Medical Marijuana
Myths and Realities

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Introduction

Marijuana has been demonized, glorified, and recently attempted to be medicalized. This presentation is divided into 2 parts. The 1st will cover basic information about M.J. covering mechanisms of action, side-effects, M.J. dependence and new approaches to treat it. The 2nd part will cover what is known about M.J. as medicine.

Marijuana

- Plant source – *Cannabis Sativa*
- Marijuana – a mixture of dried seeds, stems, leaves, & flowering top
- An old drug used at least since 2700 B.C.
- Napoleon's troops under General Kleber discovered marijuana & hashish during the Egyptian Campaign & brought it back to Europe where it became popular
- Made illegal in U.S. by Marijuana Stamp Act of 1937

Epidemiology

- More than 75 million (over 34%) of Americans 12 years or older have tried it at least once & 18 million have used it in the past month
- Average age of 1st use has been declining:
  - From 16 years to 13.6 years
- While most discontinue marijuana by their mid-20's, a subset maintain daily, long-term use
- 10% of 1st time users and 50% daily users will develop dependence
- Daily teen use highest in 30 years

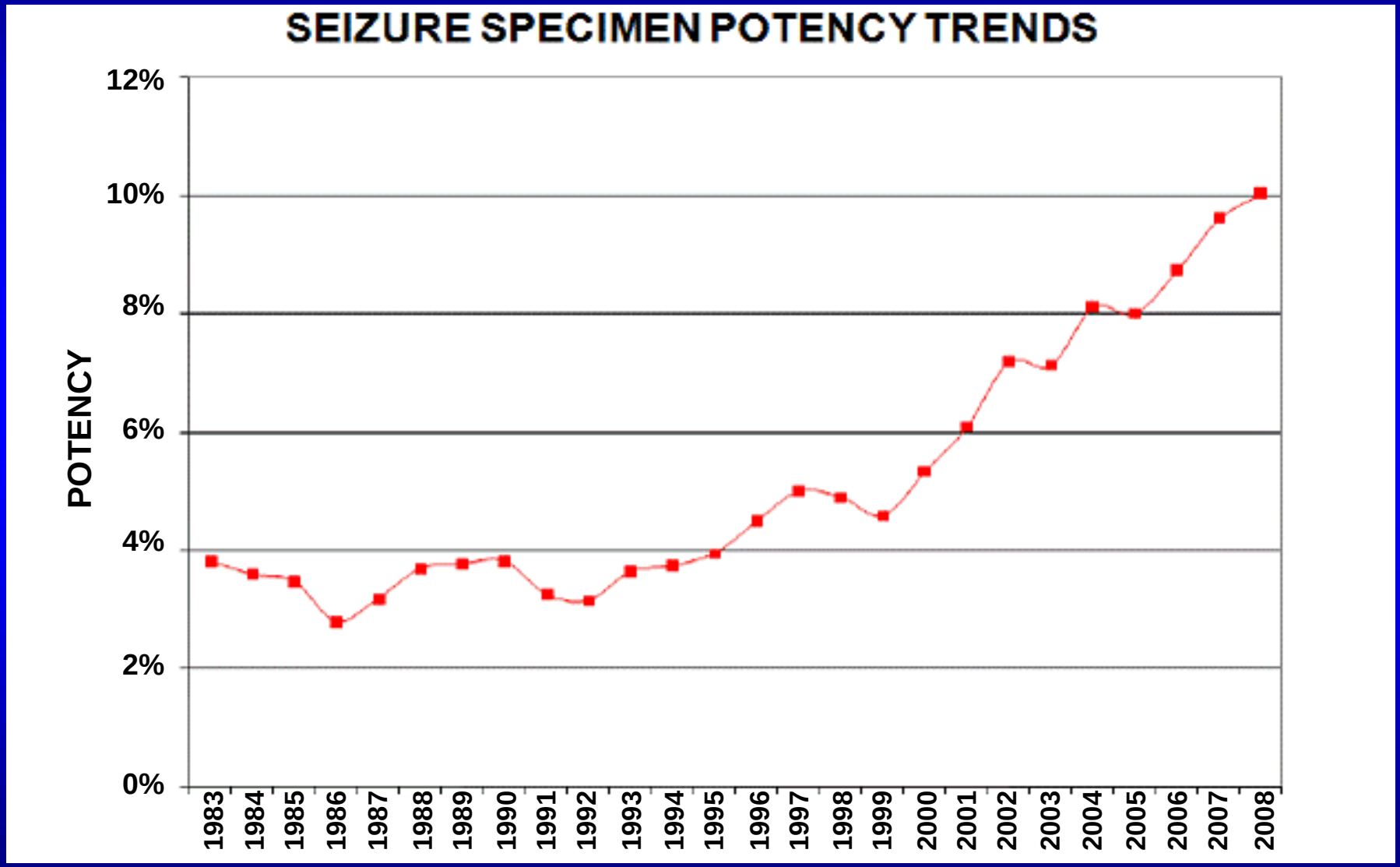
Relation between Marijuana & other Drug Use

- Early age of onset a major predictor of continued frequent marijuana use & likelihood of using other drugs
- Increased potency of marijuana may make the brain less responsive to endogenous cannabinoids, especially in the still developing adolescent brain
- Effects of higher potency – more rapid intoxication & with smaller amount – may increase brain toxicity as with vodka vs. beer
- May also increase anxiety & apathy in teens & make other drug use more attractive

Pharmacology

- Delta-9- tetrahydrocannabinol- (THC) main psychoactive component, isolated by Mechoulam in 1964
- At least 400 other compounds
- At least 60 other cannabinoids – key one is CBD- Cannabidiol
- Street potency has increased substantially in past 3 decades – from 1% THC to 5-10% & as high as 15% to 30%

Average Marijuana Seizure Potency Exceed 10%



Source: University of Mississippi Marijuana Potency Monitoring Project, Report 104, March 23, 2009

Smoked vs Oral Route

- Smoked Route
  - Rapid onset of “high,” major physiological & subjective effects take up to 30 minutes to develop
  - Peak plasma level in 10 minutes
  - Intoxication lasts 2-3 hours depending on dose
- Oral Route, e.g., Dronabinol (Schedule III)
  - Greater percentage absorbed, but less predictable effects
  - Onset 30-60 minutes
  - Peak plasma level in 2-3 hours
  - Effects last up to 8 hours

Endocannabinoid System

- CB-1 receptor cloned 1990; activated by THC
- Cannabinoid receptors: CB-1 & CB-2 cloned so far
  - Highest CB-1 concentrations in cortex (cognitive functioning), hippocampus (memory), & cerebellum (motor coordination)
  - CB-2 receptors mainly located in cells of immune system but recently identified also in brainstem, cortex, & cerebellum
- Endogenous ligands: 2 main ones characterized
  - Anandamide (Sanskrit for “bliss”)
  - (2-AG) 2-archidonoylglycerol

Endocannabinoid System & Other Addictions

- CB-1 receptors may regulate reinforcing effects of alcohol & mediate alcohol relapse. In heavy drinkers one drink leads to increased endorphins in two brain regions.
- CB-1 receptors have important role in opioid reward
- THC rewarding effects attenuated in monkeys by naltrexone
- Cross-dependence
  - Naloxone induces withdrawal in THC dependent rats
  - Rimonabant precipitates withdrawal in morphine dependent rats

Potential Side Effects

- Respiratory effects – acute, dilates bronchial tubes; chronic, decreased bronchial diameter, & worsening of breathing problems. Chronic cough & bronchitis
- Cardiac – increased heart rate & increased cardiac work load-associated with heart attacks
- Slowing of time, increased hunger (“munchies”), slowed reaction time
- Acute use increases risk-taking behavior

Potential Side Effects (cont)

- Intoxication may be associated with mild suspiciousness or paranoia
- Aggressiveness usually decreased but can increase if m.j. taken during high stress
- Increased road, rail, & air accidents
- At higher doses, hallucinations, usually visual, may occur; at times, paranoid delusions
- May lead to confusion & panic reactions
- Serious suicide attempts more common in those who meet criteria for M.J. abuse/dependence

Marijuana & Cognitive Deficits

- Short term memory deficits
- Decreases concentration, attention, & information processing
- Early onset marijuana users (before age 17): poorer cognitive performance than late onset even after month of abstinence
- Verbal IQ especially affected - largely reversible but heavy chronic use may lead to permanent impairment
- Persistent M.J. users showed broad neuropsychological decline as late as 25 years later even after stopping M.J. use
- Suggest neurotoxic effect of M.J. in adolescent brain (Meier 2012)

Marijuana Use & Psychosis

- Is marijuana a precipitating or a causative factor in the development of schizophrenia or both?
- MJ use aggravates symptoms & course of schizophrenia and increases relapse even when premorbid psychotic systems controlled for
- An episode of marijuana induced psychosis, while usually short-lived, led to subsequent psychotic episodes in 77% & a diagnosis of a schizophrenia-spectrum disorder in 45% usually within 3 years
- Associated with earlier age at 1st male psychotic episode
- Increased hazard during adolescent to early adulthood when developing brain more vulnerable

Moore, Zammit, et al., Lancet, July 28, 2007

"Cannabis use and risk of psychotic or affective mental health outcomes: A Systematic Review"

Key Findings:

- The most comprehensive meta-analysis to date of a possible causal relation between cannabis use and later psychotic illness
- An increased risk of psychosis of about 40% in participants who had ever used cannabis compared to never users.
- A clear dose-response effect with an increased risk of 50-200% in the most frequent users

Marijuana & Dependence

- Daily use associated with the hallmarks of classical dependence – heavy use, e.g., 2-10 joints/day, increased salience, impaired performance, & compulsive drug-seeking behavior
- 10% of those who have ever smoked M.J, will become dependent at some point
- Pleasure of response associated with likelihood of becoming dependent

Treatment of M.J. Dependence
Psychotherapeutic Approaches

- Motivational Enhancement (MET)
- Cognitive-Behavioral Therapy (CBT)
- Family Structural Therapy
- Contingency Management Strategies
- Regardless of the approach, after chronic heavy use cessation can be very difficult and relapse is common (71%)

Marijuana Withdrawal Symptoms

- Irritability
- Anger, increased aggression
- Depressed mood
- Headaches
- Restlessness
- Trouble sleeping & strange dreams
- Decreased appetite & weight loss
- Tobacco withdrawal similar except for opposite effects on appetite & weight

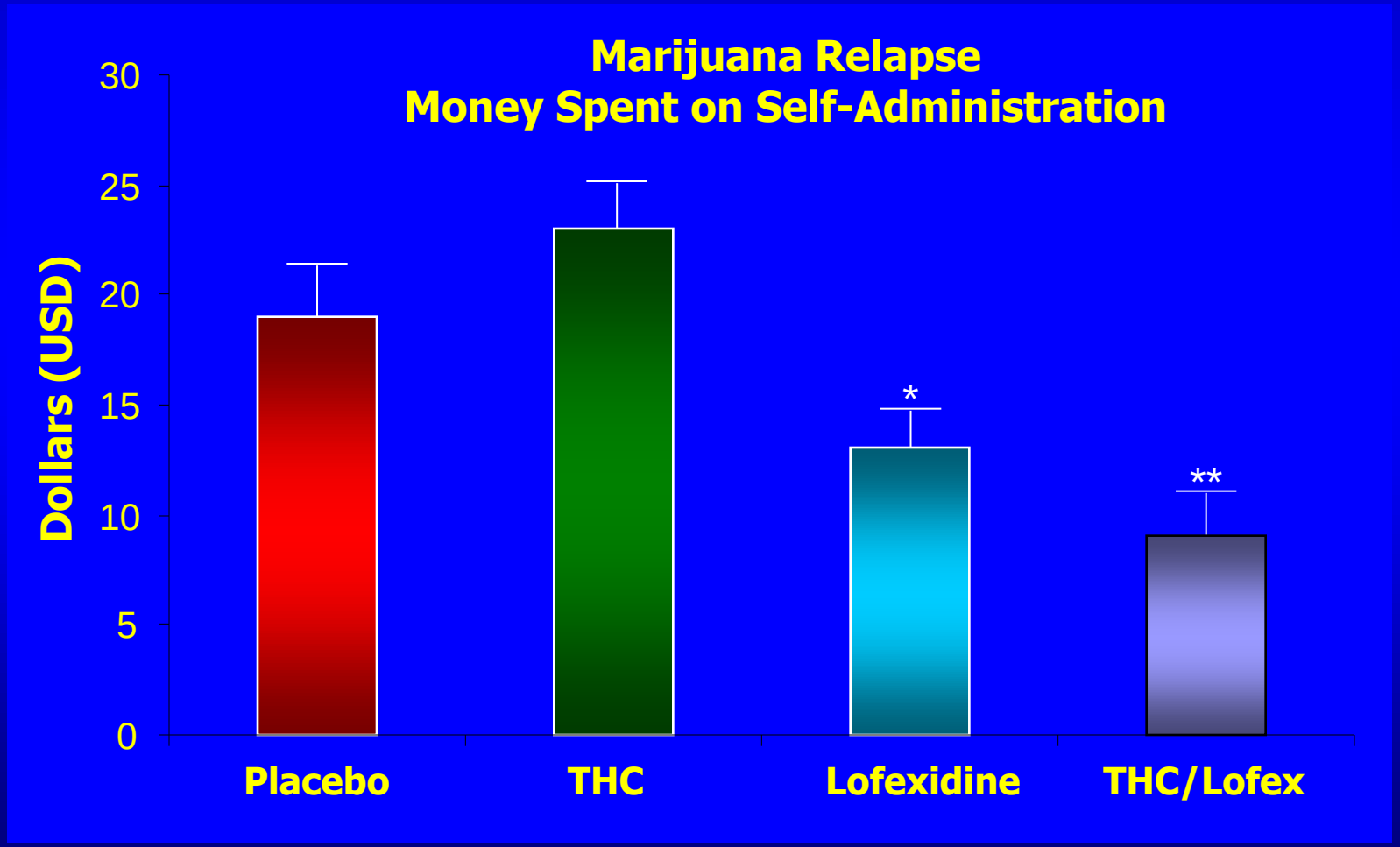
(Haney, et al., 1999, & others)

Pharmacological treatment of M.J. Dependence

- Withdrawal- M.J. withdrawal syndrome reliably documented in both clinical and human studies
- A number of negative studies, e.g. bupropion, divalproex, and nefazodone
- Most promising is combination of dronabinol (synthetic THC) and lofexidine, or nabilone
- Sativex (aerosol combining THC; cannabidiol (1:1) may be useful when available
- Given high relapse rate from psychotherapy trials, a pharmacological approach may be necessary

Effect of Dronabinol and Lofexidine in Laboratory Model of Withdrawal and Relapse

(Haney et al., 2008)



Pharmacological Treatment cont

- **Prevention of Reinstatement**
  - **Naltrexone 50 mg increased intoxicating effects but lower dose may be useful**
  - **The dronabinol/lofexidine combo might be useful**
  - **Rimonabant (cannabinoid antagonist) might have been of use but withdrawn from market because of potential surcidality)**
  - **Nabilone (Cesamet), a synthetic THC analog, compared to dronabinol has higher bioavailability, longer duration of action and urinary metabolites distinct from M.J. (Haney et al 2013)**

Pharmacological Treatment (cont)

- N-acetlycysteina (NAC)
  - Over-the-counter supplement
  - Affects neurotransmission and has anti-inflammatory properties linked to oxidative pathways. Glutamate most commonly used brain neurotransmitter.
  - Leads to increased plasma cysteine levels and increases in brain glutathione
  - 8 weeks double-blind controlled study in cannabis-dependent adolescents (n-116), NAC participants (1200mg bid) had twice the odds of negative cannabinoid urines compared to placebo
  - Subjects also received contingency management and had brief (<10minutes) cessation counseling at each visit. Rate of negative urines was 41% compared to 27% for placebo

Summary (cont)

- Over last 3 decades, MJ potency has increased, age of onset has decreased, & more are seeking treatment for abuse/dependence
- A M.J. withdrawal syndrome has now been reliably documented in both clinical & human laboratory studies
- After chronic heavy MJ use, cessation can be very difficult and relapse is common (71%).
- There is increasing evidence of the involvement of chronic MJ use in mood & anxiety disorders, earlier onset of schizophrenia, & schizophrenic relapse

Medical Marijuana
Compassionate intervention or Oxymoron
Key Issues

- **Mode of use**
  - **No other approved medication by the smoked route**
  - **Potential carcinogenicity: one M.J. cigarette deposits about as much tar as 4 of tobacco; even worse with blunts because of tobacco wrap**
  - **Difficulty of delivering exact dose**

Medical Marijuana
Key Issues

- **FDA approval vs referenda or state legislation**
  - **No other medication non-FDA since Lactrile in the 1980's which turned out to be both ineffective and potentially lethal**
  - **FDA approval has helped keep both dangerous and ineffective meds off the market**
  - **"The plural of anecdote is not data"**
  - **What does the scientific evidence show about efficacy**
  - **Objective evidence vs subjective reports**

Medical Marijuana
Key Issues

- **Issues of potency, purity and composition**
  - **5% or 15% or higher THC levels**
  - **Contamination by molds, fungi, or sprays**
  - **Which cannabinoids: especially critical re % of cannabidiol (CBD) which can be both anti-THC and anti-psychotic**
- **What indications and are there appropriate alternatives**
  - **Oral cannabinoids such as dronabinol, a schedule III since 1985 and nabilone**
  - **Other existing medications for pain, nausea, cachexia, glaucoma, etc**

Role of the Physician

- The State bills decide who gets medical M.J. using a gateway definition of medical conditions required to get it.
- Some states specify conditions, others “or any other condition for which M.J. may be helpful”
- Usually a few Drs write most of the “recommendations” (not “prescriptions because not FDA approved”)
- Because of varying potency, can’t really specify frequency, dosage, etc. Usually no pt/Dr relationship required
- In one survey, only 2 of 500 Drs say they would issue a medical m.j. card

Proposed Medical Uses of Cannabinoids

- Anti-emetic for severe nausea/vomiting associated with cancer chemotherapy or other causes
- Cachexia associated with AIDS or cancer
- Spasticity secondary to neurologic diseases such as multiple sclerosis
- Pain management, especially neuropathic pain
- Rheumatoid arthritis
- Proponents: “Anything individual feels marijuana may be useful for”
- Most medical claims anecdotal: “Plural of anecdote is not data”
- “The grass makes the other side of the hill look greener”

Proposed Medical Uses of Cannabinoids

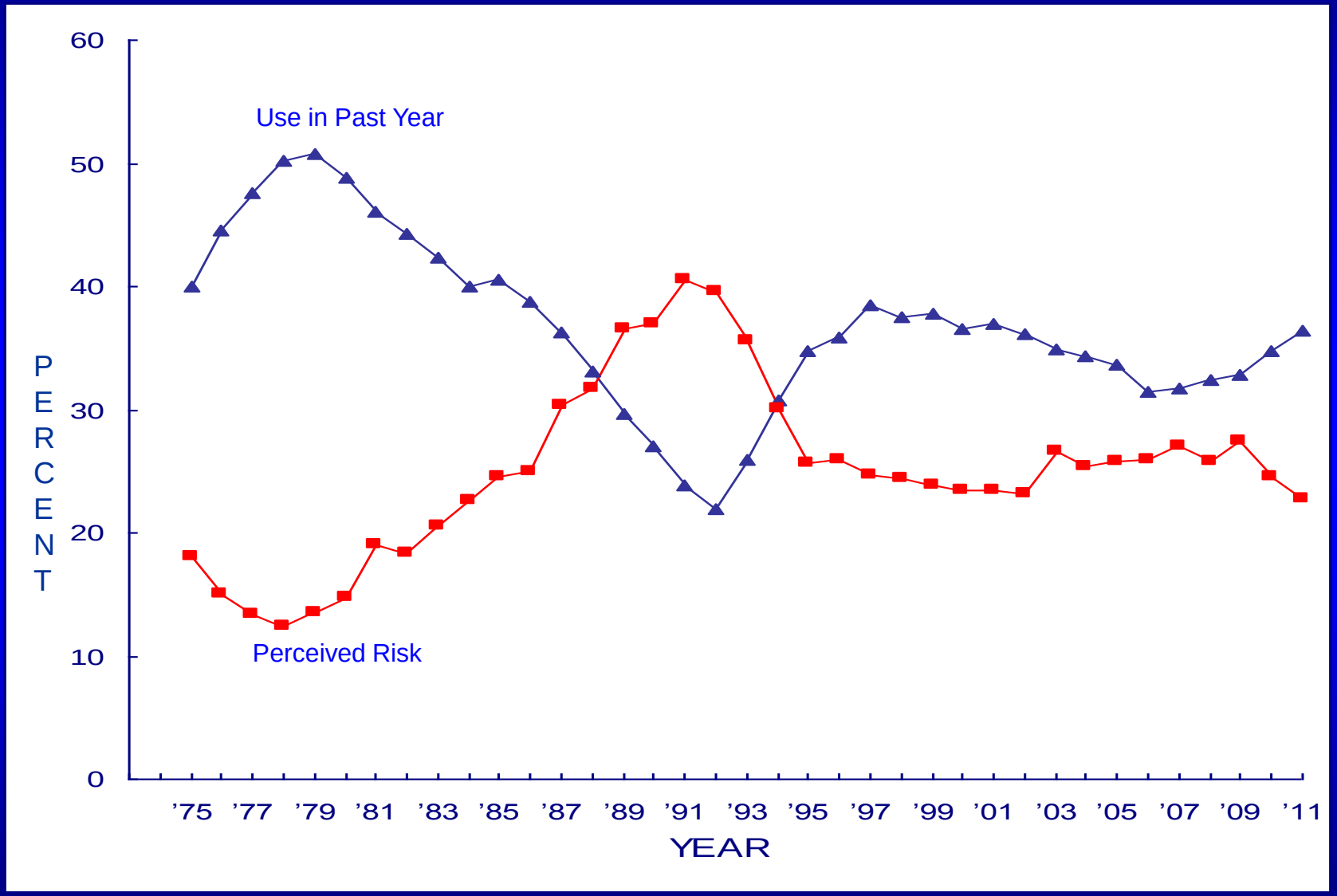
(Continued)

- Most studies have used oral THC
- Sativex – combination of THC (Cannabis Sativa) & Cannabidiol, (CBD) delivered via aerosol. Approved for muscle spasticity & pain in M.S. (Canada). Studied in U.S. for cancer-related pain
- CBD both a THC antagonist and an anti-psychotic
- Often bred out of dispensary M.J.

Key Issues

- Effect of "Medical M.J." on teen-age use
  - Best predictors of teen-age use are perceived risk and perceived social disapproval which go in opposite direction to use.
  - In 2011, the highest 12th grade daily use in 30 years
- Is "Medical M.J." primarily a stalking horse for legalization of recreational use – now in 2 states
- 20 states plus D.C. have "Medical M.J."

Trends in Annual Use of Marijuana vs Perceived Risk among 12th Graders



Source: The Monitoring the Future study, the University of Michigan.

Why are we concerned about medical marijuana?

- Increased adolescent and young adult use
- 10% of users likely to become dependent and find it difficult to stop
- Smuggling large amounts of M.J. to non-medical M.J. states
- Increased auto accidents
- Hard to close even if locality wants to because of lawyers and money, money, money

Summary of "Medical Marijuana"

- Most "Medical M.J. users do not have any of the serious conditions for which proponents claim there is a need
- Most evidence of effectiveness anecdotal
- Where it can be effective, there are existing approved medications
- Increased knowledge of endocannabinoid system should improve both treatment and use of derivatives from cannabis plant
- IOM Report "There is little future in smoked m.j. as a medically approved medication. Its future lies in its components."
- Both public and medical field have taken m.j. use too lightly, leading to increased use and more casualties