Marijuana: Clearing the Smoke on Clinical and Policy Issues

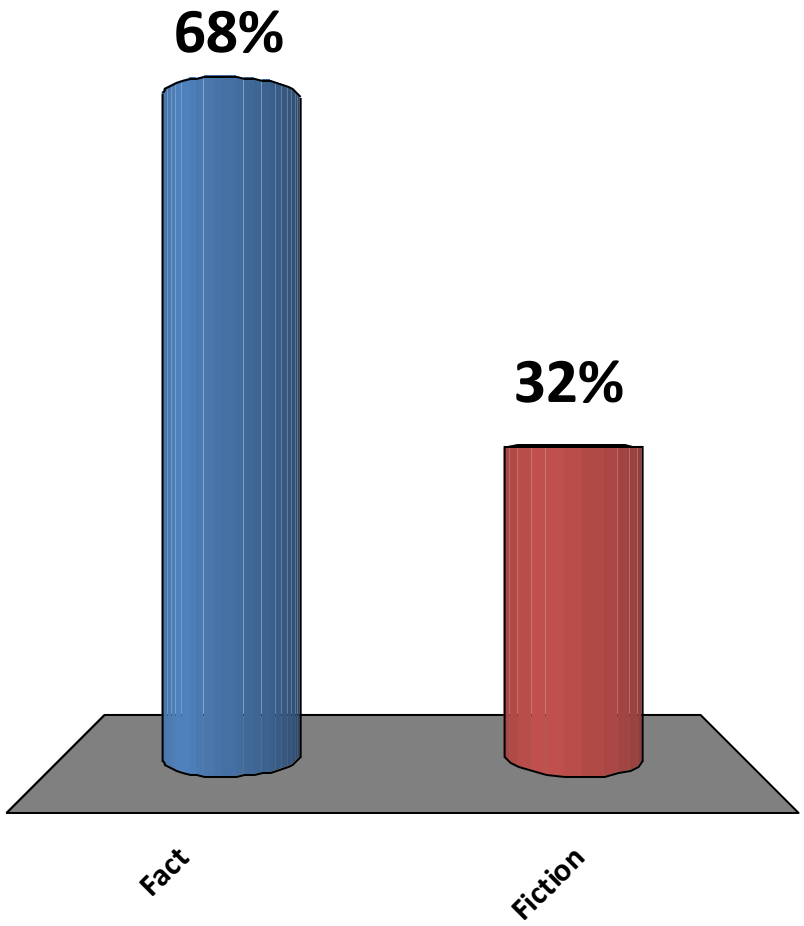
Jeanette M. Tetrault, MD FACP
Assistant Professor of Medicine
Yale University School of Medicine

Fact or Fiction?

Marijuana use is increasing…..

A. Fact

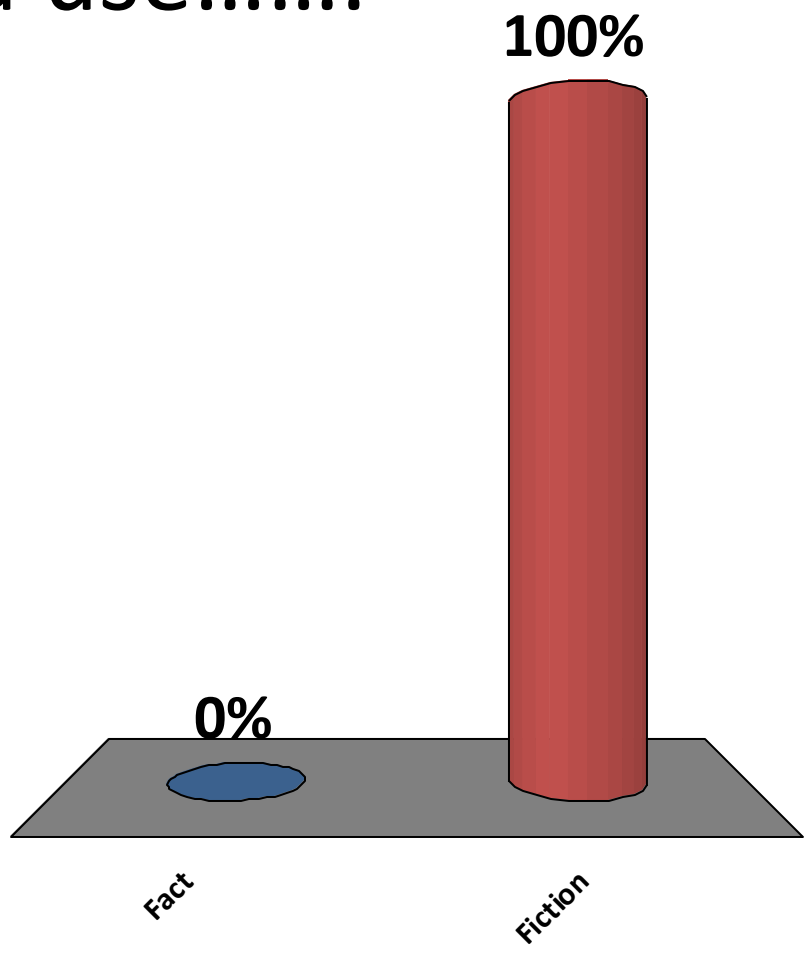
B. Fiction



Fact or Fiction?

No adverse health effects occur with marijuana use…….

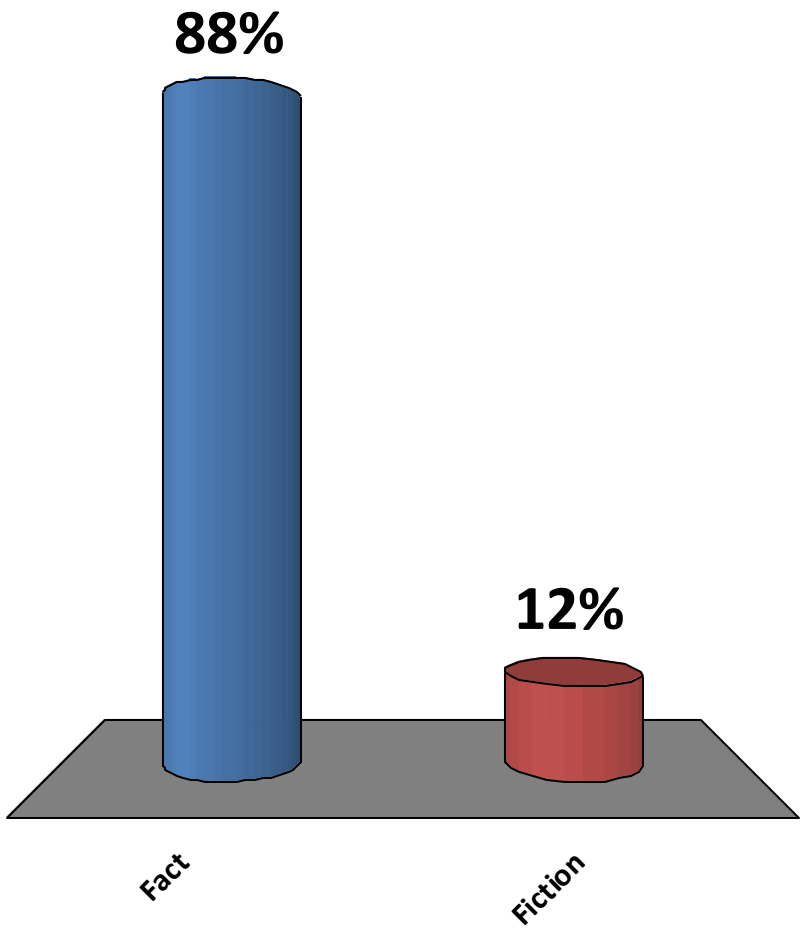
A. Fact
B. Fiction



Fact or Fiction?

Withdrawal symptoms occur with marijuana cessation……

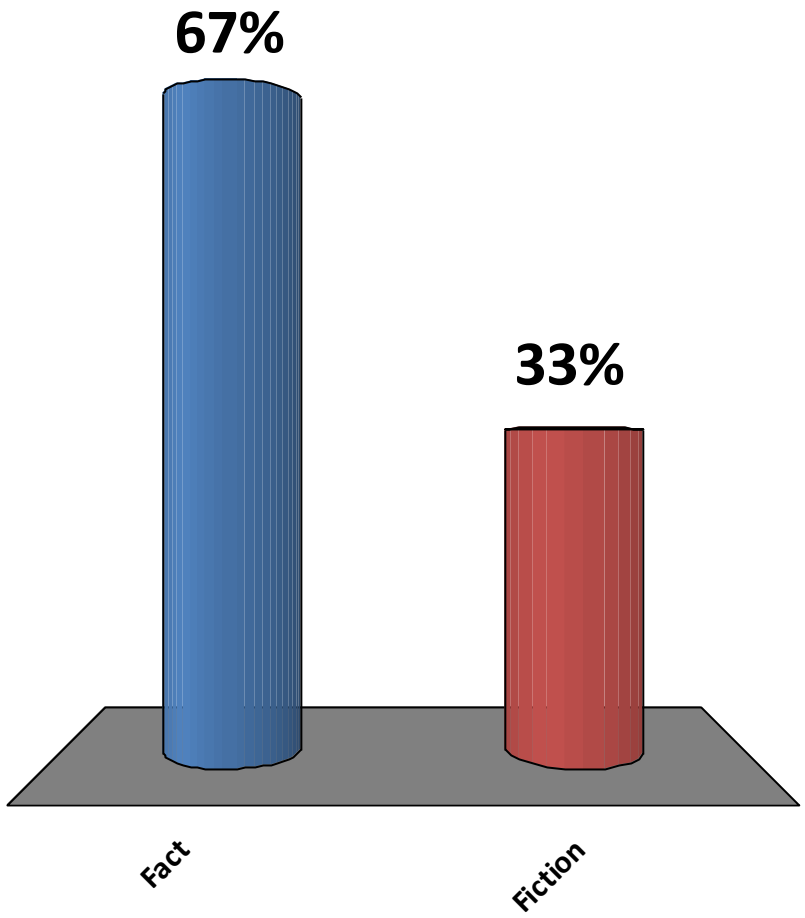
A. Fact
B. Fiction



Fact or Fiction?

You can’t overdose on marijuana……..

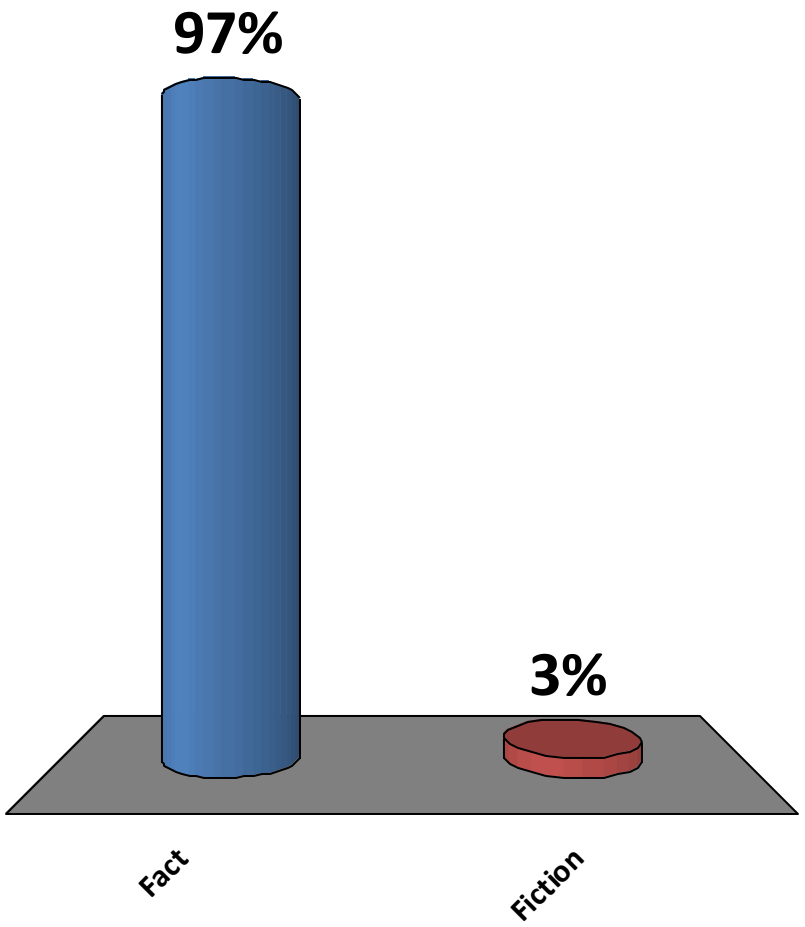
A. Fact
B. Fiction



Fact or Fiction?

Marijuana use disorders are treatable…….

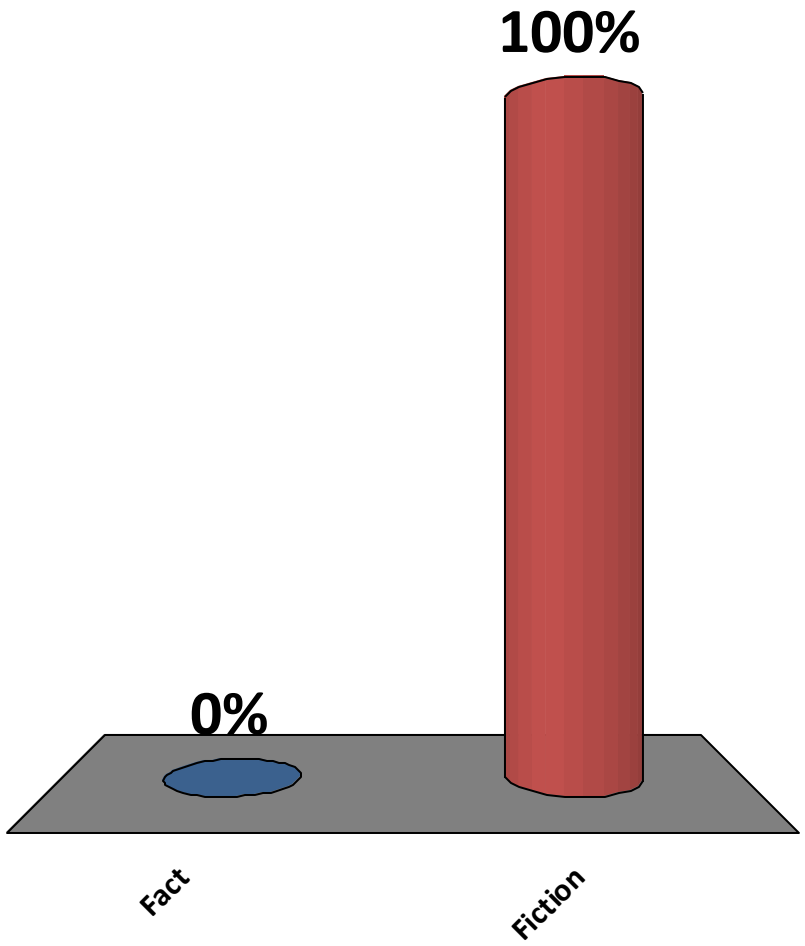
A. Fact
B. Fiction



Fact or Fiction?

Medical marijuana is approved for use nationwide……

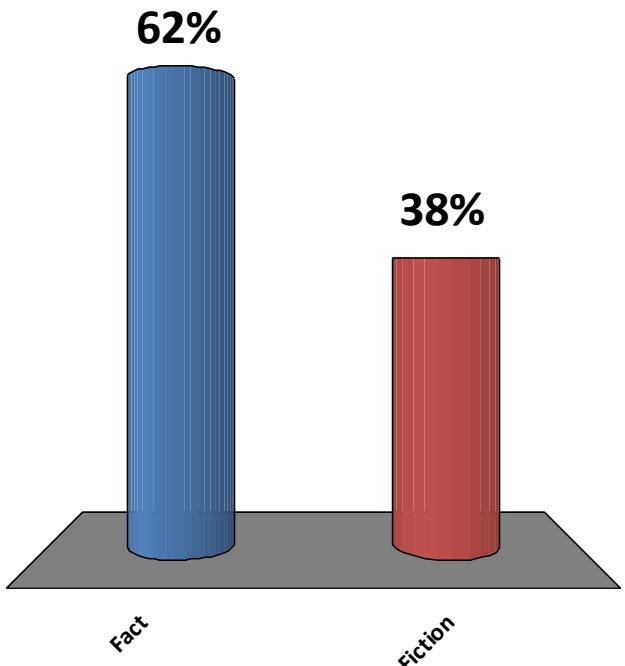
A. Fact
B. Fiction



Fact or Fiction?

There is an association between a state's legalization of recreational marijuana use and advancement of that state's football team to the super bowl……..

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

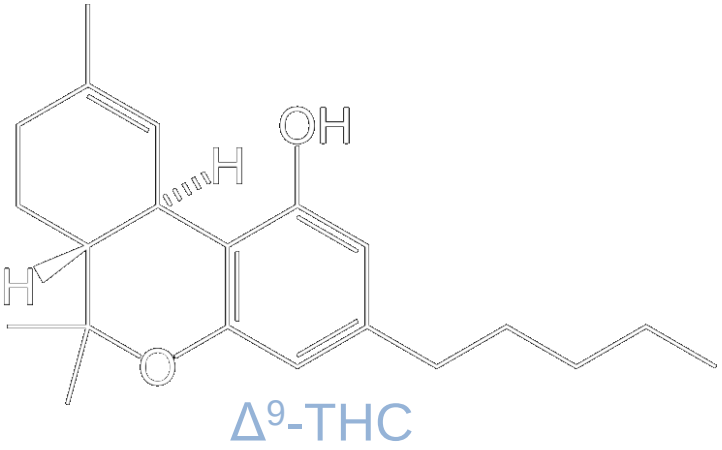
Outline

- 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
- Evidence for and against medical use of marijuana

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 Δ9-tetrahydrocannabinol (THC) and route of administration

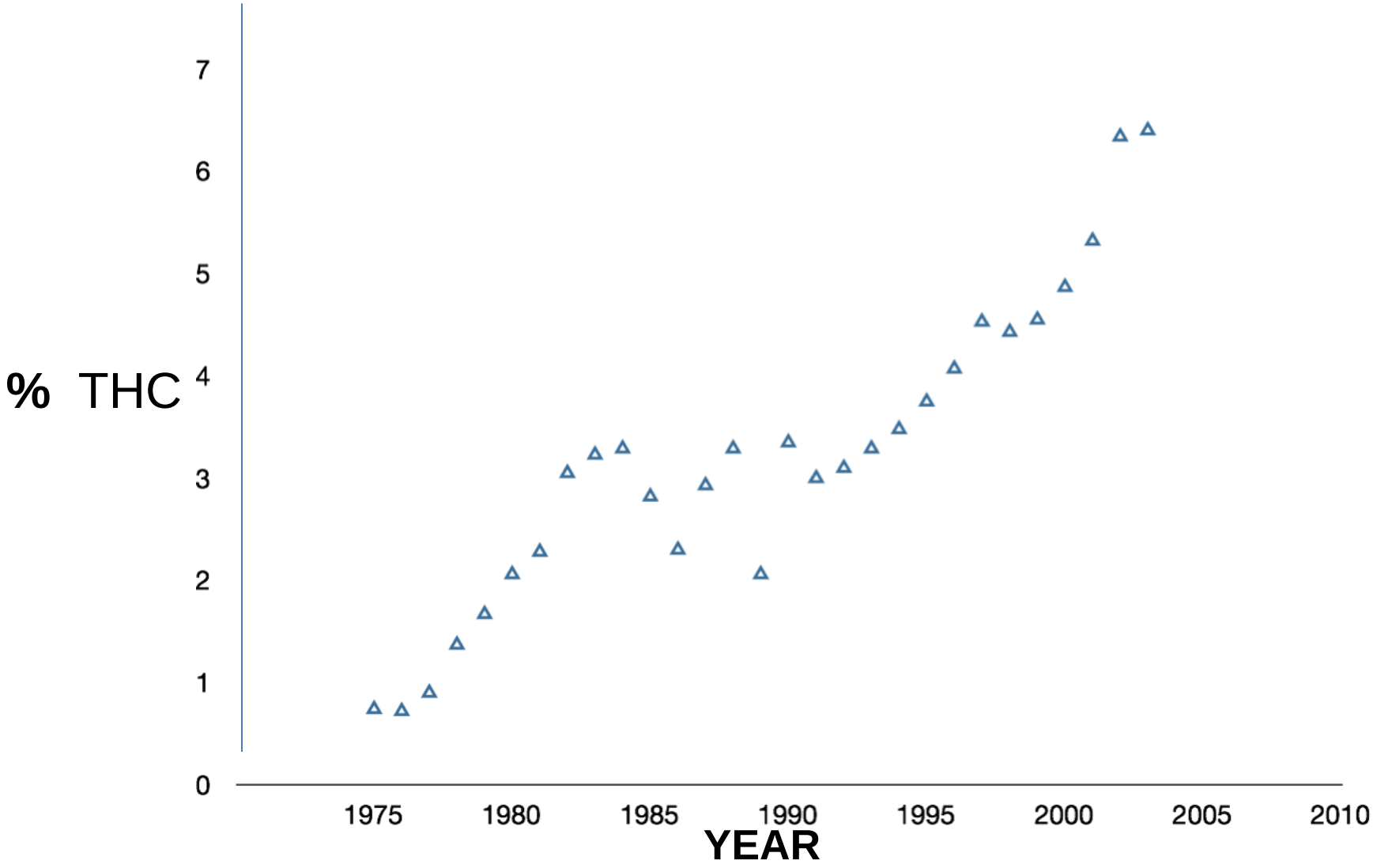
Δ^9-TETRAHYDROCANNABINOL (THC)



Δ^9-THC

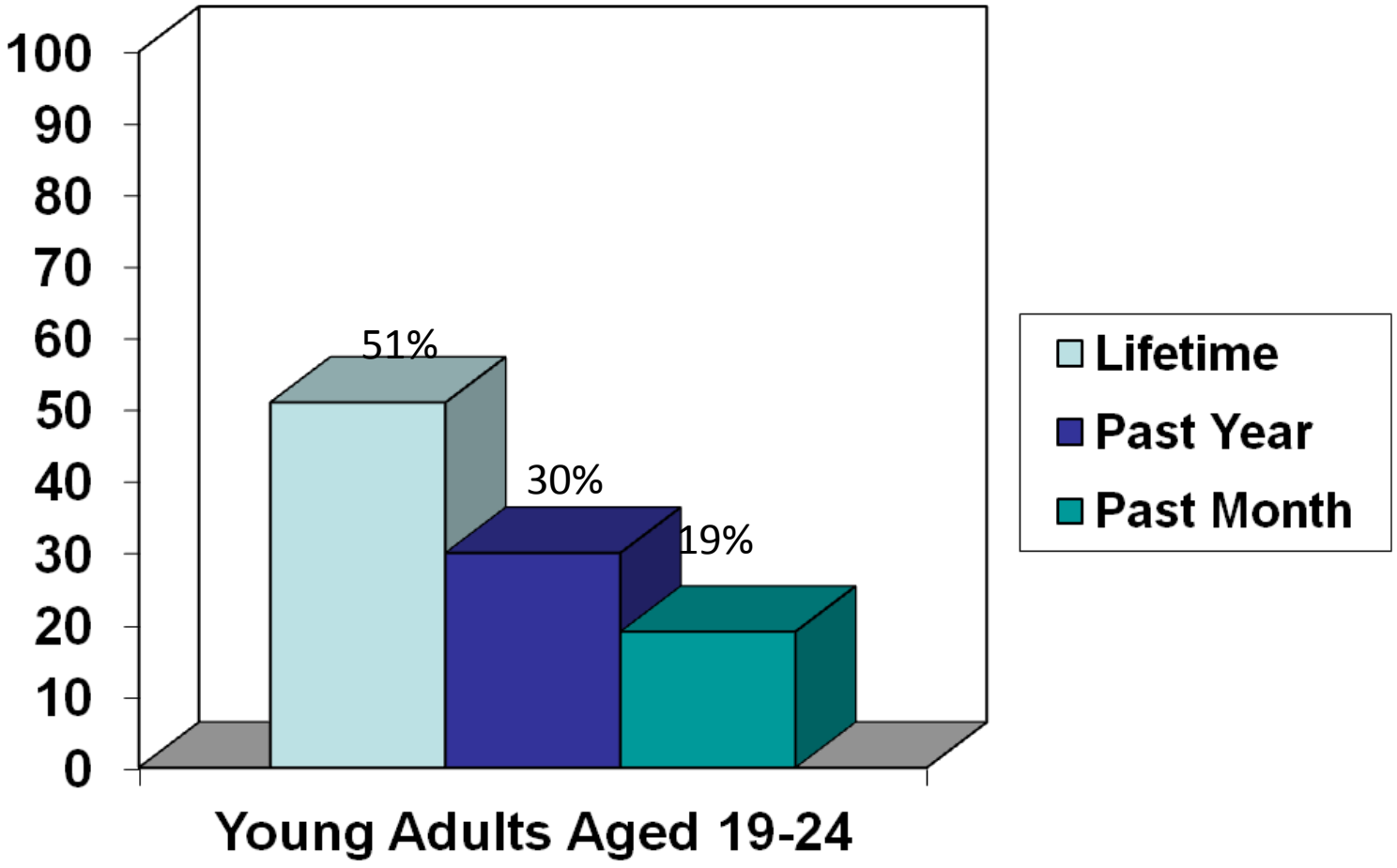
- Psychoactive ingredient in *Cannabis sativa*
- Synthetic form is active ingredient of Marinol, approved in 1985 for intractable nausea
- 70+ other cannabinoids, many of which are present to varying degrees in a single C. sativa plant; some non-THC cannabinoids *may* have medical use

Percentage THC in Marijuana Seized by DEA



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

U.S. Marijuana Use-NSDUH 2010



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

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

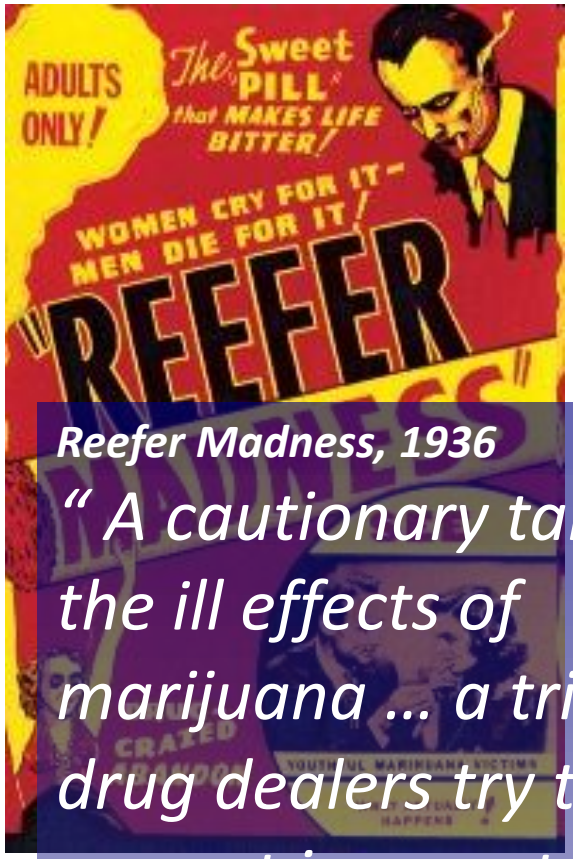
Cannabis Use Disorder, Cont'd

- 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

- 1937: Marijuana Tax Act - taxes use/possession
- Growing use 1950's by beat & jazz artists
- 1970: Controlled Substances Act passed by Congress, marijuana listed as schedule I *(i.e. no currently accepted medical use, high potential for abuse, and a lack of accepted safety even under medical supervision; limits ability to study effects)*
- 1970's widespread use; 10 states decriminalize
- 1980's "Say no to drugs," severe penalties for trafficking

US *Love-Hate* Relationship

- 1985: Marinol (synthetic THC) approved in the US for treatment of intractable nausea
- 1996: California first state to legalize medical marijuana
- 1997-2012: 18 more states + DC legalize *medical* marijuana (AK, AZ, CO, CT, DE, HI, ME, MI, MT, NV, NJ, NM, OR, RI, VT, WA); 2 legalized *recreational* use (CO, WA)
- January 1, 2014: CO opens first Marijuana shop

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 ½ PPD for two years. His mother expresses concern over his daily marijuana use.
- Should she be concerned? What should you say?

Physiologic Effects of Cannabinoids

- Neuropsychiatric
  - Mood
  - Memory
  - Cognition
  - Behavior
- Pulmonary
  - Lung function
- Cardiac
- Reproductive

- Gastrointestinal
  - Cannbinoid hyperemesis
- Oncologic risk
- Other
  - Hunger
  - Anti-nociception
  - ↓ Intra-ocular pressure
  - Immunosuppresion

Effect on Cognition

TABLE 4. Regression coefficients (β) indicating relative differences in Mini-Mental State Examination (MMSE) score change between wave 2 (1982) and wave 3 (1993–1996), by level of cannabis use, in four regression models, Baltimore Epidemiologic Catchment Area study follow-up†

Level of cannabis use	Model 1 (cannabis use)		Model 2 (cannabis use plus use of alcohol and tobacco)		Model 3 (cannabis use plus age, gender, minority status, and education)		Model 4 (cannabis use plus age, gender, minority status, education, and use of alcohol and tobacco)	
	β	SE‡	β	SE	β	SE	β	SE
Nonusers§								
Light users	0.28*	0.15	0.22	0.15	–0.001	0.16	–0.02	0.17
Light users plus use of drugs	0.25	0.19	0.17	0.19	–0.07	0.19	–0.10	0.19
Heavy users	0.35*	0.18	0.27	0.19	0.08	0.20	0.05	0.20
Heavy users plus use of drugs	0.81	0.71	0.66	0.71	0.79	0.70	0.69	0.70

* $p < 0.10$.

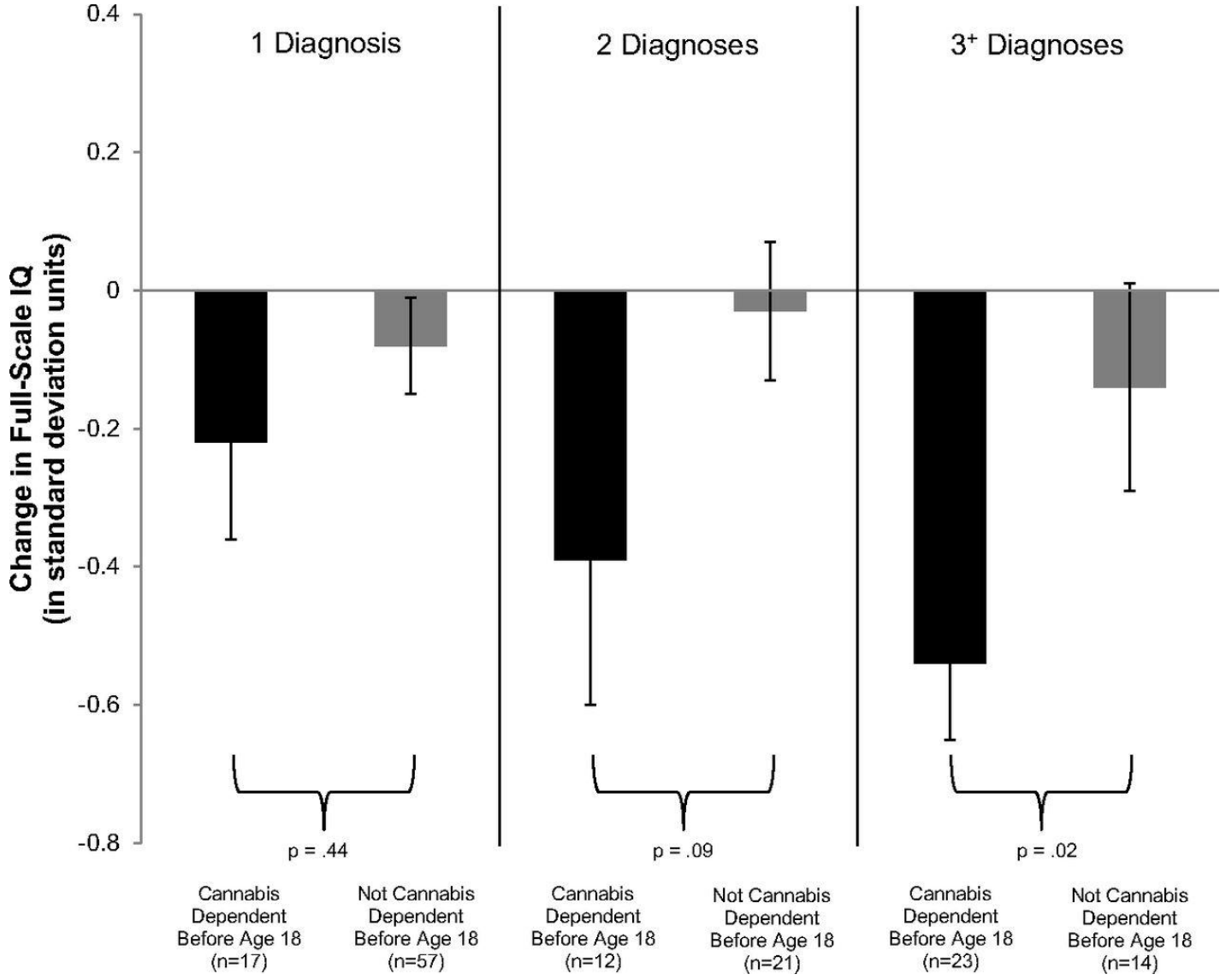
† Positive numbers indicate MMSE score increases relative to the reference group; negative numbers indicate relative decreases in MMSE score.

‡ SE, standard error.

§ Reference group.

Lyketsos CG, Am J Epidemiol 1999

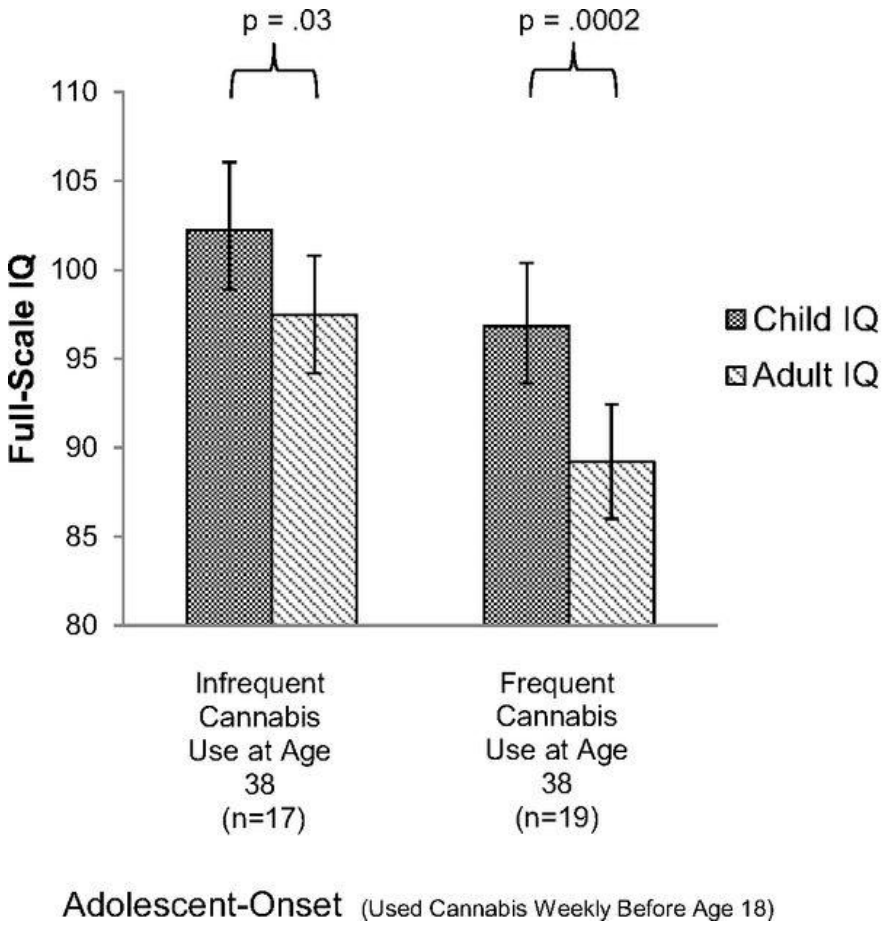
Adolescent Vulnerability in IQ Decline

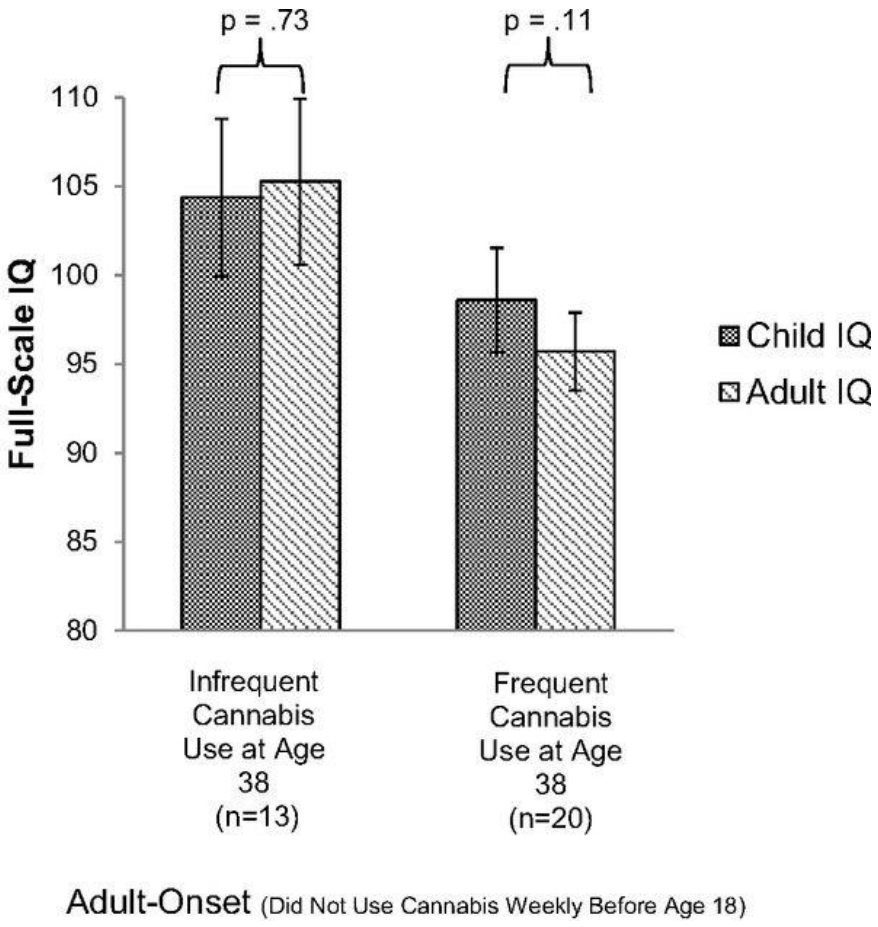


Meier M H et al. PNAS 2012

PNAS

Post-cessation IQ among Former Persistent Cannabis Users



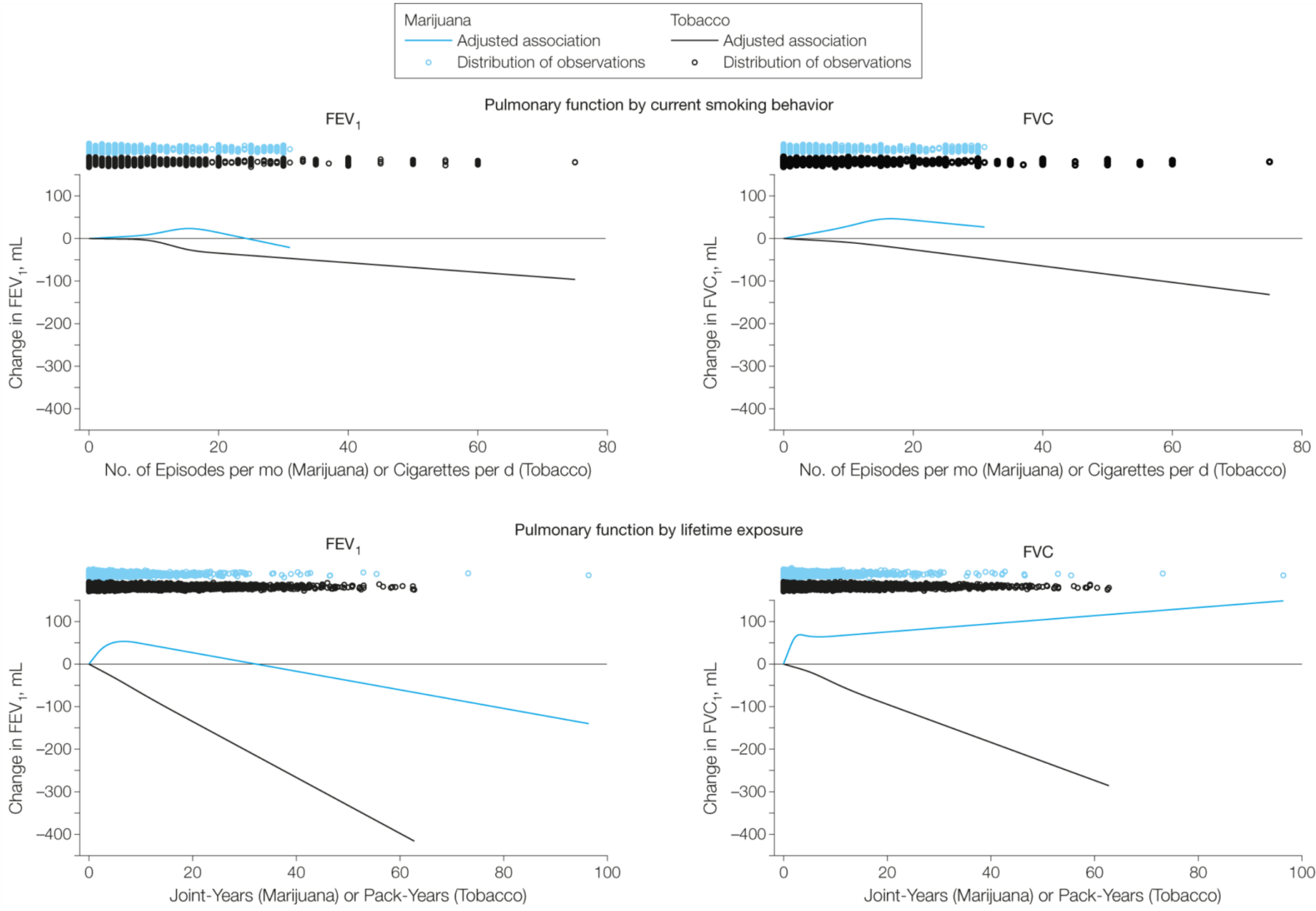


Meier M H et al. PNAS 2012

Pulmonary Effects of Smoked Marijuana

- Acute → bronchodilation (FEV_1 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_1 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



Pletcher MJ. JAMA. 2012;307(2):173-181.

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

Jouanjis, E et al. J Amer Heart Assoc 4/23/14

Cannabis and Cancer Risk

- Evidence for histopathologic changes supporting the biologic plausibility of an association of marijuana smoking with lung cancer (1)
- 2-fold increased risk of lung CA among chronic, habitual marijuana users in a 40 year cohort study
  - Adjusted for tobacco use, alcohol use, respiratory conditions, and SES (2)

1 Mehra R Archives of Int Med. 2007
2 Callaghan RC Cancer causes and control. 2012

Other Risks with Cannabis Use

- Cannabis use may lead to cannabis use disorder
  - Telescoping: Occurs more rapidly in females (1)
- 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] Schepsis, T JAM, 2011

[2] Sullivan LE, Journal of Adolescent Health 2013

[3] Asbridge M, BMJ, 2012

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 and possibly cancer
- Of concern, regular marijuana use may lead to more serious disorders, use of other illicit substances, and poorer driving skills

Fundamental tension

Well-known harms:

- Marijuana use disorders: **3.5% of all U.S. residents 12 and over** (NSDUH 2008)

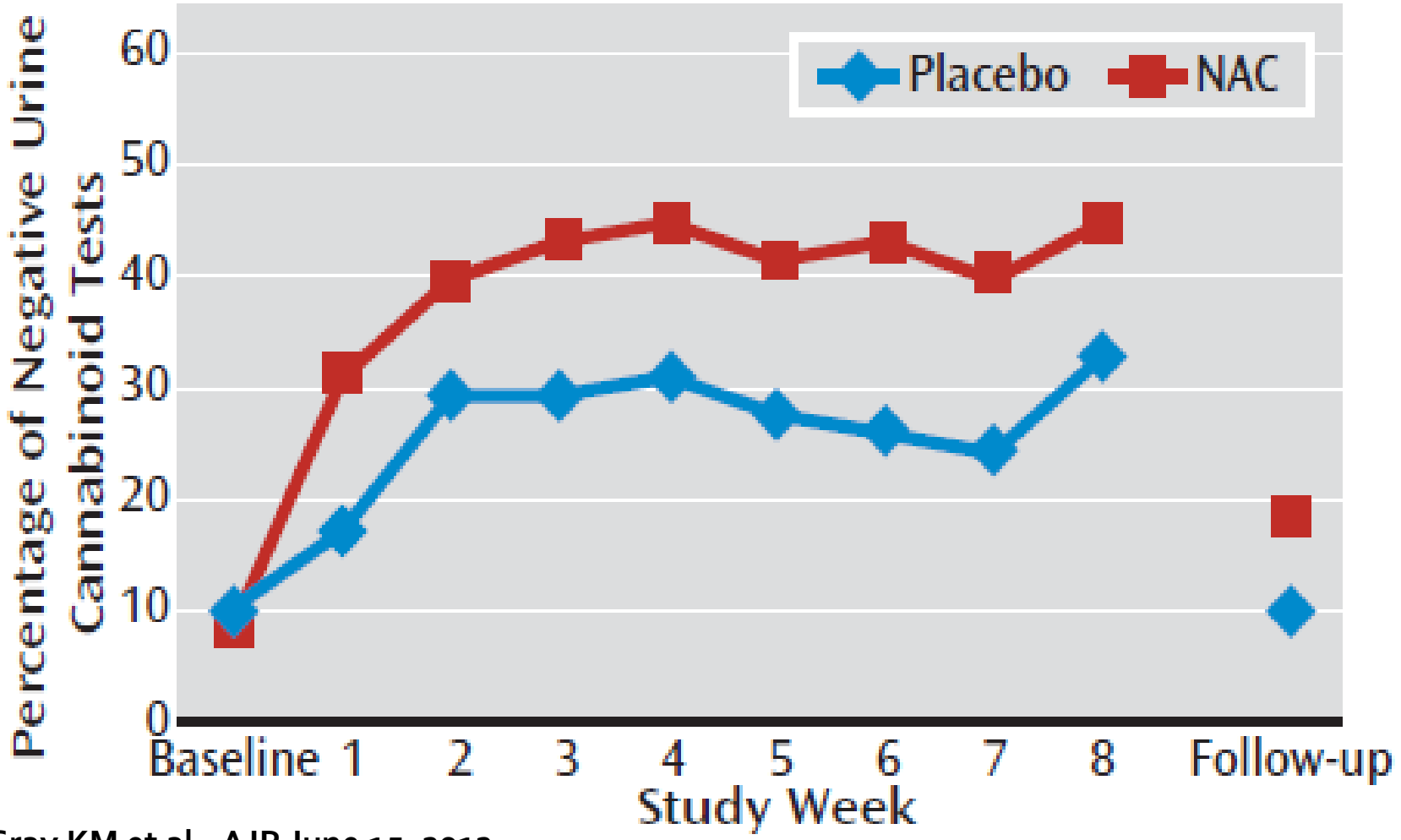
However:

- Intoxication and withdrawal 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

Treatment Options

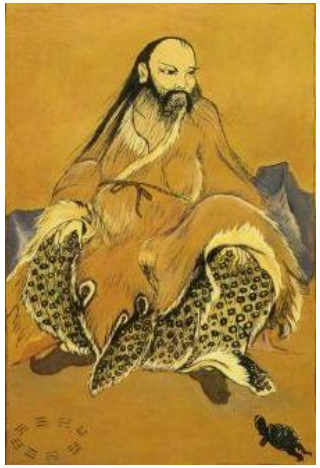
- Behavioral
  - Substance abuse treatment setting
    - cognitive-behavioral therapy, contingency management, motivational enhancement, therapeutic living
  - General medical settings
    - Brief interventions
- Pharmacotherapy
  - No currently approved medication
    - cannabinoid antagonist
    - 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.

History of Medicinal Marijuana

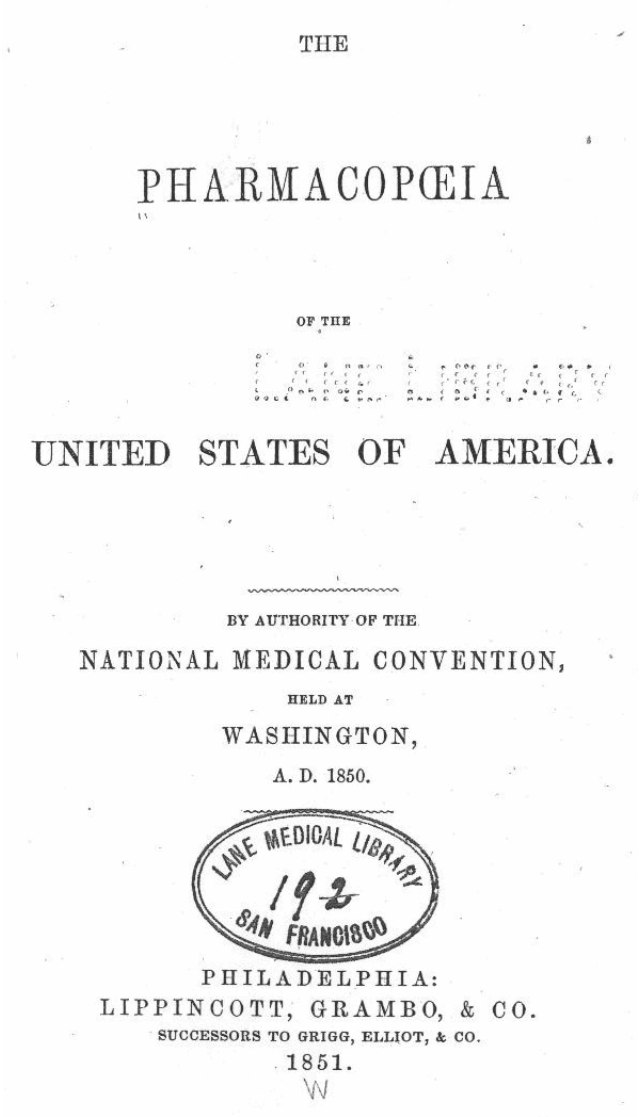


The Chinese Emperor Fu His (ca. 2900 BC) noted cannabis possessed both yin and yang.

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



THE

PHARMACOPŒIA

OF THE

UNITED STATES OF AMERICA.

BY AUTHORITY OF THE

NATIONAL MEDICAL CONVENTION,

HELD AT

WASHINGTON,

A. D. 1850.

PHILADELPHIA:

LIPPINCOTT, GRAMBO, & CO.

SUCCESSORS TO GRIGG, ELLIOT, & CO.

1851.

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.

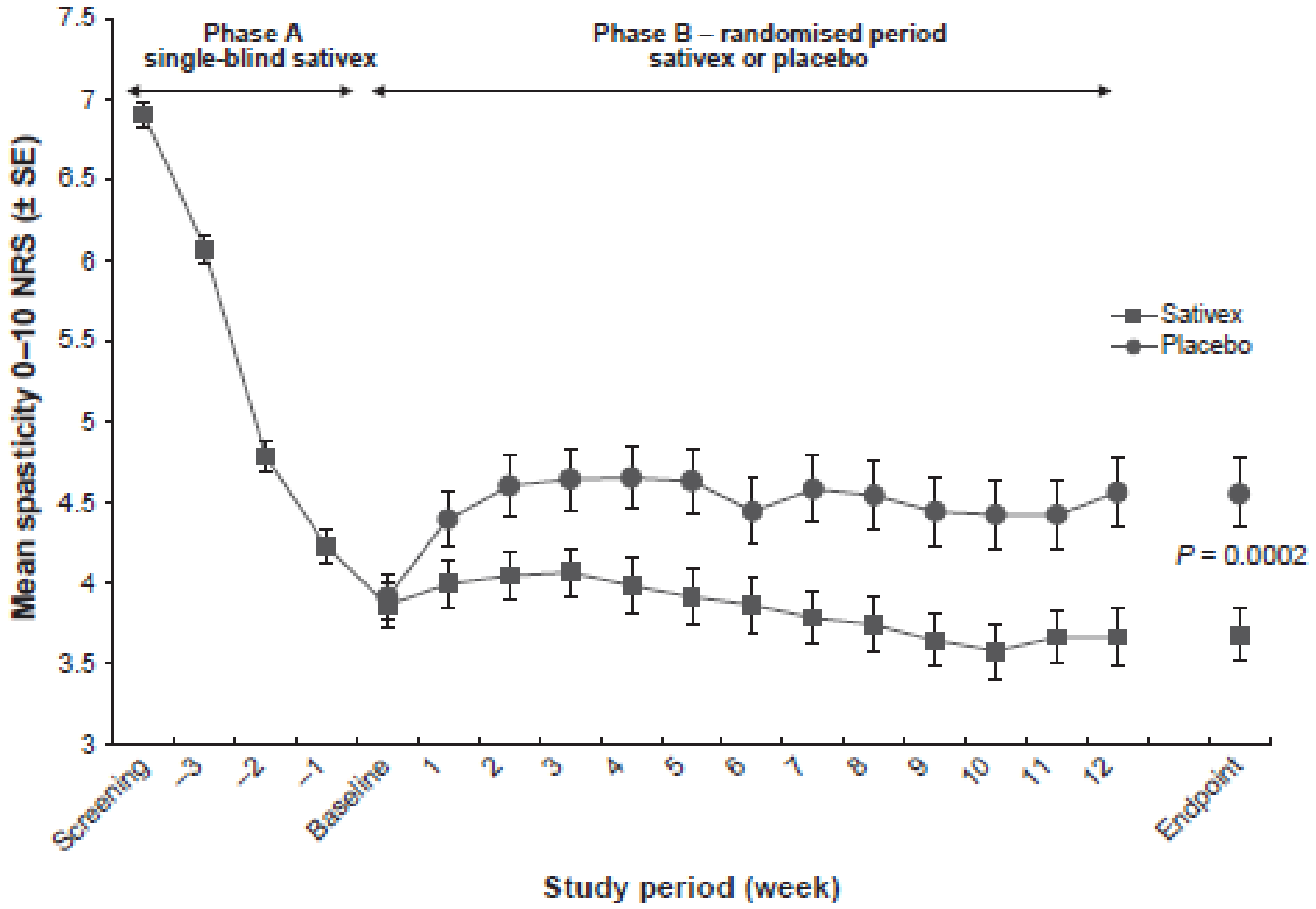
In 1942, amidst spreading reports of marijuana's alleged association with violent crime, it was removed from the U.S. Pharmacopeia.

Clinical Trials of Cannabinoids, Any Condition: 1990-2012

Study type	Positive trials	Equivocal	Negative trials	Total
Double-blind, placebo controlled	12	7	3	**22**

http://medicalmarijuana.procon.org/view.resource.php?resourceID=000884

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

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?

Policy Context *Refresher*

- 1970: Controlled Substances Act passed by Congress, marijuana listed as schedule I (i.e. no currently accepted medical use, high potential for abuse, and a lack of accepted safety even under medical supervision.)

- 1985: Marinol (synthetic THC) approved in the US for treatment of intractable nausea

- 1996: California first state to legalize medical marijuana

- 1997-2012: 17 more states + DC legalize medical marijuana (AK, AZ, CO, CT, DE, HI, ME, MA, MI, MT, NV, NJ, NM, OR, RI, VT, WA); 2 legalized recreational use

Policy Context, cont'd

2005: Supreme Court decision (Gonzales v. Raich)

Regardless of state laws, federal law enforcement has the authority under the CSA to arrest and prosecute physicians who prescribe or dispense marijuana and patients who possess or cultivate it.

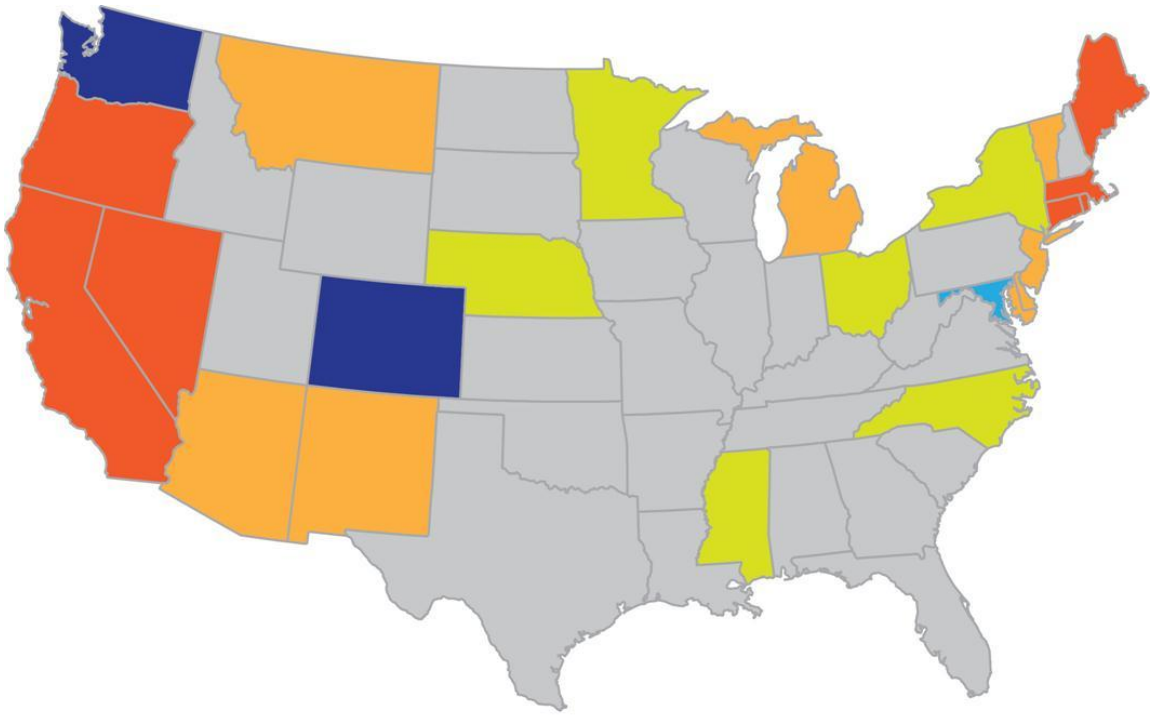
2009: Department of Justice

Issued a memorandum to U.S. Attorneys stating that federal resources should not be used to prosecute providers and patients whose actions comply with their states' laws permitting medical use of marijuana.

2008-2010: IOM, ACP, AMA

Petitioned DEA/FDA to reschedule marijuana to schedule II …it remains schedule I to this day

Current *State of the Union*



States and district with medical marijuana laws. This also includes Alaska and Hawaii. In Alaska, the state includes the right to possess modest amounts of marijuana in the home.

States that have removed jail time for possessing small amounts of marijuana.

States that both have a medical marijuana law and have removed jail time for possessing small amounts of marijuana.

Maryland has a limited medical marijuana defense for possession only.

Marijuana is legal for adult use and the state will regulate and tax marijuana sales. Colorado and Washington also have medical marijuana laws.

January 2013

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 Dept 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
8. There is an association between a state's legalization of recreational marijuana use and advancement of that state's football team to the super bowl. Further research needed

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)

Supplementary Cases

Case presentation #2

- RJ is a 48 year old man with AIDS, Hepatitis C, wasting syndrome.
- CC: nausea/vomiting, ongoing weight loss
- HPI: BMI 25 → 17 over past 6 months. Reports loss of appetite, nausea/vomiting both of which he says are partially relieved by smoking marijuana, which he started to do again recently on the recommendation of his girlfriend.
- PMHx:
  - HIV/AIDS – former IVDU. Off HAART since 2011, which he discontinued due to nausea/vomiting. CD4 = 34; VL = 1.5 million
  - HCV – type I. Failed IFN/ribavirin due to flu-like symptoms
  - Chronic low-back pain – degenerative disk disease. Percocet discontinued 2011 secondary to cocaine use
  - Gastritis

Case #2, cont'd

- Meds: ranitidine, omeprazole, metoclopramide, tramadol
- Soc Hx:
  - Retired machinist, now on SSDI
  - 1 ppd tobacco; rare alcohol
  - Reports quitting cocaine 6 months ago
- **"Doc, since marijuana has been helping, will you certify me to get medical marijuana so that I can use it legally?"**

Case # 2 Discussion

Case presentation #3

- JS is a 22-year-old woman with multiple sclerosis, bipolar disorder, generalized anxiety disorder
- CC: painful muscle spasms
- HPI: Started glatiramer acetate 6 months ago with good response: fewer acute MS flares with no hospitalizations. However, painful spasticity limits effectiveness/concentration at her job. Tizanidine caused excess drowsiness so she discontinued it.
- PMHx:
  - Relapsing-remitting MS complicated by ophthalmoplegia, ataxia, and painful spasticity
  - Bipolar disorder, no hx of hospitalization
  - Generalized anxiety disorder, well controlled on sertraline

Case #3, cont'd

- Soc Hx:
  - Works as a paralegal but missed 38 days of work last year because of health problems
  - No tobacco/alcohol, lifetime
  - Denies illicit drug use, lifetime
- Meds: glatiramer acetate, carbemazepine, sertraline
- She says, "I heard in news reports that marijuana can be used now in MS … do you think that might be worth trying?"

Case #3 Discussion

Initiates of Illicit Drugs among Persons 12 and Older: 2006