Marijuana

What Physicians Need to Know

Chief Resident Immersion Training (CRIT) 2013

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CRIT/FIT 2013

Modified from Robin Barnes, CRIT, 2006; Stephen Kertesz, CRIT 2009; Hillary Kunins, CRIT 2012; William Becker GR, 2013

Fact or Fiction?
(True or False Pre-seminar Questions)

1. Marijuana use is increasing.
2. Withdrawal symptoms occur with marijuana cessation.
3. No adverse health effects occur with marijuana use.
4. You can’t overdose on marijuana.
5. Marijuana abuse and dependence is treatable.
6. There are defined safe limits for marijuana use.
7. Physicians can prescribe marijuana for medical purposes in your state.

Outline

- Epidemiology
- US “love-hate” relationship with MJ
- Neurobiology
- Effects of marijuana
- Impact on health
- Medical Marijuana
- Treatment

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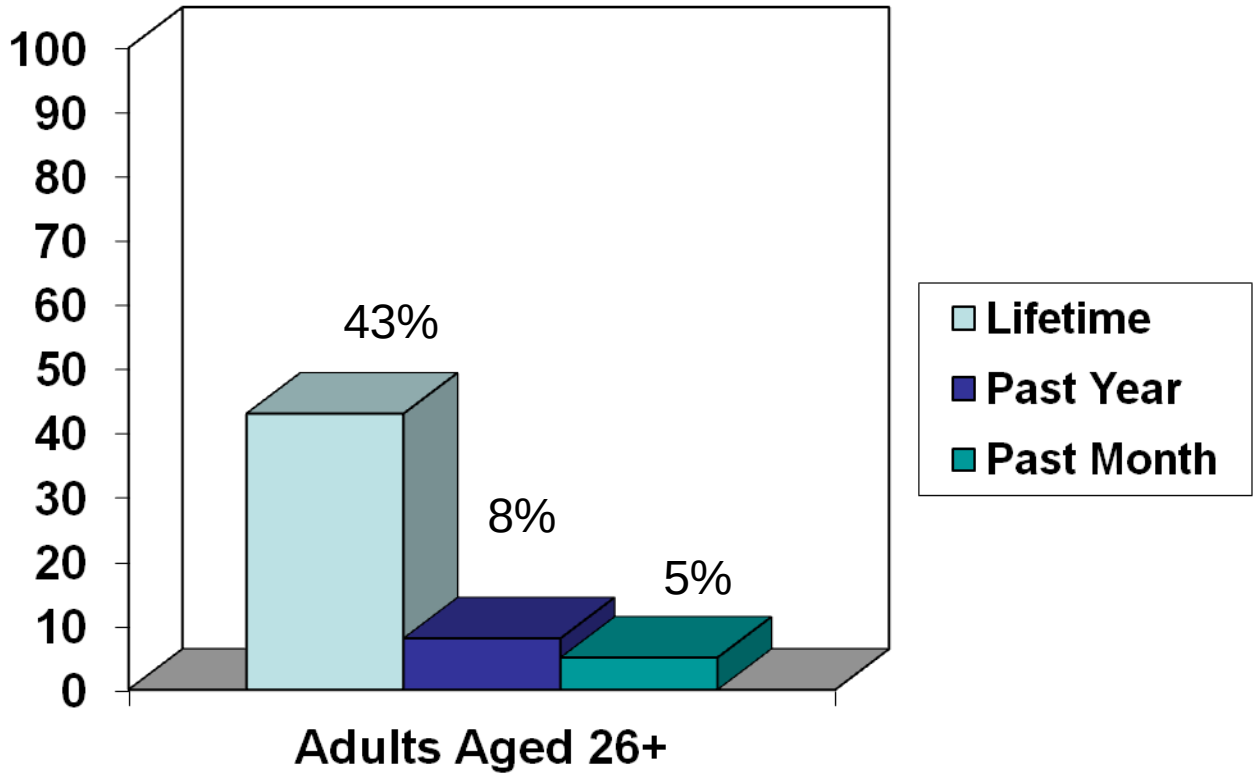
% Marijuana Use
National Survey on Drug Use and Health (NSDUH) - 2010



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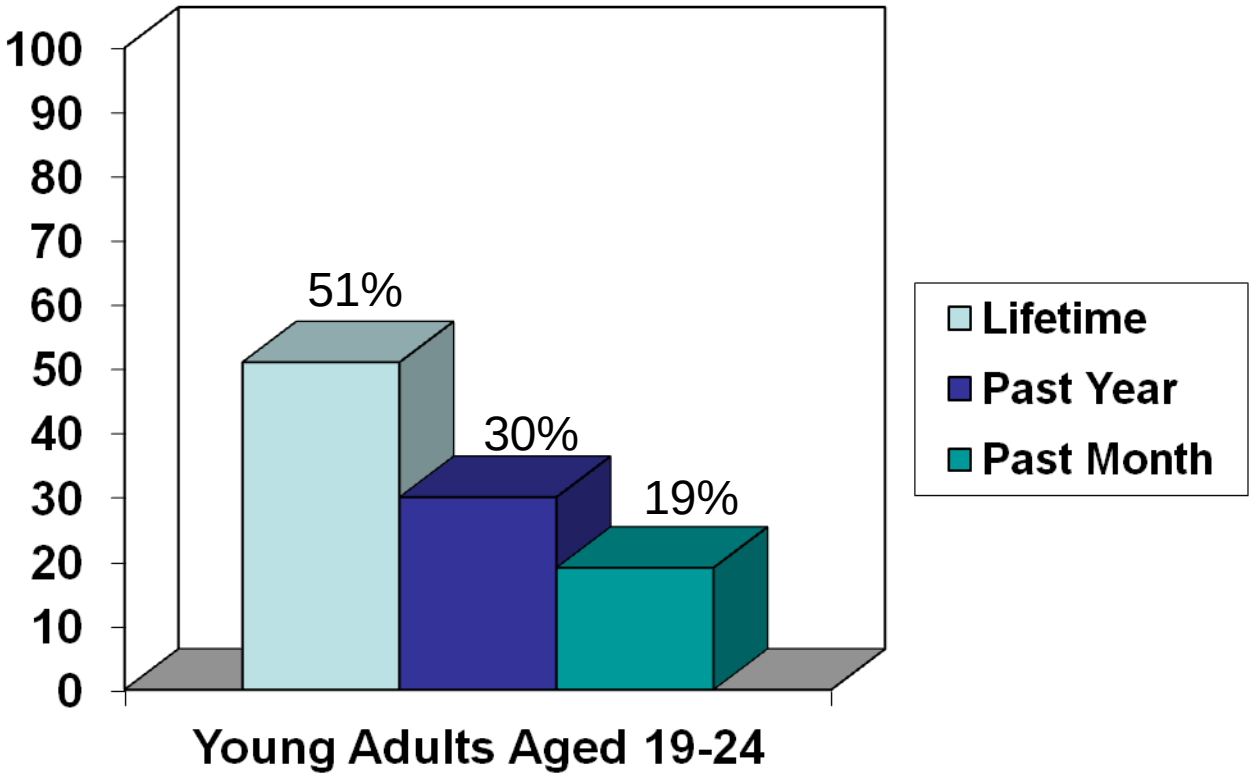
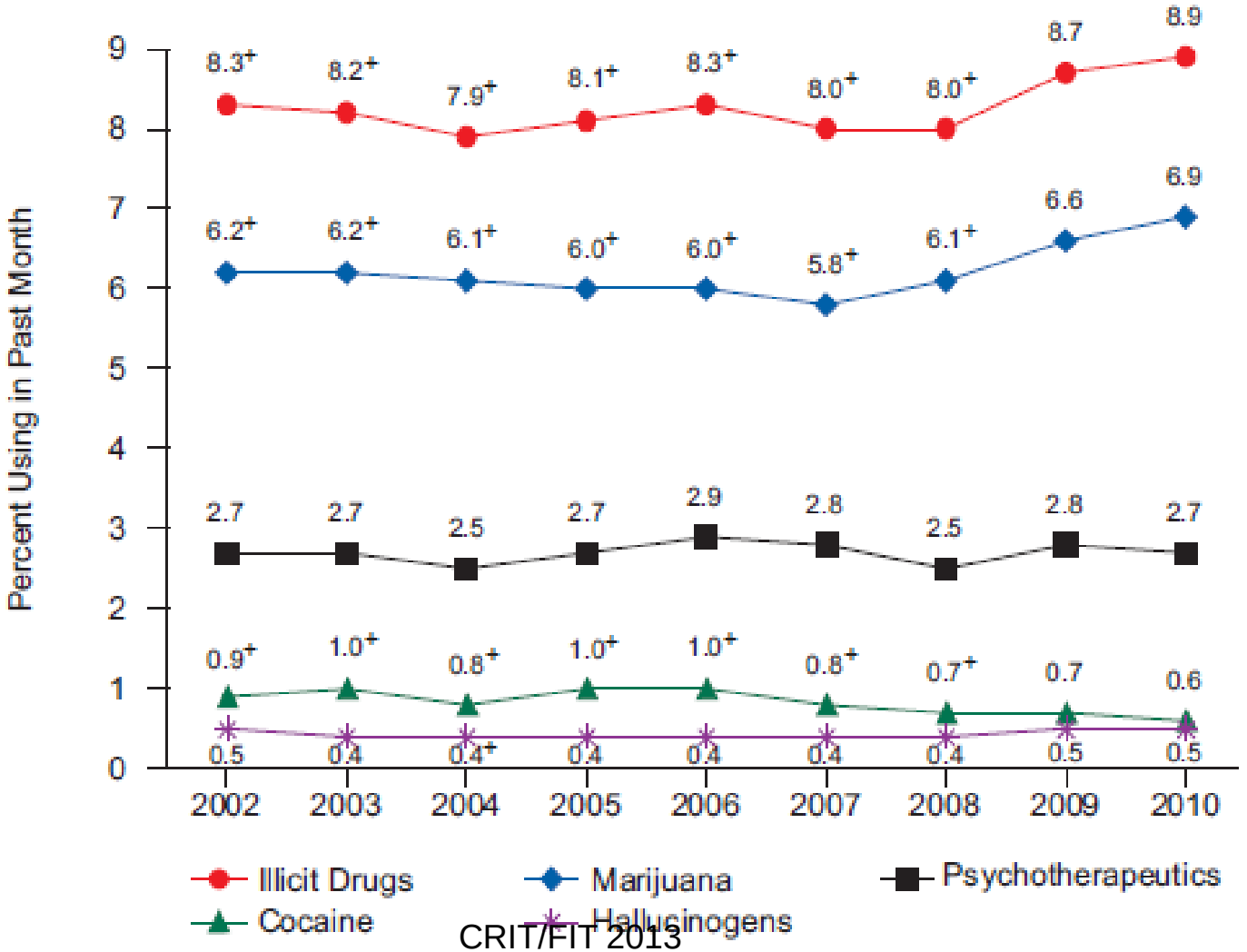
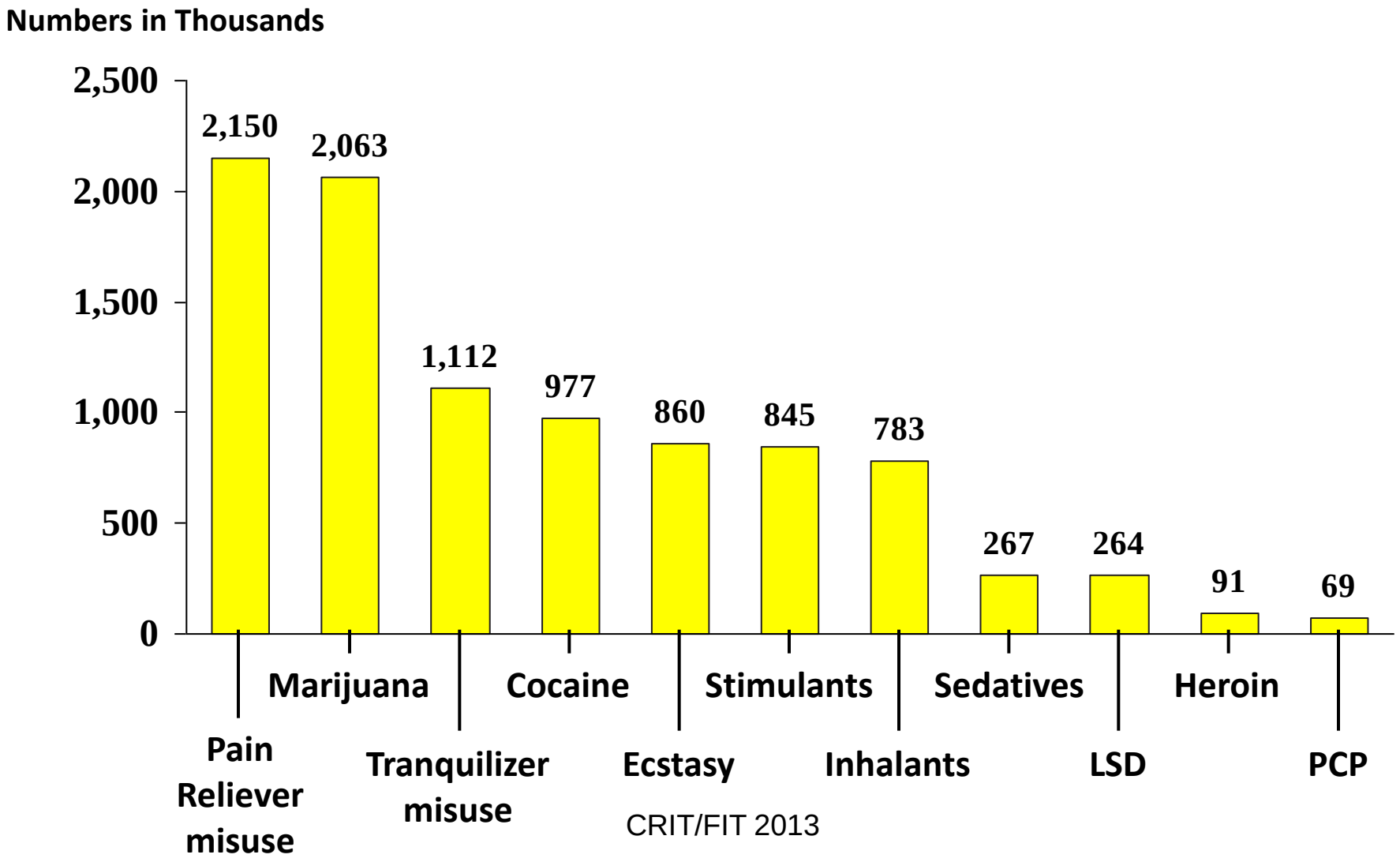


Past Month Use Illicit Drugs
Persons aged 12 and older, 2002-2010



+ Difference between this estimate and the 2010 estimate is statistically significant at the .05 level.

Past Year Initiates of Illicit Drugs among Persons 12 or Older: 2006



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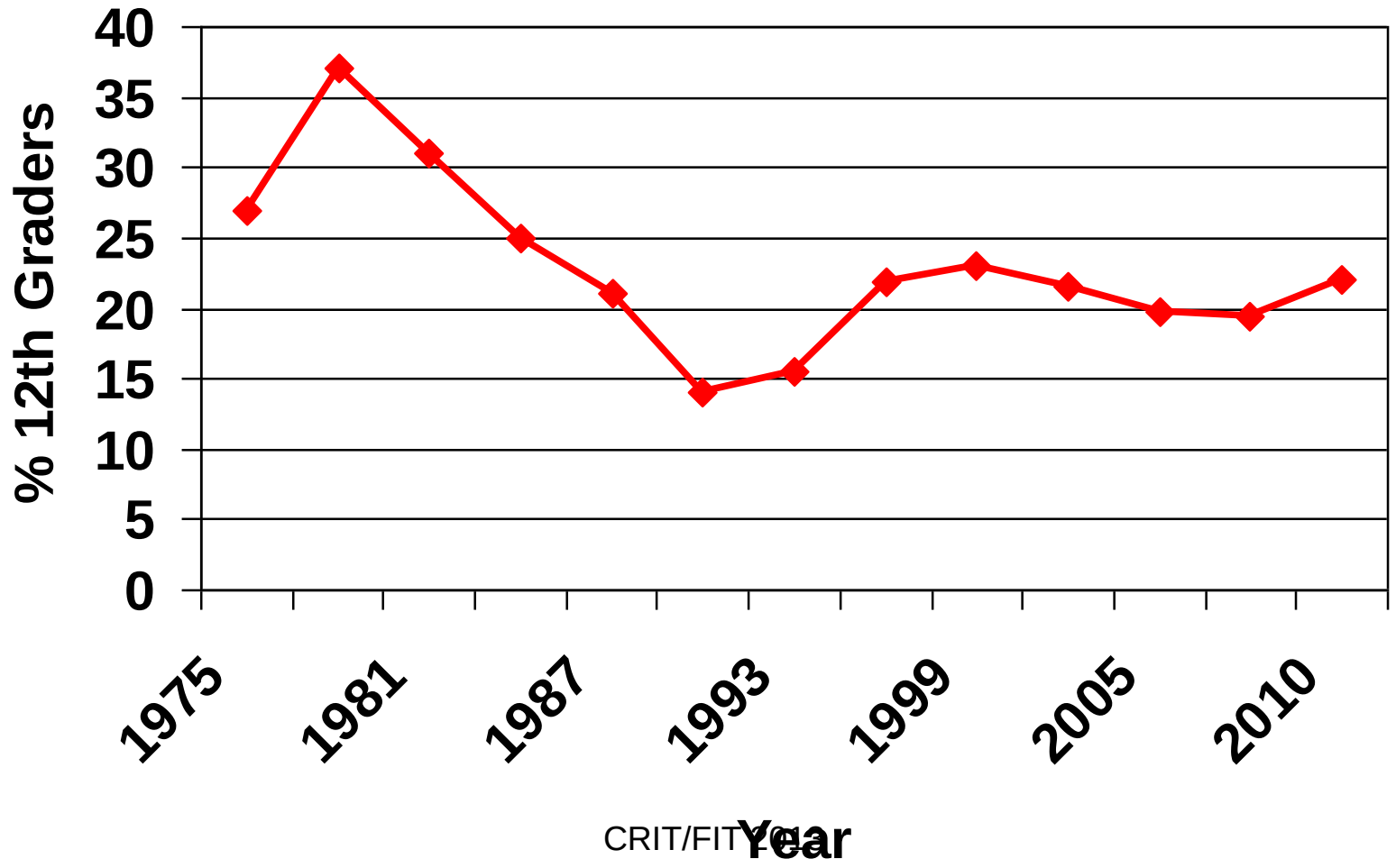
Past-Month Marijuana Use, 12th Graders



Source: Monitoring the Future

Past Year Abuse or Dependence NSDUH - 2010

- Marijuana – 4.5 million
- Pain relievers – 1.9 million
- Cocaine – 1.0 million

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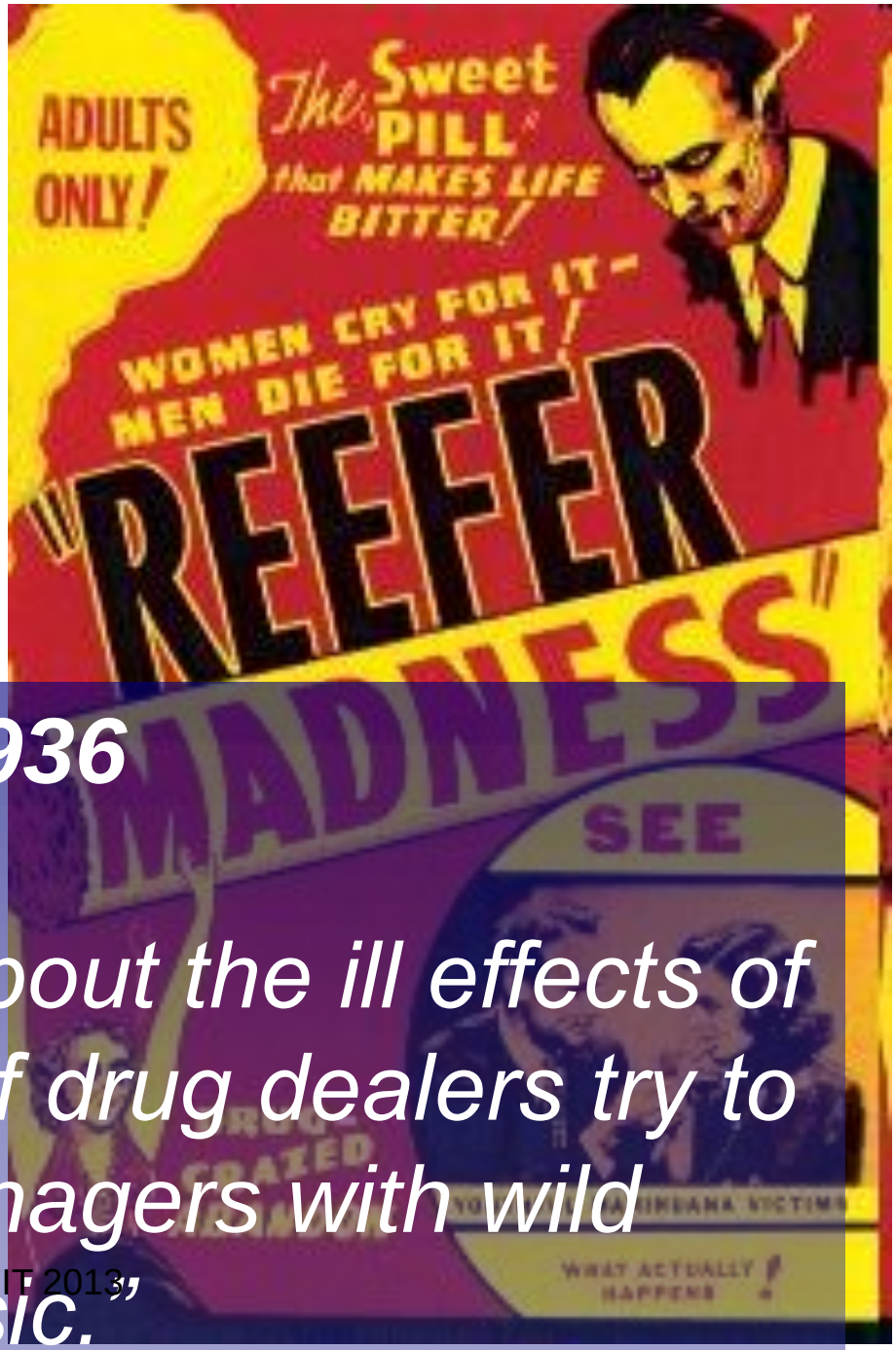
US love-hate relationship with MJ

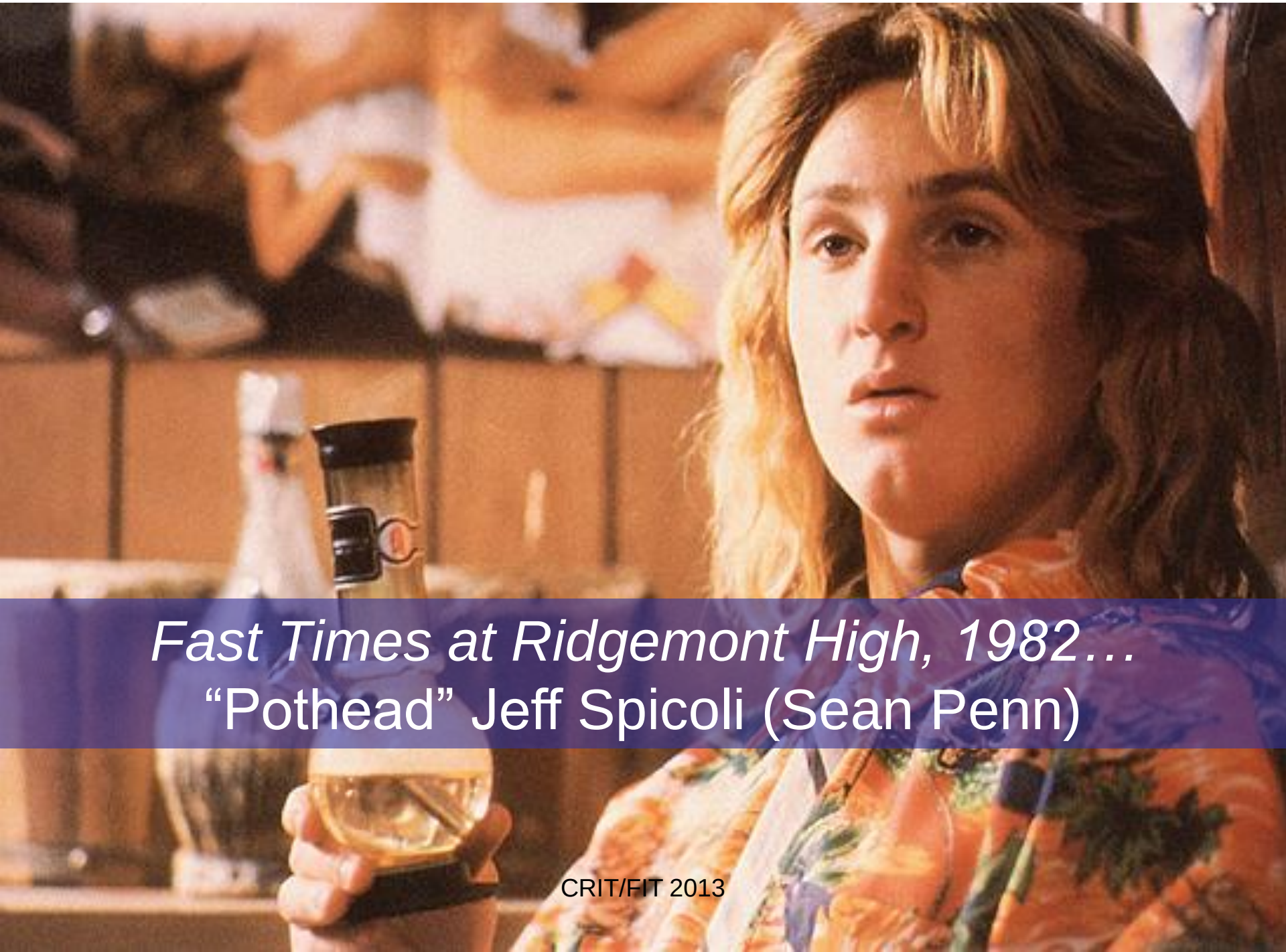
- 1937: Marijuana Tax Act - taxes use/possession
- Growing use 1950's by beat & jazz artists
- 1970: Controlled Substances Act passed by Congress, marijuana listed as schedule I (i.e. no currently accepted medical use, high potential for abuse, and a lack of accepted safety even under medical supervision;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

US: love-hate relationship with MJ



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…
"Pothead" Jeff Spicoli (Sean Penn)

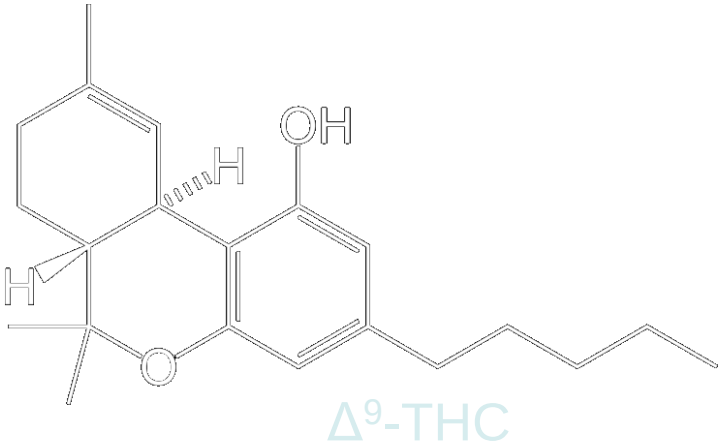
US love-hate relationship with MJ

- 1980's "Say no to drugs," severe penalties for trafficking
- 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)

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 and route of administration

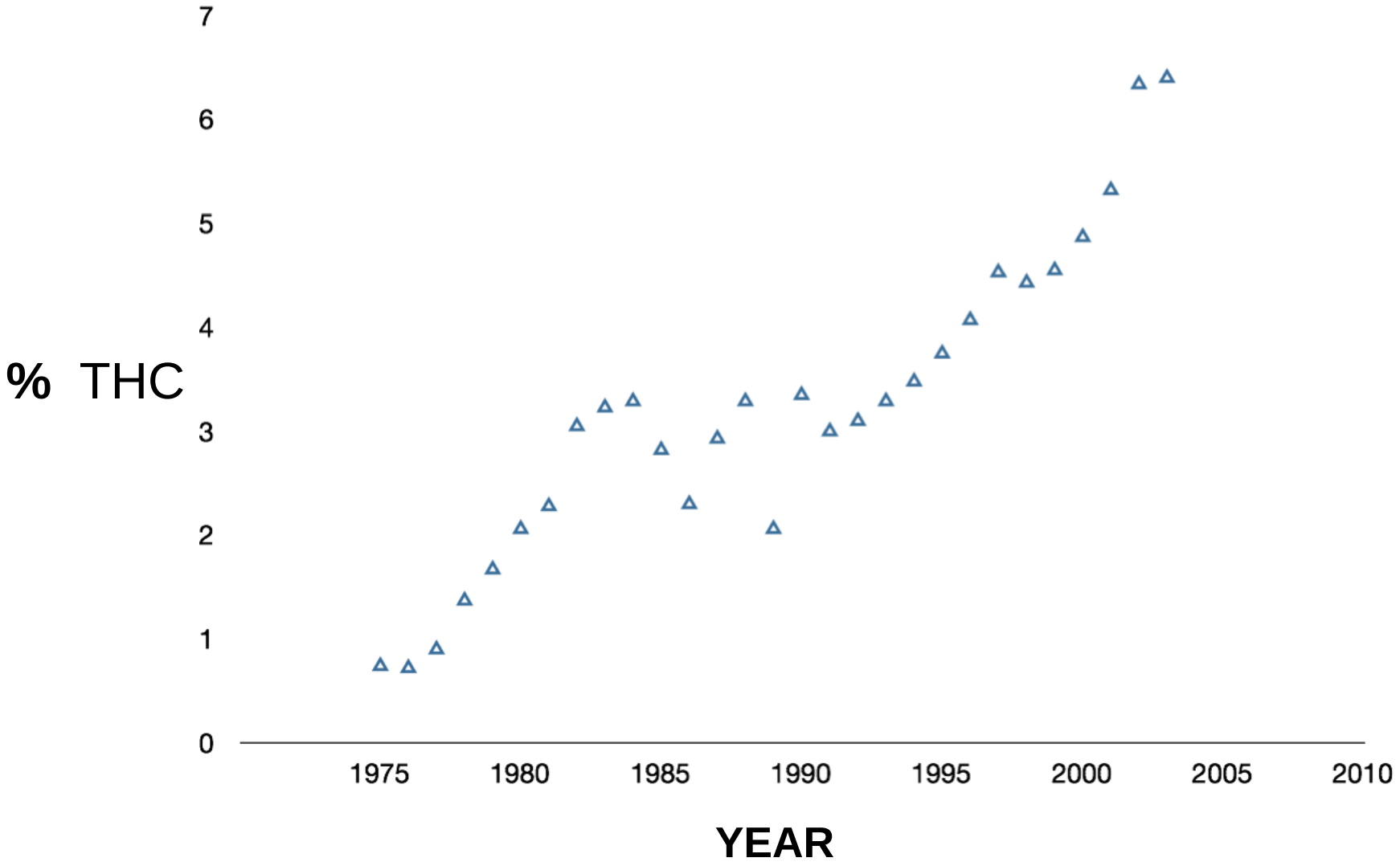
Δ^9-TETRAHYDROCANNABINOL (THC)



Δ^9-THC

- Psychoactive ingredient in *Cannabis sativa*
- 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
- Bioavailable in seconds after smoking
- 30 days to fully eliminate
- Binds CB1 receptor
- Potency: 1 joint was 10 mg THC in 1970s→150+ mg in 1990s

Percentage THC in Marijuana Seized by DEA



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

Marijuana Project at the National Center for Natural Products Research

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Cannabinoid Neurobiology

- Cannabinoid Receptors
  - Discovered in late 1980's
  - Three types (so far): CB1, CB2, GPR55
  - Locations:
    - Hippocampus
    - Basal ganglia
    - Cerebellum
    - Liver, muscle, gut, and adipose tissue
- Endogenous cannabinoids: Anandamide and 2-arachidonoylglycerol (AG2), function as neurotransmitters

Cannabinoid Neurobiolgy

- Cannabinoid antagonist: SR141617A (Rimonobant) first developed in early 1990's
  - Caused acute withdrawal syndrome in chronic MJ users
  - Caused dysphoria in MJ-naïve patients
  - Originally marketed as an anti-obesity medication but never entered US market; AE > than stated

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Physiologic Effects

- **Mood**: euphoria/relaxation; panic/paranoia at high doses and in susceptible individuals
- **Cognition**: (acute) impaired judgment, perceptual distortions; psychotic episodes, especially at high doses and in susceptible individuals; (long-term) ? memory impairment
- **Behavioral**: addiction, ? amotivation
- **Other**: increased hunger, anti-nociception, decreased intra-ocular pressure, ? immunosuppression, ? anti-inflammation

Acute Effects of *Smoked* Marijuana

- Euphoria, relaxation
- Intensity of perception
- Distortion of time and space
- Memory impairment
- Appetite stimulation, i.e., “munchies”
- No death by overdose

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Impact on Health: Cognition and Brain Function

- Transient acute effects on episodic memory & learning[1]
- Motor & Visual tracking (driving) x 2-5 hrs[2]
  - ~ 2 x odds of MVA[3]
- Persistent effects of longer-term use on cognition
  - Adolescents: slower psychomotor speed, diminished planning/sequencing after abstinence x 3 weeks[4]

[1] *Curran, Psychopharm 2002;* [2] *O'Kane 2002;* [3] *Asbridge BMJ 2012,* [4] *Medina 2007*

Impact on health: Cannabis and Psychosis

- Biologically plausible (DA release)
- Multiple epidemiologic cohort studies:
  - risk for symptoms & schizophrenia

But:

- Risk non-uniform: prior psychotic sx, genetic risk (COMT gene), early adolescent use[1]
- If prevalence rose 5x since 1970, why didn't schizophrenia rise 5x?[2]

[1] *Semple, J Psychopharm 2005;* [2] *MacLeod, Lancet 2005*

Impact on Health: Cannabis and Pulmonary Problems

- Makes biologic sense due to carcinogens/tar
  - Respiratory symptoms:
    - Cough, sputum production, and wheeze[1]
  - Lung Cancer:
    - Associated with cellular changes consistent with precancerous state
    - Associated with increased risk in combination with tobacco use[2]
- But, no consistent decline in lung function or increased risk of COPD
  - Acute bronchodilation: ~ 0.15-0.25L increase in FEV1 after smoking, higher levels of exposure, levels off[1,3]

[1]Tetrault Arch Int Med, 2007; [2] Mehra Arch Int Med, 2006; [3] Pletcher, JAMA 2012

Cannabis and Other Problems

- Head and neck cancer?
- Depressive symptoms: modest data
- Reproductive effects: Adverse in males (hormonal alterations, sperm function effects)

Early life use, later problems?

- The DEBATED **Gateway** to other drugs[1, 2]
  - Sequence (Yes)
  - Association (Yes)
  - Causation (Maybe)
  - Even if NO causation, policy & clinical focus on young marijuana users at risk remains relevant
- Adverse association with educational attainment and other drug use[3]
  - Early use of alcohol and tobacco similar effects

[1] Kandel 2003; [2] Fiellin LE, J Adol Health 2013; [3]MacLeod 2005

Physiologic Effects

- Withdrawal is real
  - Onset 8-10 hours after stopping drug; 4-14 days' duration
  - DSM-V:"cessation of cannabis use that has been heavy and prolonged," results in "clinically significant distress or impairment in social, occupational, or other important areas of functioning," and is characterized by at least three of these symptoms: irritability, anger or aggression; nervousness or anxiety; sleep difficulties (insomnia); decreased appetite or weight loss; restlessness; depressed mood; and or physical symptoms such as stomach pain, shakiness or tremors, sweating, fever, chills, and headache.

- Chronic use→ tolerance

What might be presenting problems in primary care?

- Respiratory: exacerbation of asthma, cough, increased sputum production
- Mental Health: depression, paranoia
- Problems with concentration, learning, employment/school
- Difficulty stopping or controlling use

Winstock, BMJ, 2010

Some Complexity and Uncertainty…

- Salutary effects
  - Role of medical marijuana is a hot-button issue
- Impact of medical marijuana on addressing marijuana abuse and dependence in primary care?
- Is there safe use, and for whom?

Fundamental Tension

Public health scourge:

- Past year abuse/dependence (DSM-IV defined): 3.5% of all U.S. residents 12 and over (NSDUH 2008)

However:

- Intoxication, overdose, withdrawal are not fatal
- Functional long-term use seems to be relatively frequent (compared to alcohol and other drugs)
- Risk of end-organ damage appears to be less than several other legal and illegal substances
- Therapeutic Index *may be* equal or better compared to many controlled substances

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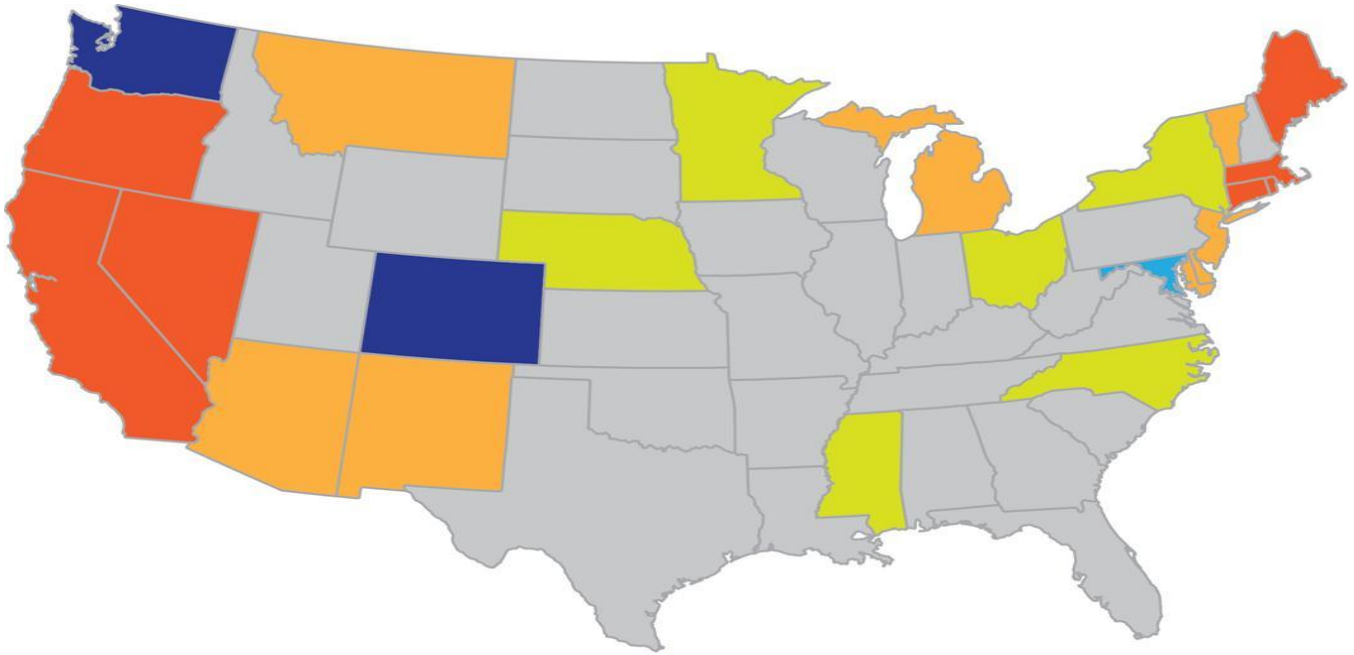
Current MJ Laws in US



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

Can It Be *Medically Useful?*

- Possible:
  - Anti-emetic
  - Appetite stimulant
  - Pain control (central) – multiple sclerosis, neuropathy
  - Anxiolytic
  - Glaucoma –mild decrease intraocular pressure
- Dronabinol (Marinol): relative effects vs. marijuana is contested

Cohen S, BMJ, 2008, Tramer MR, BMJ, 2001

Studies of Cannabinoids, Any Condition: 1990-2012

Study type	Positive trials	Equivocal	Negative trials	Total
Double-blind, placebo controlled	12	7	3	**22**
Non-blinded, controlled	25	24	30	**79**

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

Major Questions Remain…

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

Diagnosis of abuse/dependence

- Same criteria for abuse and dependence as other illicit and licit substances
  - DSM-IV
  - Dependence includes physiologic criteria
- BUT, risky versus safe use? – NOT studied
  - How to counsel and or treat in primary care?

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Treatment Options

- Pharmacotherapy
  - No currently approved medication
    - ?cannabinoid antagonist
    - ?NAC—Gray KM AJP 2012
    - ?oral THC for withdrawal, maintenance or short-term treatment?
      - ?cannabinoid agonist—Levin FR DAD 2011
- Behavioral
  - Substance abuse treatment setting
    - cognitive-behavioral therapy, contingency management, motivational enhancement
  - Ambulatory and emergency care setting
    - ?Brief interventions – similar to alcohol use? – some data

Strategies to Help Patients Cut Back or Abstain in Primary Care

- Not well-studied
- Brief intervention
- Discuss potential for withdrawal symptoms
  - How to manage?
    - Delay smoking during day
    - Extend interval between drug ingestion
    - Taper off slowly
- Refer for treatment

Fact or Fiction?

1. Marijuana use is increasing. True
2. Withdrawal symptoms occur with marijuana cessation. True
3. No adverse health effects occur with marijuana use. False
4. You can't overdose on marijuana. True
5. Marijuana abuse and dependence is treatable. True
6. There are defined safe limits for marijuana use. False
7. Physicians can prescribe marijuana for medical purposes in your state. 19 states + DC

What can you tell your patients? (fact vs fiction)

- No safe limits have been defined
- The gateway “association” is present (?causal)
  - Addiction is real; but conditional dependence low
- Medical and social complications do occur
  - Cognitive, respiratory, reproductive effects
  - There is a risk for psychotic symptoms, especially in adolescents
  - Death by OD is not reported
  - Withdrawal symptoms exist
- Behavioral treatments may help

THE AMERICAN JOURNAL OF PSYCHIATRY

psychiatryonline

From: A Double-Blind Randomized Controlled Trial of N-Acetylcysteine in Cannabis-Dependent Adolescents

Am J Psychiatry. 2012;169(8):805-812. doi:10.1176/appi.ajp.2012.12010055

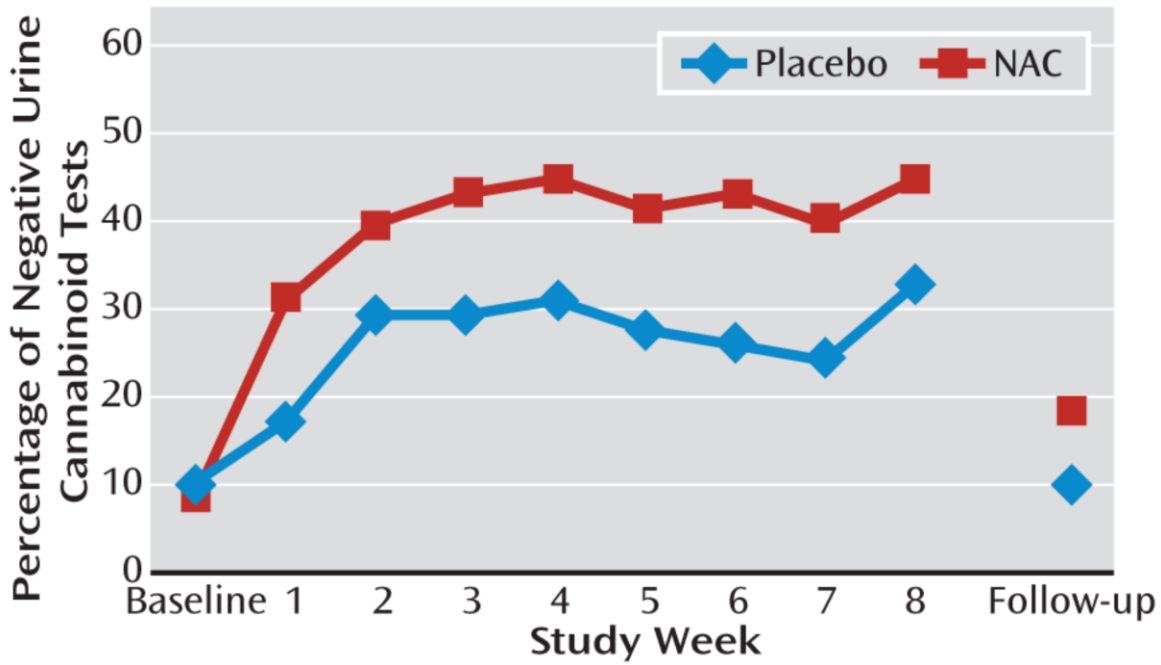

Figure Legend:

Proportion of Negative Urine Cannabinoid Tests Over Time Among Cannabis-Dependent Adolescents in a Randomized Controlled Trial of N-Acetylcysteine (NAC)[a]

[a] In this intent-to-treat analysis, all randomized participants (N=116) were included, and urine cannabinoid tests were assumed to be positive for all missed visits. With adjustment for years of cannabis use, baseline urine cannabinoid test results, and major depressive disorder, odds ratio=2.4, 95% CI=1.1–5.2; χ^2=4.72, p=0.029.

Dronabinol

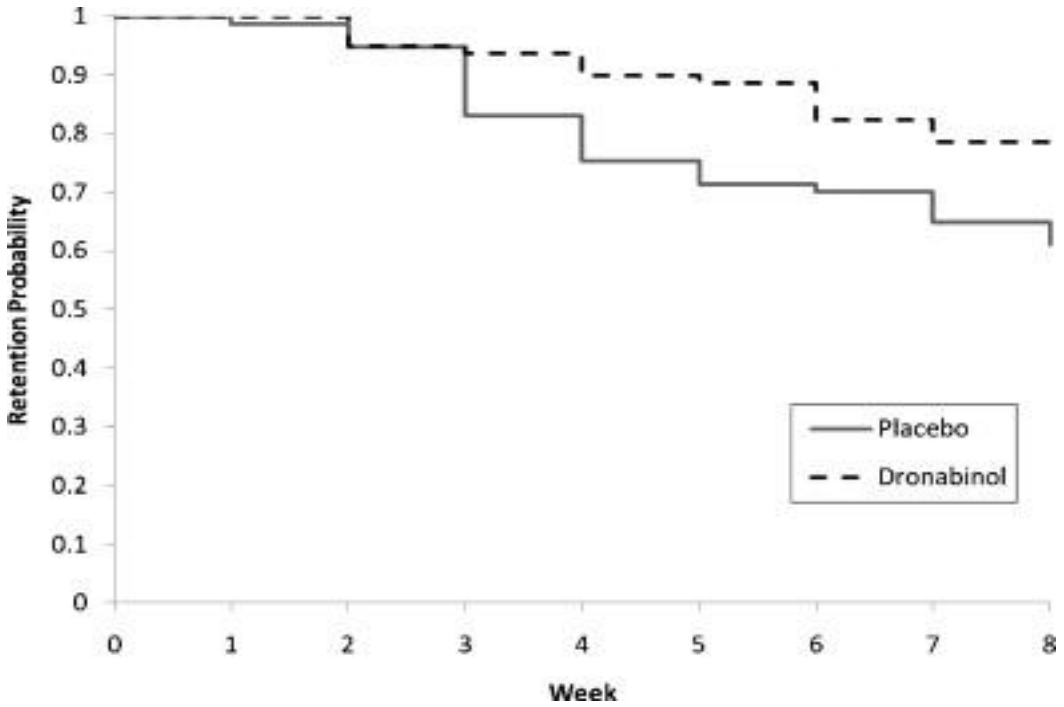

Fig. 2 Retention rates were found significantly different between the treatment groups based on log-rank statistics (<ce:italic> P</ce:italic> <ce:hsp sp="0.25"/> =<ce:hsp sp="0.25"/> .02).

Frances R. Levin , John J. Mariani , Daniel J. Brooks , Martina Pavlicova , Wendy Cheng , Edward V. Nunes

Dronabinol for the treatment of cannabis dependence: A randomized, double-blind, placebo-controlled trial
Drug and Alcohol Dependence Volume 116, Issues 1?3 2011 142 - 150

http://dx.doi.org/10.1016/j.drugalcdep.2010.12.010