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Marijuana: Clearing the Smoke on Clinical and Policy Issues

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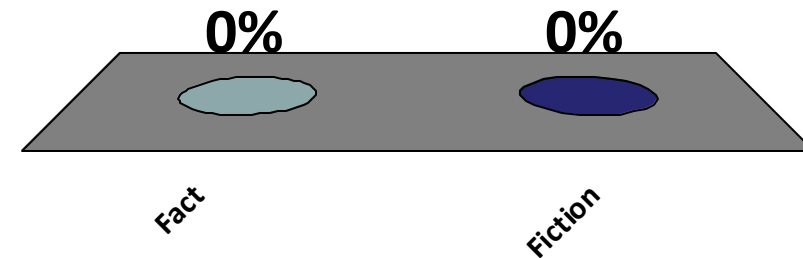
Program Director, Addiction Medicine Fellowship Program
Yale University School of Medicine



Fact or Fiction?

Marijuana use is increasing.....

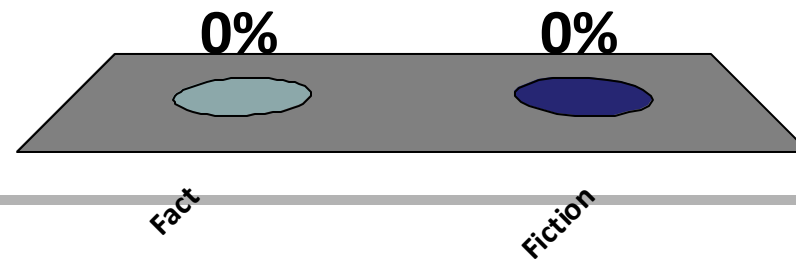
- A. Fact
- B. Fiction



Fact or Fiction?

No adverse health effects occur with marijuana use.....

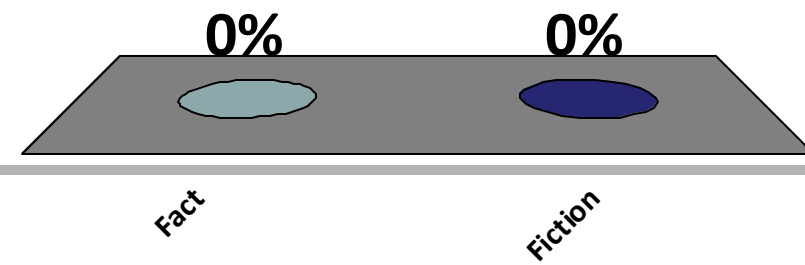
- A. Fact
- B. Fiction



Fact or Fiction?

Withdrawal symptoms occur with marijuana cessation.....

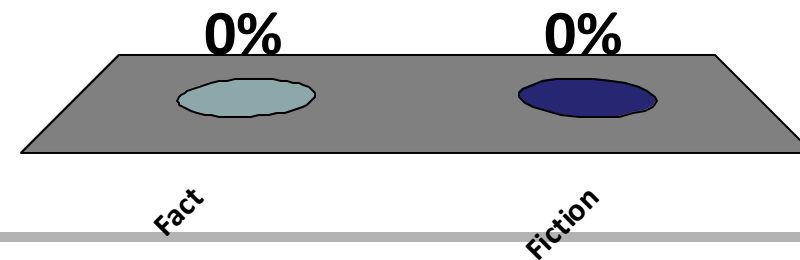
- A. Fact
- B. Fiction



Fact or Fiction?

You can't overdose on marijuana.....

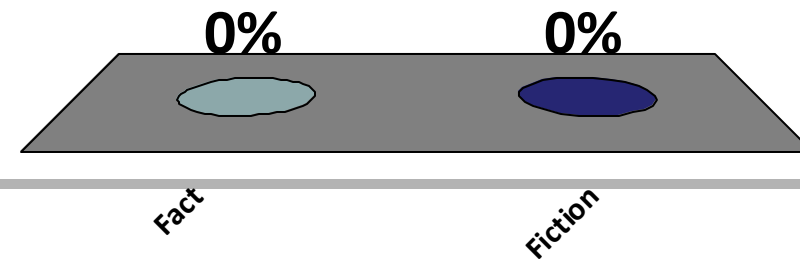
- A. Fact
- B. Fiction



Fact or Fiction?

Marijuana use disorders are treatable.....

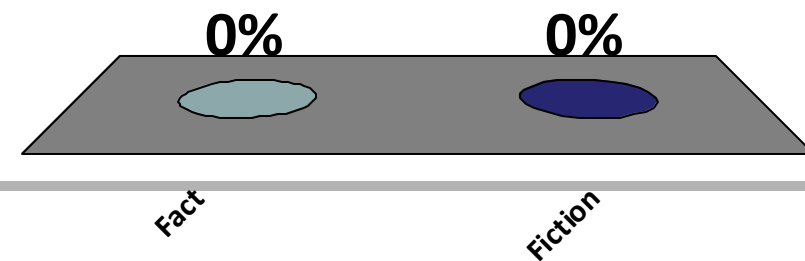
- A. Fact
- B. Fiction



Fact or Fiction?

Medical marijuana is approved for use nationwide.....

- A. Fact
- B. Fiction



Why Talk about Marijuana?

- Clinical and political
- Timely
- Treatment for marijuana use vs. marijuana use for treatment
- Your patients want to know



Learning objectives

- Define the key components of marijuana as a substance and review relevant epidemiology and terminology
- Explore US love-hate relationship with marijuana and national policy history
- Summarize neurobiology and physiologic 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

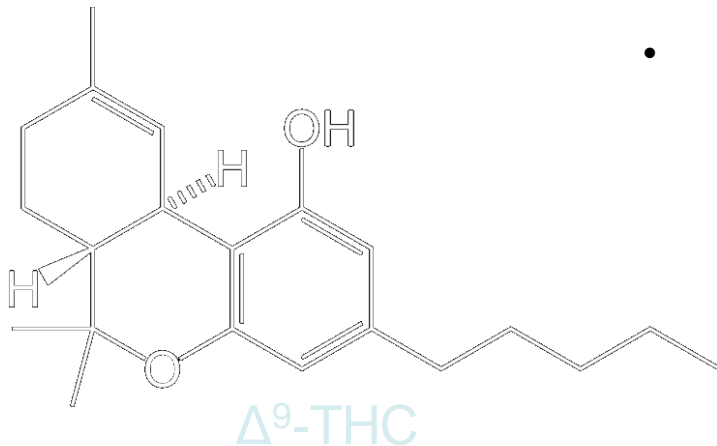
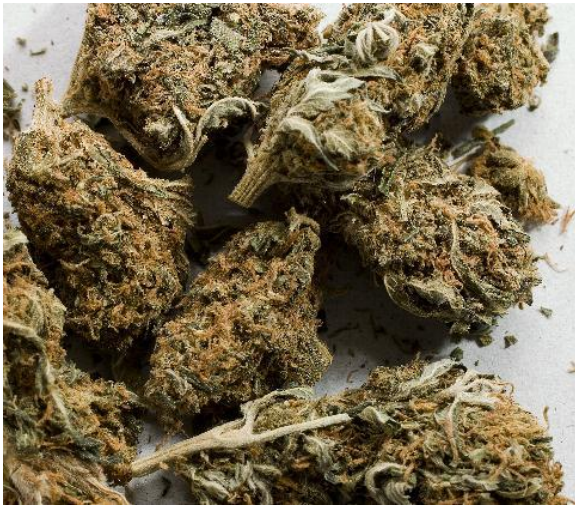


What is Marijuana?

- 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 Δ 9-tetrahydrocannabinol (THC) and route of administration



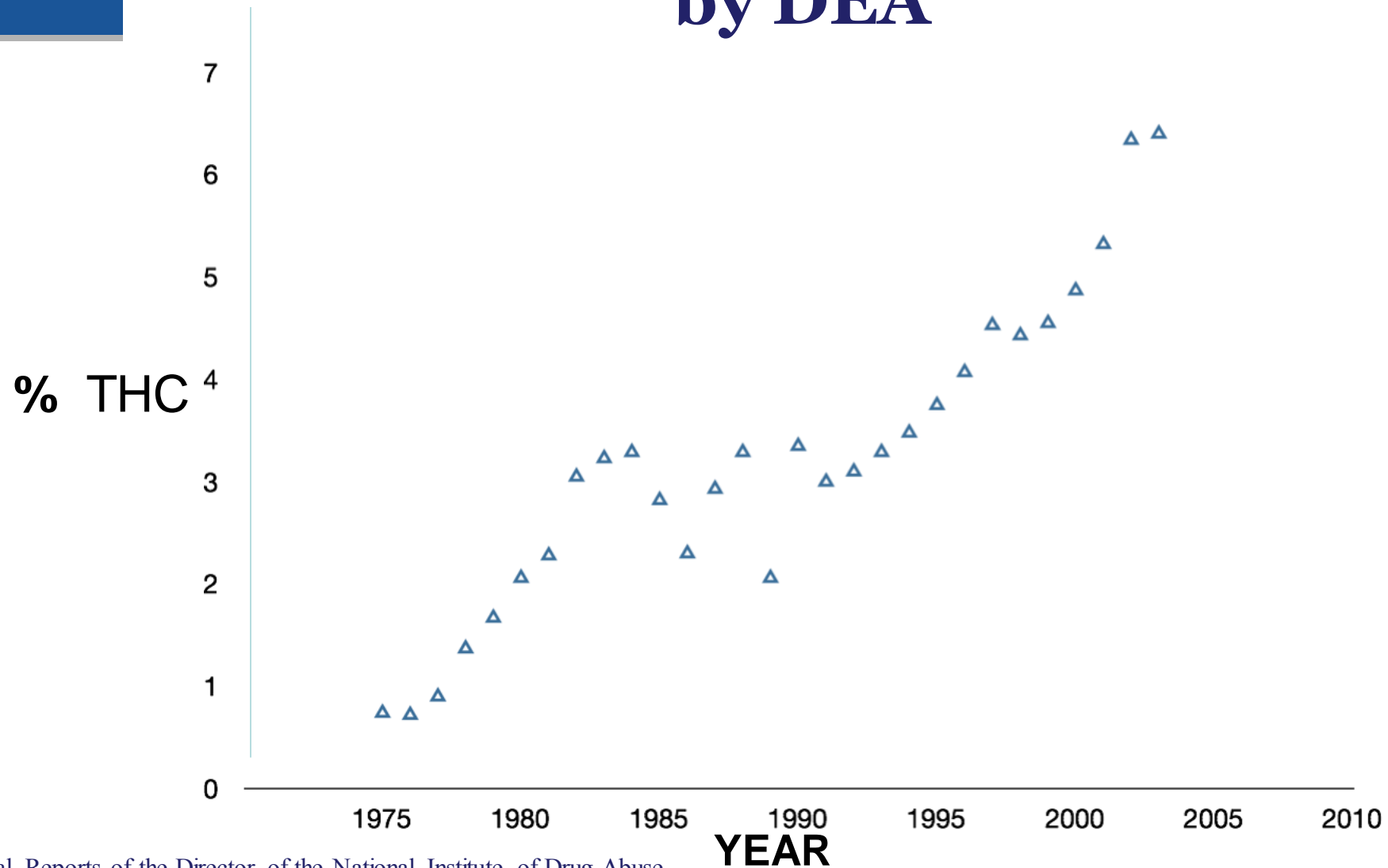
Δ^9 -TETRAHYDROCANNABINOL (THC)



- 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



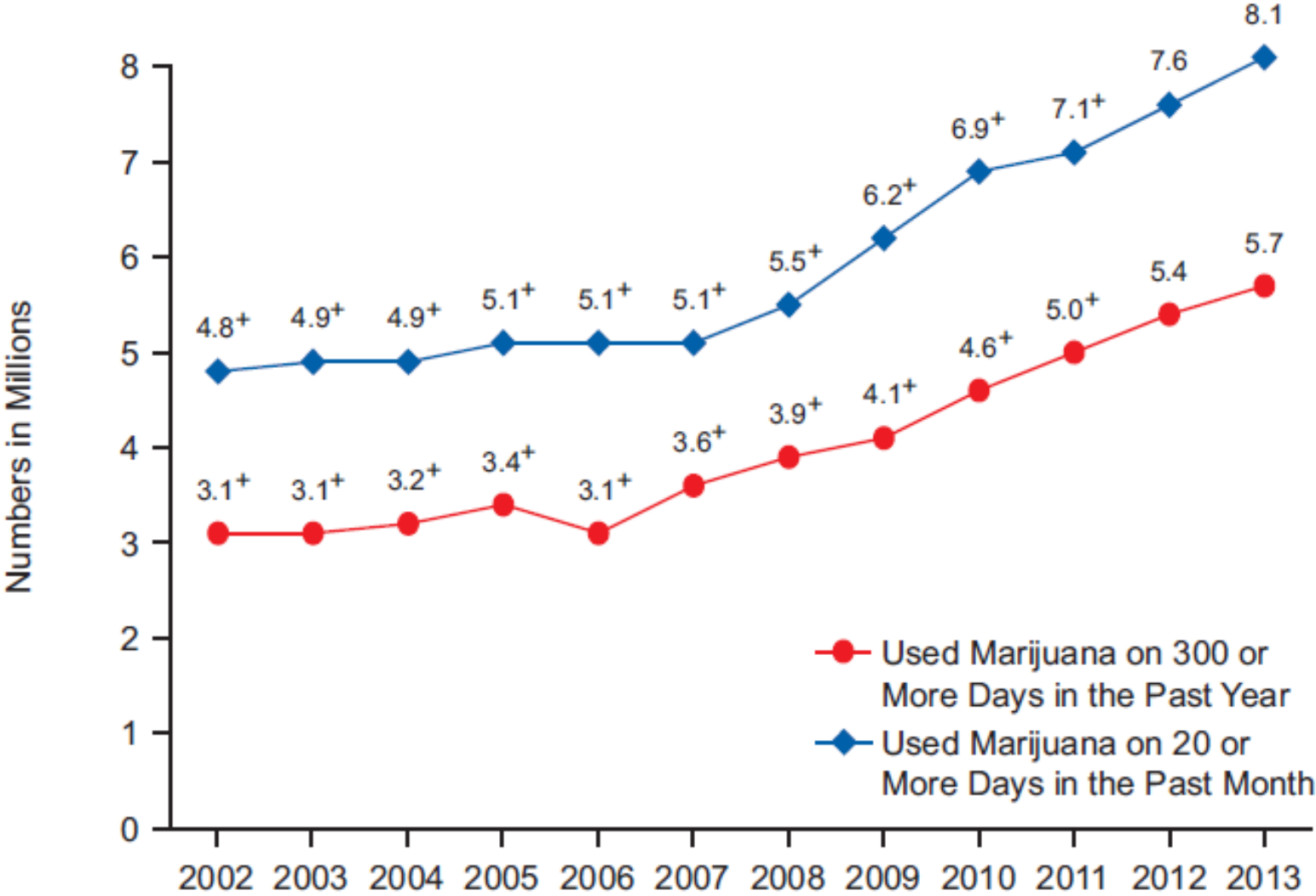
Percentage THC in Marijuana Seized by DEA



From the compiled Annual Reports of the Director of the National Institute of Drug Abuse



Density of Marijuana use age 17 or older

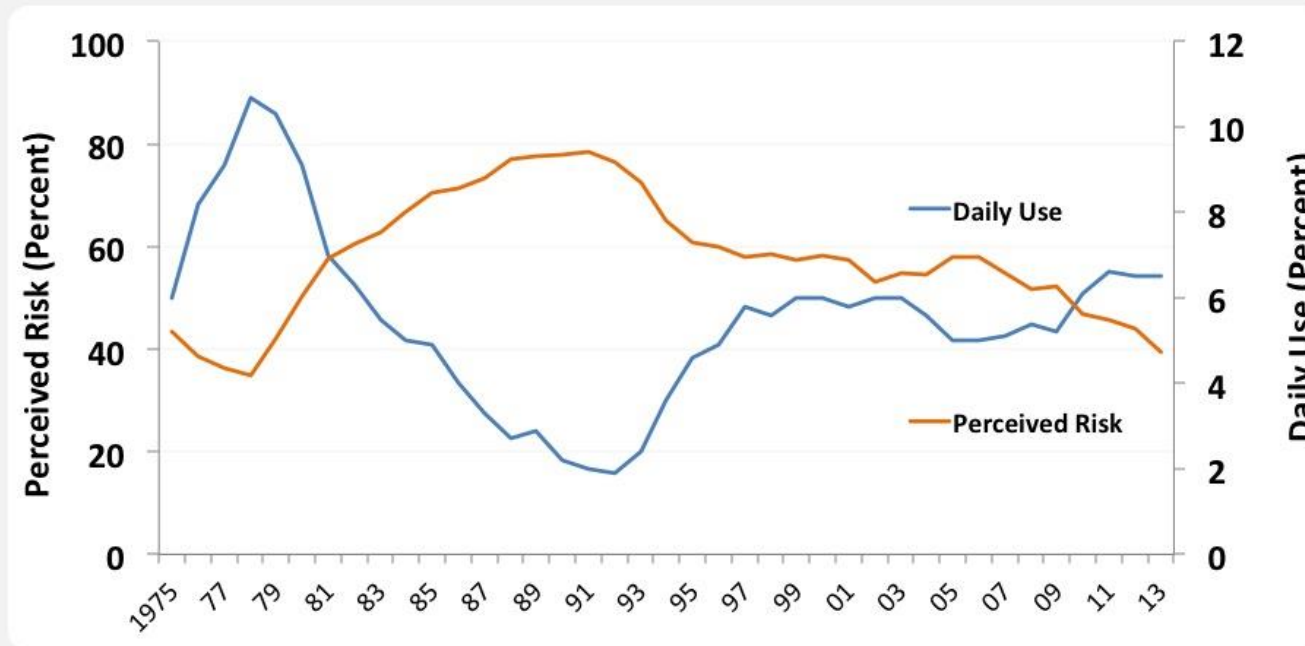


NSDUH 2013



Why the increase?

Daily Marijuana Use vs. Perceived Risk of Regular Marijuana Use among 12th 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

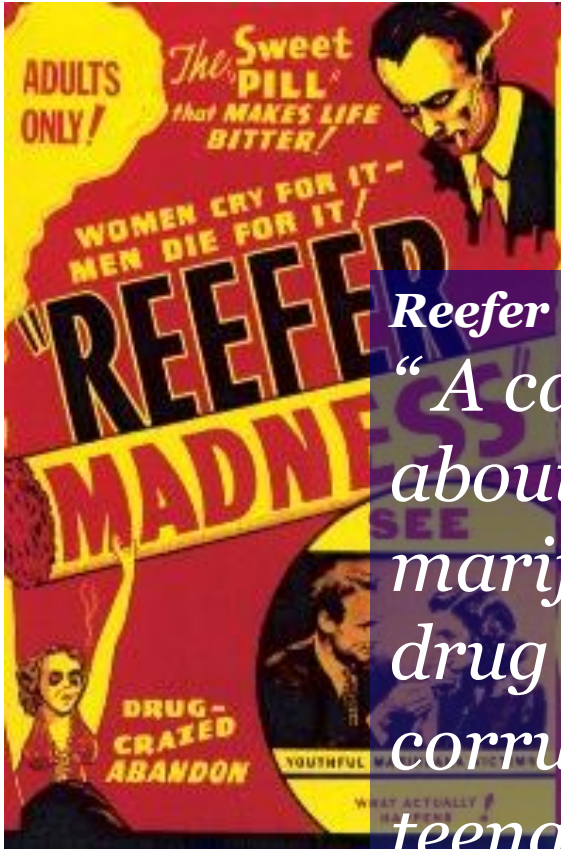


Cannabis Withdrawal: New to DSM 5

- 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

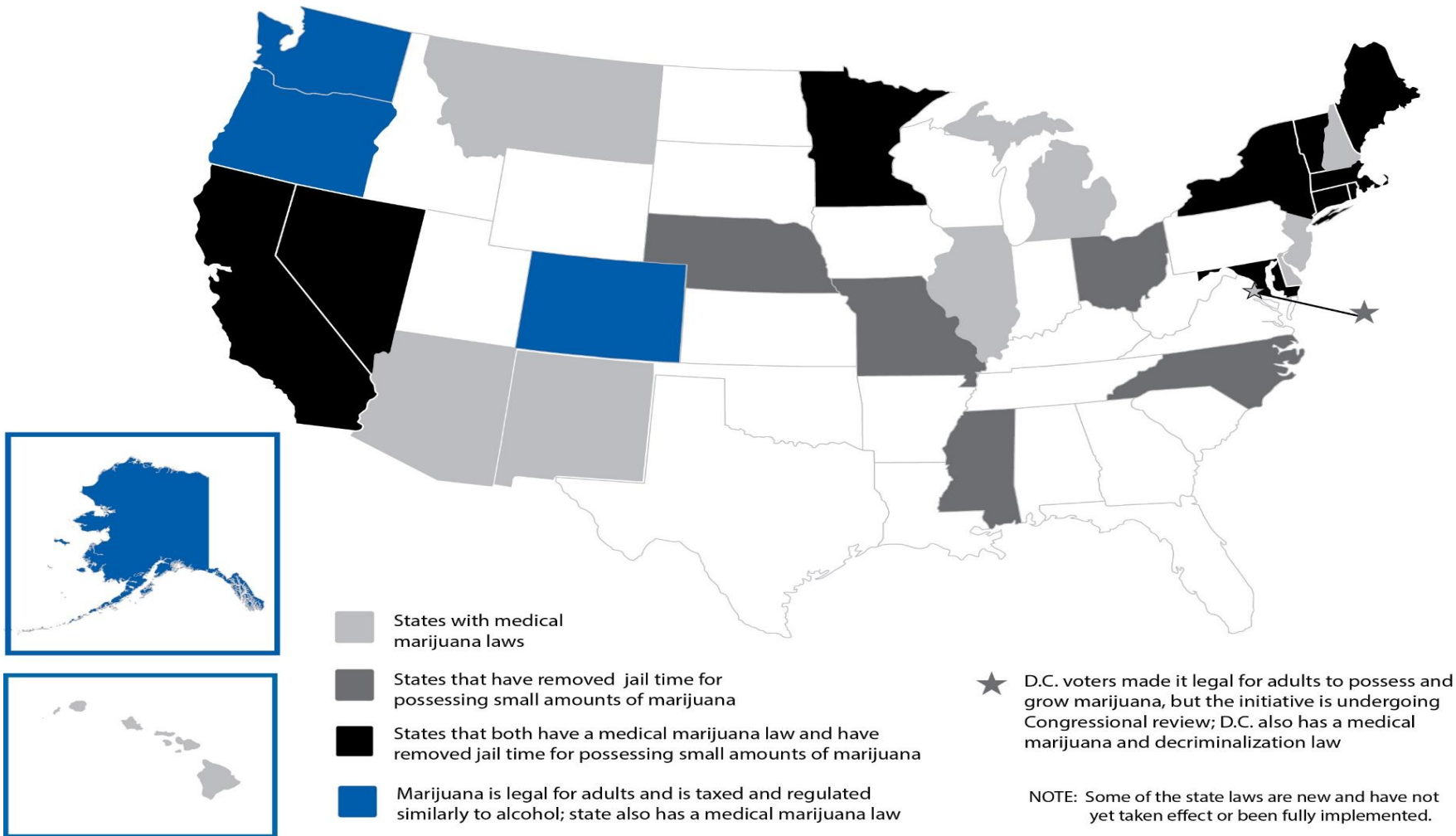


Policy timeline

- 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: 23 states + PR medical marijuana, 4 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: CAREERS bill introduced in Senate
 - Bipartisan group of senators introduced bill to reschedule marijuana



Current *State of the Union*: 23 states medical marijuana laws, 4 states and D.C. with recreational laws



Cannabinoid Neurobiology

- Cannabinoid Receptors
 - CB1, CB2, GPR55
 - Location:
 - Hippocampus
 - Basal ganglia
 - Cerebellum
 - liver, muscle, gut, and adipose tissue
- Endogenous cannabinoids
 - Anandamide
 - 2-arachidonoylglycerol (AG2)
- SR141617A (Rimonabant) : Cannabinoid ***antagonist***
 - Caused acute withdrawal syndrome in chronic MJ users
 - Caused dysphoria in MJ-naïve patients



Case Presentation #1

- MD is a 19 yo male who comes to your clinic to establish primary care. He is accompanied by his mother. He has no relevant PMH or FH. He takes no medications and has no allergies. He denies alcohol use and smokes 1/2 PPD for two years. His mother expresses concern over his daily marijuana use.
- Should she be concerned? What should you say?



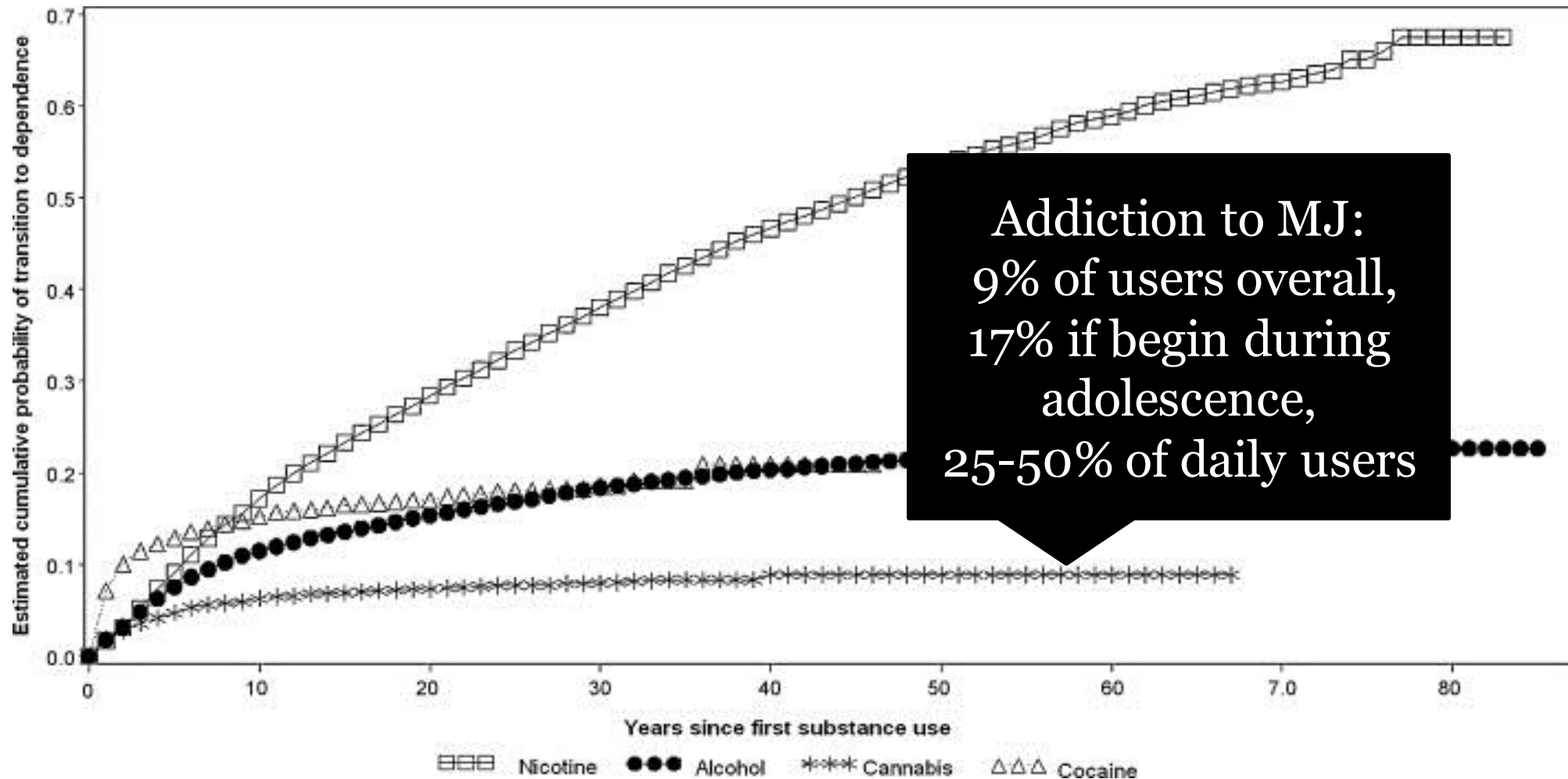
Adverse effects of marijuana use

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



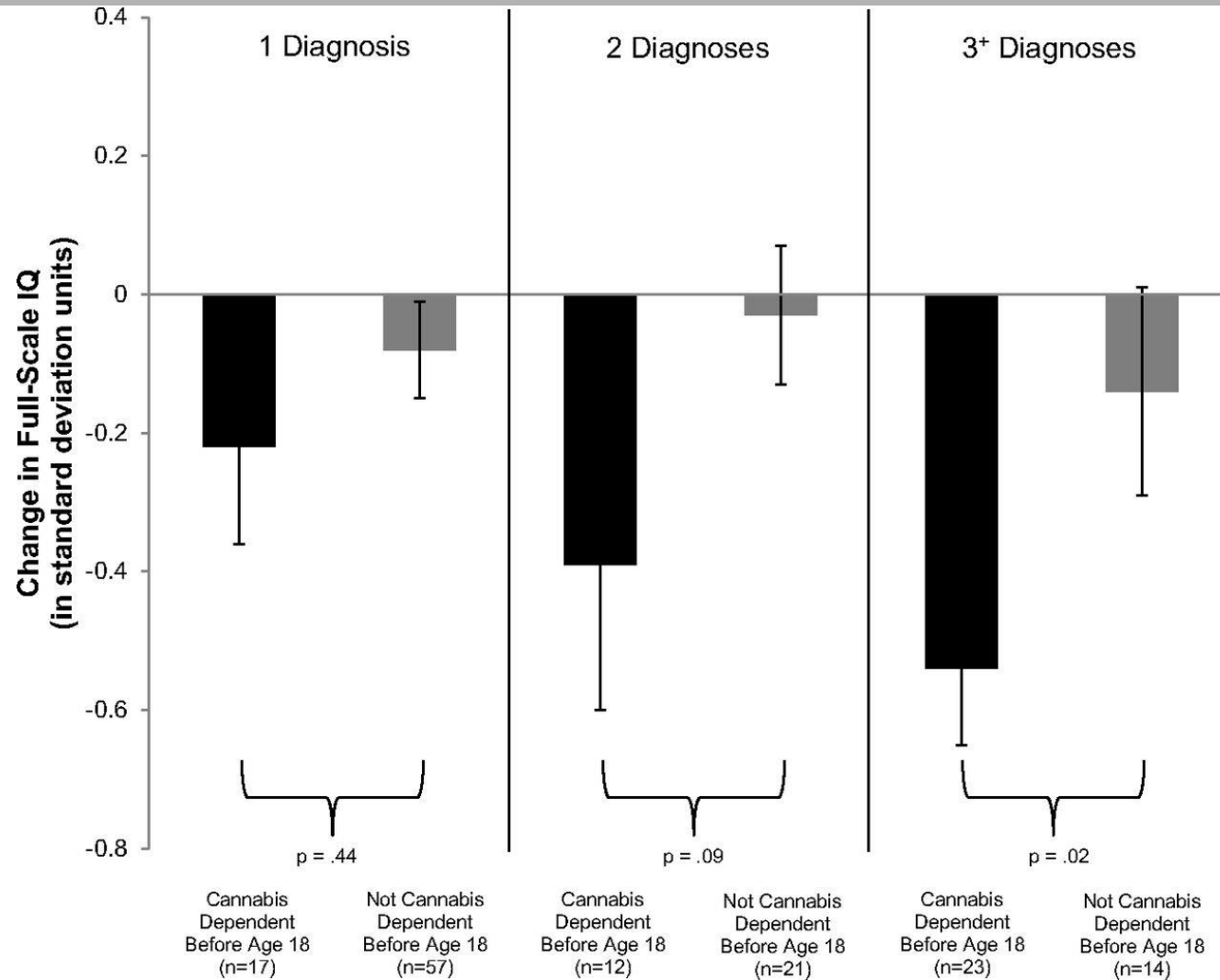
Cumulative Probability of Transitioning to Substance Use Disorder for Nicotine, Alcohol, Marijuana and Cocaine



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



Adolescent vulnerability in IQ decline

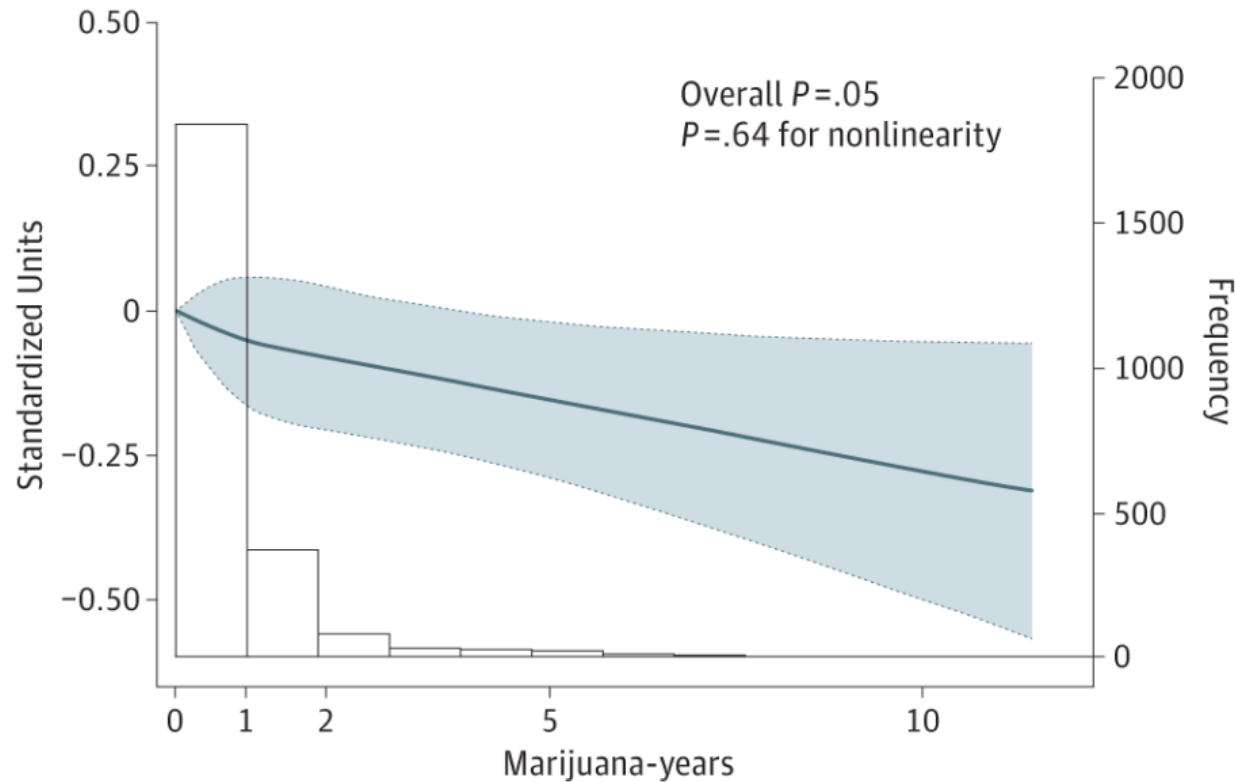


Meier M H et al. PNAS 2012

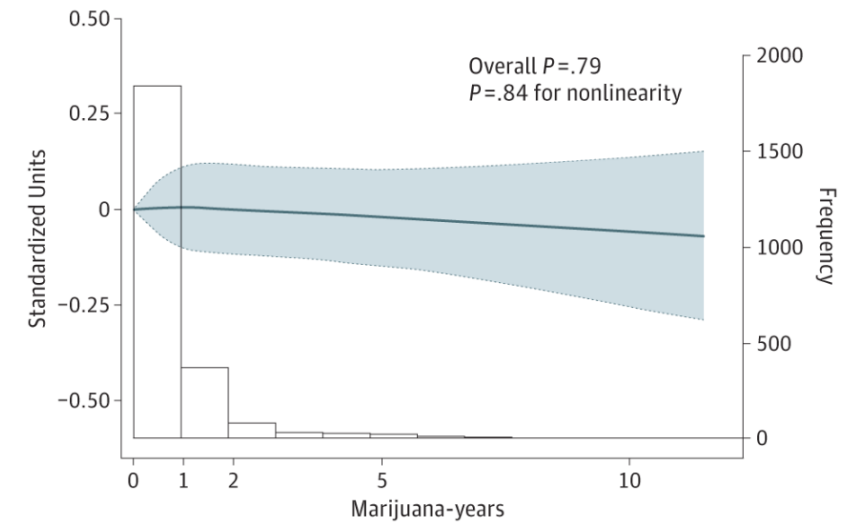


Association Between Lifetime Marijuana Use and Cognitive Function in Middle Age: The CARDIA Study

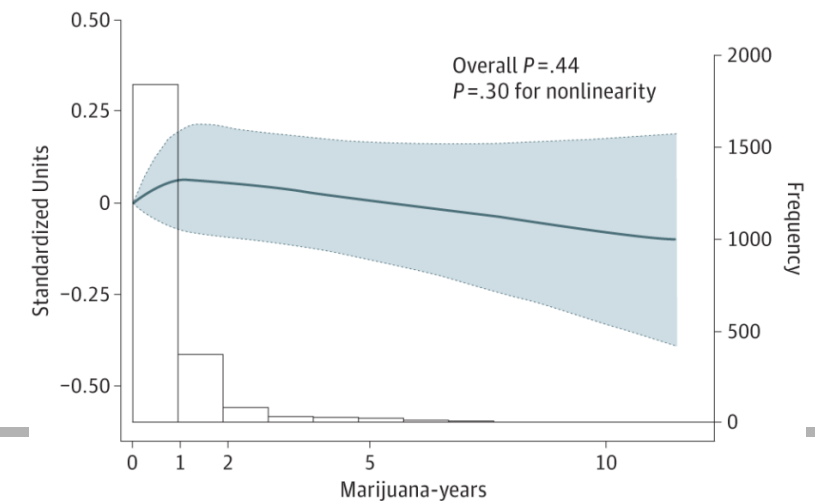
A Rey auditory verbal test



B Digital symbol substitution test



C Stroop test



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

Prevalence of psychiatric disorders among individuals who use marijuana

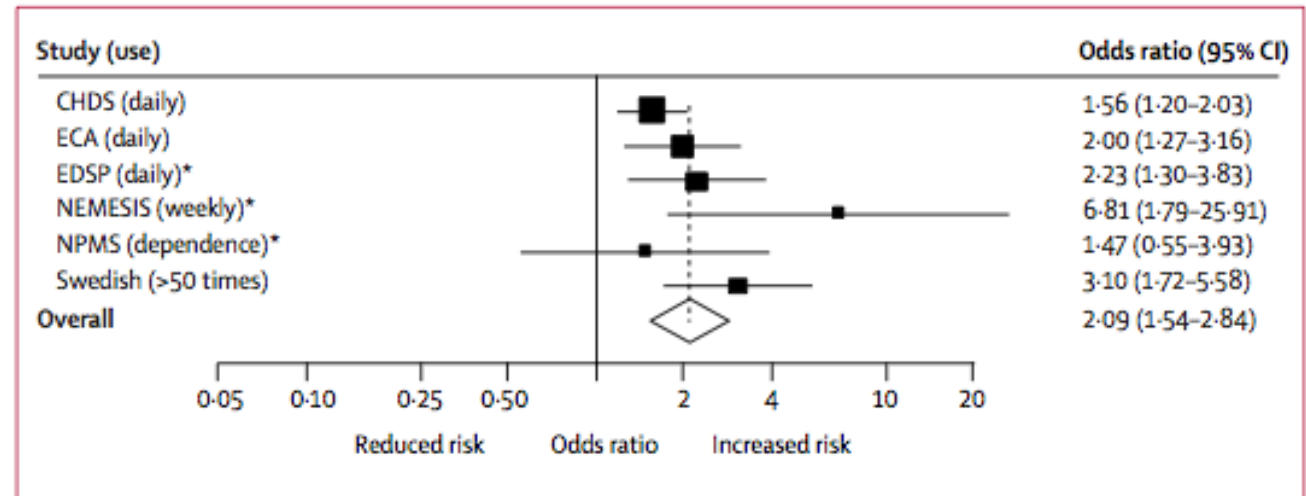
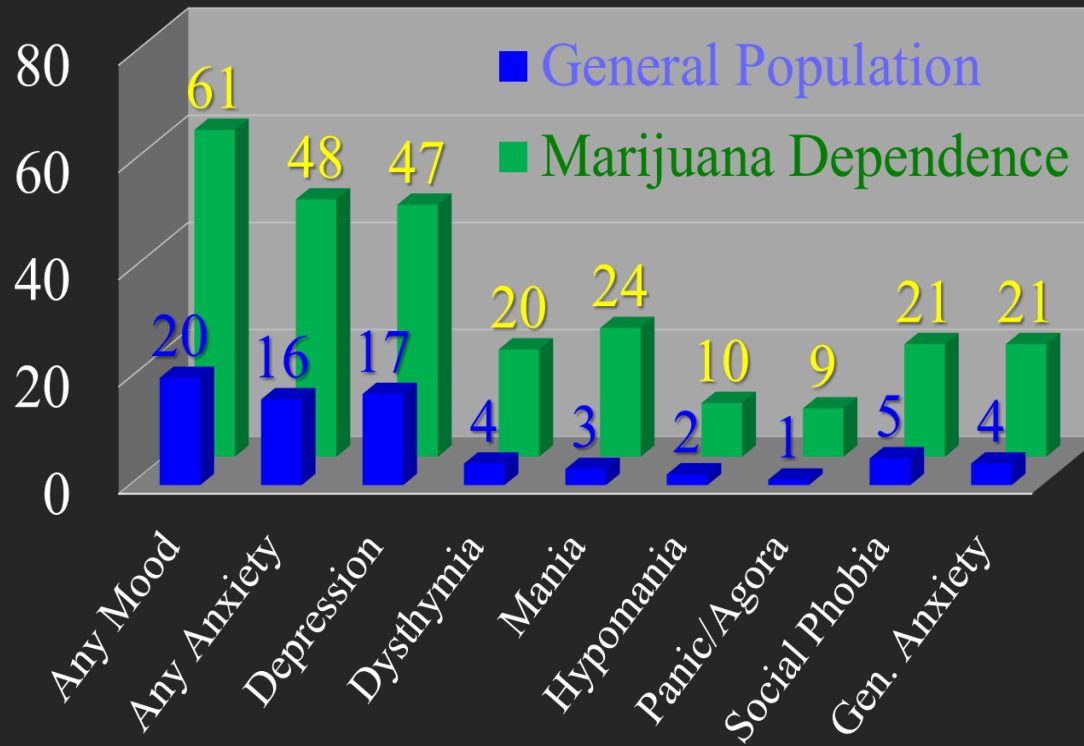
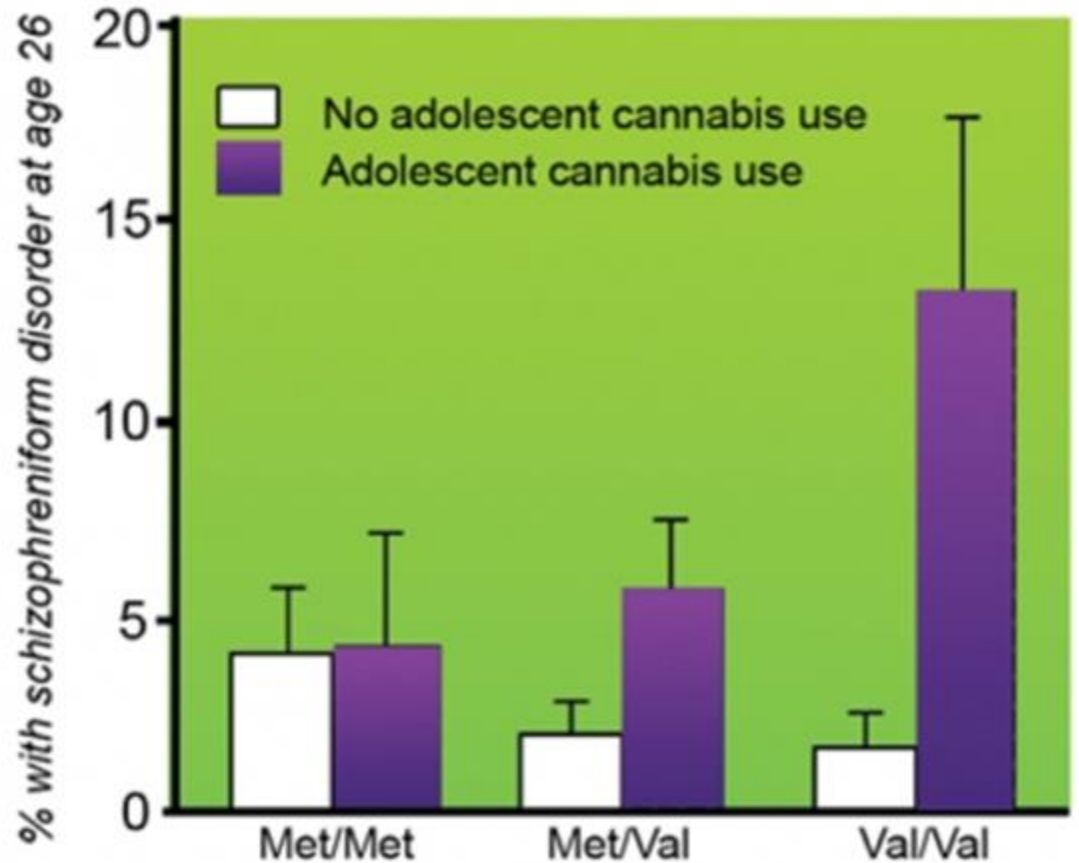


Figure 2: Forest plot showing adjusted odds ratios and 95% CI for any psychosis outcome according to most frequent use of cannabis in individual studies

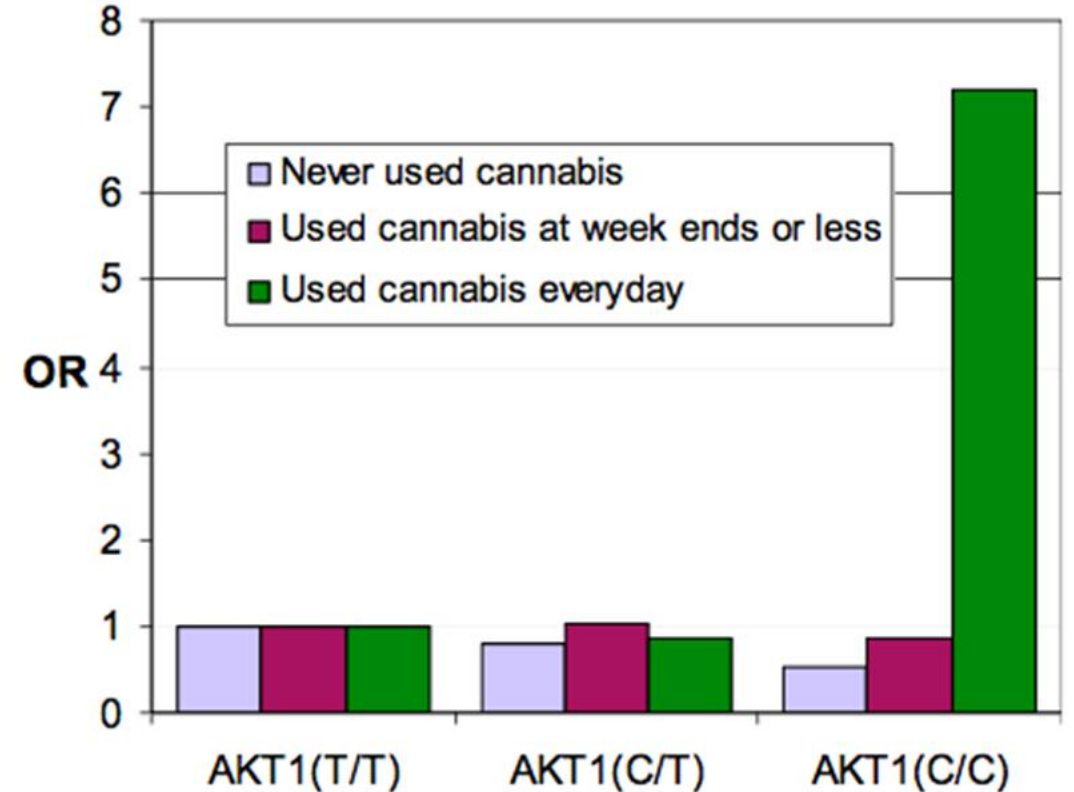
Conway 2006; Moore et al., Lancet 2007



Genetic variation influences harmful effects of marijuana



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



BIOL PSYCHIATRY 2012;72:811-816



Pulmonary Effects of Smoked Marijuana

- Acute → bronchodilation (FEV₁ 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, FEV₁ 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



Marijuana and Cancer Risk

- Evidence for histopathologic changes supporting biologic plausibility of association between marijuana smoking with lung cancer
- Increased risk of lung CA among chronic, habitual marijuana users in a single 40 year cohort study
 - However risk is lower than seen with tobacco use
- Association between MJ use and testicular cancer risk (OR 1.94 95% CI: 1.02-3.68) in population based case control study
 - Non-seminoma and mixed histology tumors

1 Mehra R Archives of Int Med. 2007

2 Callaghan RC Cancer causes and control. 2012

3 Lacson JCA et al *Cancer*, 2012



Other Risks with Marijuana Use

- Associated with use of other substances in adolescents (1)
 - Enrollment in extracurricular activities protective
- Gateway: 2.5 increase risk of subsequent use of prescription opioids (2)
- 2-fold increase MV crash risk (3)
 - Elevated if alcohol also involved

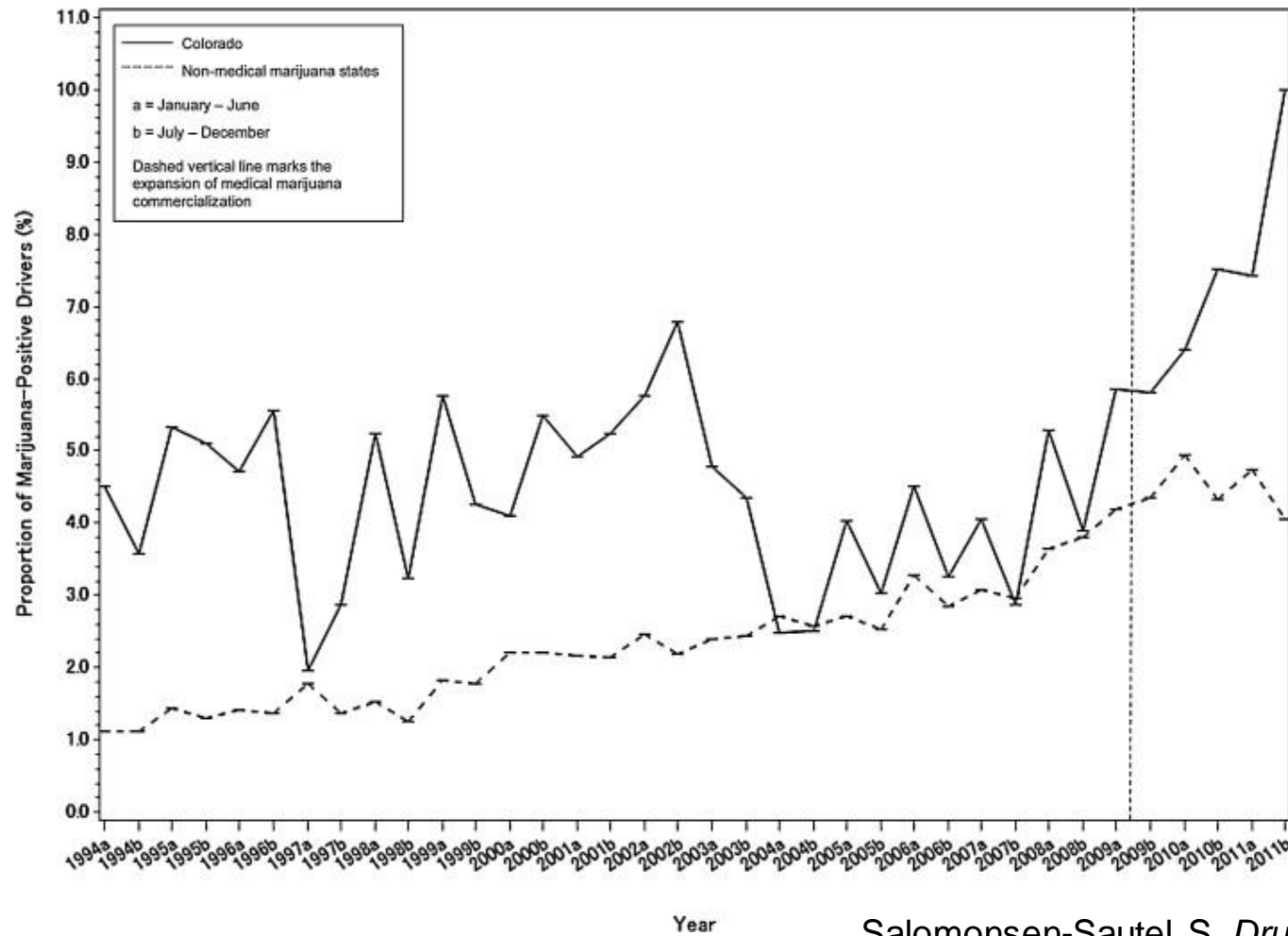
¹ Schepesis, T JAM, 2011

³Asbridge M, BMJ, 2012

² Sullivan LE, Journal of Adolescent Health 2013



Trends in Fatal Motor Vehicle Crashes Before and After Marijuana Commercialization in CO



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



Return to Case #1

- There may be an effect on IQ which may be persistent even with cessation
- Smoked marijuana may lead to increased respiratory symptoms
- Of concern, regular marijuana use may be associated with more serious disorders, use of other illicit substances, and poorer driving skills

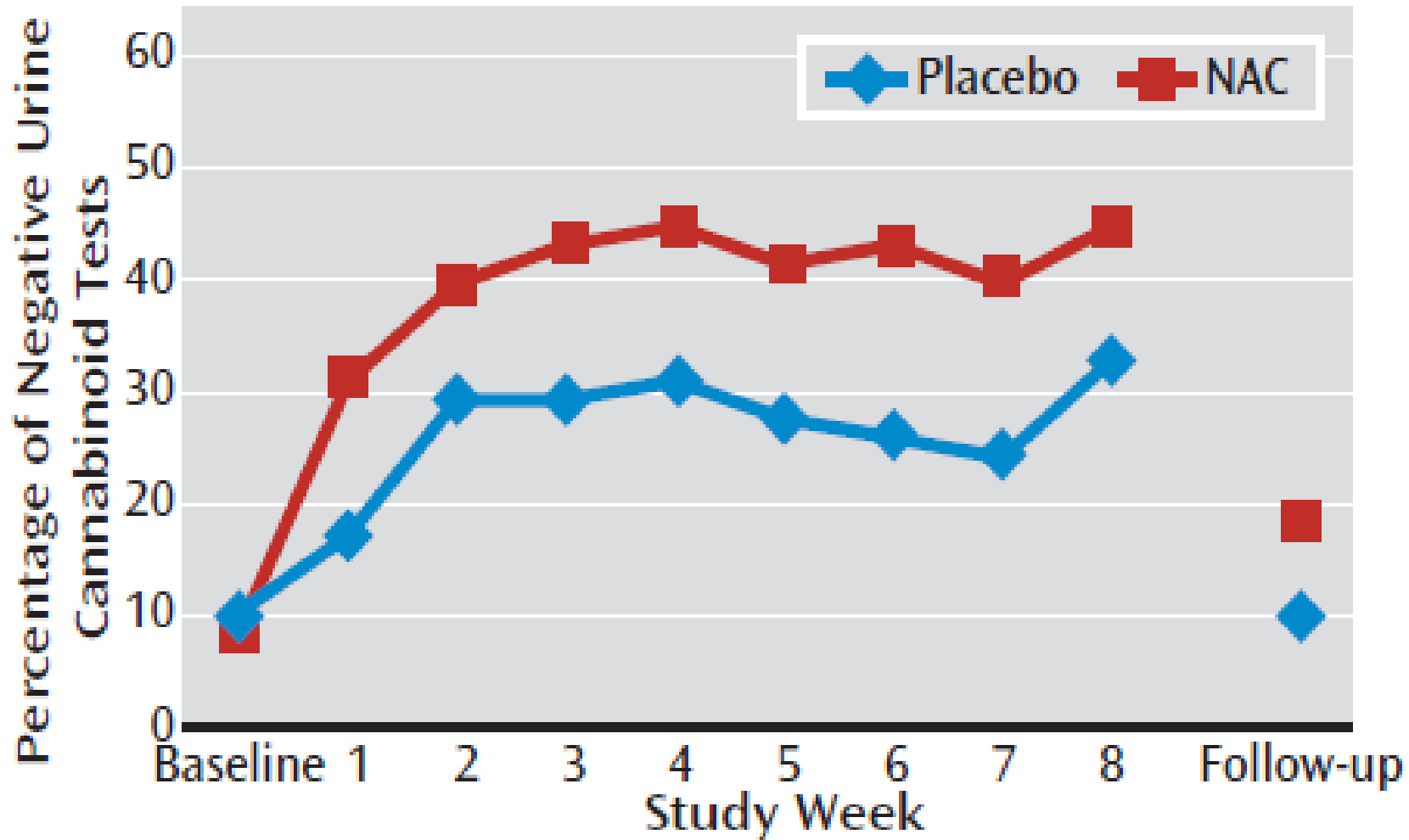


Treatment Options

- 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



A Double-Blind RCT of N-Acetylcysteine in Cannabis-Dependent Adolescents



Gray KM et al., AJP June 15, 2012.



Synthetic marijuana

The New York Times

Potent 'Spice' Drug Fuels Rise in Visits to Emergency Room



By [ALAN SCHWARZ](#) APRIL 24, 2015

A photo provided by Karen Stallings of her sons, Joey Stallings, left, and Jeffrey Stallings. Both were hospitalized this month after using a synthetic substance called spice that mimics marijuana but is far more potent.

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

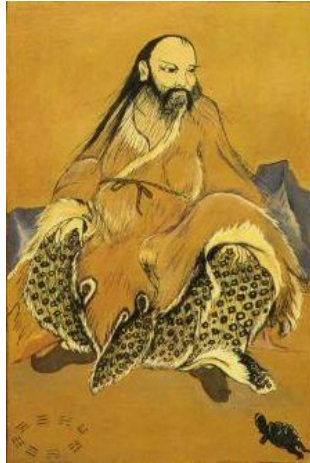


Fundamental tension

- 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



History of Medicinal Marijuana



The Chinese Emperor Fu His (ca. 2900 BC) noted cannabis possessed both yin and yang.

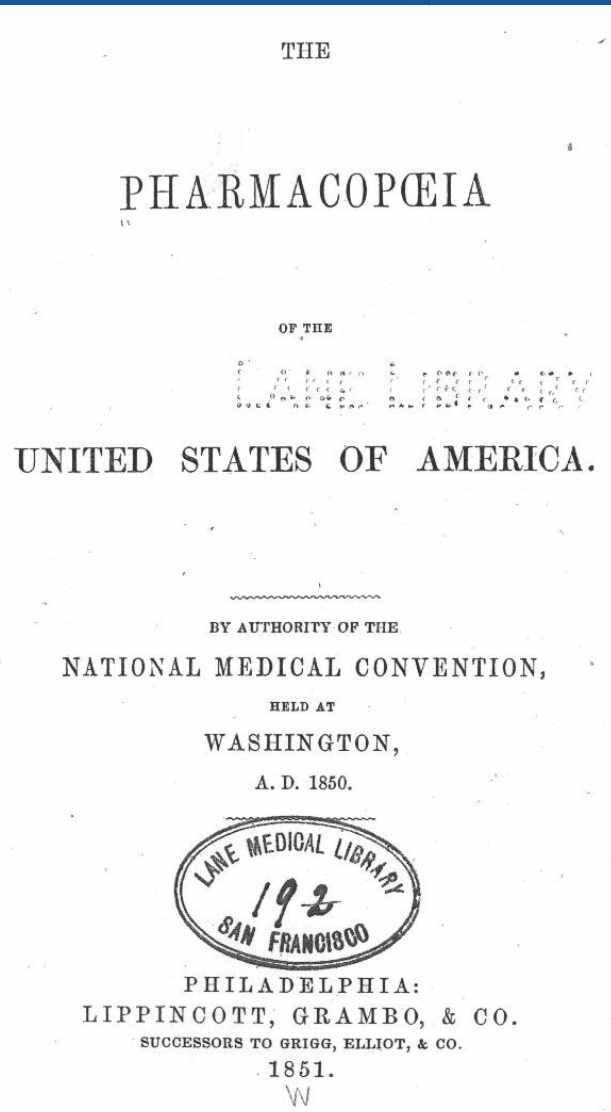


Cannabis pollen was found on the mummy of Ramesses II, who died in 1213 BC. Prescriptions for cannabis in Ancient Egypt included treatment for glaucoma and inflammation.

Deitch, R. *Hemp: American History Revisited: The Plant with a Divided History*, 2003

Lise Manniche, PhD. *An Ancient Egyptian Herbal*, 1989





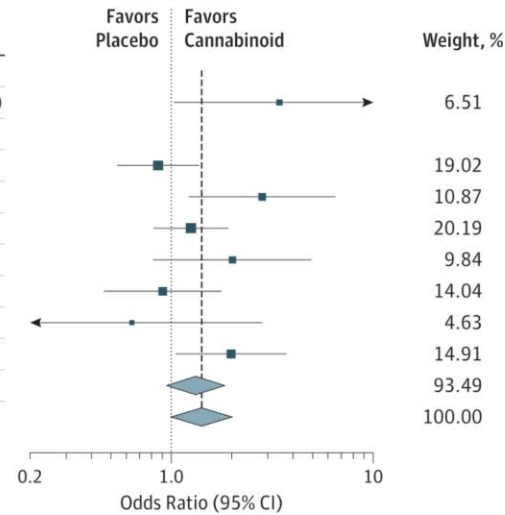
In 1850, the U.S. Pharmacopoeia listed marijuana as treatment for neuralgia, tetanus, typhus, cholera, rabies, dysentery, alcoholism, opiate addiction, anthrax, leprosy, incontinence, gout, convulsive disorders, tonsillitis, insanity, excessive menstrual bleeding, and uterine bleeding, among others.

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

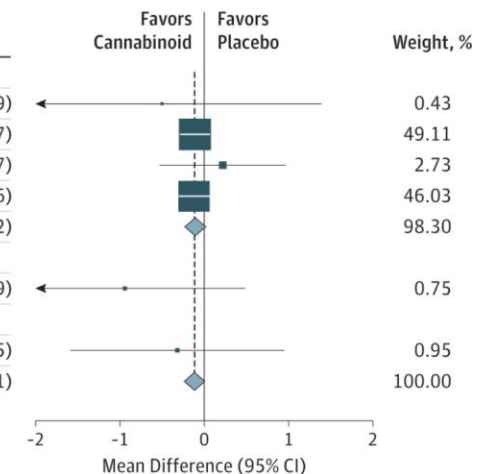


Cannabinoids for medical use: Pain and spasticity

Improvement in Pain With Cannabinoid vs Placebo by Study	Cannabinoid Events		Placebo Events		Odds Ratio (95% CI)
	No.	Total No.	No.	Total No.	
Tetrahydrocannabinol (smoked)					
Abrams et al, ⁷⁷ 2007	13	25	6	25	3.43 (1.03-11.48)
Nabiximols					
GW Pharmaceuticals, ²² 2005	54	149	59	148	0.86 (0.54-1.37)
Johnson et al, ⁶⁹ 2010	23	53	12	56	2.81 (1.22-6.50)
Langford et al, ⁶⁵ 2013	84	167	77	172	1.25 (0.81-1.91)
Nurmikko et al, ⁷⁶ 2007	16	63	9	62	2.00 (0.81-4.96)
Portenoy et al, ⁶⁷ 2012	22	90	24	91	0.90 (0.46-1.76)
Selvarajah et al, ⁷⁰ 2010	8	15	9	14	0.63 (0.14-2.82)
Serpell et al, ⁸⁸ 2014	34	123	19	117	1.97 (1.05-3.70)
Subtotal $I^2=44.5%$, ($P=.094$)	241	660	209	660	1.32 (0.94-1.86)
Overall $I^2=47.6%$, ($P=.064$)	254	685	215	685	1.41 (0.99-2.00)



Score Change With Cannabinoid vs Placebo by Study	Cannabinoid		Placebo		Mean Difference (95% CI)
	No. of Patients	Mean (SD) Score Change	No. of Patients	Mean (SD) Score Change	
Nabiximols					
Collin, ¹²⁵ 2010	156	-3.3 (9.25)	160	-2.8 (7.81)	-0.50 (-2.39 to 1.39)
Collin, ¹²⁷ 2007	114	-.64 (.56)	63	-.53 (.58)	-0.11 (-0.29 to 0.07)
Wade, ¹²⁹ 2004	73	-.37 (2.51)	70	-.59 (2.04)	0.22 (-0.53 to 0.97)
Berman, ⁸⁷ 2007	40	-.13 (.43)	44	-.01 (.42)	-0.12 (-0.30 to 0.06)
Subtotal $I^2=0.0%$, ($P=.082$)	383		337		-0.11 (-0.23 to 0.02)
Dronabinol					
Zajicek, ¹³¹ 2003	197	-1.86 (7.95)	207	-.92 (6.56)	-0.94 (-2.37 to 0.49)
Tetrahydrocannabinol/cannabidiol					
Zajicek, ¹³¹ 2003	207	-1.24 (6.6)	207	-.92 (6.56)	-0.32 (-1.59 to 0.95)
Overall $I^2=0.0%$, ($P=.80$)	590		544		-0.12 (-0.24 to 0.01)



CUPID Trial

The Cannabinoid Use in Progressive Inflammatory brain Disease (CUPID) trial: a randomised double-blind placebo-controlled parallel-group multicentre trial and economic evaluation of cannabinoids to slow progression in multiple sclerosis

Health Technology Assessment, No. 19.12; Feb 2015

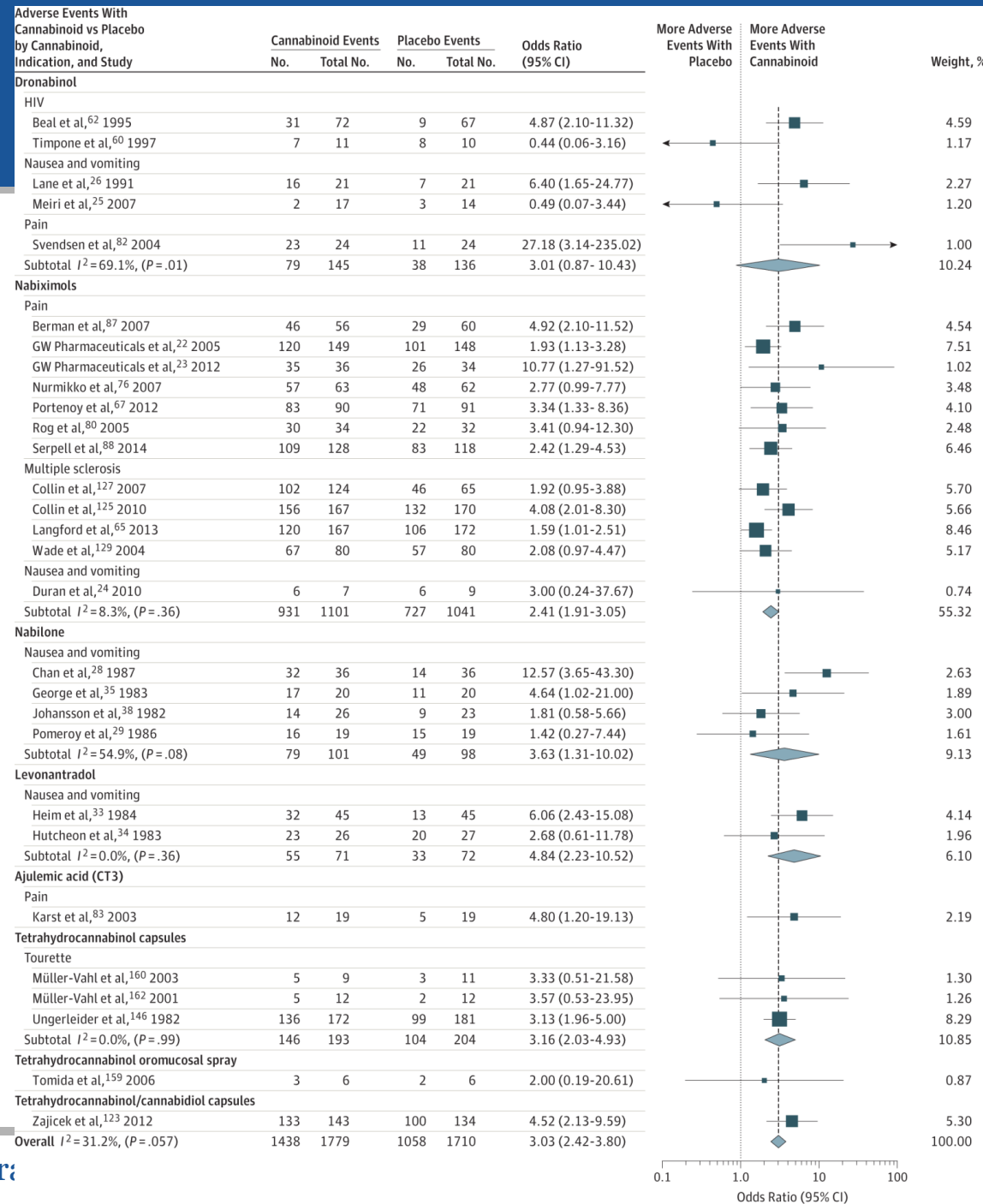
Susan Ball, Jane Vickery, Jeremy Hobart, Dave Wright, Colin Green, James Shearer, Andrew Nunn, Mayam Gomez Cano, David MacManus, David Miller, Shahrukh Mallik, and John Zajicek.

Headline

The study found that oral dronabinol did not slow down the progression of progressive multiple sclerosis. No major safety concerns were identified in the use of dronabinol.



Odds of Adverse Events



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



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 ^a	Percentage Difference in Age-Adjusted Opioid Analgesic Overdose Mortality in States With vs Without a Law		
	Primary Analysis	Secondary Analyses	
	Estimate (95% CI) ^b	Estimate (95% CI) ^c	Estimate (95% CI) ^d
Medical cannabis law	-24.8 (-37.5 to -9.5) ^e	-31.0 (-42.2 to -17.6) ^f	-23.1 (-37.1 to -5.9) ^e
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) ^e	-3.9 (-21.7 to 18.0)
Annual state unemployment rate ^g	4.4 (-0.3 to 9.3)	5.2 (0.1 to 10.6) ^e	2.5 (-2.3 to 7.5)

^a All models adjusted for state and year (fixed effects).

^b $R^2 = 0.876$.

^c 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; $R^2 = 0.873$.

^d Findings include all heroin overdose deaths, even if no opioid analgesic was

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

^e $P \leq .05$.

^f $P \leq .001$.

^g An association was calculated for a 1-percentage-point increase in the state unemployment rate.

Bachhuber MA et al. JAMA 2014



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?



State Level Variation

- Physician recommendation 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



Quiz Answers

1. Marijuana use is increasing. **T**
2. Withdrawal symptoms occur with marijuana cessation. **T**
3. No adverse health effects occur with marijuana use. **F**
4. You can't overdose on marijuana. **T**
5. Marijuana use disorders are treatable. **T**
7. Medical marijuana is approved for use nationwide. **F**



Conclusions

- Marijuana use and marijuana use disorders are prevalent
- Physicians should be aware of the potential physiologic implications of marijuana use
- Treatments are available for marijuana use disorders
- Medical marijuana and decriminalization and legalilzation policies differ statewide



Addiction is the elephant in the room....

Treat addiction



Reduce stigma

Save lives

Thank you

Questions?

Acknowledgements: several slides adapted from Dr. William Becker (Yale) and Dr. Hilary Kunins (CRIT), Dr. Jeffrey Hunt (Brown)

