

# Marijuana: Clearing the Smoke on Clinical and Policy Issues

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# Learning objectives

- Define the key components of marijuana as a substance and review relevant epidemiology and terminology
- Explore US policy regarding MJ decriminalization to legalization
- Summarize adverse health effects and other potential risks of marijuana use (and touch on synthetic MJ)
- Examine the tension between treatment for marijuana use disorders vs. marijuana as medicine

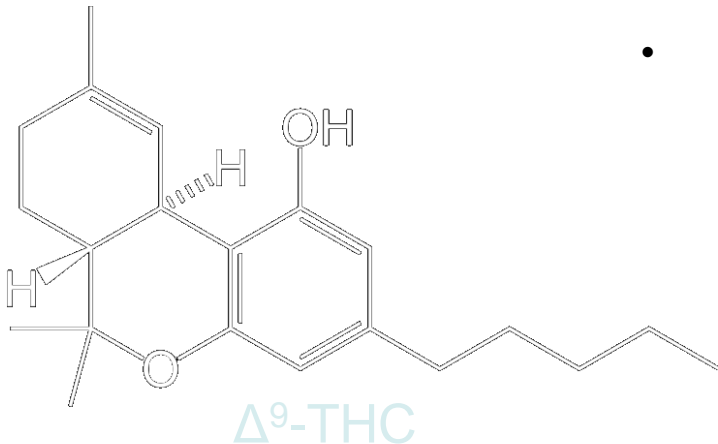
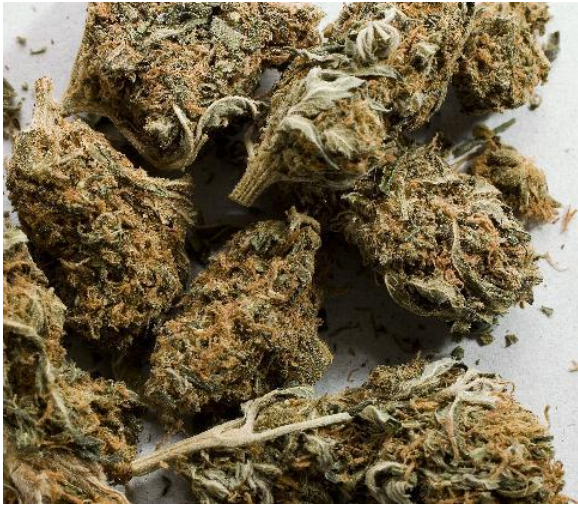


# What is marijuana?

- Dried flowers, leaves, stems and seeds of the *Cannabis sativa* plant
- Usually smoked as a cigarette or in a pipe; can be orally ingested
- More concentrated, resinous form: hashish
- Sticky black liquid: hash oil
- Potency related to concentration of  $\Delta^9$ -tetrahydrocannabinol (THC) and route of administration



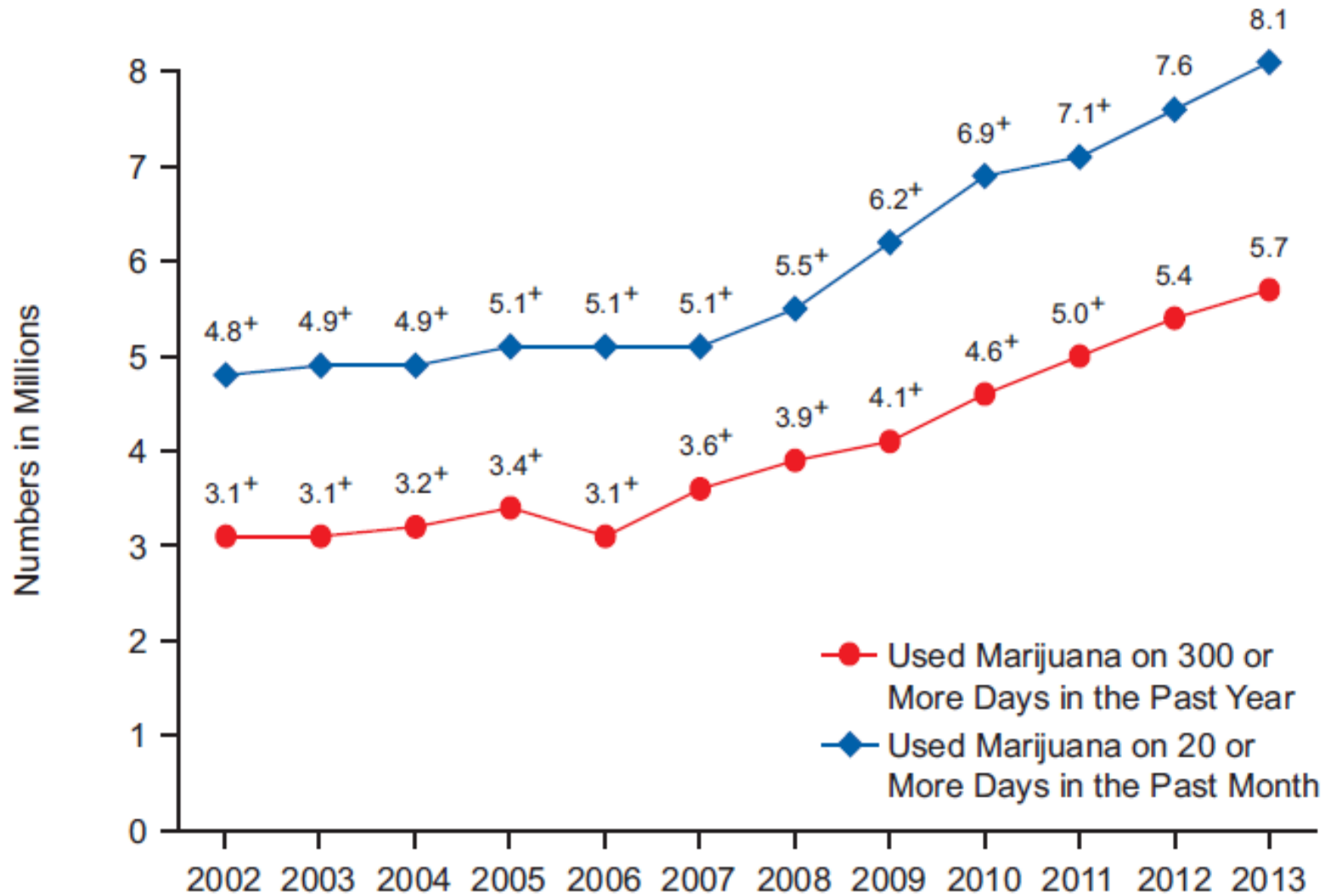
# $\Delta^9$ -TETRAHYDROCANNABINOL (THC)



- Psychoactive ingredient in *Cannabis sativa*
- Synthetic form is active ingredient of Marinol, approved in 1985 for intractable nausea
- 70+ other cannabinoids, many of which are present to varying degrees in a single *C. sativa* plant; **some non-THC cannabinoids *may* have medical use**



# Marijuana use among individuals age 17 or older

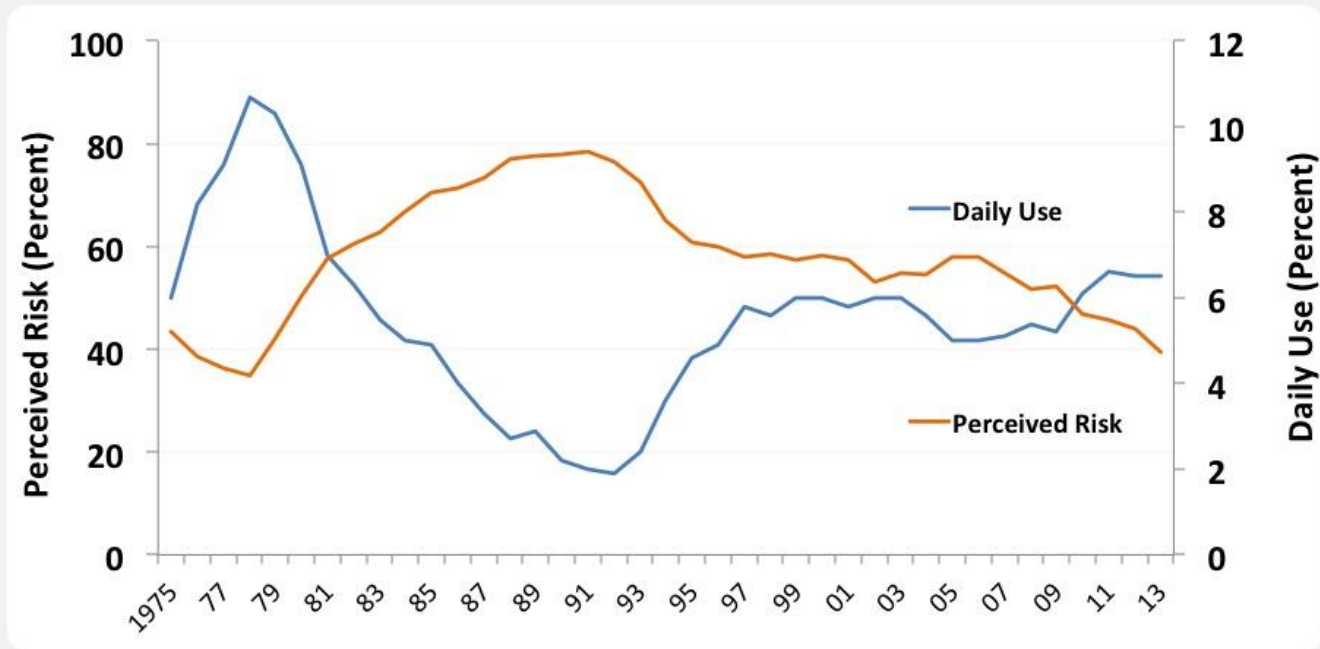


NSDUH 2013



# Why the increase?

## Daily Marijuana Use vs. Perceived Risk of Regular Marijuana Use among 12<sup>th</sup> Graders, 1975-2013



Source: University of Michigan, 2013 Monitoring the Future Study



# Cannabis Use Disorder DSM 5

A problematic pattern of cannabis use leading to clinically significant impairment or distress, as manifested by two or more of the following within a 12-month period:

- Cannabis is often taken in larger amounts or over a longer period than was intended
- There is a persistent desire or unsuccessful efforts to cut down or control cannabis use
- A great deal of time is spent in activities necessary to obtain cannabis, use cannabis, or recover from its effects
- Craving, or a strong desire or urge to use cannabis



# Cannabis Use Disorder, Cont'd

- Recurrent cannabis use resulting in a failure to fulfill major role obligations at work, school, or home
- Continued cannabis use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of cannabis
- Important social, occupational, or recreational activities are given up or reduced because of cannabis use
- Recurrent cannabis use in situations in which it is physically hazardous
- Continued cannabis use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by use
- Tolerance
- Withdrawal





# Cannabis withdrawal: New to DSM 5

- Cessation of cannabis use that has been heavy and prolonged
- Three or more of the following signs and symptoms develop within approximately one week after the cannabis cessation:
  - Irritability, anger, or aggression
  - Nervousness or anxiety
  - Sleep difficulty (eg, insomnia, disturbing dreams)
  - Decreased appetite or weight loss
  - Restlessness
  - Depressed mood
  - At least one of the following physical symptoms causing significant discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills, or headache
- Cause distress or impairment
- No other explanation for symptoms



# US *Love-Hate* Relationship



*Reefer Madness, 1936*  
“A cautionary tale about the ill effects of marijuana ... a trio of drug dealers try to corrupt innocent teenagers with wild parties and jazz music.”



*Fast Times at Ridgemont High, 1982...*  
Jeff Spicoli



# US *Love-Hate* Relationship



*Reefer Madness, 1936*  
“A cautionary tale about the ill effects of marijuana ... a trio of drug dealers try to corrupt innocent teenagers with wild parties and jazz music.”



# Policy timeline

- 1970: Controlled Substances Act passed by Congress, marijuana listed as schedule I drug
- 1985: dronabinol (synthetic THC) approved in the US for treatment of intractable nausea
- 1996-2015: 28 states + PR medical marijuana, 8 states and D.C. legalize recreational use
- 2005: Supreme Court decision (Gonzales v. Raich)
  - Federal law enforcement has the authority to arrest and prosecute MDs or patients
- 2009: Department of Justice Memorandum
  - Federal resources should not be used to prosecute providers and patients who comply with states laws
- 2008-2010: IOM, ACP, AMA
  - Petitioned DEA/FDA to reschedule marijuana to schedule II ...it remains schedule I to this day
- March, 10 2015: CARERS bill introduced in Senate
  - Bipartisan group of senators introduced bill to reschedule marijuana





# Moderate acute effects

- Acute marijuana intoxication
  - agitation, psychosis, and anxiety
  - tachycardia and hypertension
- Cannabinoid Hyperemesis Syndrome
- Pediatric Exposures

Kim & Monte Annals of Em Med 2016

Yale School of Medicine, Section of General Internal Medicine

## Cannabinoid Hyperemesis Syndrome



### Symptoms:

- Cyclic Vomiting (Can last for hours or days)
- Abdominal Pain
- Excessive thirst
- Nausea
- Gastric Pain
- Compulsive bathing (to ease the pain)

### THE PARADOX?

Marijuana can help with nausea and appetite

But not when it is consumed in

## EXCESS



GREEN RUSH DAILY

<https://www.greenrushdaily.com/2016/08/17/cannabinoid-hyperemesis-syndrome-cannabis/>

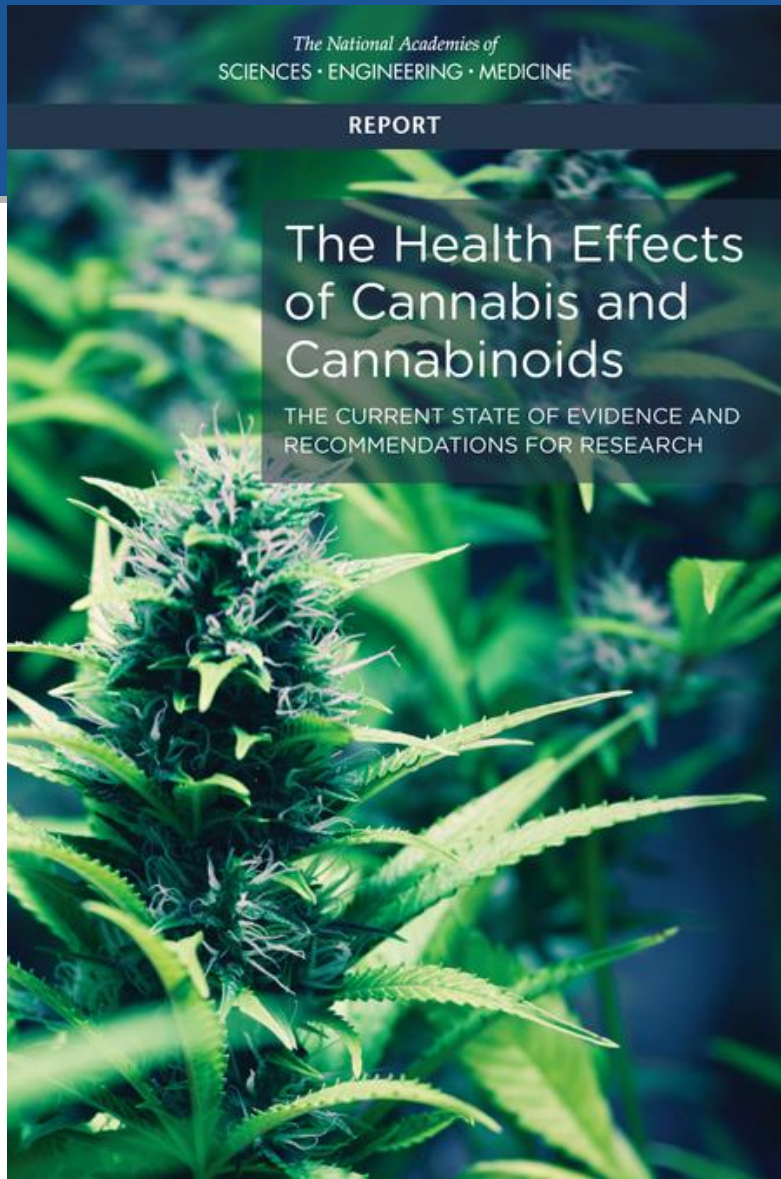


# Adverse effects of marijuana use

**Table 2.** Level of Confidence in the Evidence for Adverse Effects of Marijuana on Health and Well-Being.

Effect	Overall Level of Confidence*
Addiction to marijuana and other substances	High
Abnormal brain development	Medium
Progression to use of other drugs	Medium
Schizophrenia	Medium
Depression or anxiety	Medium
Diminished lifetime achievement	High
Motor vehicle accidents	High
Symptoms of chronic bronchitis	High
Lung cancer	Low





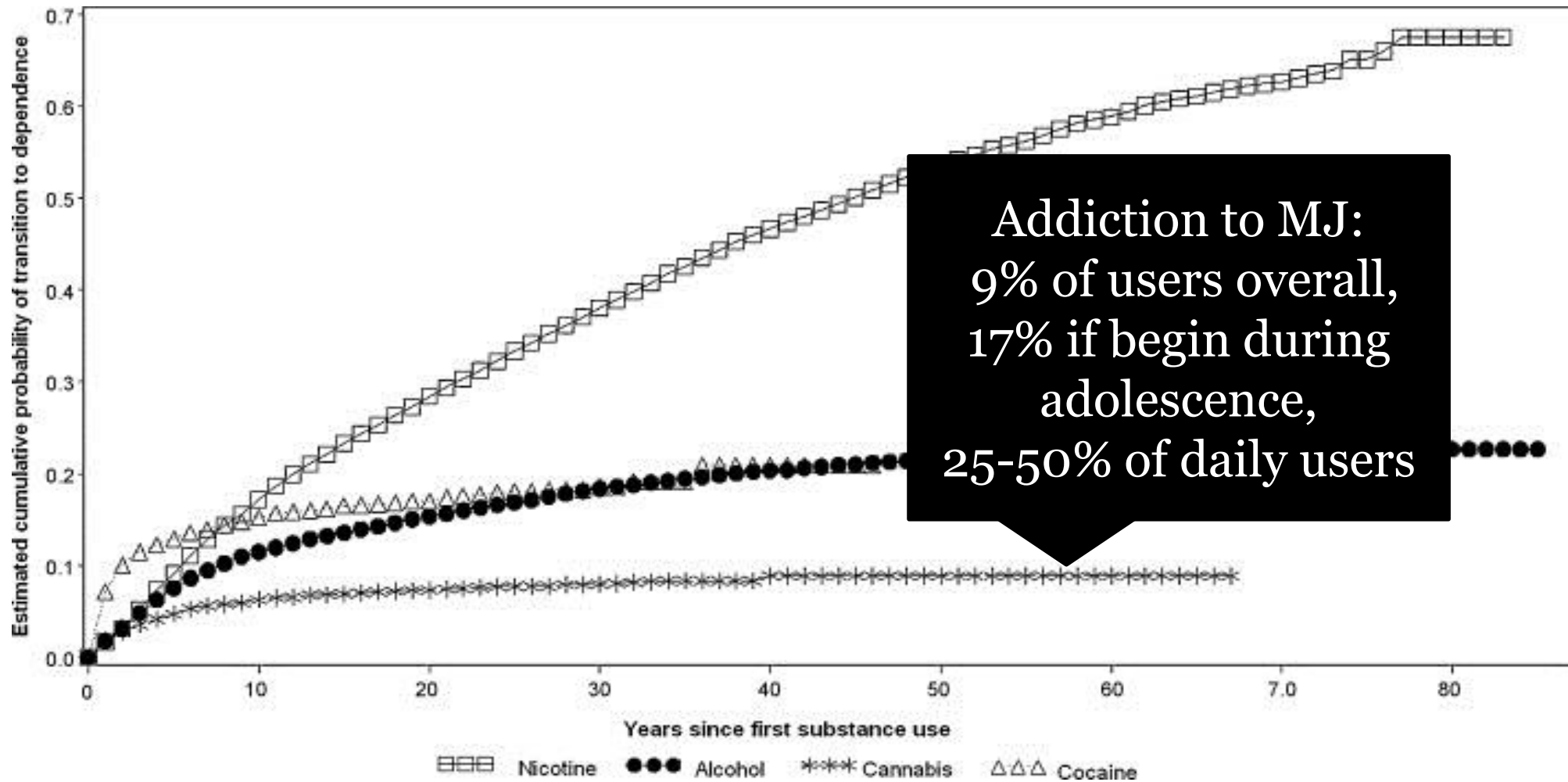
- 16 person committee reviewed > 10,000 abstracts published since 1999
- Focused on recently published systematic reviews and high quality primary research for 11 groups of health effects including both harms and therapeutic effects

Report of National Academies of Science, Engineering and Medicine.  
Health Effects of Cannabis and Cannabinoids. 2017





# Cumulative Probability of Transitioning to Substance Use Disorder for Nicotine, Alcohol, Marijuana and Cocaine



Addiction to MJ:  
9% of users overall,  
17% if begin during  
adolescence,  
25-50% of daily users

Lopez-Quintero, C. et al. *Drug & Alcohol Dependence* 2011



# Health effects of cannabis and cannabinoids: SUD

## **There is substantial evidence that:**

- Initiating cannabis use at an earlier age is a risk factor for the development of problem cannabis use

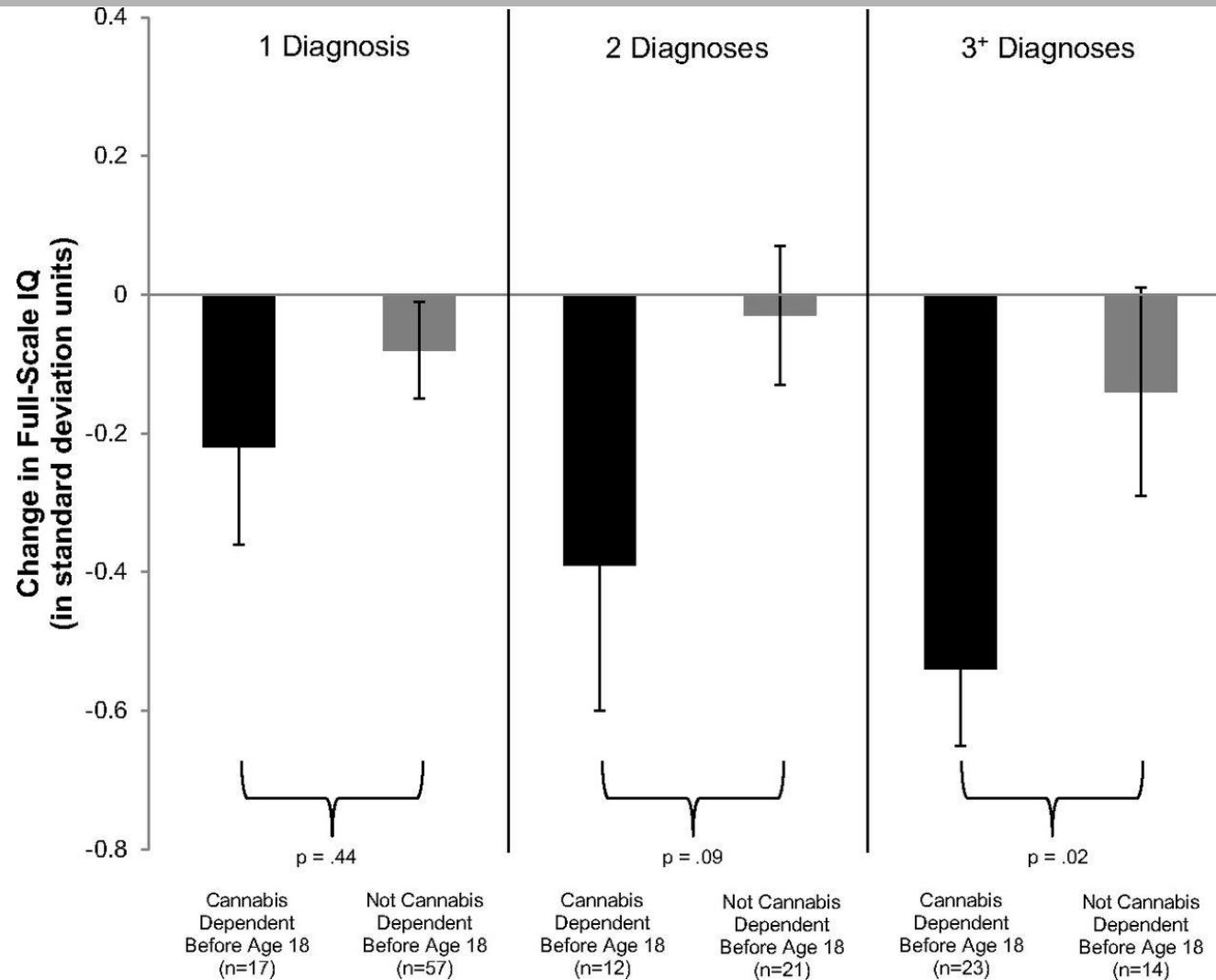
## **There is moderate evidence of a statistical association between cannabis use and:**

- The development of substance use disorder for substances, including alcohol, tobacco, and other illicit drugs

Report of National Academies of Science, Engineering and Medicine.  
Health Effects of Cannabis and Cannabinoids. 2017



# Adolescent vulnerability in IQ decline



Meier M H et al. PNAS 2012



# Other cognitive effects of marijuana

- In a large study of 5115 adults at 18-30yo at baseline followed up for 25 years
- Current use of marijuana associated with worse verbal memory and processing speed
- Cumulative lifetime exposure was associated with worse performance in verbal memory, processing speed and executive function
- For each 5 years of past exposure, verbal memory was 0.13 standardized units lower (95% CI, -0.24 to -0.02;  $P = .02$ )
  - corresponds to **remembering 1 word less from a list of 15, for every 5 years of use.**

Auer R et al. JAMA Intern Med. 2016;176(3):352-361



# Health effects of cannabis and cannabinoids: Psychosocial domains

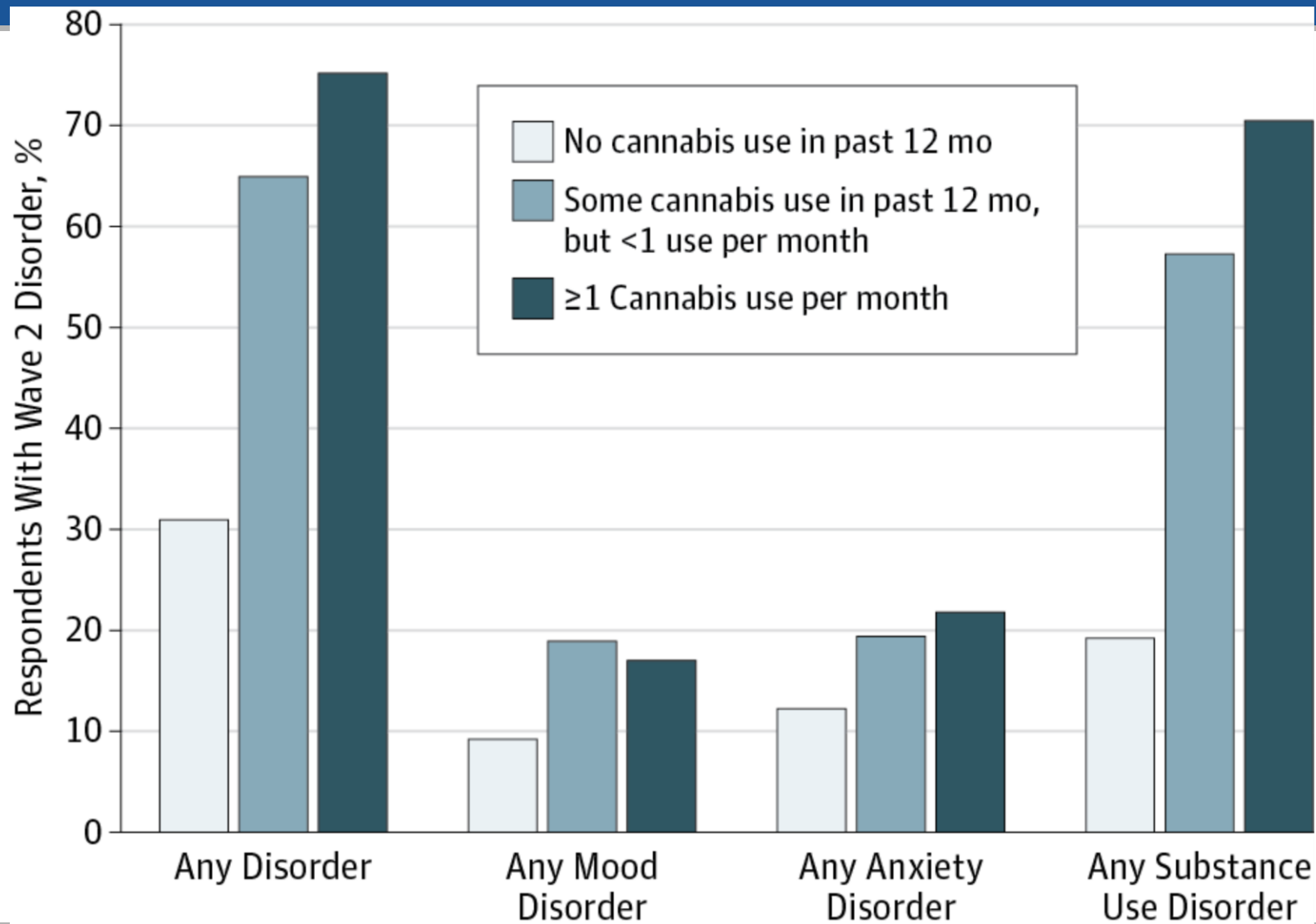
**There is moderate evidence of a statistical association between cannabis use and:**

- The impairment in the cognitive domains of learning, memory, and attention (acute cannabis use)

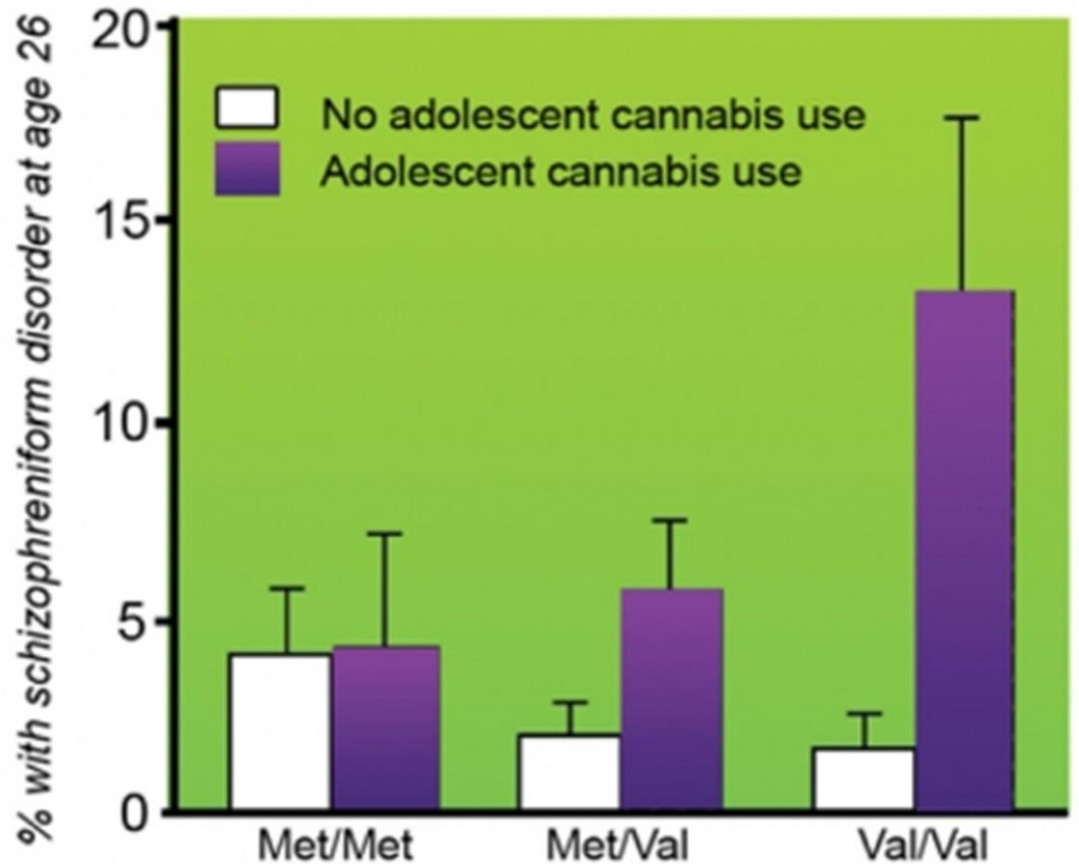
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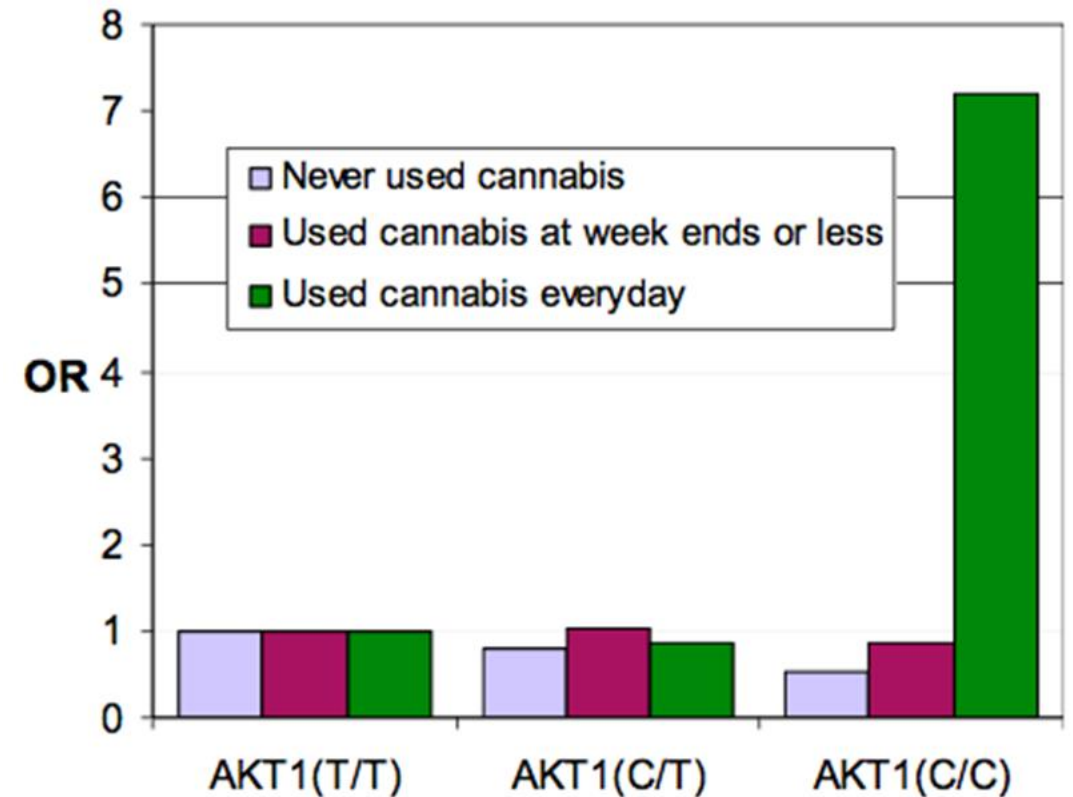
# Association between mood disorder and MJ



# Genetic variation influences harmful effects of marijuana



adapted from Caspi et.al. *Biol. Psych*, May 2005.



BIOL PSYCHIATRY 2012;72:811-816



# Health effects of cannabis and cannabinoids: Mental Health

**There is substantial evidence of a statistical association between cannabis use and:**

- The development of schizophrenia or other psychoses, with the highest risk among the most frequent users

**There is moderate evidence of a statistical association between cannabis use and:**

- Better cognitive performance among individuals with psychotic disorders and a history of cannabis use
- Increased symptoms of mania and hypomania in individuals diagnosed with bipolar disorders (regular cannabis use)
- A small increased risk for the development of depressive disorders
- Increased incidence of suicidal ideation and suicide attempts with a higher incidence among heavier users
- Increased incidence of suicide completion
- Increased incidence of social anxiety disorder (regular cannabis use)
- Major depressive disorder is a risk factor for the development of problem cannabis use



# Pulmonary effects of smoked marijuana

- Acute → bronchodilation (FEV<sub>1</sub> increase ~ 0.15-0.25L)
- Long-term → cough (OR 2.0, 95% CI 1.32-3.01), phlegm, wheeze; however data were inconclusive regarding an association between long-term marijuana smoking and airflow obstruction(1)
- At low levels of exposure, FEV<sub>1</sub> increased by 13 mL/joint-year and FVC by 20 mL/joint-year, but at higher levels of exposure, airflow obstruction was observed(2)

1. Tetrault JM et al. Archives IM 2007

2. Pletcher MJ et al. JAMA 2012



# Health effects of cannabis and cannabinoids: Respiratory disease

**There is substantial evidence of a statistical association between cannabis smoking and:**

- Worse respiratory symptoms and more frequent chronic bronchitis episodes (long-term cannabis smoking)

**There is moderate evidence of a statistical association between cannabis smoking and:**

- Improved airway dynamics with acute use, but not with chronic use
- Higher forced vital capacity (FVC)

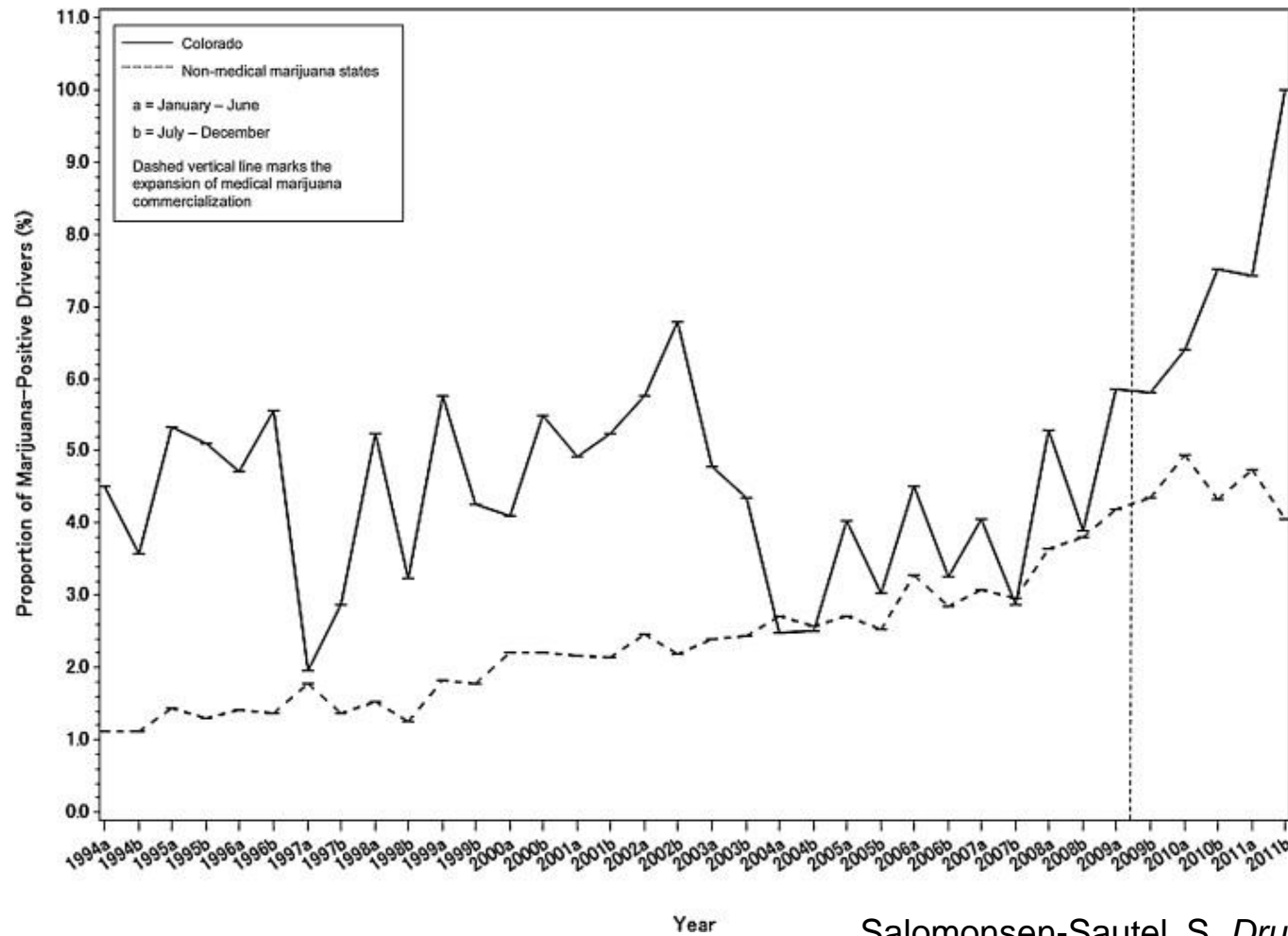
**There is moderate evidence of a statistical association between *the cessation* of cannabis smoking and:**

- Improvements in respiratory symptoms

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Health Effects of Cannabis and Cannabinoids. 2017



# Trends in fatal motor vehicle crashes before and after marijuana commercialization in CO



Salomonsen-Sautel, S. *Drug & Alcohol Dependence*, 2014



# Health effects of cannabis and cannabinoids: Injury and death

**There is substantial evidence of a statistical association between cannabis use and:**

- Increased risk of motor vehicle crashes

**There is moderate evidence of a statistical association between cannabis use and:**

- Increased risk of overdose injuries, including respiratory distress, among pediatric populations in U.S. states where cannabis is legal (9-4b)

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Health Effects of Cannabis and Cannabinoids. 2017



# Health effects of cannabis and cannabinoids: Other effects

**There is substantial evidence of a statistical association between maternal cannabis smoking and:**

- Lower birth weight of the offspring

**There is limited evidence of a statistical association between maternal cannabis smoking and:**

- Pregnancy complications for the mother
- Admission of the infant to the neonatal intensive care unit (NICU)

**There is moderate evidence of *no* statistical association between cannabis use and:**

- Incidence of lung cancer (cannabis smoking)
- Incidence of head and neck cancers

Report of National Academies of Science, Engineering and Medicine.  
Health Effects of Cannabis and Cannabinoids. 2017



# Treatment Options

- Behavioral
  - Substance abuse treatment setting
    - cognitive-behavioral therapy, contingency management, motivational enhancement, therapeutic living
  - General medical settings
    - Brief interventions
- Pharmacotherapy
  - No currently approved medication
    - cannabinoid antagonist
    - oral THC for withdrawal, maintenance or short-term treatment?
      - cannabinoid agonist—Levin FR DAD 2011
    - N-Acetylcysteine



# Synthetic marijuana: K2, Spice, etc.



- General Information:
  - Marketed as safe legal alternative to marijuana; easily accessible; multiple names (Moon Rocks, Yucatan Fire) generally smoked; very common among adolescents
- Effects:
  - Mild euphoria and relaxation
  - The ‘giggles’
  - Increased sensitivity to external stimuli
  - Distortion of time perception
  - Frank, vivid hallucinations
- Neurobiology: CB receptor agonist; lasts up to 6 hrs
- Adverse effects:
  - Dry mouth, palpitations, rapid heart rate, vomiting, agitation, confusion
  - **Evolving chemically and difficult to test for in urine**
  - May be adulterated with heavy metal residues

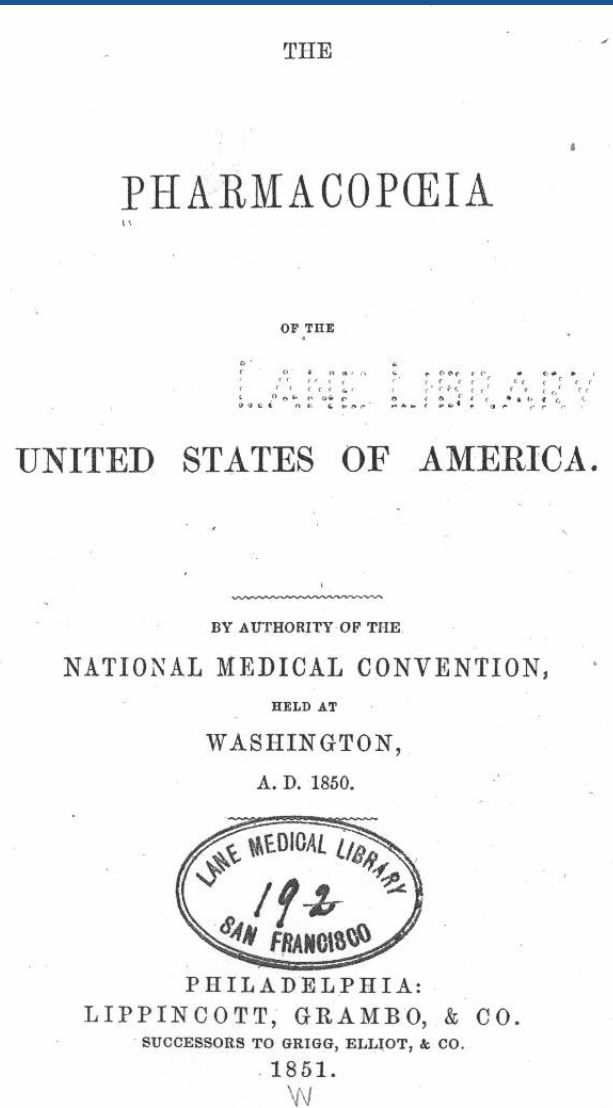


# Fundamental tension

- Intoxication and withdrawal of marijuana are not fatal
- Overdose is unlikely
- Long-term, moderate use seems to be relatively frequent (compared to other drugs)
- Risk of end-organ damage appears to be lower than several other legal and illegal substances
- Ratio of medical benefit to harm *may be* equal or better than some controlled substances







In 1850, the U.S. Pharmacopoeia listed marijuana as treatment for neuralgia, tetanus, typhus, cholera, rabies, dysentery, alcoholism, opiate addiction, anthrax, leprosy, incontinence, gout, convulsive disorders, tonsillitis, insanity, excessive menstrual bleeding, and uterine bleeding, among others.

In 1942, amidst spreading reports of marijuana's alleged association with violent crime, it was removed from the U.S. Pharmacopoeia.



# Health effects of cannabis and cannabinoids: Therapeutic effects

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

- For the treatment of chronic pain in adults (cannabis)
- As antiemetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids)
- For improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids)

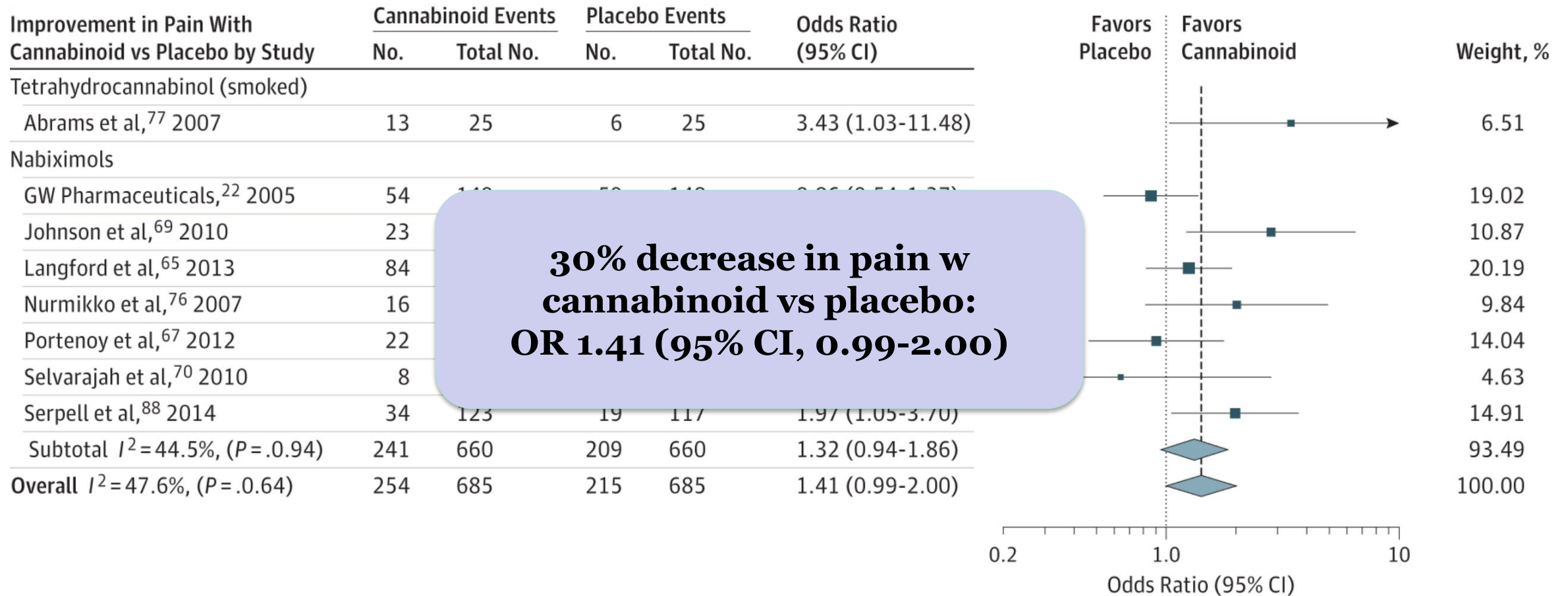
**There is moderate evidence that cannabis or cannabinoids are effective for:**

- 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)

Report of National Academies of Science, Engineering and Medicine.  
Health Effects of Cannabis and Cannabinoids. 2017



# Cannabinoids for medical use: Pain



# Medical Marijuana and OD risk

Table. Association Between Medical Cannabis Laws and State-Level Opioid Analgesic Overdose Mortality Rates in the United States, 1999-2010

Independent Variable <sup>a</sup>	Percentage Difference in Age-Adjusted Opioid Analgesic Overdose Mortality in States With vs Without a Law		
	Primary Analysis	Secondary Analyses	
	Estimate (95% CI) <sup>b</sup>	Estimate (95% CI) <sup>c</sup>	Estimate (95% CI) <sup>d</sup>
Medical cannabis law	-24.8 (-37.5 to -9.5) <sup>e</sup>	-31.0 (-42.2 to -17.6) <sup>f</sup>	-23.1 (-37.1 to -5.9) <sup>e</sup>
Prescription drug monitoring program	3.7 (-12.7 to 23.3)	3.5 (-13.4 to 23.7)	7.7 (-11.0 to 30.3)
Law requiring or allowing pharmacists to request patient identification	5.0 (-10.4 to 23.1)	4.1 (-11.4 to 22.5)	2.3 (-15.4 to 23.7)
Increased state oversight of pain management clinics	-7.6 (-19.1 to 5.6)	-11.7 (-20.7 to -1.7) <sup>e</sup>	-3.9 (-21.7 to 18.0)
Annual state unemployment rate <sup>g</sup>	4.4 (-0.3 to 9.3)	5.2 (0.1 to 10.6) <sup>e</sup>	2.5 (-2.3 to 7.5)

<sup>a</sup> All models adjusted for state and year (fixed effects).

<sup>b</sup>  $R^2 = 0.876$ .

<sup>c</sup> All intentional (suicide) overdose deaths were excluded from the dependent variable; opioid analgesic overdose mortality is therefore deaths that are unintentional or of undetermined intent. All covariates were the same as in the primary analysis;  $R^2 = 0.873$ .

<sup>d</sup> Findings include all heroin overdose deaths, even if no opioid analgesic was

involved. All covariates were the same as in the primary analysis.  $R^2 = 0.842$ .

<sup>e</sup>  $P \leq .05$ .

<sup>f</sup>  $P \leq .001$ .

<sup>g</sup> An association was calculated for a 1-percentage-point increase in the state unemployment rate.

Bachhuber MA et al. JAMA 2014



# State Level Variation

- Physician certification for patients with certain qualifying diagnoses
- Patient may possess only a one month supply (varies from state to state)
  - CT=2.5 oz; WA=12 oz
- Growers are certified by Department of Consumer Protection to cultivate MJ
  - Application fee often prohibitive
- Pharmacists able to obtain a dispensing license from DCP
  - State regulates amount of licenses



# Challenges in conducting research on adverse health effects or therapeutic effects of cannabis

- There are specific regulatory barriers, including the classification of cannabis as a Schedule I substance, that impede the advancement of cannabis and cannabinoid research
- It is often difficult for researchers to gain access to the quantity, quality, and type of cannabis product necessary to address specific research questions on the health effects of cannabis use
- A diverse network of funders is needed to support cannabis and cannabinoid research that explores the beneficial and harmful health effects of cannabis use
- To develop conclusive evidence for the effects of cannabis use on short- and long-term health outcomes, improvements and standardization in research methodology (including those used in controlled trials and observational studies) are needed

Report of National Academies of Science, Engineering and Medicine.  
Health Effects of Cannabis and Cannabinoids. 2017



# Interactive teaching scenario: Morning report/role play

- Set up a “spicy,” public health debate regarding legalization of recreational marijuana using the following citation as a spring board for discussion:

Kilmer B. Recreational Cannabis — Minimizing the Health Risks from Legalization. Perspective. NEJM. February 23, 2017
- Assign report participants to one of two groups:
  - Recreational marijuana SHOULD be legalized in all states nationwide
    - Citing adverse effects of criminalization and potential for increasing state budgets through taxation, potential impact on opioid epidemic
  - Recreational marijuana SHOULD NOT be legalized in all states nationwide
    - Citing current research on adverse health effects and natural experiment data from states that have already legalized recreational marijuana
- All arguments need to be evidence-based and factual



# Thank you

# Questions?

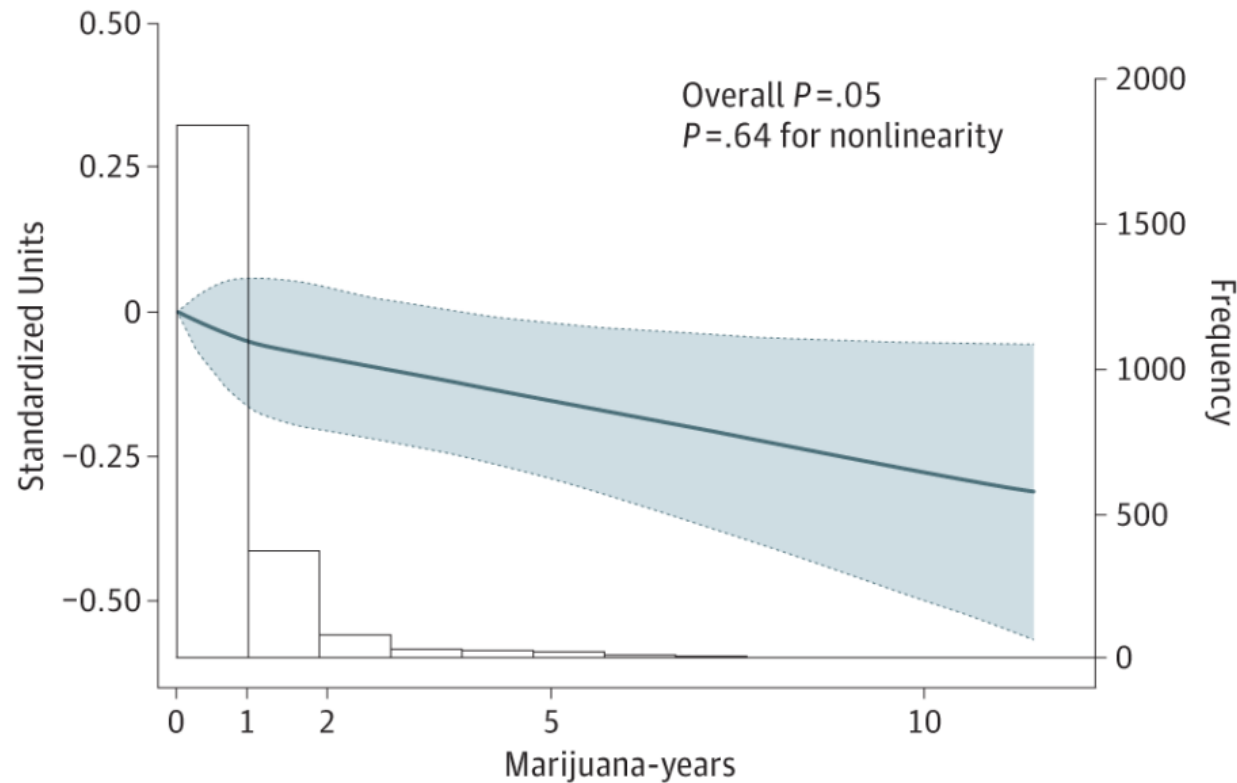
*Acknowledgements: several slides adapted from Dr. William Becker (Yale),  
Dr. Hilary Kunins (NY DPH), Dr. Jeffrey Hunt (Brown), Dr. Zoe Weinstein (BU)*



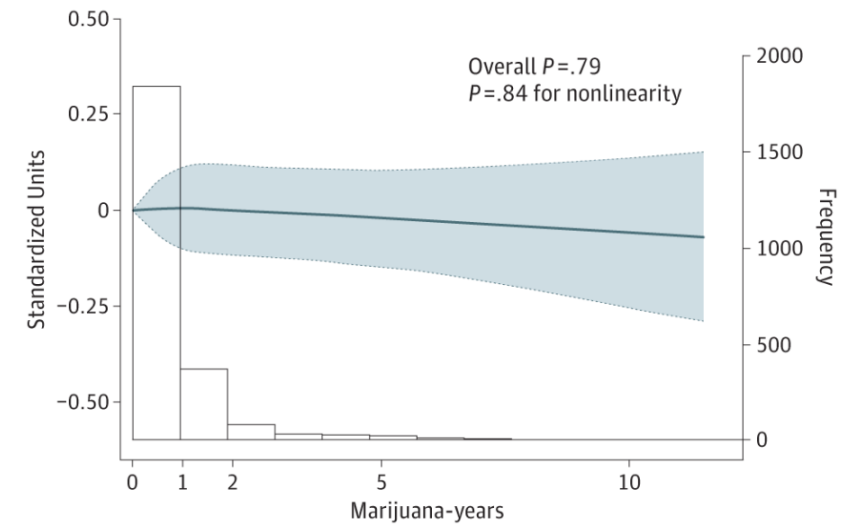


# Association between lifetime marijuana use and cognitive function in middle age: The CARDIA Study

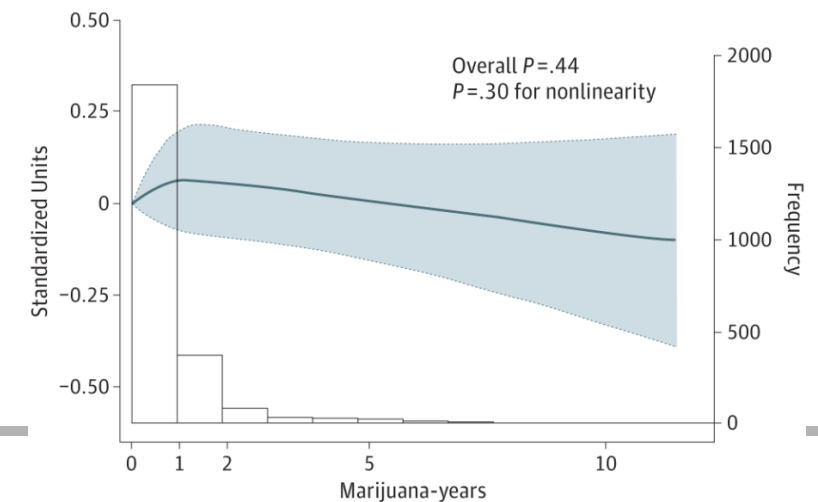
**A** Rey auditory verbal test



**B** Digital symbol substitution test



**C** Stroop test



Auer R et al. JAMA Intern Med. 2016;176(3):352-361

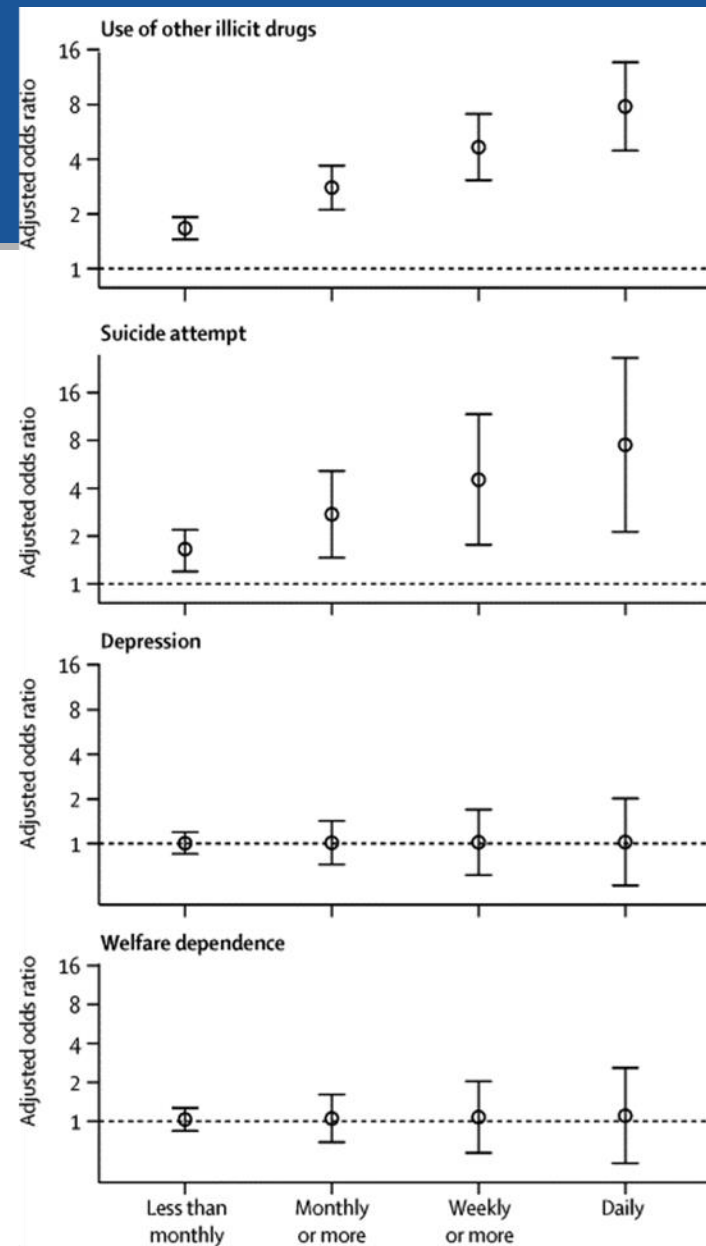
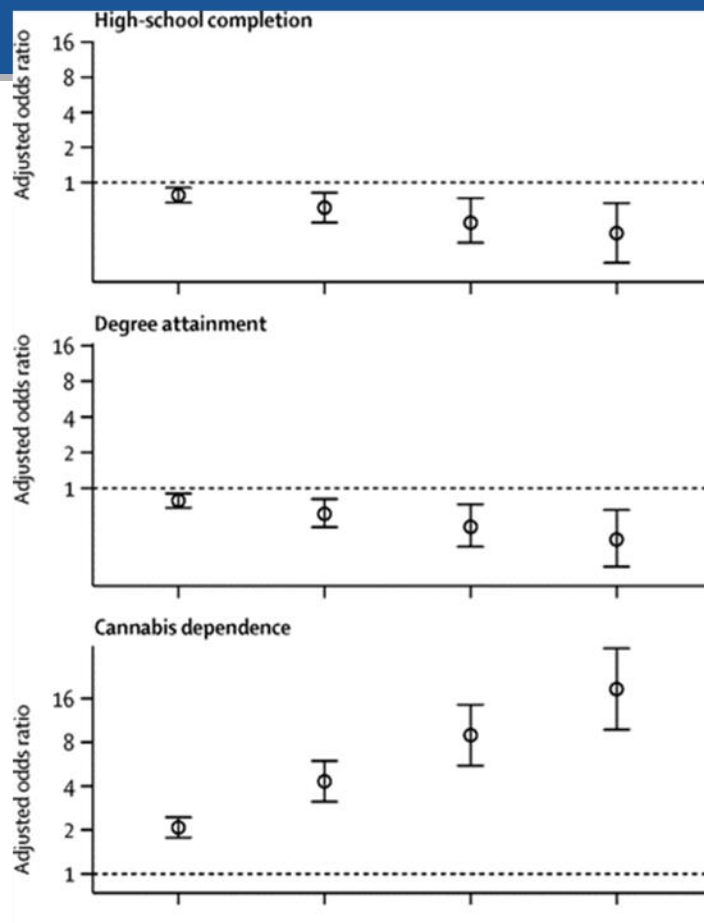
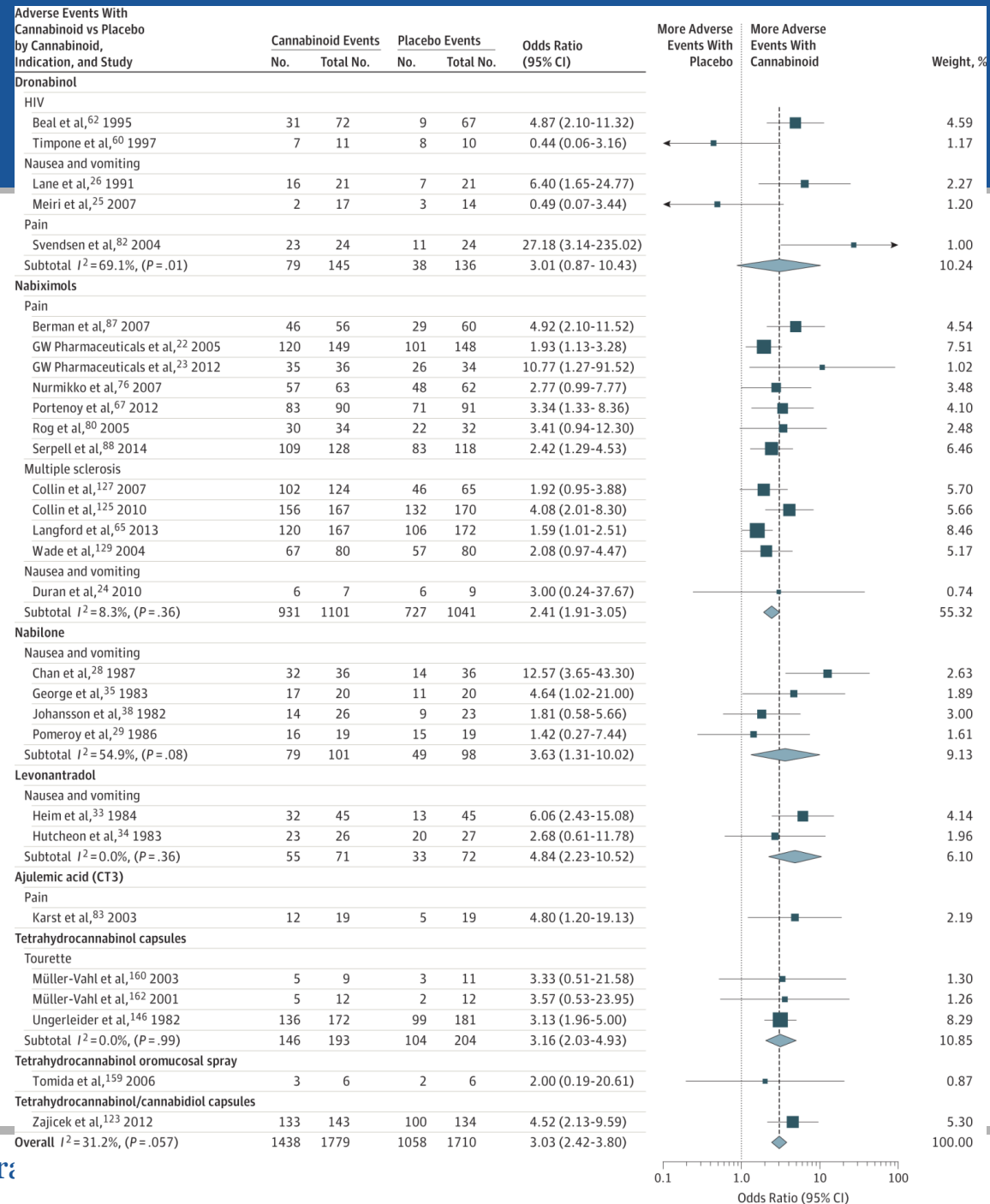


Figure 2. Adjusted odds ratios (log scale) between maximum frequency of cannabis use before age 17 years and young adult outcomes in combined data, compared with individuals who have never used cannabis. Error bars show 95% CIs.



# Odds of Adverse Events



Whiting PF et al. JAMA. 2015;313(24):2456-2473



# Major Questions Remain

- Does marijuana provide sustained benefit?
- What are the long term effects in medical populations?
- Is smoked marijuana more effective than synthetic formulations?
- What is the comparative effectiveness of marijuana vs. established treatments?
- What are the appropriate doses for various conditions?

