

Marijuana: Clearing the Smoke on Clinical and Policy Issues

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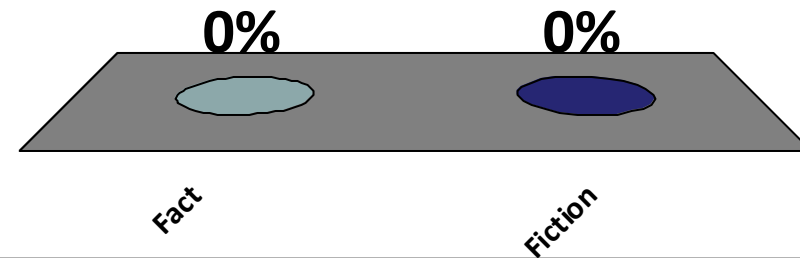
Yale University School of Medicine



Fact or Fiction?

Marijuana use is increasing.....

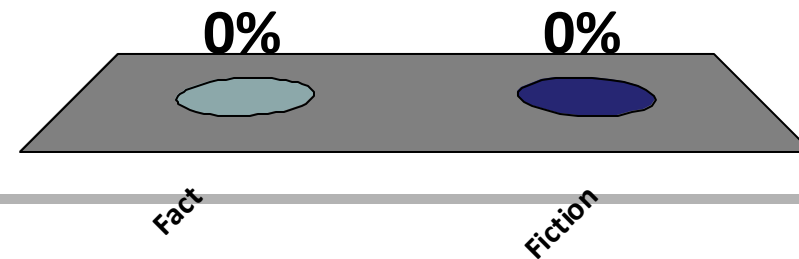
- A. Fact
- B. Fiction



Fact or Fiction?

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

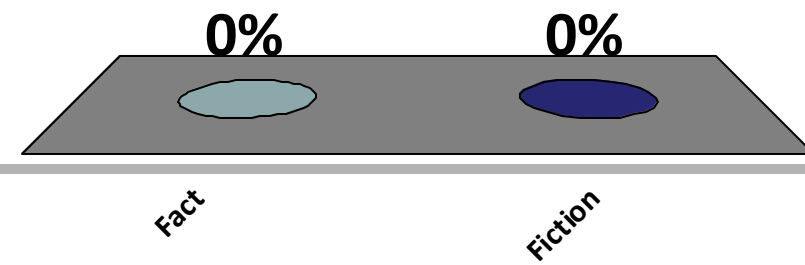
- A. Fact
- B. Fiction



Fact or Fiction?

Withdrawal symptoms occur with marijuana cessation.....

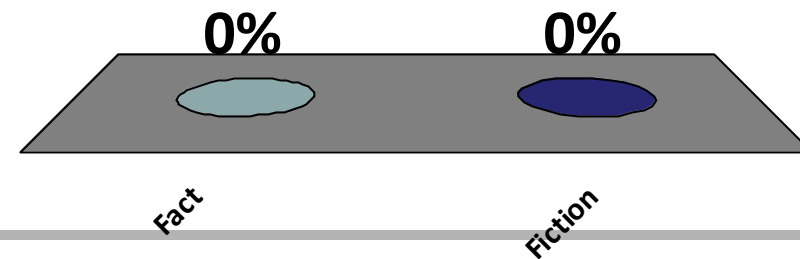
- A. Fact
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Fact or Fiction?

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

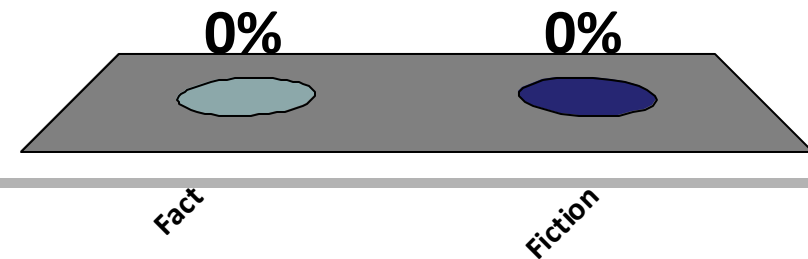
- A. Fact
- B. Fiction



Fact or Fiction?

Marijuana use disorders are treatable.....

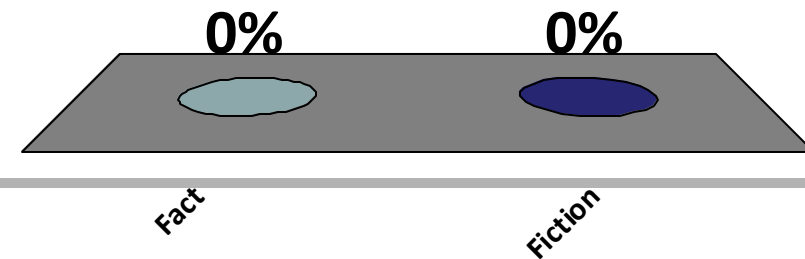
- A. Fact
- B. Fiction



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



Outline

- What is marijuana?
- Epidemiology and terminology
- U.S. *love-hate* relationship with marijuana
- Neurobiology
- Physiologic effects and other potential risks of marijuana use
- Treatment for marijuana use disorders
- Marijuana as medicine?

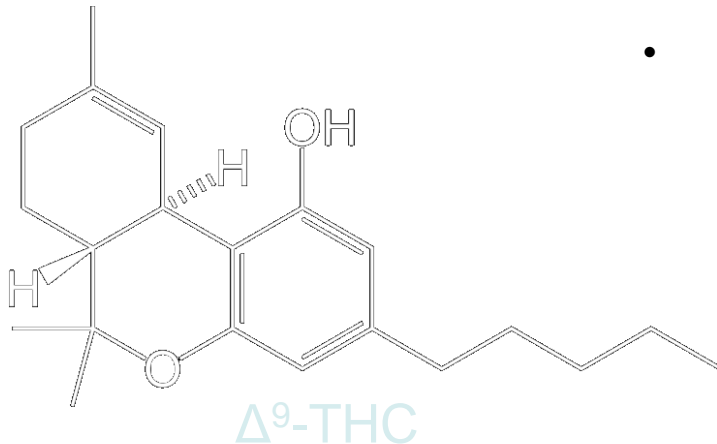


What is Marijuana?

- 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



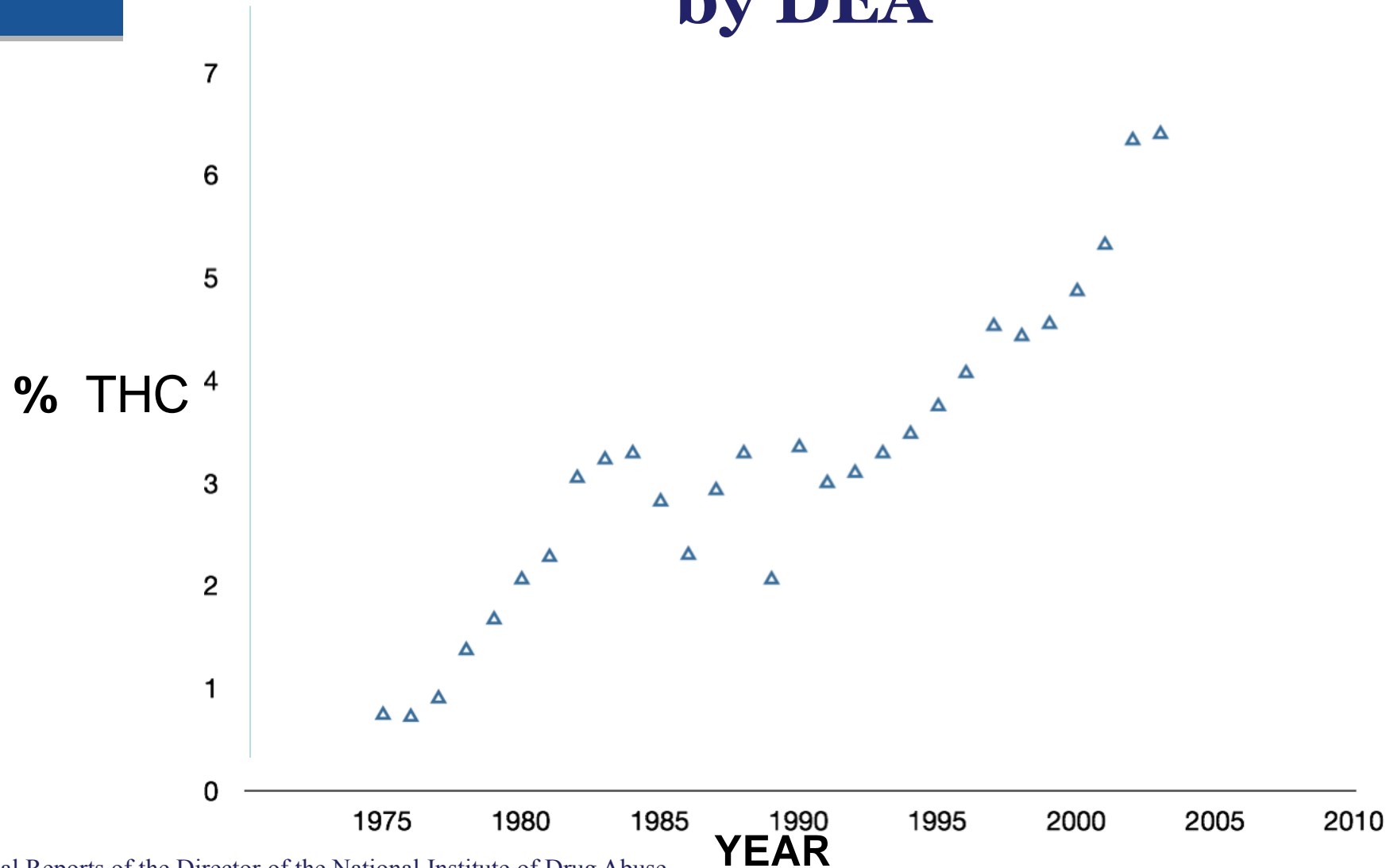
Δ^9 -TETRAHYDROCANNABINOL (THC)



- 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



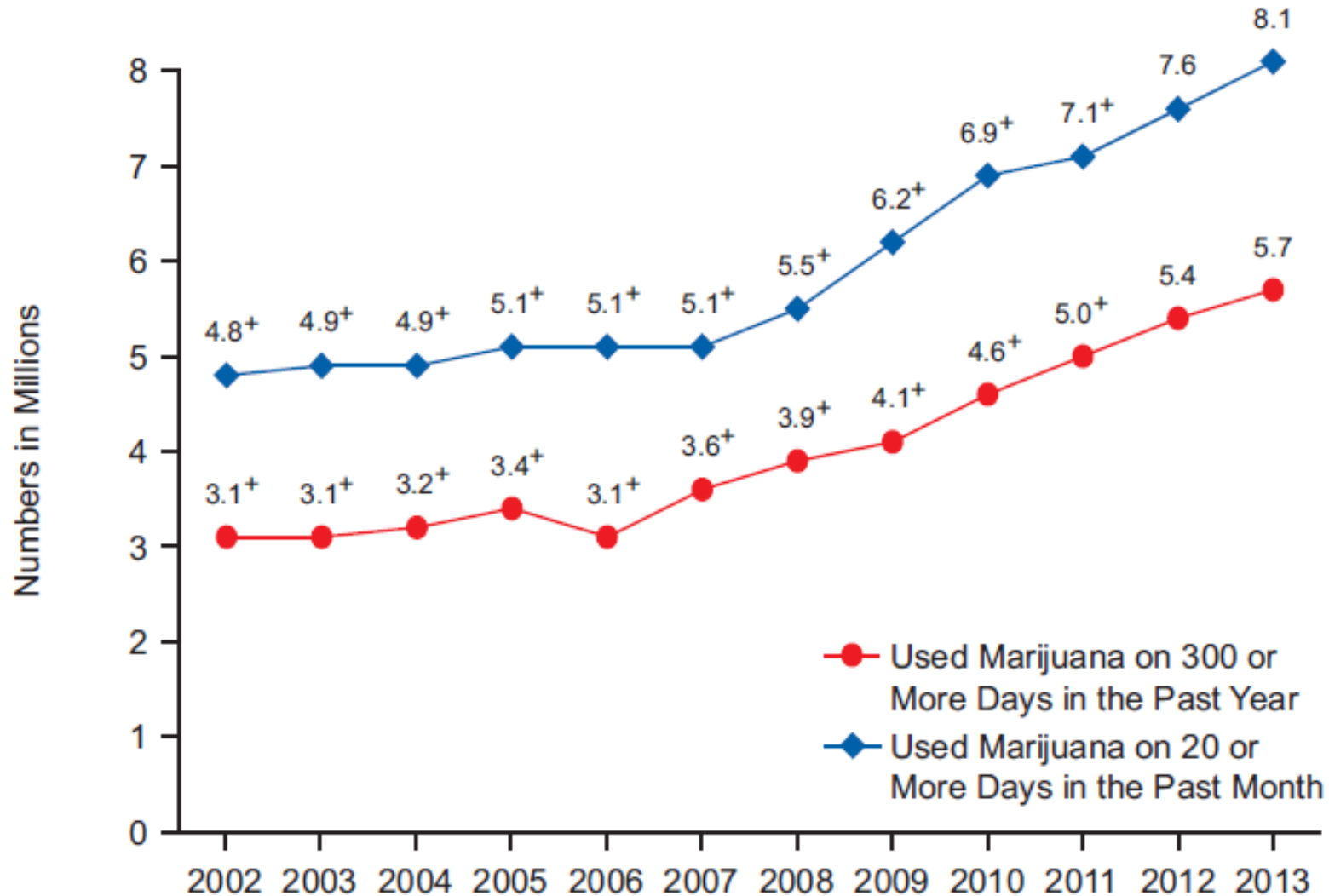
Percentage THC in Marijuana Seized by DEA



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



Density of Marijuana use age 17 or older

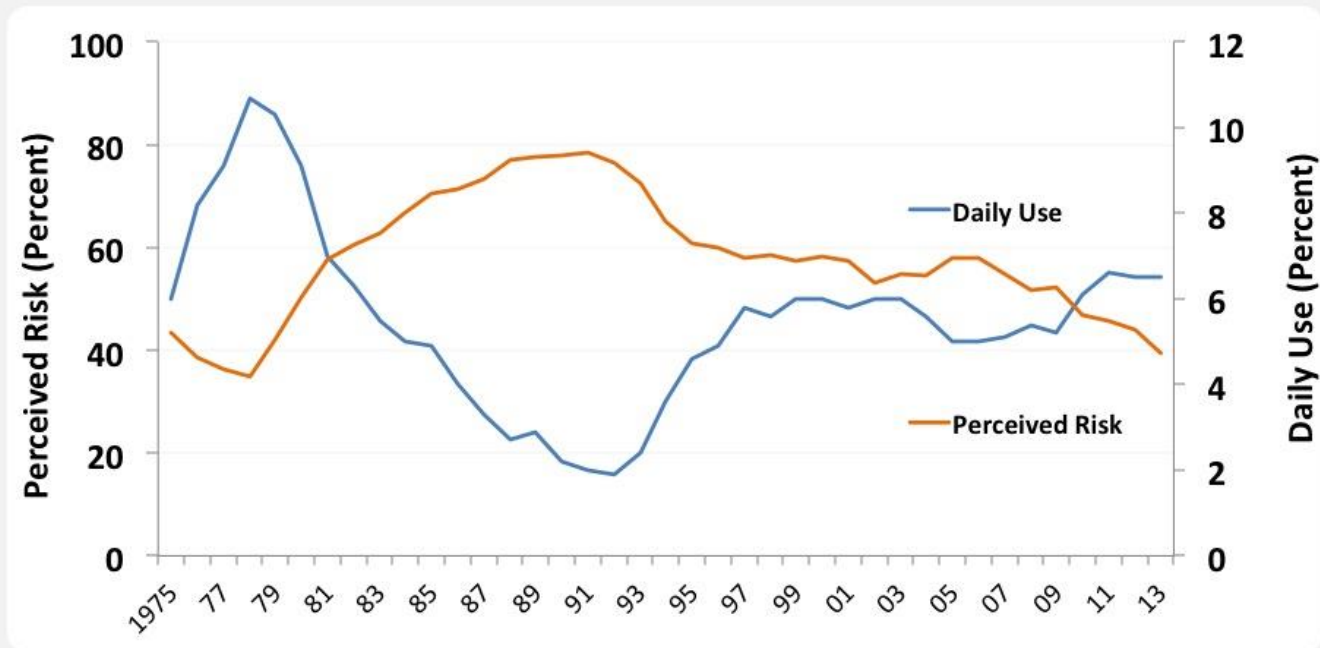


NSDUH 2013



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

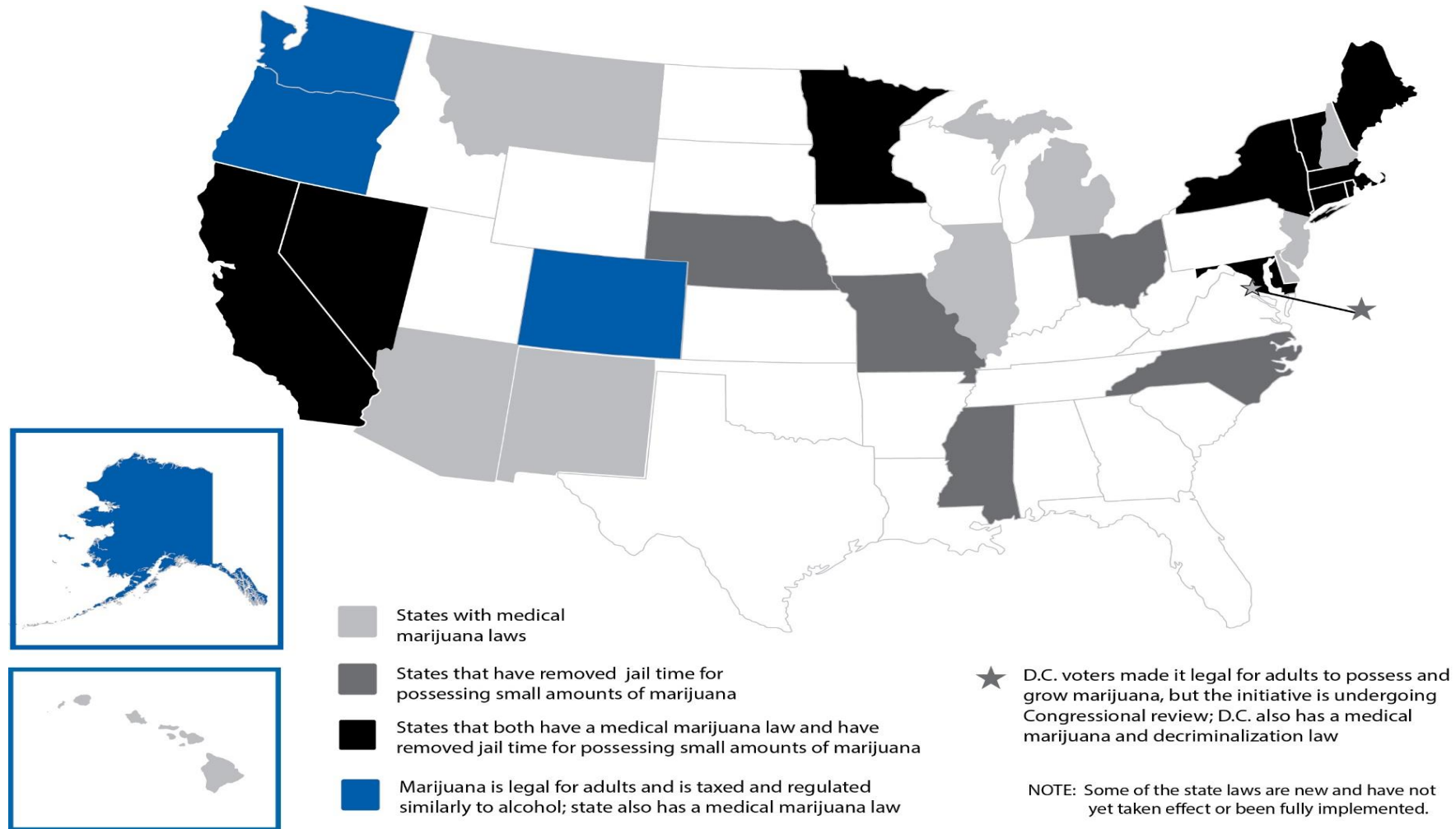


Policy timeline

- 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: CARERS 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?



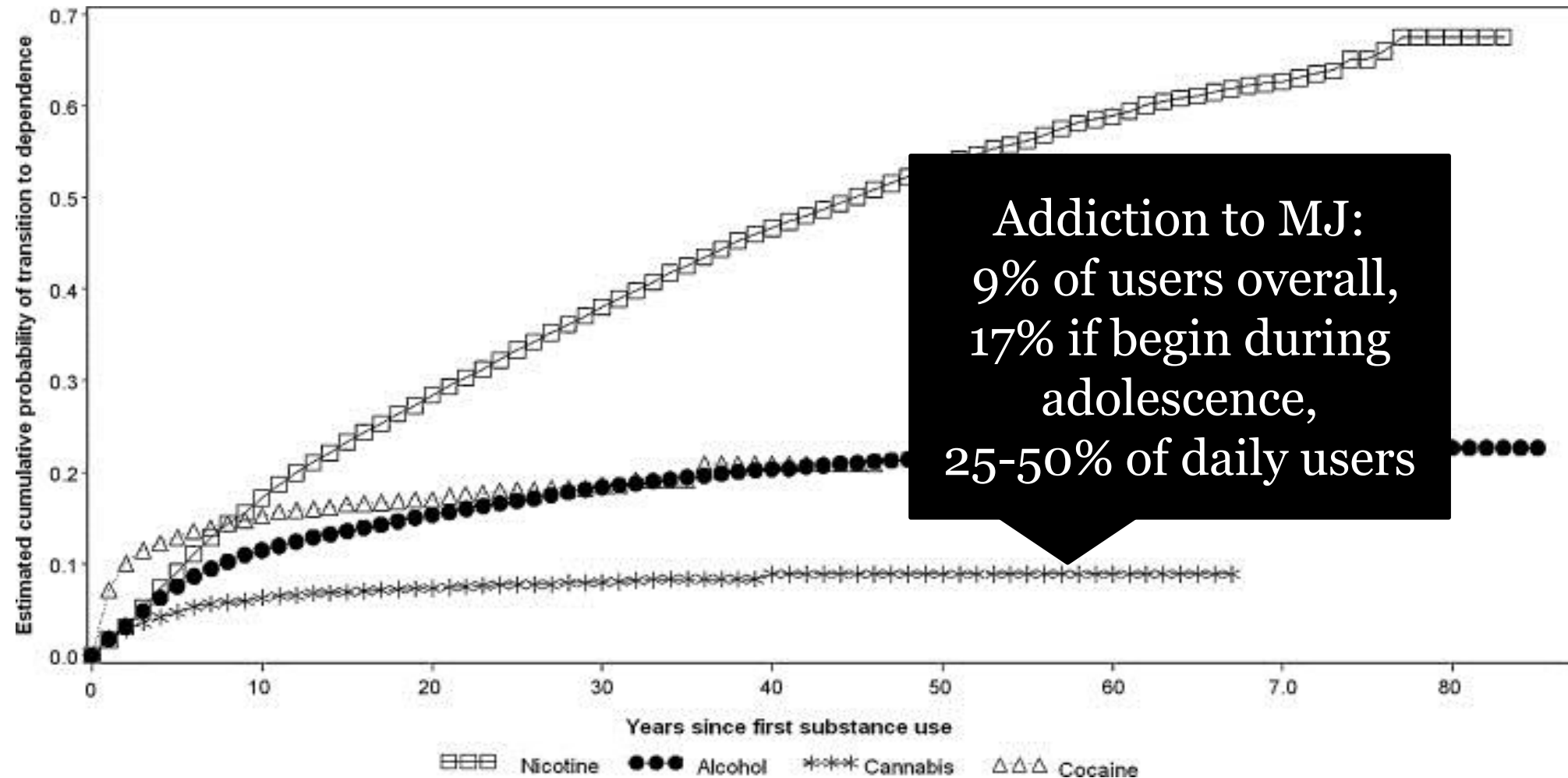
Adverse effects of marijuana use

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

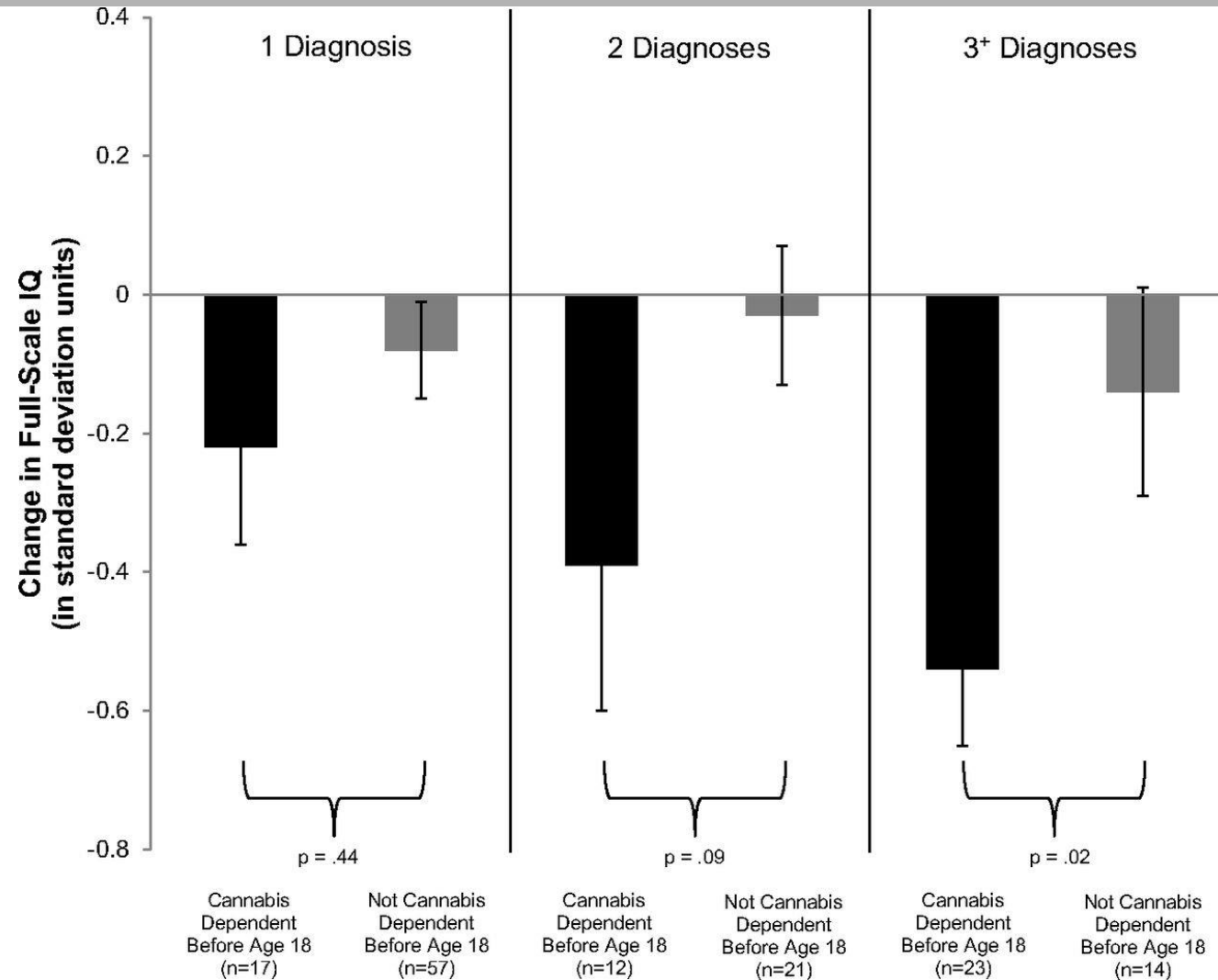


Addiction to MJ:
9% of users overall,
17% if begin during
adolescence,
25-50% of daily users

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



Adolescent vulnerability in IQ decline



Meier M H et al. PNAS 2012



Prevalence of psychiatric disorders among individuals who use marijuana

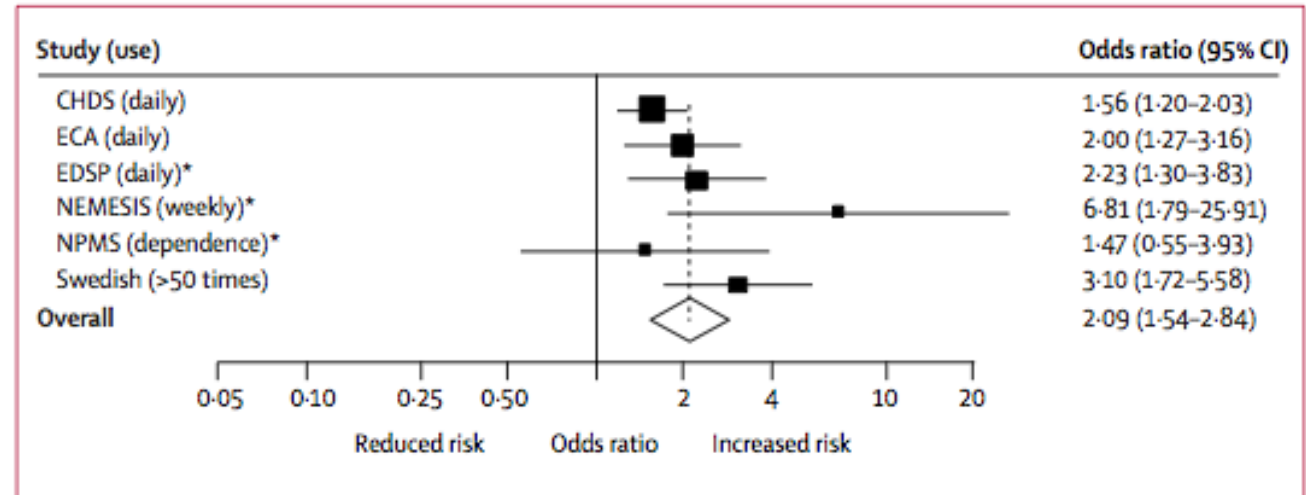
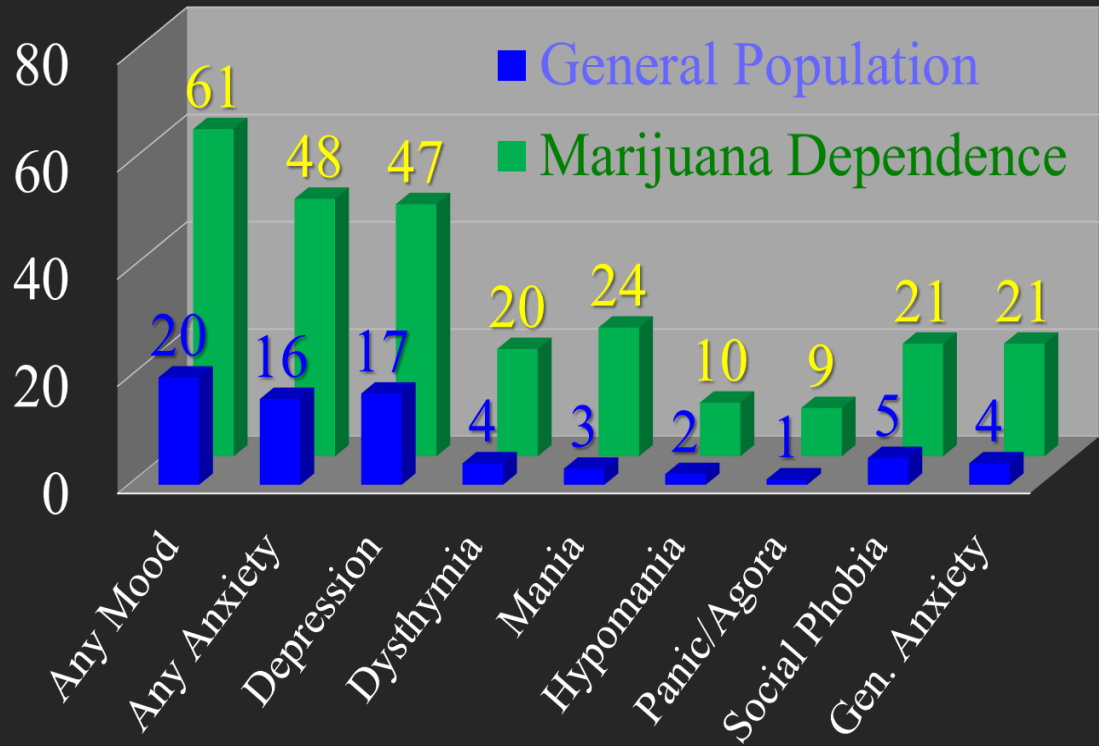
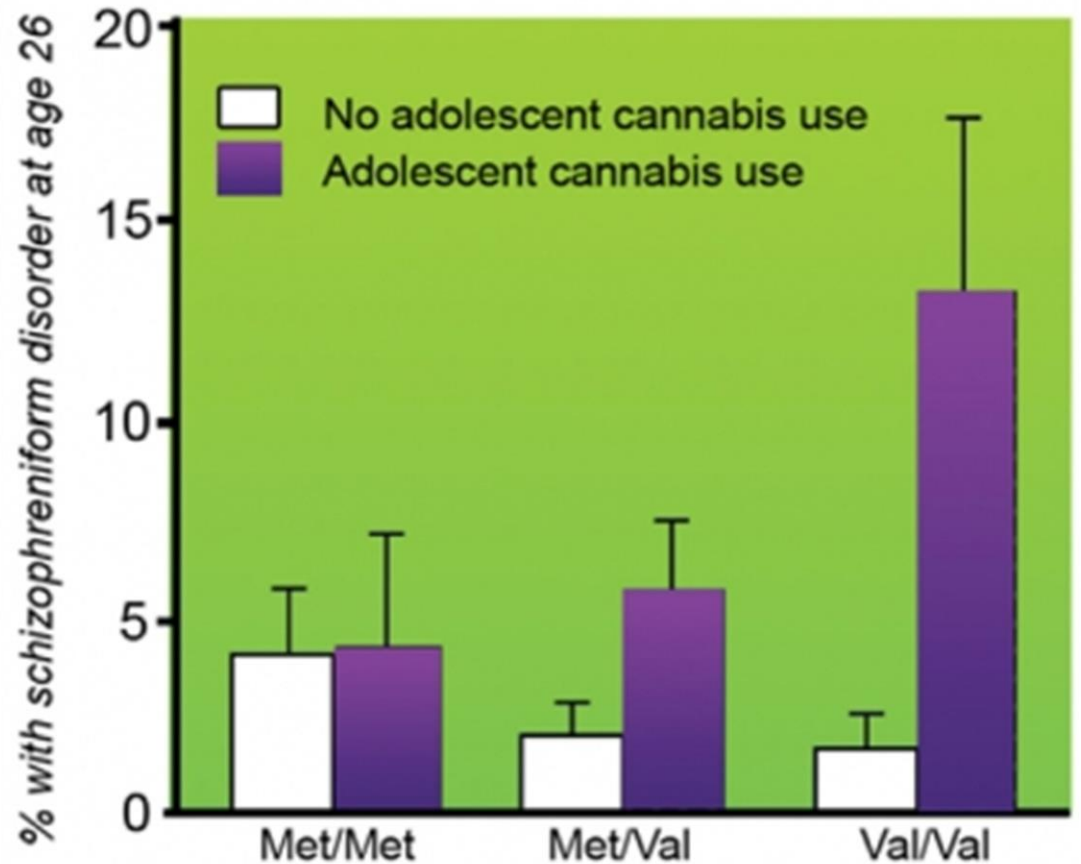


Figure 2: Forest plot showing adjusted odds ratios and 95% CI for any psychosis outcome according to most frequent use of cannabis in individual studies

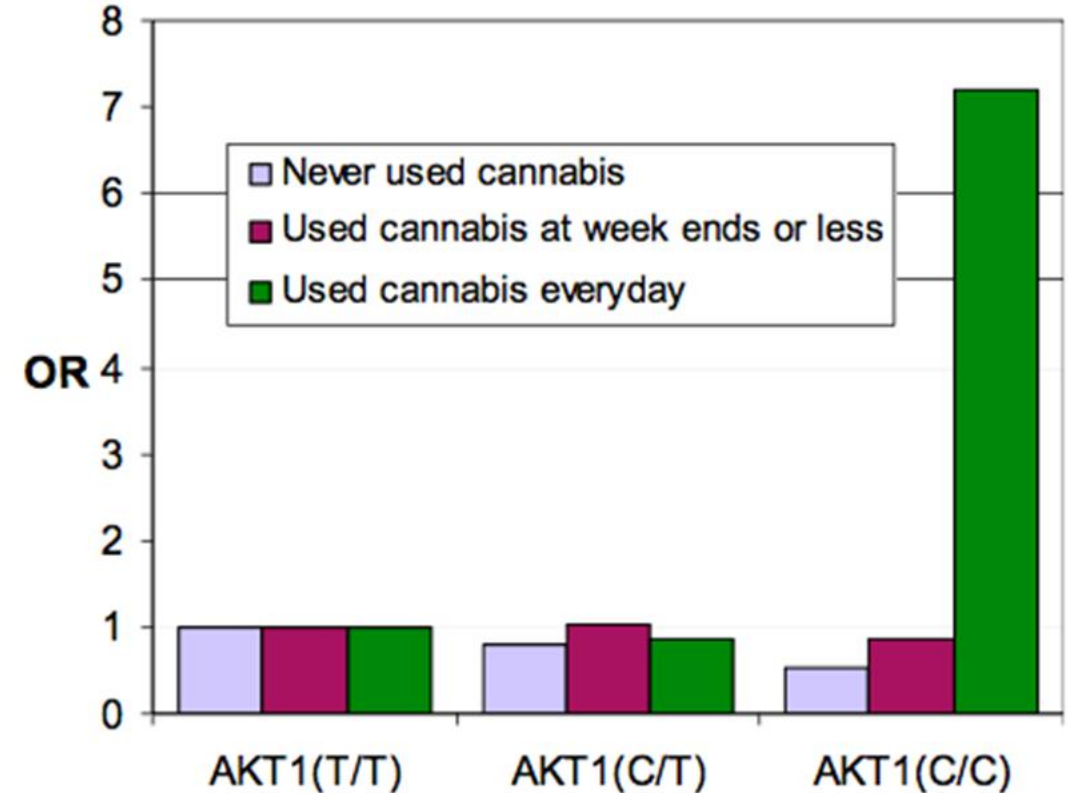
Conway 2006; Moore et al., Lancet 2007



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



Cannabis 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 Cannabis 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

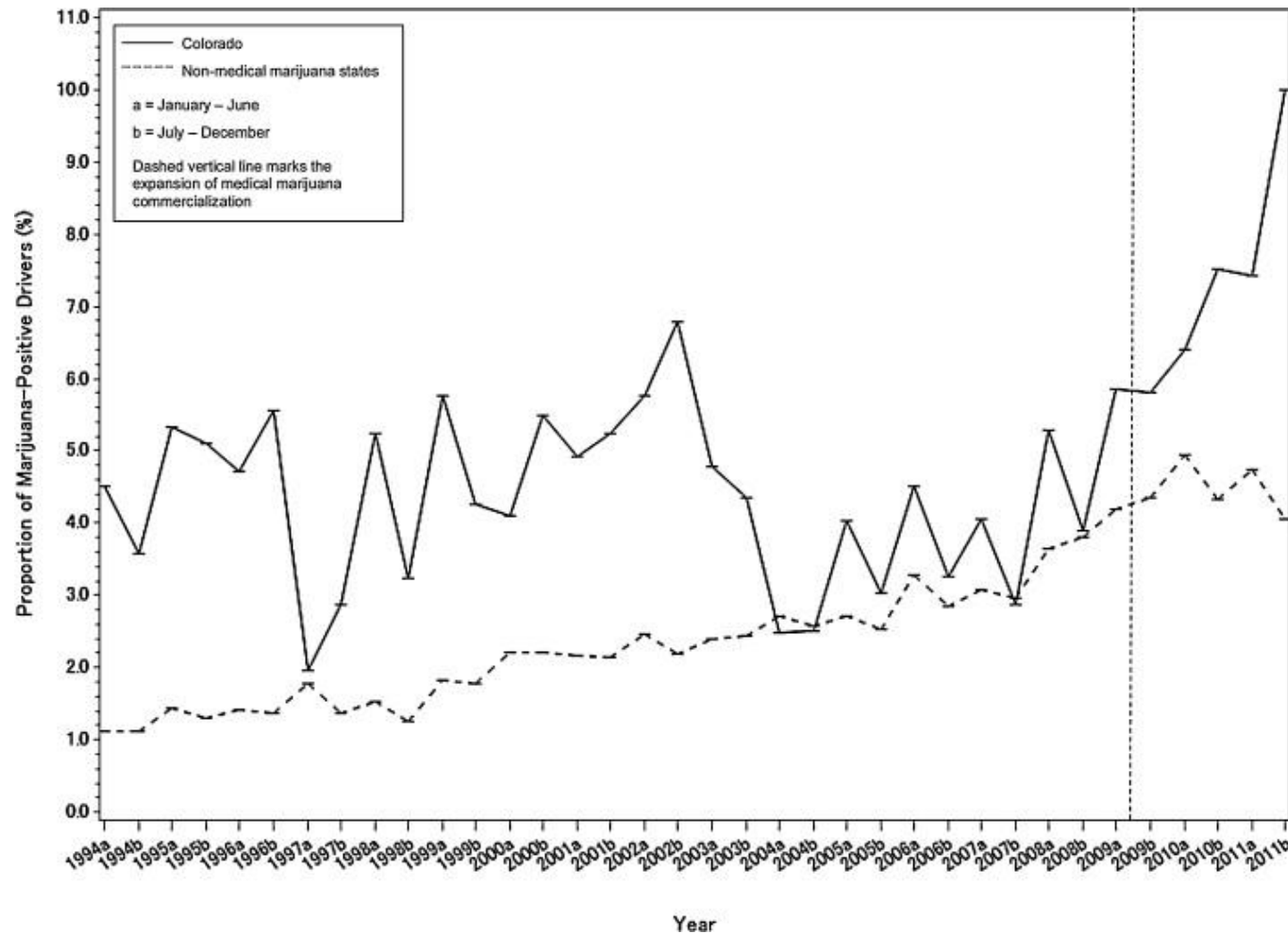
¹ Schepesis, T JAM, 2011

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



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

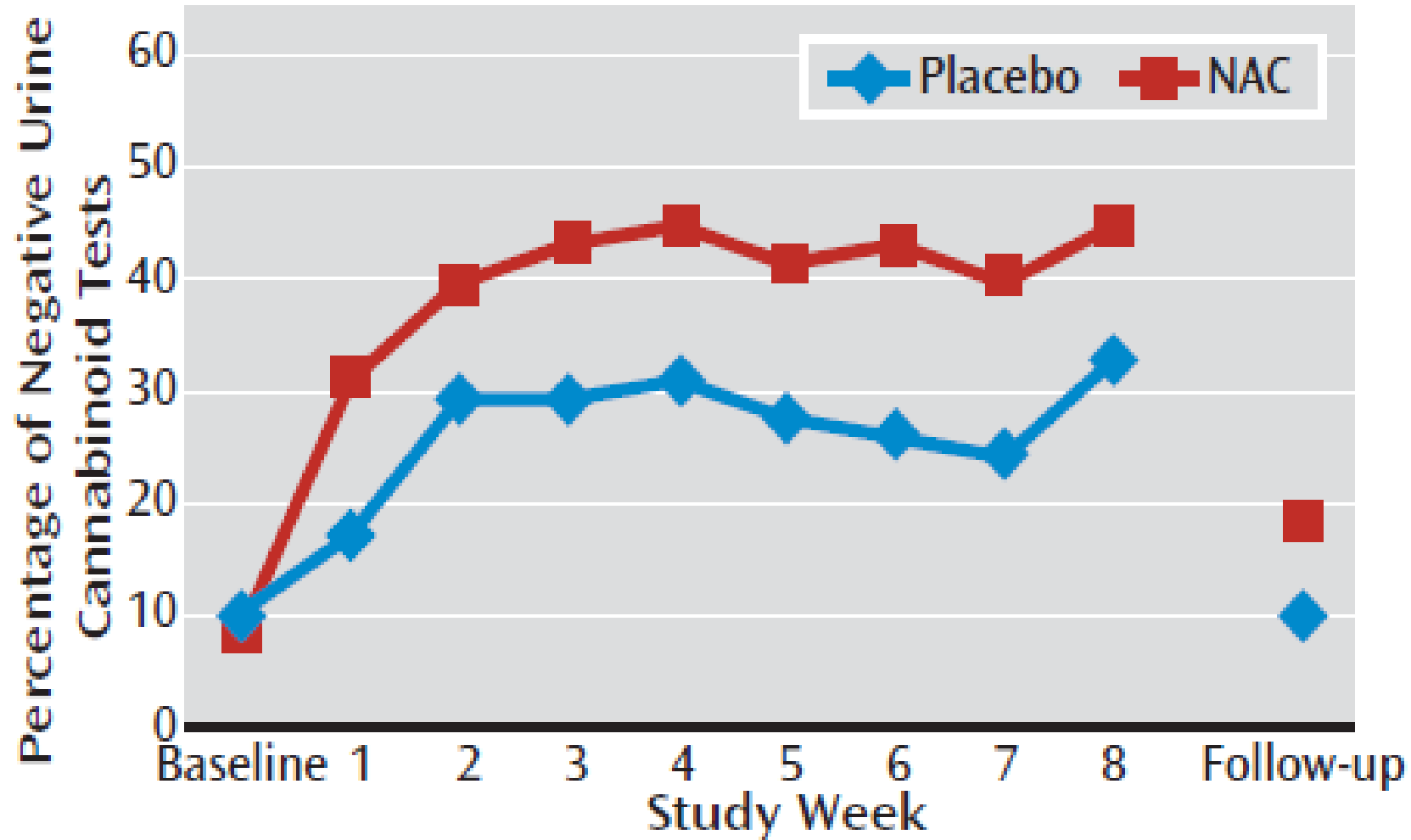


Treatment Options

- 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.



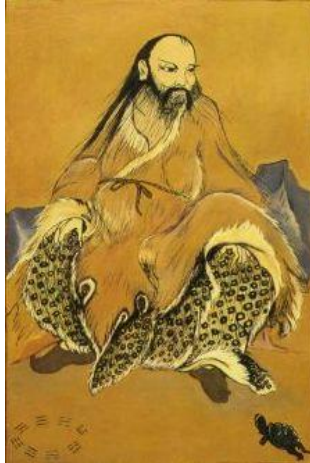
- General Information:
 - Marketed as safe legal alternative to marijuana; easily accessible; multiple names (Moon Rocks, Yucatan Fire) generally smoked; very common among adolescents
- Effects:
 - Mild euphoria and relaxation
 - The ‘giggles’
 - Increased sensitivity to external stimuli
 - Distortion 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



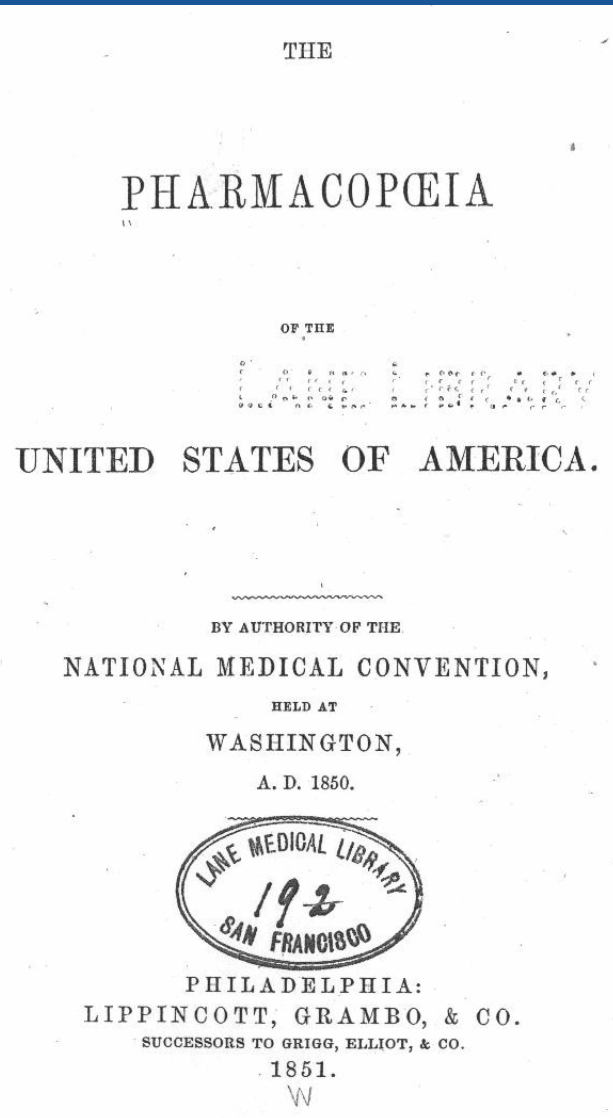
The Chinese Emperor Fu His (ca. 2900 BC) noted cannabis possessed both yin and yang.



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. Pharmacopeia 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. Pharmacopeia.

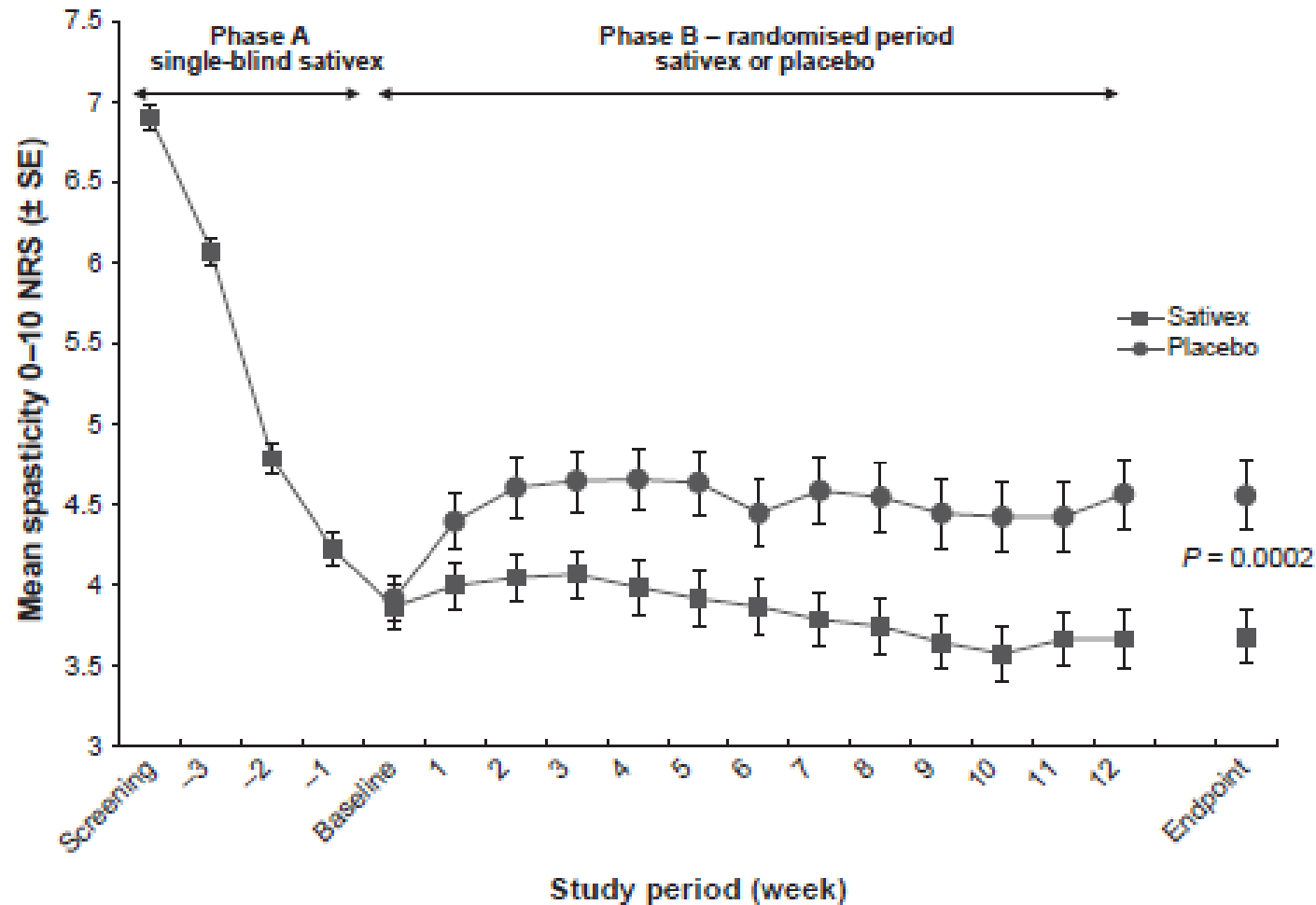


Review of clinical studies with cannabis and cannabinoids 2005-2009

Indication	# of studies	# of patients	Findings	# of studies of smoked MJ
Chronic pain or neuropathic pain	11	631	7 - improved symptoms 1 - worsened symptoms	2
Experimental pain	4	63	2- no effect 1-synergistic with opioids	1
Multiple sclerosis or spasticity	9	1300	5- improvement of spasticity or OAB or incontinence	0
HIV/AIDS	4	118	4-improved pain or caloric intake	4
Glaucoma	1	6	1- reduction of intraocular pressure	0
Intestinal dysfunction	2	82	2-decrease colonic motility	0
Nausea/vomiting/appetite	2	228	1-similar to ondansetron	0
Schizophrenia	2	55	1- reduce acute psychosis 1-increase symptoms	0
Other indications	2	80	2-sx improvement for pts with GBM, pts on IFN for HCV	1
Total	37	2563		



A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex[®]), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis



Novotna, et al. European Journal of Neurology 2011, 18: 1122-1131



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.



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



Thank you

Questions?

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



Extra Slides



Street Names for Marijuana and Other Terminology

- Pot
- Weed
- Mary-Jane
- Reefer
- Ganga
- Hash
- Chronic
- Green
- Wacky-tabacky
- Maui-wowy
- Joint
- Bong
- Blunt
- Roach
- Pipe
- Pot-brownies



Cardiovascular Complications

Characteristics	Total	Cardiac		Cerebral	Peripheral
		ACS	HRD		
N	35	20	2	3	10
Age (mean±SD)	34.3±8.8	35.5±9.0	32.5±13.4	25.3±3.1	35.2±8.0
Male	30	20	1	2	7
Exposure (A/R/D)	13/6/16	10/2/8	2/0/0	0/0/3	1/4/5
Cardiovascular history	9	4	0	0	5
Associated substances (as quoted in medical file)	24	12	1	2	9
Tobacco/alcohol	21/6	11/2	0/0	2/2	8/2
None declared	11	9	1	0	1
Cocaine	1	1	0	0	0
Benzodiazepine	1	0	1	0	0
Ecstasy	1	0	0	0	1
Lysergic acid diethylamide (LSD)	1	0	0	0	1
Hospitalization, n (mean duration in days)	18 (15)	10 (20)	0 (0)	3 (2)	5 (9)
Death	9	8	1	0	0



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.

