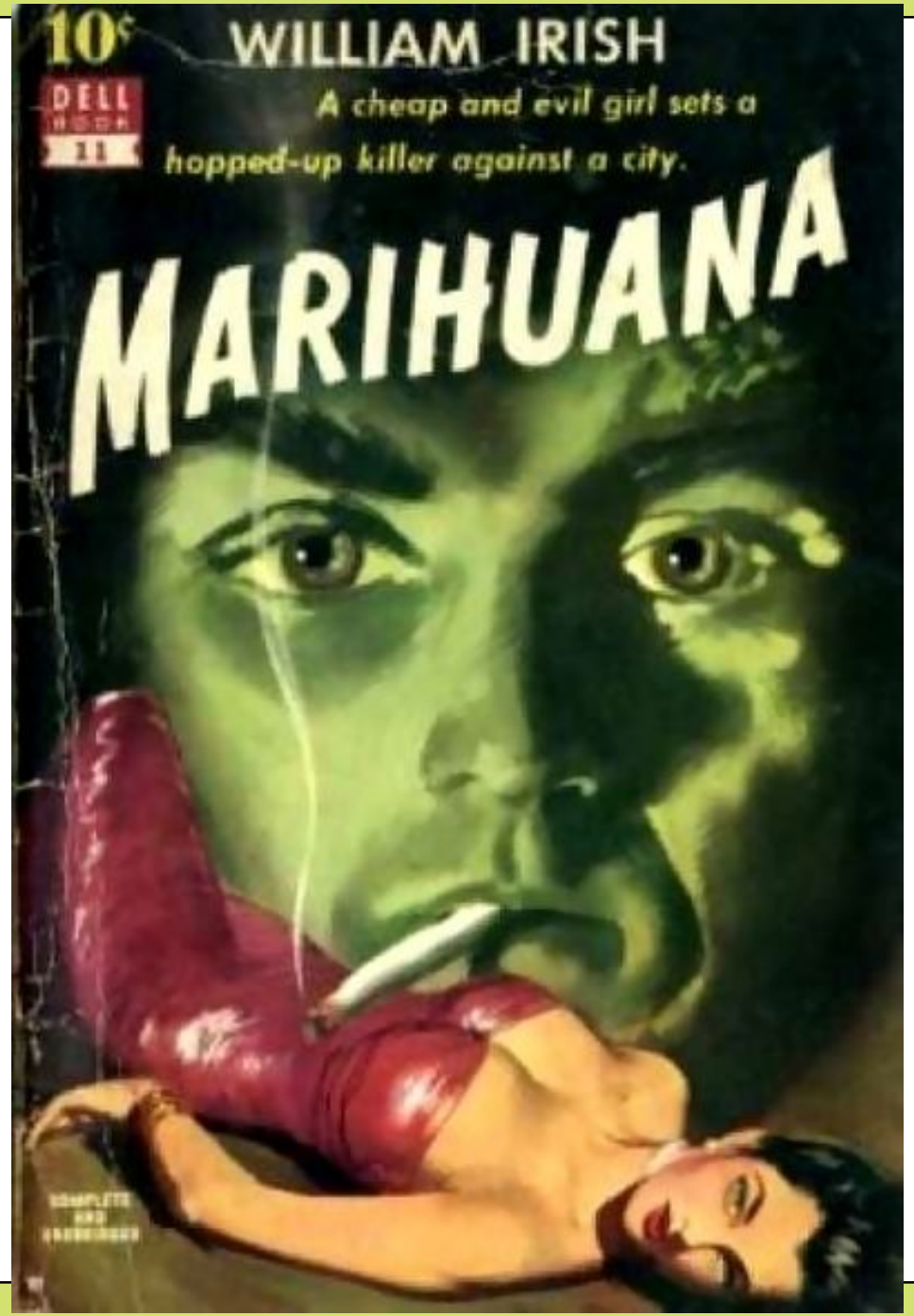

Percentage of U.S. 12 Grade Students Reporting Daily Marijuana Use vs. Perceived Risk of Regular Marijuana Use
Perceived Risk (Percent)
100
80
60
40
20
0
12
10
8
6
4
2
0
Daily Use (Percent)
Daily Use
Perceived Risk
1975
77
79
81
83
85
87
89
91
93
95
97
99
01
03
05
07
09
11
13
Source: The Monitoring the Future study, the University of Michigan

Youth Risk Behavior Surveys 1991-2017 ~203,000 9th to 12th graders

- **Trends in Single, Dual, and Poly Use of Alcohol, Cigarettes, and Marijuana**
- **MJ only**
  - 0.6 → 6.3%
  - Both ETOH and TOB only declined
- **MJ + ETOH**
  - 3.6 → 7.6%
  - ETOH + TOB declined
- **MJ + ETOH +TOB**
  - 9.4 → 4.4%
- **Racial Disparity**
  - Black 11.5% ↑
  - Hispanic 8.1% ↑
  - Non-Hispanic White 3.4% ↑

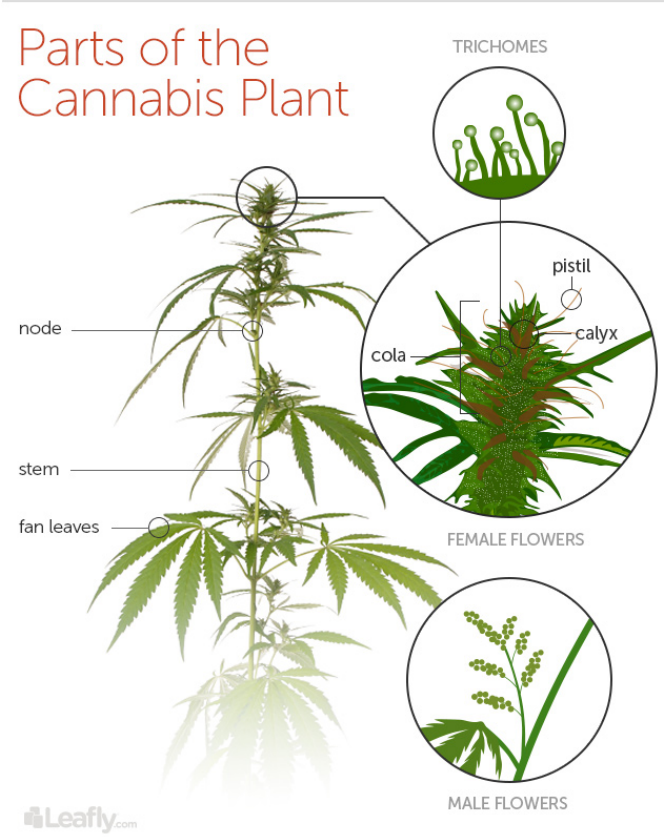
Hongying Dai, Am J Public Health. 2019 Aug;109(8):1138-1140

What Is It?


10¢
WILLIAM IRISH
DELL
A cheap and evil girl sets a
hopped-up killer against a city.
MARIHUANA

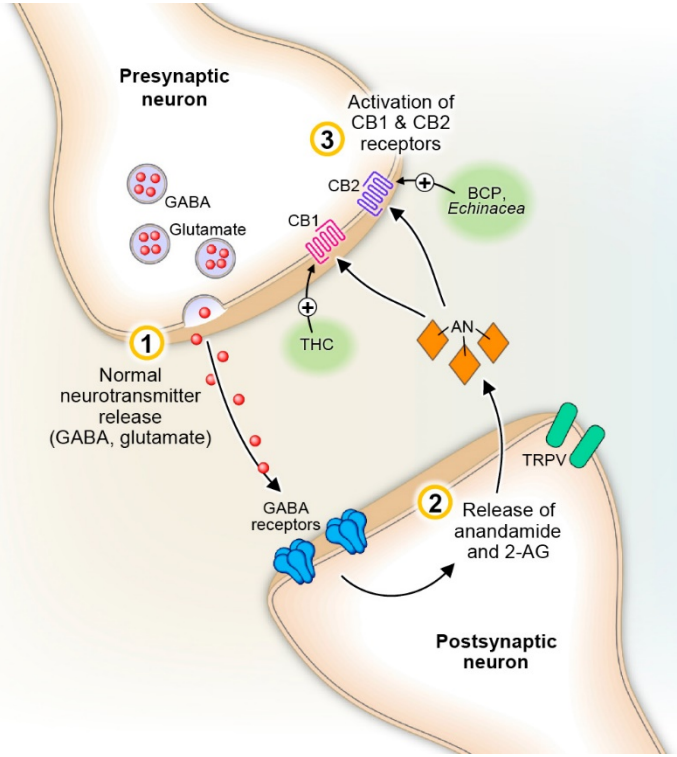
Marijuana – The Parts

- > 400 compounds (60 pharmacologically active)
- Δ^9-THC (tetrahydrocannabinol) + 103 other cannabinoids
- Each has individual, interactive and entourage effects
- Clinical trials w/ individual cannabinoids can't be extrapolated to MJ
- Composition varies among product



Elsohly MA, Slade D. Chemical constituents of marijuana. *Life Sci.* 2005;78(5):539-548

D'Souza D, Ranganathan M. Medical Marijuana: Is the Cart Before the Horse?. *JAMA*. 2015;313(24):2431-2432. doi:10.1001/jama.2015.6407.



Cannabinoids

Endocannabinoids (brain derived)

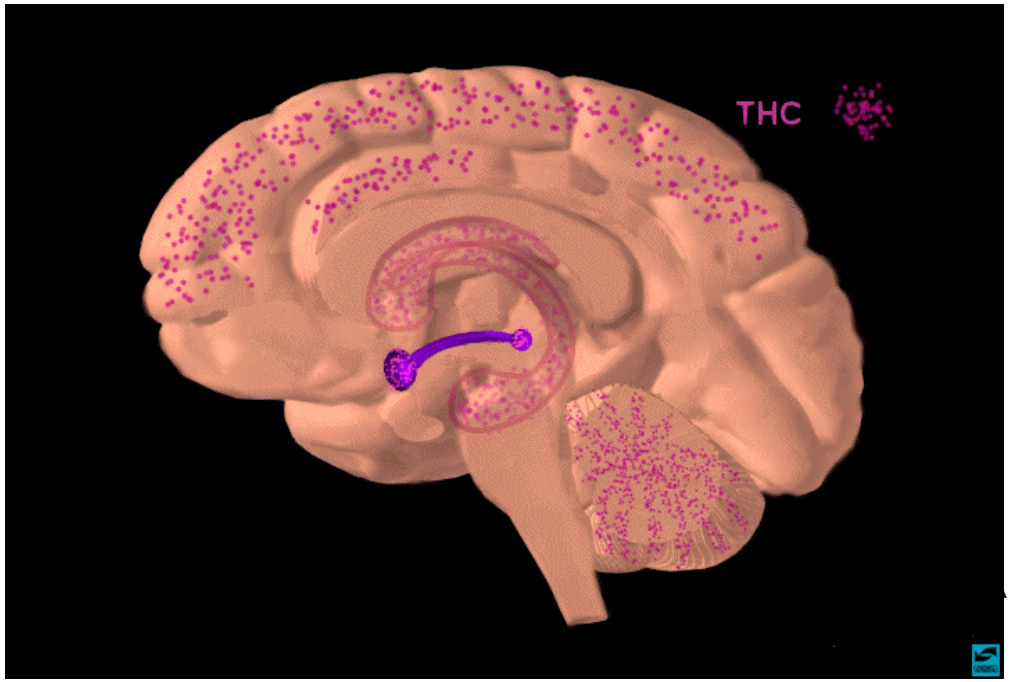
- Anandamide (AEA)
- 2-Arachidonylglycerol (2-AG)

Phytocannabinoids (plant derived)

- Cannabidiol (CBD)
- Tetrahydrocannabinol (THC)
- Cannabichromene (CBC)
- Cannabigerol (CBG)
- Many others

Synthetic cannabinoids (laboratory derived)

- Dronabinol
- Nabilone



Mayo Clinic Proceedings 2019 94, 1840-1851DOI: (10.1016/j.mayocp.2019.01.003)

Cannabinoid Drug-Drug Interactions

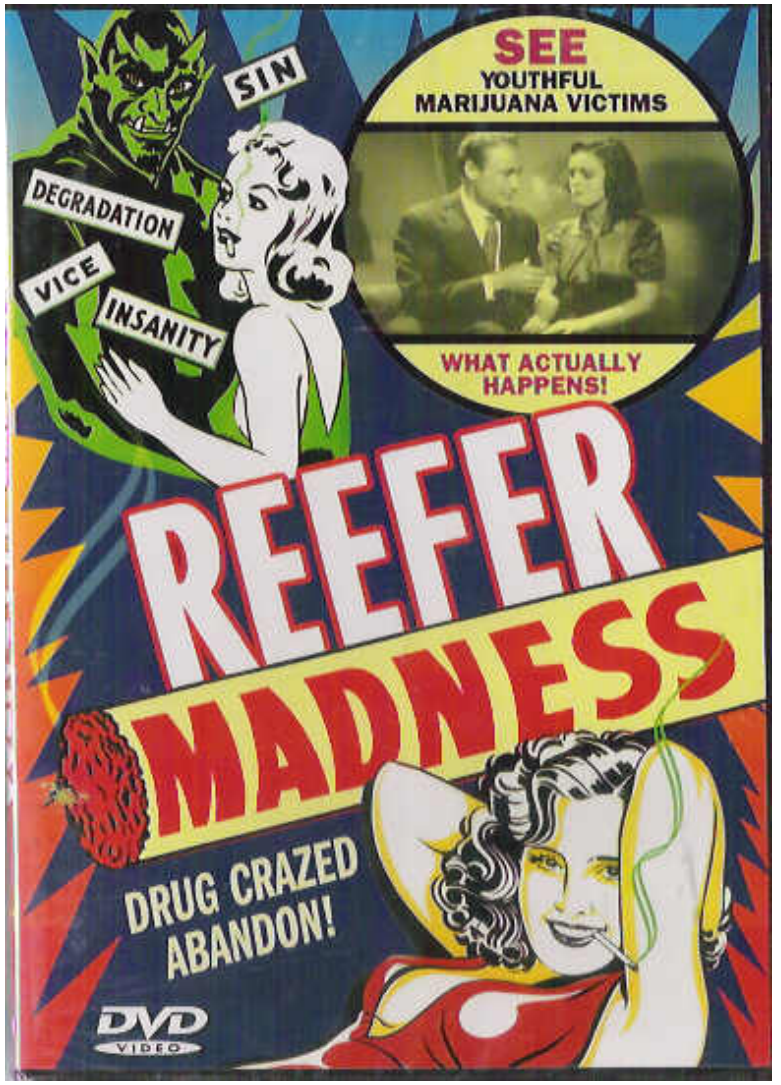
Cannabinoid	CYP-2C9	CYP-2C19	CYP-3A4
Δ9-THC	X		X
Δ8-THC	X		X
CBD		X	X
CBN	X		X

- Chlorpromazine
- Clozapine
- CNS depressants
- Disulfiram
- Hydrocortisone
- Ketoconazole
- MAO inhibitors
- Phenytoin
- Protease inhibitors
- Theophylline
- Tricyclic antidepressants
- Warfarin

1. Colorado Department of Public Health and Environment. *Monitoring Health Concerns Related to Marijuana in Colorado: 2016.*https://www.colorado.gov/cdphe/marijuana-health-report.
2. Stout SM et al. *Drug Metab Rev*. 2014;46(1):86–95.

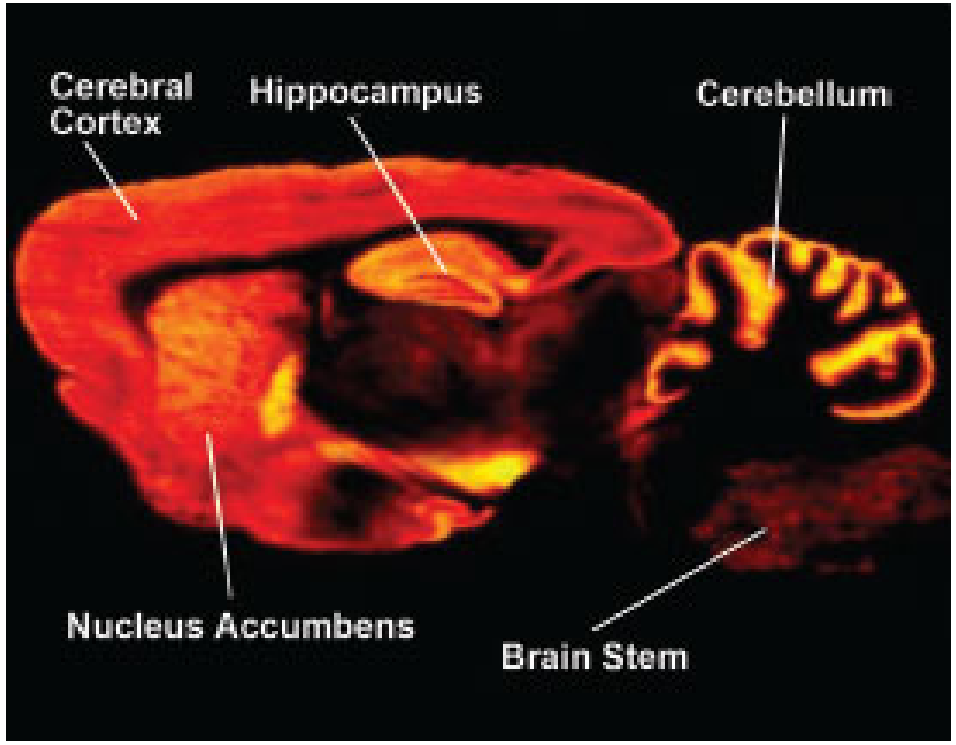
M.Garofoli Slide

What are the RISKS?



Rat Brain

- Exposure to THC around birth or adolescence demonstrates impaired learning and memory later in life
- Hippocampus changes
- Altered reward system

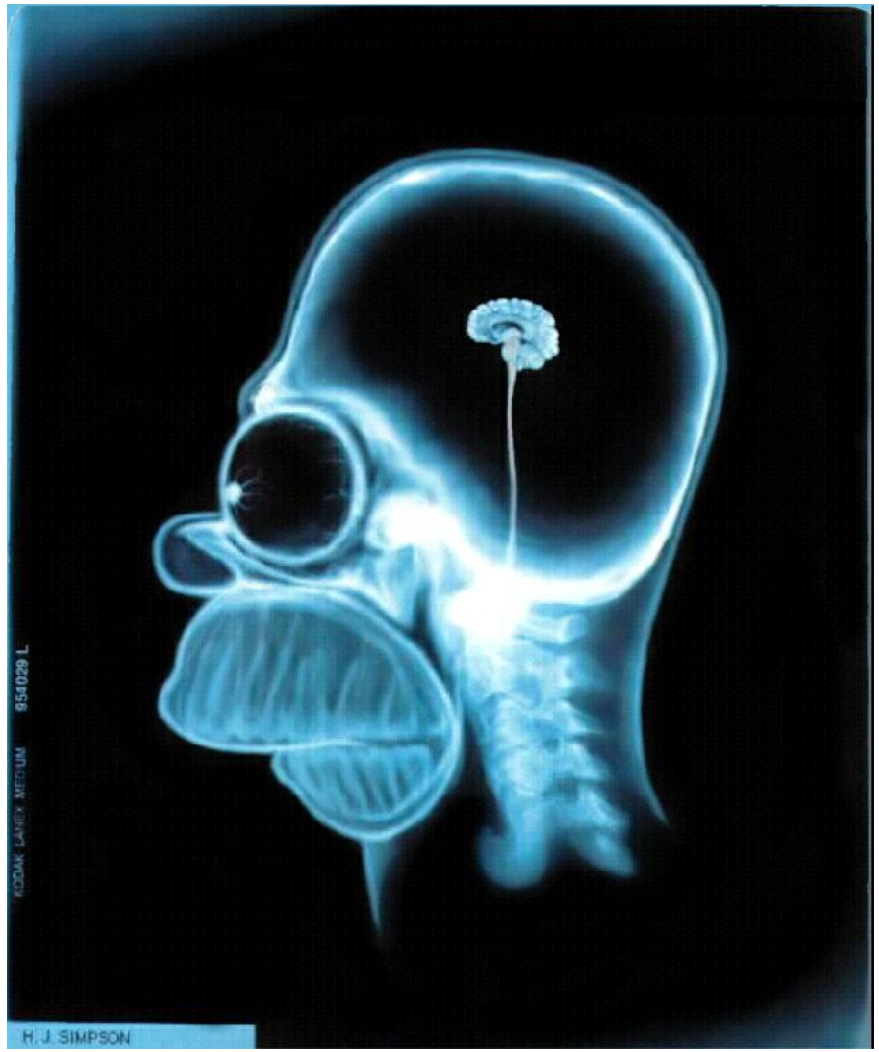


Dinieri JA, Hurd YL. Rat models of prenatal and adolescent cannabis exposure. Methods Mol Biol 2012;829:231-242

https://www.drugabuse.gov/publications/research-reports/marijuana/how-does-marijuana-use-affect-your-brain-body

Human Brain

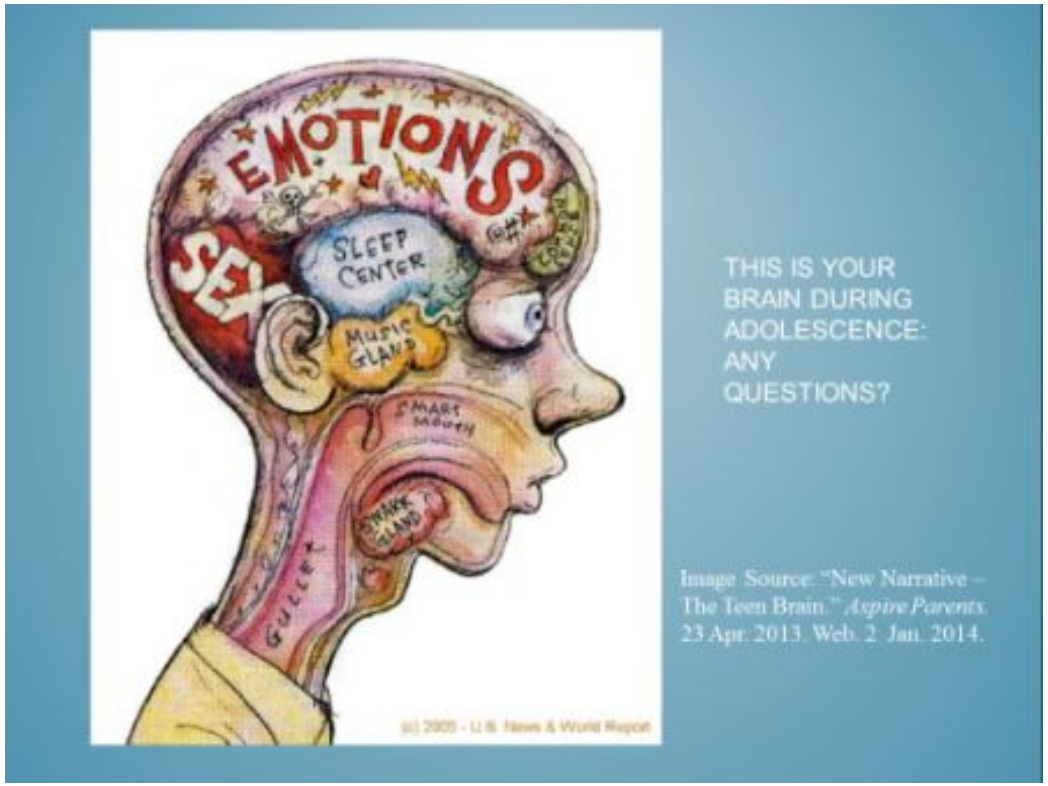
- **Inconclusive**
- Some suggest connectivity and reduced volume in certain regions (memory, learning and impulse control)
- Others found no structural differences
- Several suggest functional impairment in cognition
  - Age initiated, how much, how long



Volkow ND, Swanson JM, Evins AE, et al. Effects of Cannabis Use on Human Behavior, Including Cognition, Motivation, and Psychosis: A Review. JAMA Psychiatry. February 2016. doi:10.1001/jamapsychiatry.2015.3278.

Developing Brain

- <u>CARDIA study</u>
  ~4,000 young adults over 25 years
  - Lower scores on verbal memory
  - No affect on processing speed or executive function
- <u>New Zealand longitudinal study</u>
  ~1000 babies over 25 years
  - Persistent use beginning in adolescence resulted in loss of 8 IQ points in mid-adulthood
  - Those who quit as adults did not recover loss IQ
  - Confounders?



Auer R, Vittinghoff E, Yaffe K, et al. Association Between Lifetime Marijuana Use and Cognitive Function in Middle Age: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. JAMA Intern Med. February 2016. doi:10.1001/jamainternmed.2015.7841.
Meier MH, Caspi A, Ambler A, et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. Proc Natl Acad Sci U S A. 2012;109(40)

A Population-Based Analysis of the Relationship Between Substance Use and Adolescent Cognitive Development

Jean-François G. Morin, B.A., Mohammad H. Afzali, Ph.D., Josiane Bourque, M.Sc., Sherry H. Stewart, Ph.D., Jean R. Séguin, Ph.D., Maeve O'Leary-Barrett, Ph.D., Patricia J. Conrod, Ph.D.

- N=3,826 (7th graders over 4y)
- ETOH and MJ related to cognition
- Common vulnerabilities for both on all domains
- MJ (but not ETOH!) use had:
  - Lagged neurotoxic effects on inhibitory control and working memory
  - Concurrent effects of delayed memory and perceptual reasoning
- MJ effects were independent of ETOH effects

"Beyond the role of cognition in vulnerability to substance use, the concurrent and lasting effects of adolescent cannabis use can be observed on important cognitive functions and appear to be more pronounced than those observed for alcohol."

Am J Psychiatry. 2019 Feb 1;176(2):98-106

JAMA Psychiatry | Original Investigation

Association of Cannabis Use in Adolescence and Risk of Depression, Anxiety, and Suicidality in Young Adulthood

A Systematic Review and Meta-analysis

Gabriella Gobbi, MD, PhD; Tobias Atkin, BA; Tomasz Zytynski, MD; Shouao Wang, MSc; Sorayya Askari, PhD; Jill Boruff, MLIS; Mark Ware, MD, MSc; Naomi Marmorstein, PhD; Andrea Cipriani, MD, PhD; Nandini Dendukuri, PhD; Nancy Mayo, PhD

- Meta-analysis of 11 studies (n=23,317)
- Adolescent consumption associated with **increased risk of developing depression and suicidal behavior** later in life, even in the absence of a premorbid condition.
- There was no association with anxiety.

…the high prevalence of adolescents consuming cannabis generates a large number of young people who could develop depression and suicidality attributable to cannabis. This is an important public health problem and concern, which should be properly addressed by health care policy.

JAMA: *Preadolescents and adolescents should avoid using cannabis as use is associated with a significant increased risk of developing depression or suicidality in young adulthood*

Gobbi G. *JAMA Psychiatry.* Published online February 13, 2019.76(4):426–434

Youths Who Use Marijuana Are at Increased Risk for Acute Psychotic Symptoms

- N=527 of 14-18 y/o
- ~27% reported hallucinations
- ~33% reported paranoia or anxiety
- ~43% reported having at least 1 symptom
- None was associated with confounders of age, sex, race, general health or SES.
- Respondents with CUD reported more hallucinations or paranoia

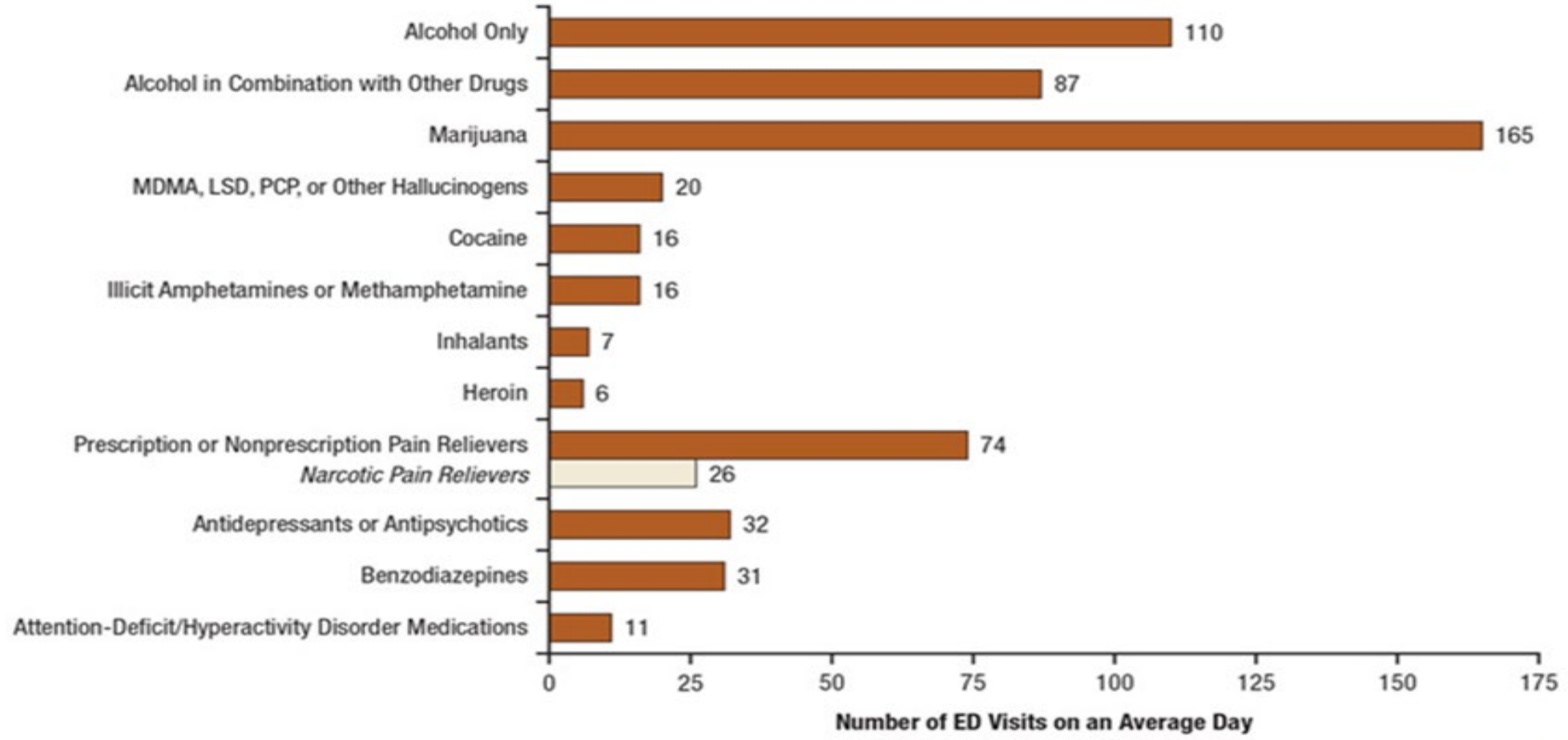
Levy S. JAMA Pediatr. 2019 Feb 1;173(2):185-186

Gateway Substance?

- **NSDUH** 2004 to 2014 survey of 12-21 y/o (n=275,559)
- Self reported age of **first** use: Marijuana, Tobacco, ETOH
  - **MJ** as 1st : doubled from 4.8% to 8.8%
  - **Cigarettes** as 1st : dropped from 21.4% to 8.9%
  - **ETOH** as 1st : constant around 30%
- Using MJ as first:
  - increased odds of CUD and heavy current MJ use
  - equal to tobacco for developing TUD
- As youth aged, they were more likely to start with MJ
- Compared to tobacco, using MJ or ETOH as 1st were more likely to use other drugs

Fairman, BJ et al. When Marijuana Is Used before Cigarettes or Alcohol: Demographic Predictors and Associations with Heavy Use, Cannabis Use Disorder, and Other Drug-related Outcomes. Prev Sci May 2018

Adolescents and ED Visits



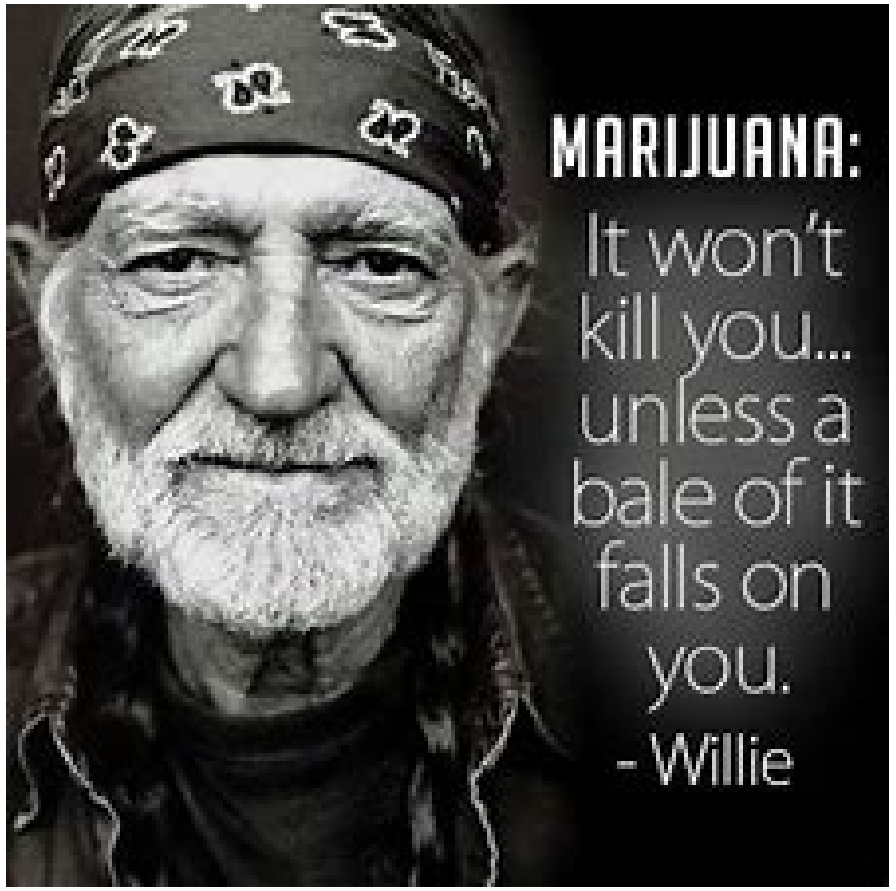
Source: 2011 SAMHSA Drug Abuse Warning Network (DAWN).

Adolescence

- Poorer educational outcomes
- Less likely to finish high school or obtain a degree
- Higher chance of using other drugs
- Higher chance of attempting suicide
- Higher chance of psychosis
- Lower income, unemployment, criminality, lower life satisfaction

Schweinsburg AD, et al. The influence of marijuana use on neurocognitive functioning in adolescents. *Curr Drug Abuse Rev*. 2008;1(1):99-111.
Macleod J, et al. Psychological and social sequelae of cannabis and other illicit drug use by young people: a systematic review of longitudinal, general population studies. *Lancet Lond Engl*. 2004;363(9421):1579-1588.
Silins Eet al. Young adult sequelae of adolescent cannabis use: an integrative analysis. *Lancet Psychiatry*. 2014;1(4):286-293.
Fergusson DM, Boden JM. Cannabis use and later life outcomes. *Addict Abingdon Engl*. 2008;103(6):969-976;

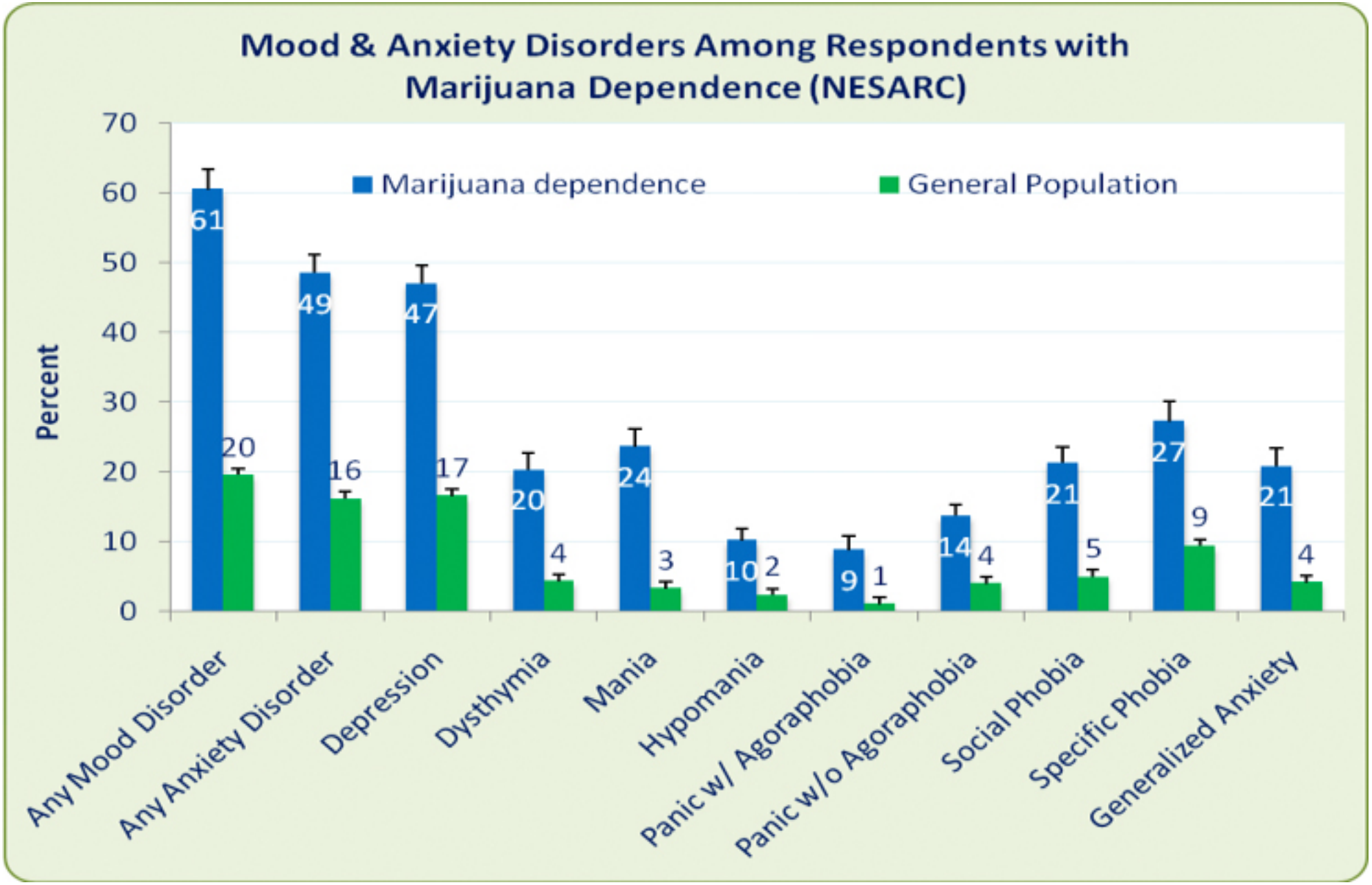
ADULTS


MARIJUANA:
It won't kill you... unless a bale of it falls on you.
- Willie

Mental Health

- Several studies linking increased risk, but difficult to attribute causation
- Strongest evidence is with SUD and psychotic d/o with preexisting vulnerability
- Worsens course of illness in schizophrenia
- Use can produce acute psychosis

Delforterie MJ, et al. The relationship between cannabis involvement and suicidal thoughts and behaviors. *Drug Alcohol Depend*. 2015;150:98-104.
Borges G, et al. A literature review and meta-analyses of cannabis use and suicidality. *J Affect Disord*. 2016;195:63-74



https://www.acpeds.org/marijuana-use-detrimental-to-youth

Psychosis, Depression, and Anxiety

ADDICTION
SSA SOCIETY FOR THE STUDY OF ADDICTION
RESEARCH REPORT
doi:10.1111/add.14459

Age-varying effects of cannabis use frequency and disorder on symptoms of psychosis, depression and anxiety in adolescents and adults

Bonnie J. Leadbeater[1], Megan E. Ames[1] & Ashley N. Linden-Carmichael[2]

Department of Psychology, University of Victoria, Victoria, BC, Canada[1] and Department of Biobehavioral Health, Edna Bennett Pierce Prevention Research Center, 303 Biobehavioral Health, The Pennsylvania State University, University Park, PA, USA[2]

- N=662 random sample of adolescents during a 10 year period in Canada
- N-=36,309 cross-sec data from NESARC in US adults

"Significant Association between CU frequency and CUD and psychotic and depressive symptoms in late adolescence and young adulthood extend across adulthood, and include anxiety"

Addiction. 2019 Feb;114(2):278-293

Association of Cannabis With Long-Term Clinical Symptoms in Anxiety and Mood Disorders:

A Systematic Review of Prospective Studies

- Review of 11 studies (n=11,959)
- Worse outcomes and poorer treatment response
- **PTSD**
  - greater severity of symptoms
- **Bipolar Disorder**
  - greater severity of symptoms
  - Higher recurrence of mania
  - Shorter time to mania recurrence
- **Major Depressive Disorder**
  - More depressive symptoms
  - Especially, anhedonia and sleep disturbance

Mammen G. J Clin Psychiatry. 2018 Jun 5;79(4).

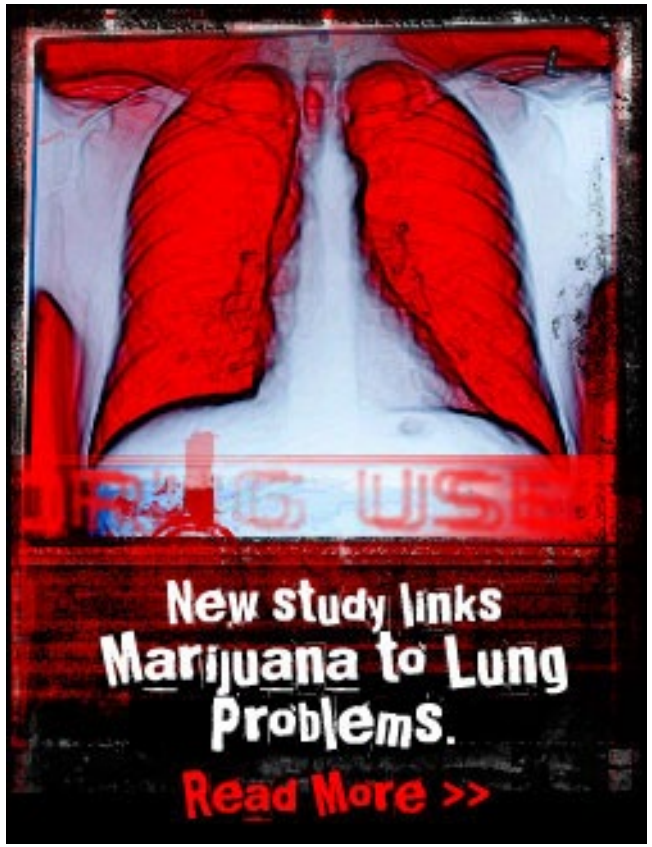
Effects on the Heart

- Increases heart rate
- Increases cardiac output
- Risk of MI is rare, however, for those who had one the risk was 5X higher w/i 1st hour after smoking
- Orthostatic Hypotension

Thomas G, Kloner RA, Rezkalla S. Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana inhalation: what cardiologists need to know. Am J Cardiol 2014;113:187-190

Triggering myocardial infarction by marijuana. Mittleman MA, Circulation. 2001;103(23):2805.

Effects on Lungs



- Many of same problems that tobacco smokers have
  - Daily cough and phlegm production
  - Frequent acute chest illness
  - Heightened risk of lung infections
  - Greater tendency for obstructed airways
- Increase lung Cancer?

Respiratory effects of marijuana and tobacco use in a U.S. sample. Moore BA, Gen Intern Med. 2005;20(1):33.

The association between marijuana smoking and lung cancer: a systematic review.Mehra R, Arch Intern Med. 2006;166(13):1359.

Testicular Cancer

- Clear link with MJ use in adolescence and increased risk
- Non-seminomatous testicular germ cell tumor
- Men carry THC in sperm for 6 months

Lacson JCA, et al. Population-based case-control study of recreational drug use and testis cancer risk confirms an association between marijuana use and nonseminoma risk. *Cancer*. 2012;118(21):5374-5383.
Daling JR, et al. Association of marijuana use and the incidence of testicular germ cell tumors. *Cancer*. 2009;115(6):1215-1223.

Pregnancy

- Women who used during pregnancy:
  - Moms more likely to be **anemic**
  - Babies more likely to have **lower birth weight**
  - Babies more likely to require **NICU**
  - Babies display altered responses to visual stimuli, increased tremulousness, and a high-pitched cry
- Link between prenatal exposure and school years:
  - **Impulse control**
  - **Visual memory**
  - **Attention**
- THC is excreted in breast milk

De Moraes Barros MC, et al. Neurobehavioral profile of healthy full-term newborn infants of adolescent mothers. *Early Hum Dev*. 2008;84(5):281-287. Goldschmidt L, et al. Effects of prenatal marijuana exposure on child behavior problems at age 10. *Neurotoxicol Teratol*. 2000;22(3):325-336. Richardson GA, et al. Prenatal alcohol and marijuana exposure: effects on neuropsychological outcomes at 10 years. *Neurotoxicol Teratol*. 2002;24(3):309-320.
Schempf AH, Strobino DM. Illicit Drug Use and Adverse Birth Outcomes: Is It Drugs or Context? *J Urban Health Bull N Y Acad Med*. 2008;85(6):858-873.

Injuries and Accidents

- Postal worker study (n=2537)
  - Pos UDS for THC pre-employment:
    - 55% more industrial accidents
    - 85% more injuries
    - 75% more absenteeism

Zwerling C, et al.The efficacy of preemployment drug screening for marijuana and cocaine in predicting employment outcome. *JAMA*. 1990;264(20):2639-2643.

Driving

- Most frequent substance found in blood tests following accidents
- Relationship between blood THC levels and performance in simulated driving
  - Impairment worst during 1st hour
- 2 Large Euro studies with UDS pos THC
  - 2X likely to cause fatal accident
  - ? Role of ETOH, urine and time
- Several meta-analyses demonstrated significant risk after MJ use
- A large case-control by National Highway Traffic Safety Administration found no increased risk when controlling for age, gender, race and ETOH

Lenne MG, Dietze PM, Triggs TJ, Walmsley S, Murphy B, Redman JR. The effects of cannabis and alcohol on simulated arterial driving: influences of driving experience and task demand. Accid Anal Prev 2010;42:859-866

Brady JE, Li G. Trends in Alcohol and Other Drugs Detected in Fatally Injured Drivers in the United States, 1999–2010. Am J Epidemiol. January 2014:kwt327.

Biecheler M-B, et. al.SAM survey on "drugs and fatal accidents": search of substances consumed and comparison between drivers involved under the influence of alcohol or cannabis. Traffic Inj Prev. 2008;9(1):11-21.

DRUID Final Report: Work Performed, Main Results and Recommendations. EU DRUID Programme; 2012. http://www.roadsafetyobservatory.com/Evidence/Details/10940

Elvik R. Risk of road accident associated with the use of drugs: a systematic review and meta-analysis of evidence from epidemiological studies. Accid Anal Prev. 2013;60:254-267. Compton RP, Berning A. Drug and Alcohol Crash Risk. Washington, DC: National Highway Traffic Safety Administration; 2015. DOT HA 812 117.

Association between medical cannabis laws and opioid overdose mortality has reversed over time

Chelsea L. Shover[a,1], Corey S. Davis[b], Sanford C. Gordon[c], and Keith Humphreys[a,d]

Medical cannabis has been touted as a solution to the US opioid overdose crisis since Bachhuber et al. [M. A. Bachhuber, B. Saloner, C. O. Cunningham, C. L. Barry, *JAMA Intern. Med.* 174, 1668–1673] found that from 1999 to 2010 states with medical cannabis laws experienced slower increases in opioid analgesic overdose mortality. That research received substantial attention in the scientific literature and popular press and served as a talking point for the cannabis industry and its advocates, despite caveats from the authors and others to exercise caution when using ecological correlations to draw causal, individual-level conclusions. In this study, we used the same methods to extend Bachhuber et al.'s analysis through 2017. Not only did findings from the original analysis not hold over the longer period, but the association between state medical cannabis laws and opioid overdose mortality reversed direction from −21% to +23% and remained positive after accounting for recreational cannabis laws. We also uncovered no evidence that either broader (recreational) or more restrictive (low-tetrahydrocannabinol) cannabis laws were associated with changes in opioid overdose mortality. We find it unlikely that medical cannabis—used by about 2.5% of the US population—has exerted large conflicting effects on opioid overdose mortality. A more plausible interpretation is that this association is spurious. Moreover, if such relationships do exist, they cannot be rigorously discerned with aggregate data. Research into therapeutic potential of cannabis should continue, but the claim that enacting medical cannabis laws will reduce opioid overdose death should be met with skepticism

Proceedings of the National Academy of Sciences Jun 2019, 116 (26)

Cannabis Use and Risk of Prescription Opioid Use Disorder in the United States

- NSDUH **2015**
  - Medical MJ more likely use prescription drugs (RR=1.62)
  - and misuse prescription drugs (RR=2.12)
- NESARC data **2001/2002** compared to **2004/2005**
  - ***Illicit*** Cannabis use associated with:
    - Increased **nonmedical** Rx opioid (OR=5.78)
    - Increased **OUD** (OR=7.76)
- Washington State study - medical and nonmedical had similar rates:
  - Depression (64/62%),
  - Violent behavior (14/15%),
  - Hallucinations (8/9%)

Caputi TL, Humphreys K. Medical marijuana users are more likely to use prescription drugs medically and nonmedically. [published online April 17, 2018] J Addict Med.

Olfson M, Wall MM, Liu SM, Blanco C. Cannabis use and risk of prescription opioid use disorder in the United States. *Am J Psychiatry*. 2018;175(1):47-53

Compton WM, Han B, Hughes A, et al: Use of marijuana for medical purposes among adults in the United States. JAMA 2017; 317:209–211

Roy-Byrne P, Maynard C, Bumgardner K, et al: Are medical marijuana users different from recreational users? The view from primary care. Am J Addict 2015; 24:599–606

Addiction

- NESARC 2012-2014
- 1/4 of **nonmedical** and 1/3 **medical** users meet criteria for past-year CUD
- 10% in both groups had another SUD
- ½ of all users had ETOH and Tobacco Use Disorders

Author's findings:

- Many medical users appear to be long-term recreational users
- Physical and health problems may in part be due to CUD stemming from adolescence

"the high rates of marijuana use disorder, other substance use disorder, and mental disorders among medical and non-medical marijuana users, especially young adults, are worrisome because polysubstance use/misuse and co-occurring substance use and mental disorders tend to be associated with high-risk behaviors and negative physical, mental, and cognitive health outcomes"

Choi, N. G., DiNitto, D. M. and Marti, C. N. (2017), Nonmedical versus medical marijuana use among three age groups of adults: Associations with mental and physical health status. Am J Addict, 26: 697–706

Addiction

- Initiate ***after*** 18y/o – **9%** eventually meet DSM criteria
- Initiate ***before*** 18 y/o – **17%** become addicted within 2 years
- Daily use – 35-50% rate of addiction
- Increased MJ addiction predicts increase risk of using other drugs

Hall W, Degenhardt L. Adverse health effects of non-medical cannabis use. Lancet 2009;374:1383-1391

Hall W, Degenhardt L. Prevalence and correlates of cannabis use in developed and developing countries. Curr Opin Psychiatry 2007;20:393-397

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

The American Journal of Psychiatry

CBD=Epidiolex

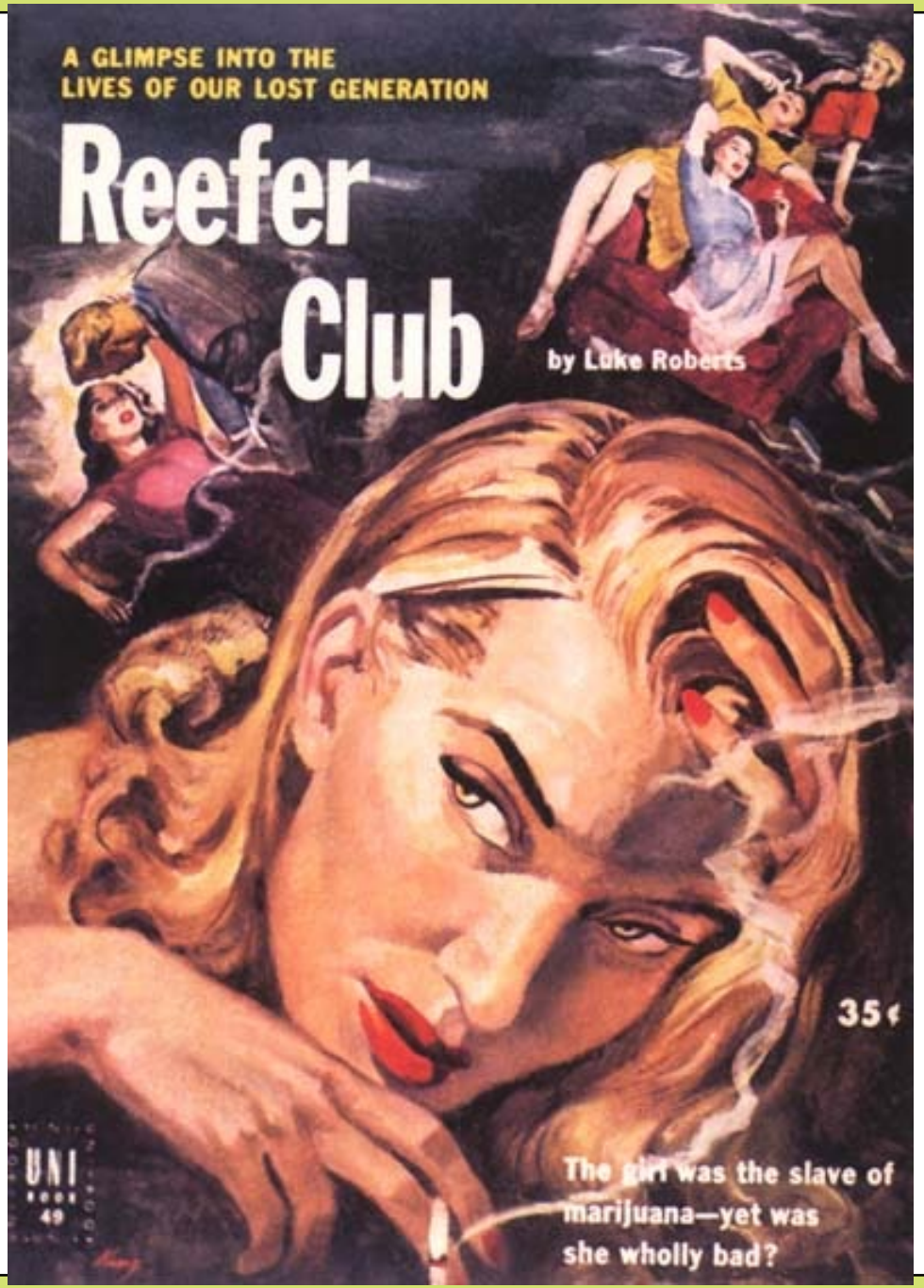
- N=50
- 400mg or 800mg q day
- Assessed acute (1h, 2h, 24h), short term (3 consecutive days), and protracted (7 days after the 3 days)
- Reduced craving and anxiety
- Reduced cue-induced physiological measures of HR and cortisol
- No significant cognitive effects or side effects

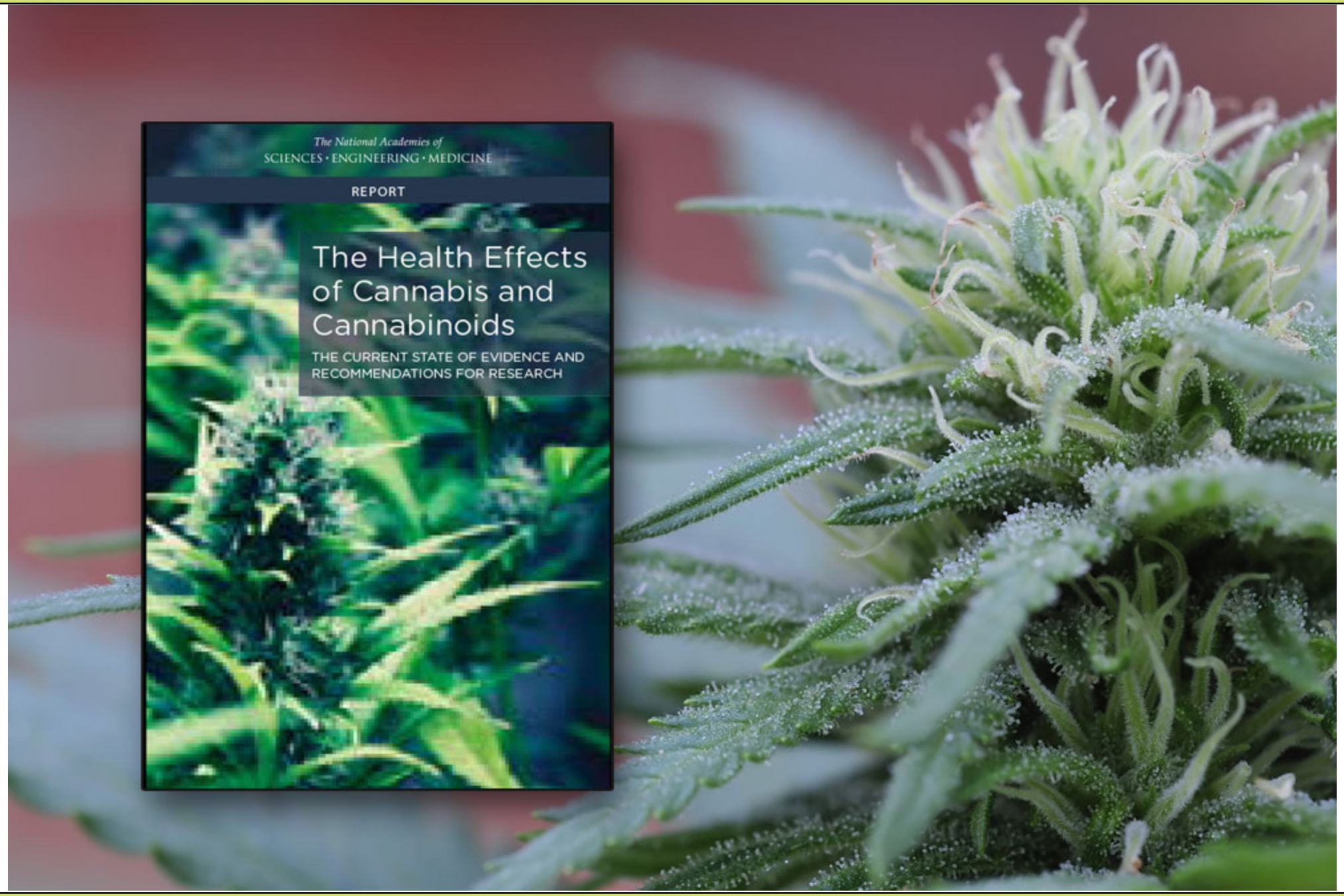
Hurd YL. Am J Psychiatry. 2019 May 21

CANNABIS WITHDRAWAL

- **Cessation of use that has been heavy and prolonged** (i.e. daily or almost daily over a few months)
- **3 of following s/s develop w/i ~ 1wk of stop:**
  - Irritability, anger, or aggression
  - Nervousness or anxiety
  - Sleep difficulty (e.g. insomnia, disturbing dreams)
  - Decreased appetite or weight loss
  - Restlessness
  - Depressed mood
  - At least 1 of the following physical symptoms causing significant discomfort:
    - Abdominal pain, shakiness/tremors, sweating, fever, chills, or headache
- **Cause clinically significant distress or impairment in social occupational, or other important areas of functioning**

What's the Evidence?




The National Academies of
SCIENCES · ENGINEERING · MEDICINE
REPORT
The Health Effects of Cannabis and Cannabinoids
THE CURRENT STATE OF EVIDENCE AND RECOMMENDATIONS FOR RESEARCH

There is conclusive or substantial evidence that cannabis or cannabinoids are effective:

- For the treatment for chronic pain in adults (cannabis) (4-1)
- Antiemetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids) (4-3)
- For improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)

There is moderate evidence that cannabis or cannabinoids are effective for:

- Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis (cannabinoids, primarily nabiximols) (4-19)

There is limited evidence that cannabis or cannabinoids are effective for:

- Increasing appetite and decreasing weight loss associated with HIV/AIDS (cannabis and oral cannabinoids) (4-4a)
- Improving clinician-measured multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)
- Improving symptoms of Tourette syndrome (THC capsules) (4-8)
- Improving anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders (cannabidiol) (4-17)
- Improving symptoms of posttraumatic stress disorder (nabilone; one single, small fair-quality trial) (4-20)

There is limited evidence of a statistical association between cannabinoids and:

- Better outcomes (i.e., mortality, disability) after a traumatic brain injury or intracranial hemorrhage (4-15)

There is limited evidence that cannabis or cannabinoids are *ineffective* for:

- Improving symptoms associated with dementia (cannabinoids) (4-13)
- Improving intraocular pressure associated with glaucoma (cannabinoids) (4-14)
- Reducing depressive symptoms in individuals with chronic pain or multiple sclerosis (nabiximols, dronabinol, and nabilone) (4-18)

There is conclusive or substantial evidence that cannabis or cannabinoids are effective:

- For the treatment for chronic pain in adults (cannabis) (4-1)
- Antiemetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids) (4-3)
- For improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)

REALLY???

Original Investigation

Cannabinoids for Medical Use
A Systematic Review and Meta-analysis

JAMA. 2015 Jun 23-30;313(24):

Penny F. Whiting, PhD; Robert F. Wolff, MD; Sohan Deshpande, MSc; Marcello Di Nisio, PhD; Steven Duffy, PgD; Adrian V. Hernandez, MD, PhD; J. Christiaan Keurentjes, MD, PhD; Shona Lang, PhD; Kate Misso, MSc; Steve Ryder, MSc; Simone Schmidlkofer, MSc; Marie Westwood, PhD; Jos Kleijnen, MD, PhD

- 79 RCTs on use of cannabinoids for medical indications (n=6,462)
- Chemo-related nausea/vomiting (28 studies; n=1,772)
- Chronic pain (28 studies; n=2,454)
- Spasticity (14 studies; n=2,280)
- Nabiximols (19), nabilone (20), Dronabinol (13), **Cannabis (2)**
- most were placebo-controlled
- 34 were parallel-group; 45 were crossover studies
- Only 4 were considered low risk of bias (mostly due to study dropout)

Benefits Summary

- **Chemo-related nausea/vomiting**
  - Superior to placebo (OR=3.82)
  - Quality of evidence: Low
- **Pain**
  - Slightly superior to placebo (OR=1.41)
  - QOE: Moderate
- **Spasticity in MS or paraplegia**
  - Failed to outperform placebo
  - QOE: Low to Moderate
- **Weight Gain, sleep, tics in Tourette's**
  - Benefits inconsistent
  - QOE: Low
- **Anxiety or depression**
  - Scant evidence that did not encourage use

Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use. JAMA. doi:10.1001/jama.2015.6358.

Adverse Events Summary

Cannabinoids were associated with more AEs (OR=3.03), more serious AEs (OR=1.41) and more dropouts (OR 2.94)

Adverse Effect	Odds Ratio (Approximate)
Disorientation	**5**
Dizziness	**5**
Dry Mouth	**4**
Euphoria	**4**
Drowsiness	**4**
Confusion	**4**
Somnolence	3
Balance Issues	3
Hallucinations	2
Nausea	2
Fatigue	2
Vomiting	2
Diarrhea	2

Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use. JAMA. doi:10.1001/jama.2015.6358.

Systematic Reviews and Meta-Analyses

PAIN

Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies

Pain. 2018;159(10)

Emily Stockings[a,*], Gabrielle Campbell[a], Wayne D. Hall[b,c], Suzanne Nielsen[a], Dino Zagic[a], Rakin Rahman[a], Bridin Murnion[d,e], Michael Farrell[a], Megan Weier[a], Louisa Degenhardt[a]

47 RCTs, 57 observational studies

N= 9958

Neuropathic Pain, Fibromyalgia, RA, Other CNCP (MS, Visceral Pain, Mixed or Undefined)

NNT to benefit= 24 (Benefit defined as 30% reduction in pain: 29%CB vs 26% placebo)

For 50% reduction in pain: No significant difference from placebo

NN to harm= 4 (81%CB vs 66.2% placebo)

No benefit on physical or emotional functioning

"It seems unlikely that cannabinoids are highly effective medicines for CNCP. There is moderate- to high-grade evidence supporting use of nabiximols to achieve modest reductions in pain as adjunctive therapy in MS-related pain. However, NNTBs were high and NNTHs low, with high rates of dropout for AEs, and long-term efficacy and safety is unknown. We also found minimal evidence that cannabinoids are effective in improving other important domains in people with CNCP such as emotional and physical functioning. Cannabinoids are unlikely to be a monotherapy for CNCP. People living with CNCP often have complex comorbidities, and multidisciplinary treatment that includes physical and psychological therapy rather than reliance on medicines alone is likely to be most effective"

Clinical Review & Education

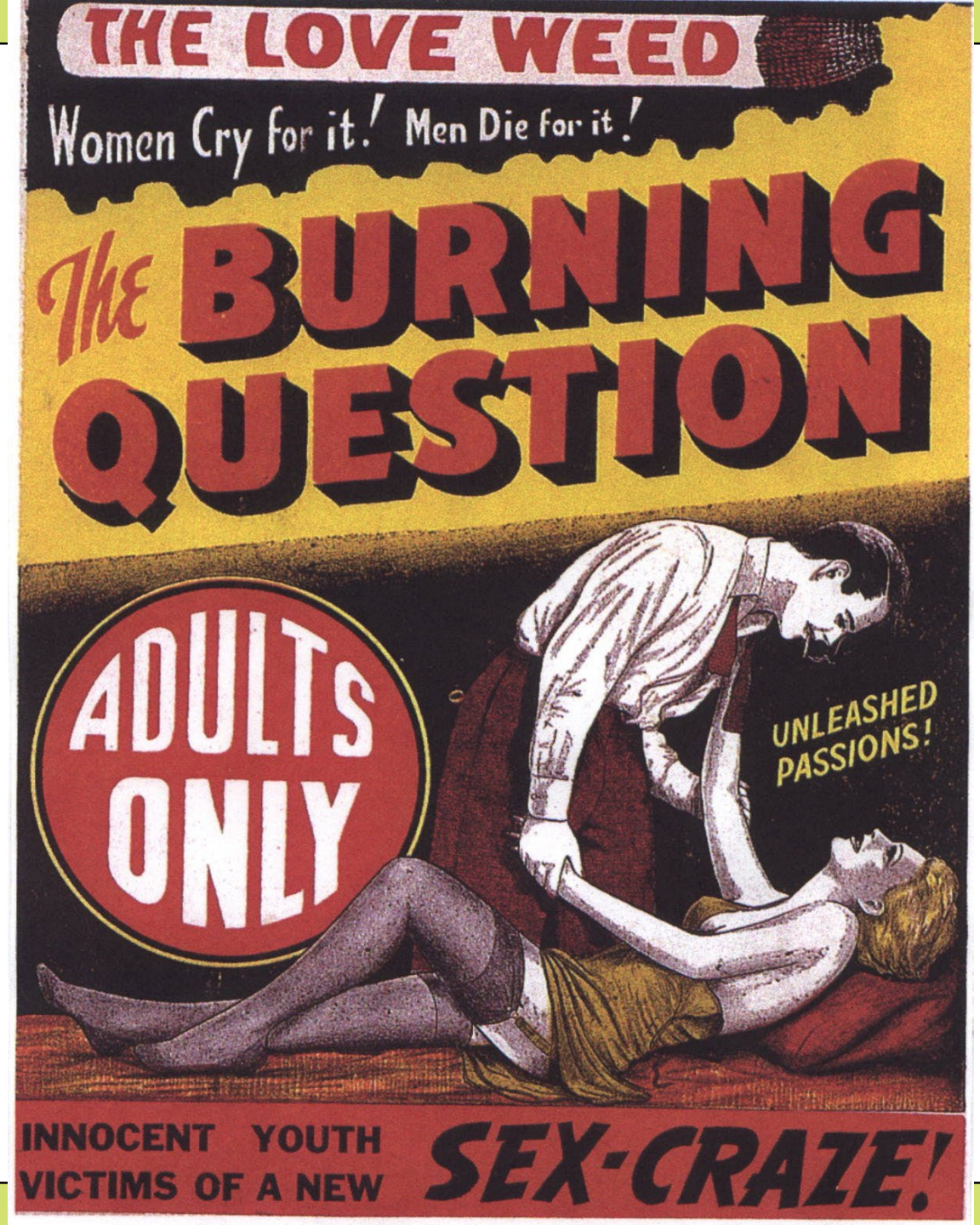
JAMA Insights

August 9, 2019

Medical Use of Cannabis in 2019

Kevin P. Hill, MD, MHS

- The cannabis plant is not a medication
- More research is needed!!!
- Need Psycho-Social treatments
- Don’t use if have a psychiatric d/o
- Don’t use if have a SUD
- Don’t use if a teenager
- First Do No Harm


THE LOVE WEED
Women Cry For it! Men Die For it!
THE BURNING QUESTION
ADULTS ONLY
UNLEASHED PASSIONS!
INNOCENT YOUTH VICTIMS OF A NEW SEX-CRAZE!