©Addiction as a Brain Disease Implications for Drug Policy

Bertha K Madras, PhD
Professor of Psychobiology
Department of Psychiatry
Harvard Medical School

Δ6-THC, Stable Cannabinoid, Found in Ashes at Archeological Site (1,600 Years old)

- **Over millennia, our ancestors, foraging for food, serendipitously discovered that certain ingested plants were a source of unique rewarding sensations and of medicine.**

- **Evidence that marijuana was used medicinally 1400 years ago.**

- **An archeological site Beit Shemesh near Jerusalem excavated the skeleton of a ~14 year old girl;**

- **full term baby; pelvis was 7-7.5 cm but need 9 cm anterior-posterior to give birth vaginally;**
- **coins were 315 -392 CE**
- A metabolite of marijuana was found in the ashes near her nose

Cannabis burned to promote uterine contractions?

Ancient Egyptian usage?

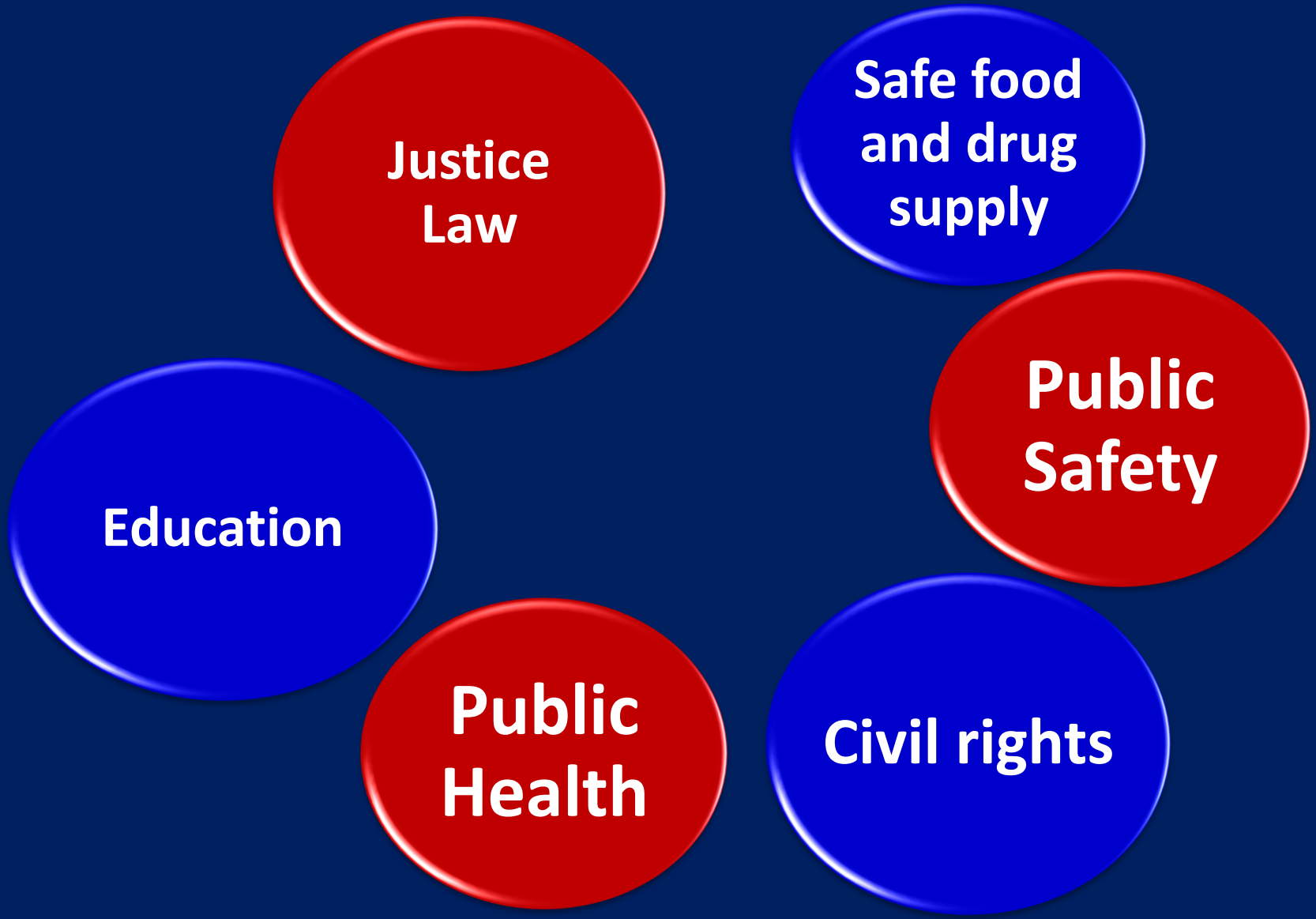
Source: Zias J, Stark H, Sellgman J, Levy R, Werker E, Breuer A, Mechoulam R. Early medical use of cannabis. Nature. 1993 May 20;363(6426):215

Demand Reduction (Prevention, Intervention, Treatment) Is a Major Challenge

Effective Prevention	Effective Intervention	Effective Treatment	Human consequences
Costs	Specific populations	Emerging drugs	Research voids
Scalability	Controversies	International Policies	

Madras BK. Office of National Drug Control Policy: a scientist in drug policy in Washington, DC. Ann N Y Acad Sci. 2010 Feb;1187:370-402. Review.

Drugs and Government Responsibility



I. Drug Biology

WHY DO PEOPLE USE DRUGS?

DRUGS: ACUTE EFFECTS

DRUG USE: LONG TERM EFFECTS

ADDICTION AS A BRAIN DISEASE

WHY DO PEOPLE USE DRUGS?

A focus on science

Drug Rewards Are Universally Sensed in Animal Brains (from insects to humans)

DRUG	HUMAN	ANIMAL
Caffeine	Yes	Yes
Alcohol	Yes	[Yes]
Nicotine	Yes	[Yes]
Marijuana	Yes	Yes
Cocaine	Yes	Yes
Heroin	Yes	Yes
Hallucinogens	Yes	Some
Inhalants	Yes	?
Benzodiazepines	Yes	Yes

People Take Drugs for Many reasons

- ***To have novel*** feelings sensations experiences **AND *To share them***
- ***To alleviate*** **anxiety worries fears**
- ***To alleviate*** **sadness depression hopelessness**

TO FEEL GOOD

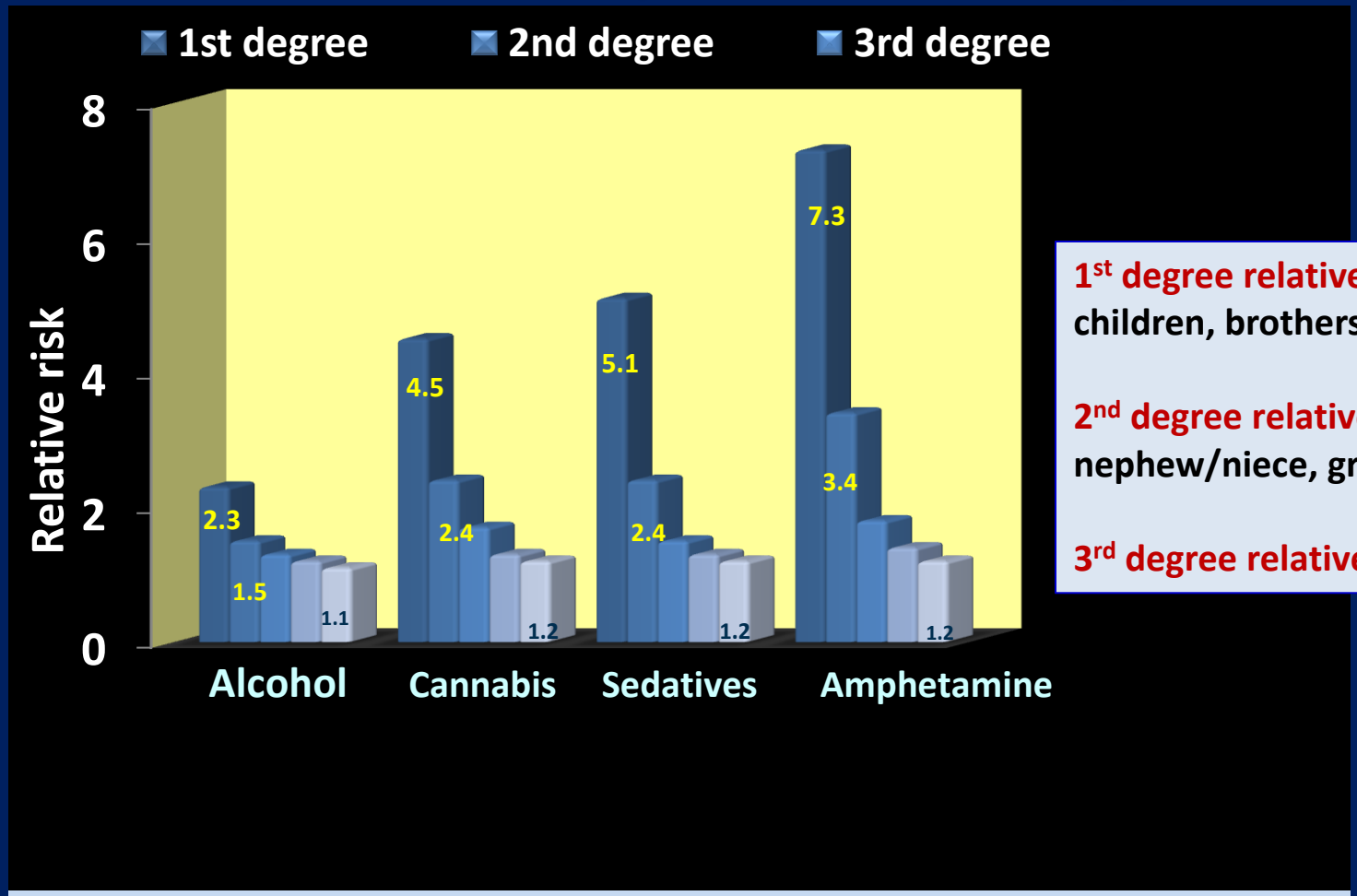
TO FEEL BETTER

Self-medication or chemical coping

RISK FACTORS

Risk factors: Person and Genetics

Relative risks of substance dependence: 1st - 5th degree relatives



1st degree relative: parents, children, brothers, sisters

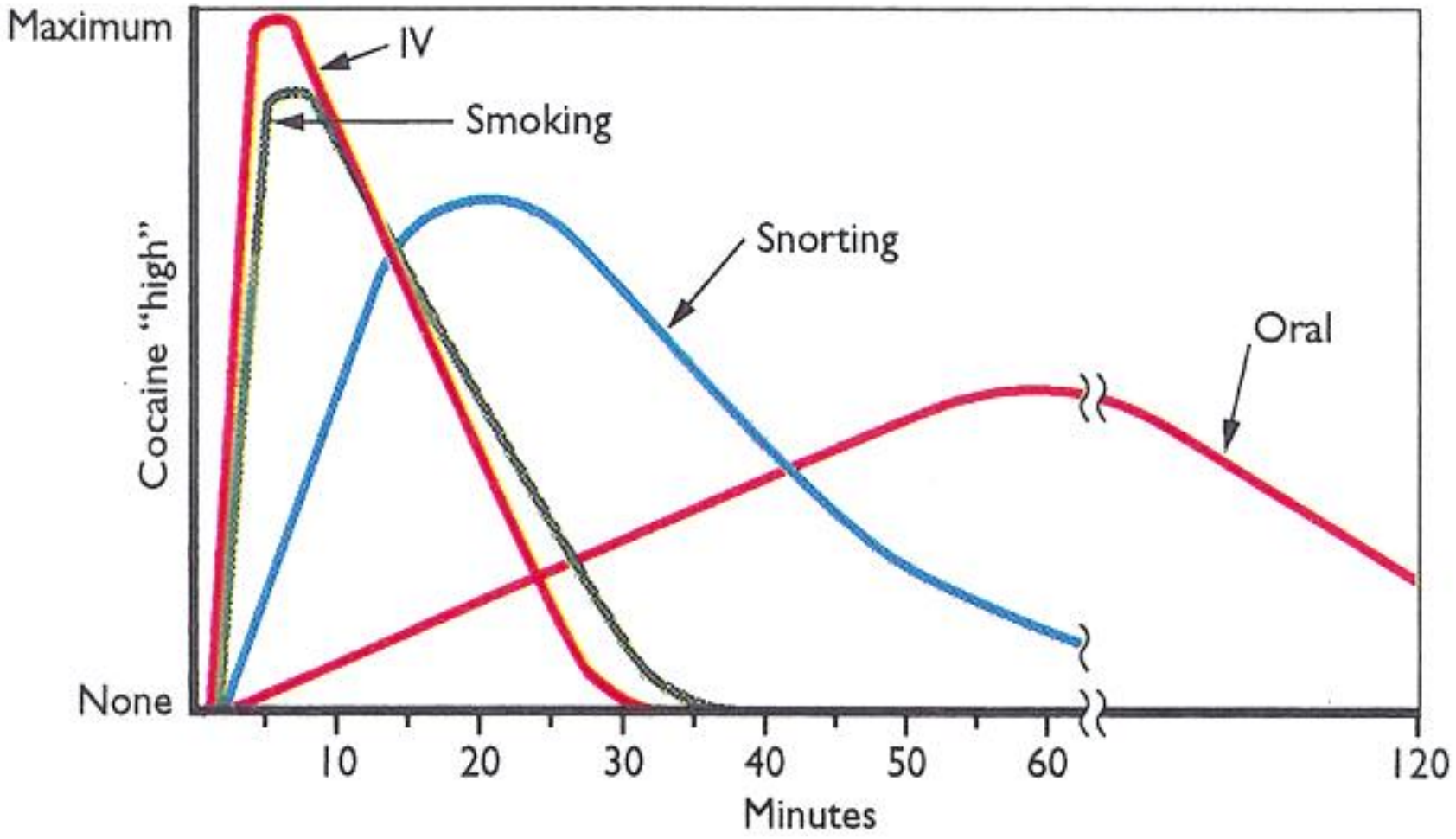
2nd degree relative: aunt/uncle, nephew/niece, grandparent

3rd degree relative: cousin

Tyrfingsson et al. Addictions and their Familiality in Iceland. Ann N Y Acad Sci. 2010 Feb;1187:208-17.

Risk Factor: DRUG

Risk Factor: DRUG



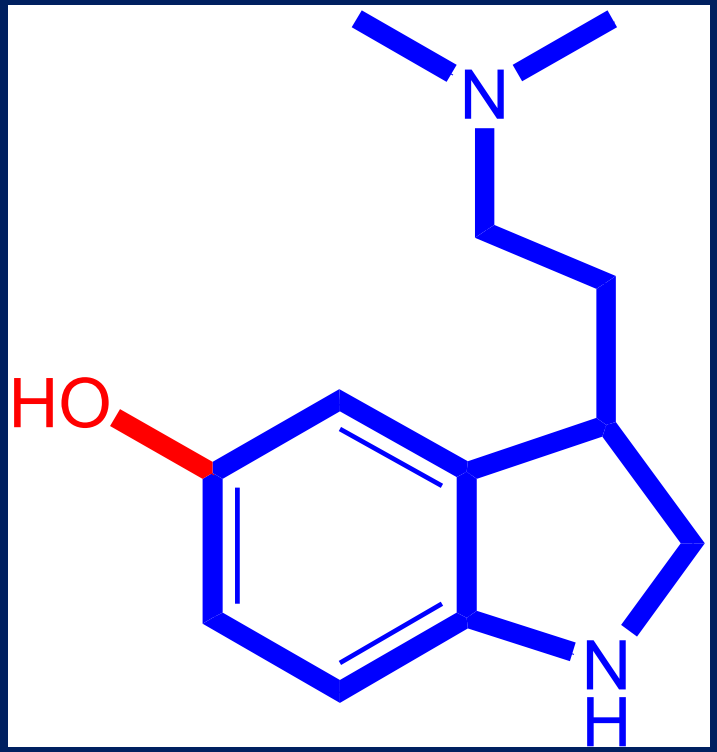
DRUGS: ACUTE EFFECTS

How do Drugs Affect the Brain?

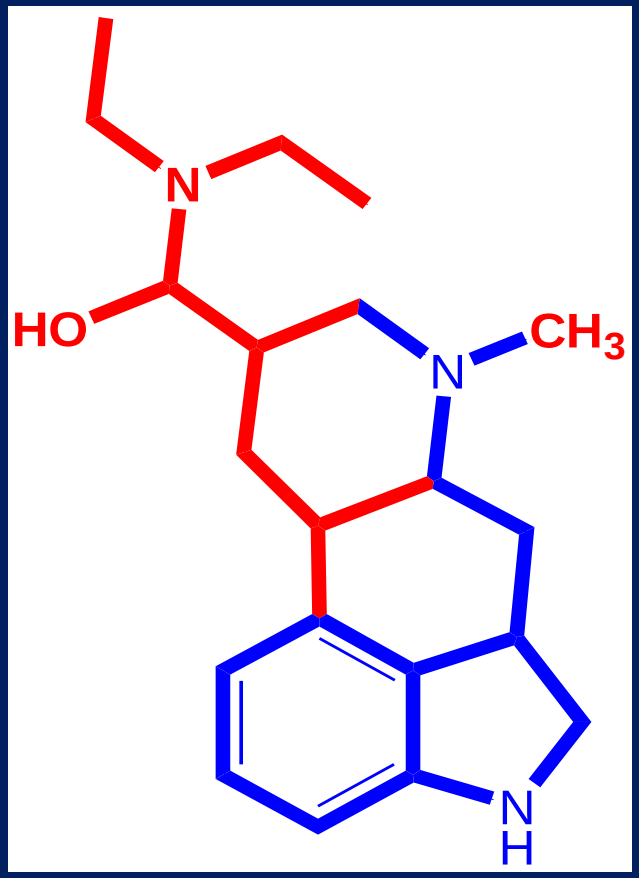
- Communication among people, within the body is the key to understanding drug effects.
- The earliest life forms on earth remained a single microscopic cell, until they developed and ability to communicate.
- When two cells were able to signal by sending chemical messages to each other, they could join together and search for food or avoid danger in unison.
- With the emergence of large complex animals, came a vast and complicated brain and nervous system to coordinate billions of cells.
- The key to this communication are chemical messages sent by one nerve cell to another, received, and interpreted.

Drugs are "Imposters" of Brain Chemical Messages

SEROTONIN

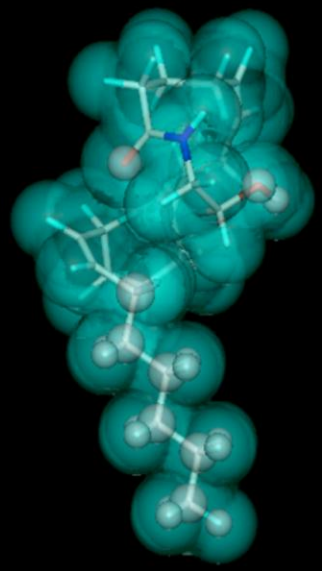


LSD



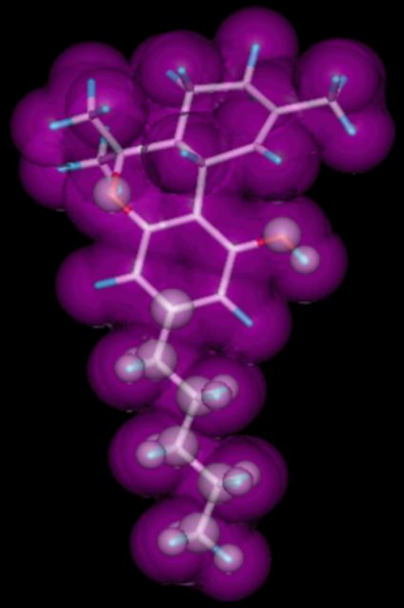
Drugs are "Imposters" of Brain Chemical Messages

Made by the brain



Anandamide

THC made by Cannabis Sativa



THC

Summary: Immediate Effects of Drugs

Many drugs of abuse are imposters of brain chemical messages

Drugs affect, modify brain communication.

These changes produce positive sensations

Normal brain signaling ≠ drug signaling

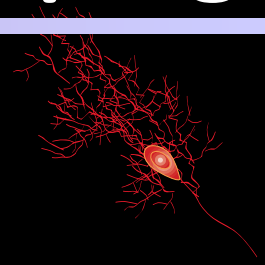
Drug-induced signals promote adaptation...
Adaptation changes the brain, behavior

DRUG USE: LONG TERM EFFECTS

- Acute effects of drugs (crime, car accidents, child neglect) are critical and help to shape public policy.

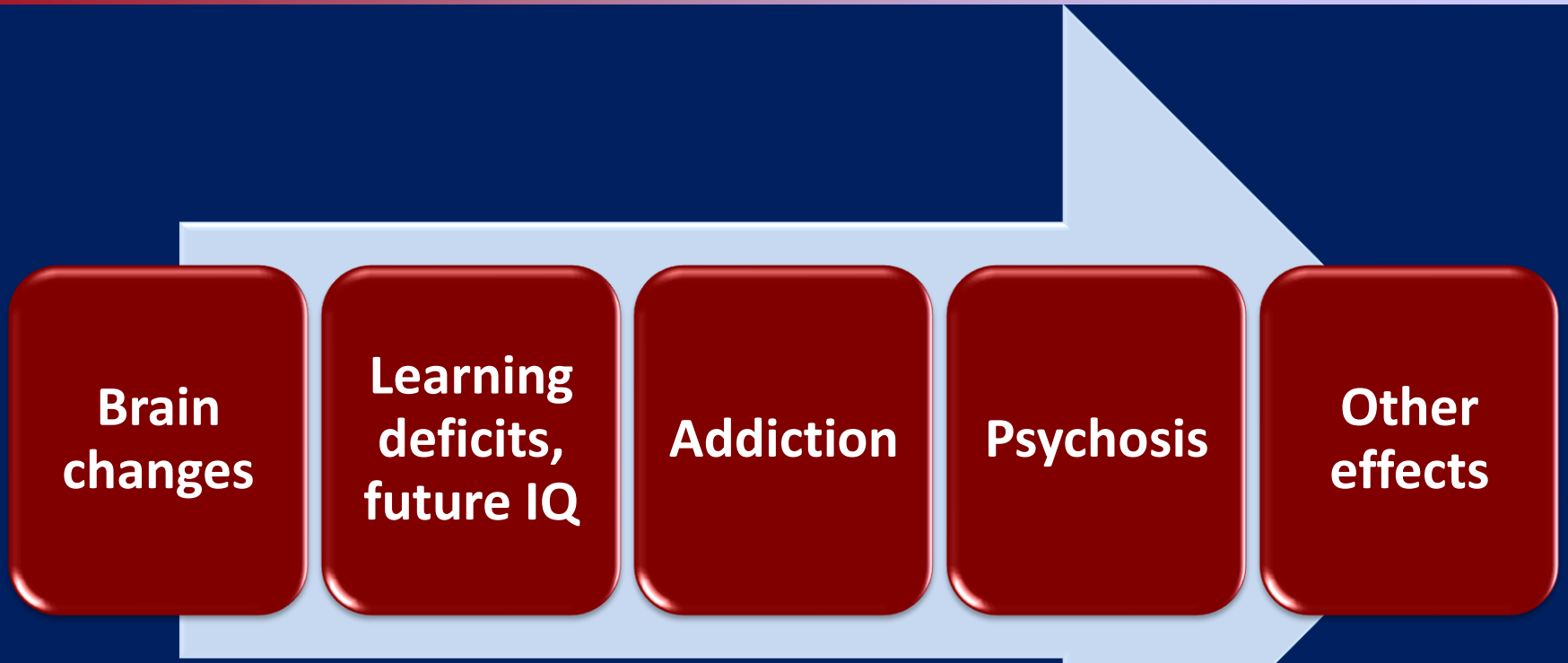
- But the longer drugs are consumed by individuals, the greater their personal problems and problems for society

Adolescents Are Major Concern Because Their Brains Are Developing



- Adolescents are a major concern because their brain is undergoing rapid development.
- Brain development is an exquisitely regulated progression of formation of circuits and connections.
- The brain contains over 100 billion nerve cells and each cell may have a few or upward of 10,000 connections with other cells.
- With meticulous precision, a family of proteins steers the complex formation of neural circuits, some by lengthening, others by stopping or directing the wires (axons) that connect nerve cells.
- Increasing evidence indicates that the introduction of drugs during adolescence may alter the normal trajectory of adolescent brain development, leading to a much higher vulnerability to addiction and to other consequences.

Drugs Affect Adolescents More Than Adults



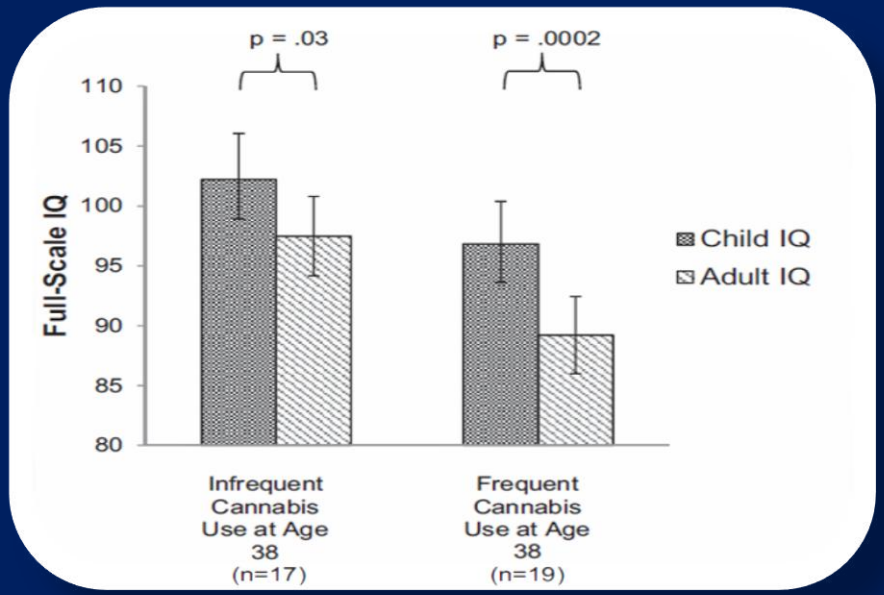
Arseneault et al., 2002; van Os et al, 2002; Zammit et al., 2002; Henquet et al., 2005; Stefanis et al., 2004; Rubino and Parolaro, 2008; Konings et al., 2008; Andreasson et al., 1987; Moore et al, 2007; McGrath J, et al. Arch Gen Psychiatry. 2010 May;67(5):440-7. Association between cannabis use and psychosis-related outcomes using sibling pair analysis in a cohort of young adults

Adolescent Marijuana Users Have Enlarged Brain Cerebellum: Association with Poor Executive Function

- 16-18 years , repeated marijuana use, one month after last dose of marijuana.
- Cerebellum (vermis 8-10) is greatly enlarged compared with non-marijuana users.
- The more the enlargement, the poorer adolescents perform on cognitive (executive) function.
- Marijuana interferes with normal pruning process in this brain region?

Source: Medina KL, Nagel BJ, Taper SF. Abnormal cerebellar morphometry in abstinent adolescent marijuana users. Psychiatry Research: Neuroimaging 182: 152-159, 2010.

Early Marijuana Use Associated With Persistent, Irreversible Lower IQ

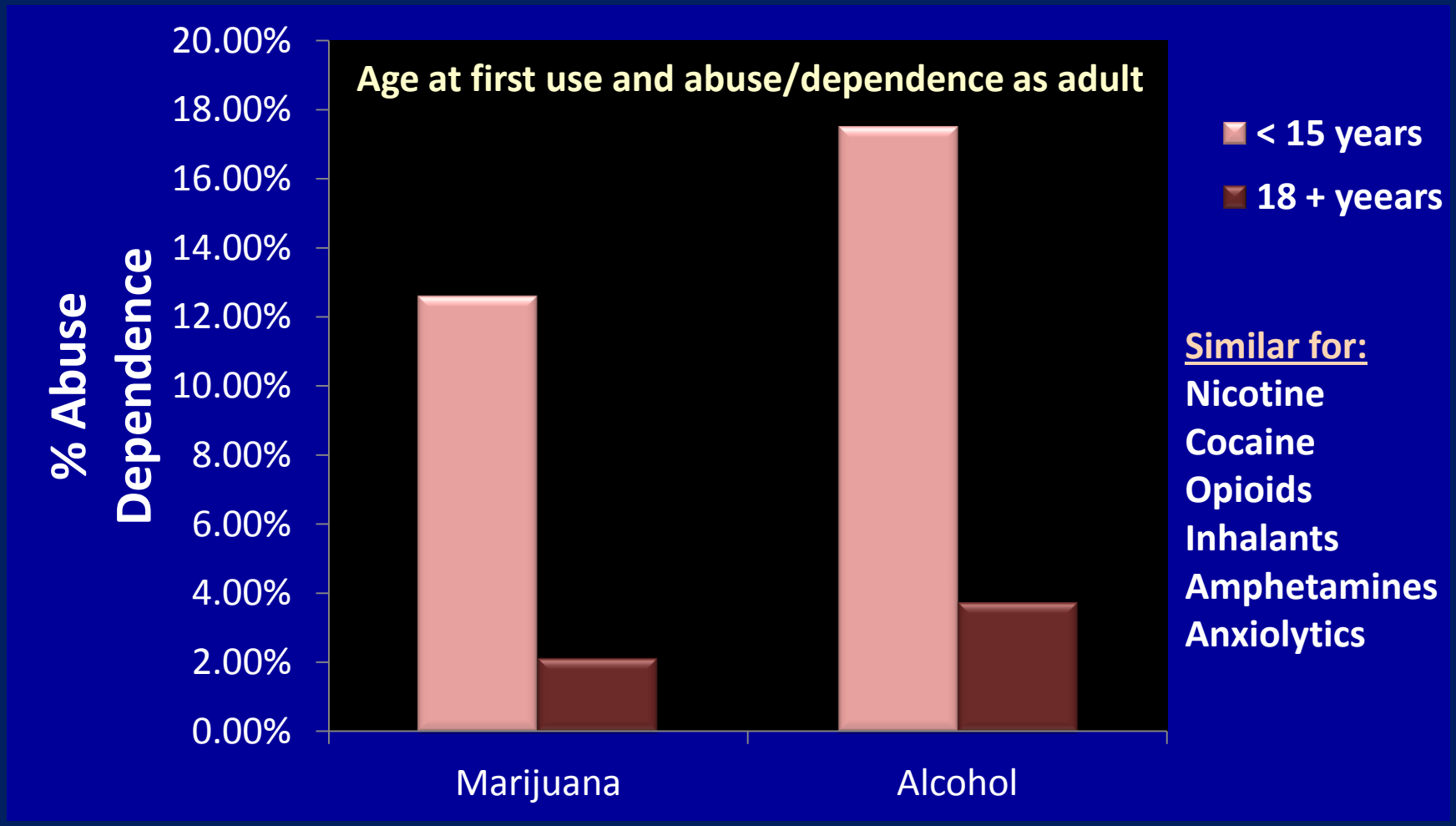


13 yr **18 yr** **21 yr** **32 yr** **38 yr**

Meier et al, Persistent cannabis users show neuropsychological decline from childhood to midlife. Proc. Natl. Acad. Sci *USA,* [epub August 27, 2012]

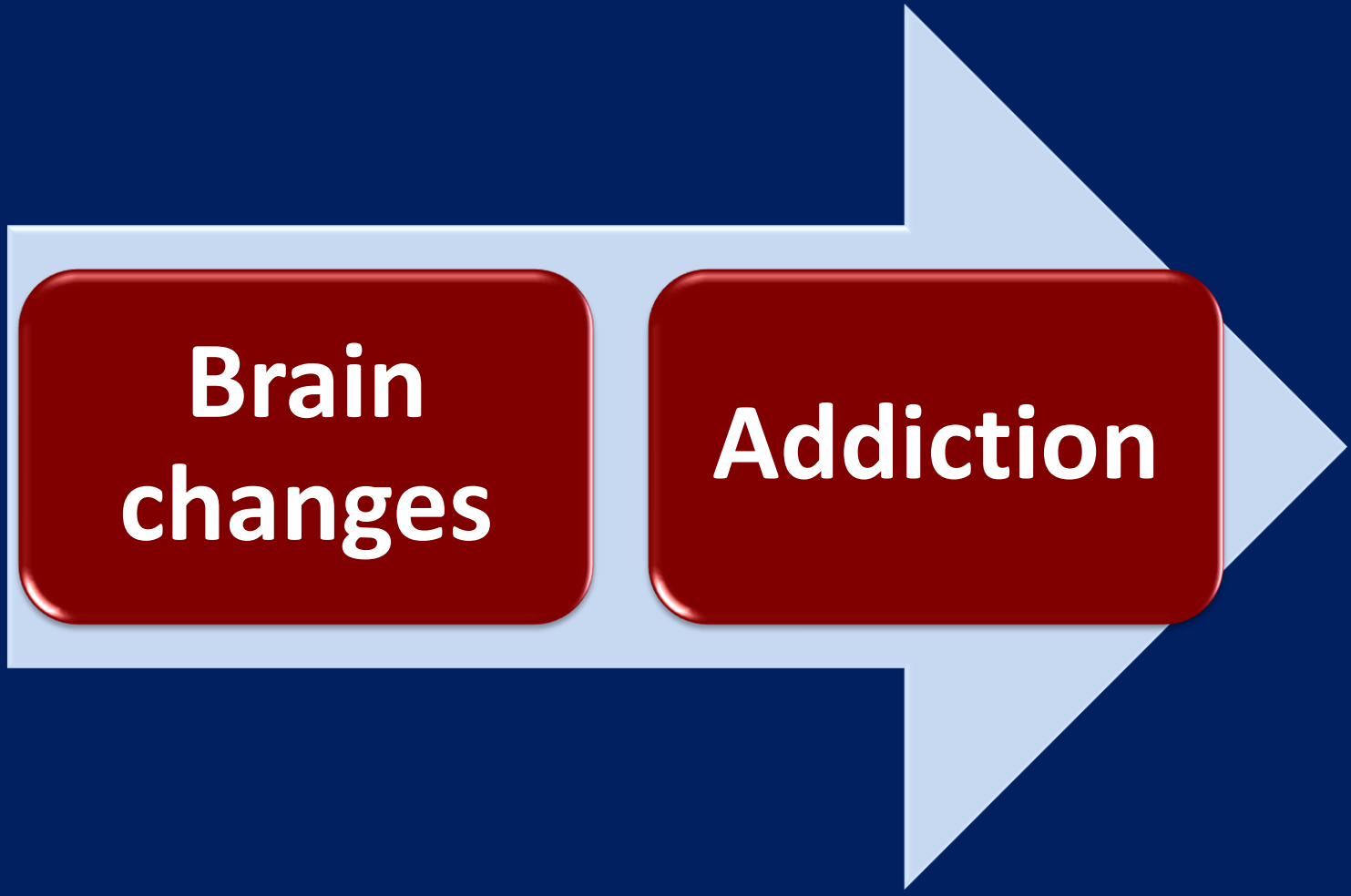
Early Drug Use Associated with Higher Addiction in Adulthood

5-6 Times Higher if Teenager Starts Using at Age 14 or Less



2010 National Survey Drug Use and Health, NSDUH Sept 2011; Anthony and Petronis, Drug Alcohol Depend. 40: 9 -15,1995

Drugs Adversely Affect Wide Populations

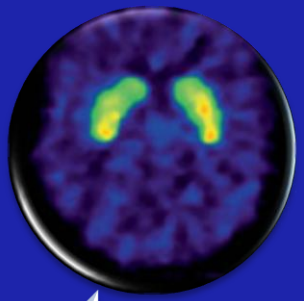


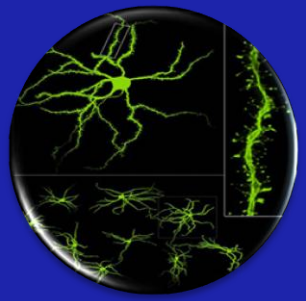
Drugs Change the Brain

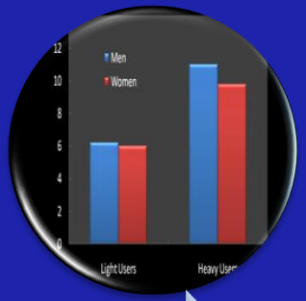
- **Brain receptors (examples)**
  - **Brain dopamine D2 receptors are reduced in methamphetamine and cocaine abusers. Mu-opiate receptor availability of detoxified alcoholic patients, is reduced compared with healthy volunteers.**
- **Brain connections (example)**
  - **Diffusion-weighted magnetic resonance imaging and brain connectivity mapping techniques were performed in 59 heavy cannabis users and 33 matched controls. Axonal connectivity was impaired in the hippocampus (fornix), associated with the age at which regular cannabis use commenced. Long-term cannabis use is hazardous to the white matter of the developing brain**
- **Blood flow**
  - **F18 FDG in occasional and frequent marijuana users. An occasional user shows minimal increase of glucose metabolism 30-40 minutes after iv THC. A chronic heavy (1-5/day; 4-7 times/week) increased glucose metabolism after iv THC. In most brain regions.**
- **Brain size**
  - Cerebellar vermis increased, hippocampus reduced in adolescent chronic marijuana users
- **Brain genes**
  - **Many examples of changes of gene expression after repeated use of drugs**

Modified from Volkow ND, Fowler JS, Wang GJ, Baler R, Telang F. Neuropharmacology. 2009;56(Suppl 1):3–8. Andrew M et al 2012: 135; 2245–2255. From Heinz A,Reimold M, Wrase J, et al. Arch Gen Psychiatry 2005;62(1):59. Chang and Chronicle, Neuroscientist 13: 422, 2007.

The Brain Adapts to Repeated Drug Exposure







Biology

Communication

Brain size

Brain circuits

Behavior

Brain function

Cycle of Addiction

Initiation

Adaptation, toxicity

Abuse

Addiction

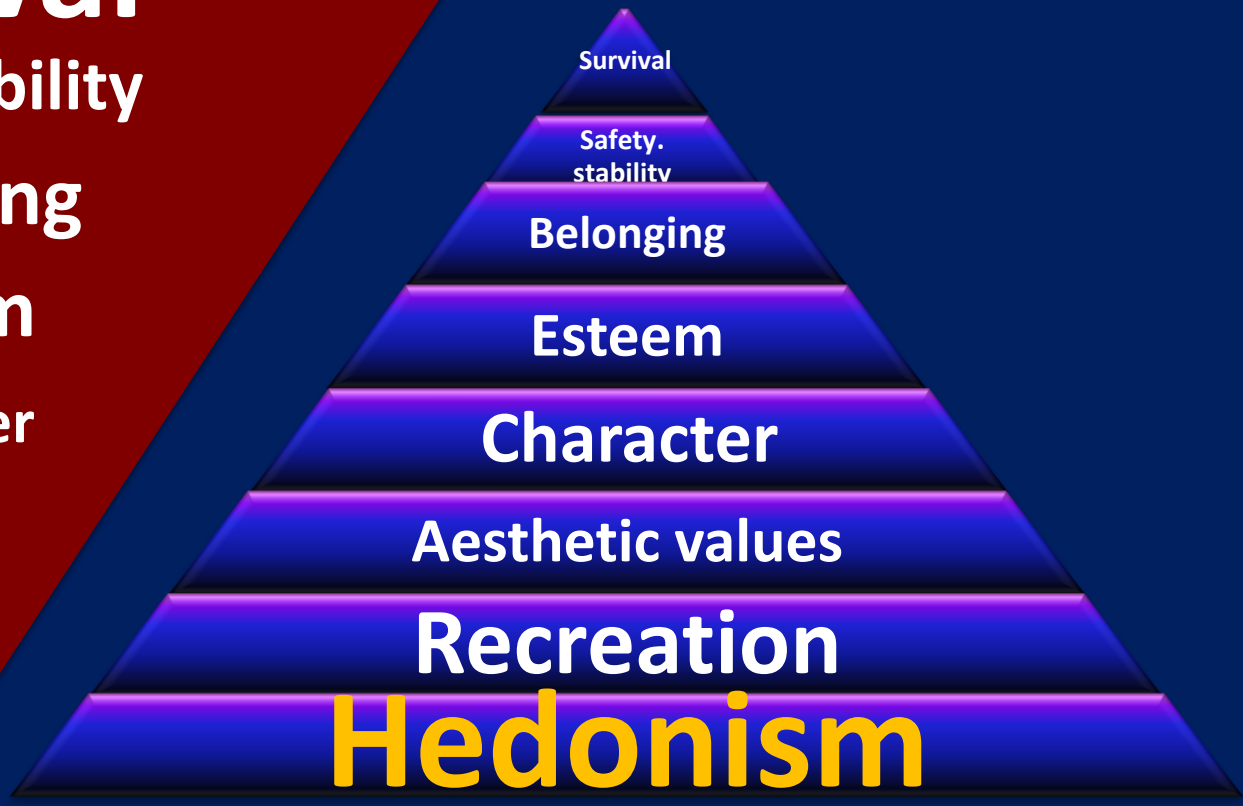
Withdrawal

Treatment

Craving

Relapse

Addiction: A Shift in Values



Addiction as a Brain Disease?

Loss of Control

- Compulsive drug seeking
- Compulsive use
- Inability to control
- Use more than intended

Adverse Consequences

- Health, social, educational
- Use instead of important life activities
- Spend emotional or physical time drug-seeking

Tolerance Withdrawal

Addiction falls along a spectrum from less to more severe

Biology of Addiction: Common Theories
None is Correct and Many Questions

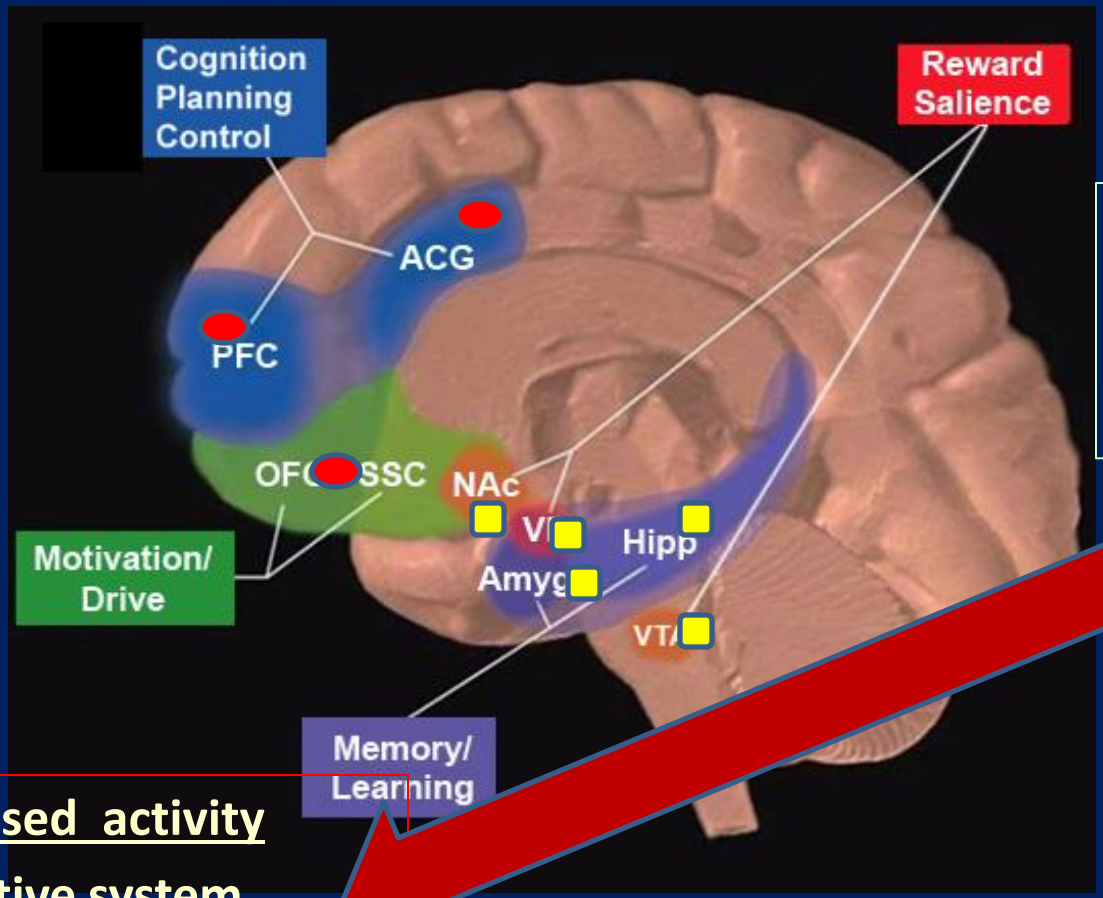
Addiction

1. Deficits in self-control, judgment, decision-making

2. Deficits in learning, memory, motivation, attention

Addiction as a Deficit in Self-control

The Brain Adapts To Drugs: Alcohol, Cocaine, Marijuana



Increased activity

impulsive system

Signals immediate pain or pleasure

Decreased activity

reflective system

Signals long-term pain or pleasure

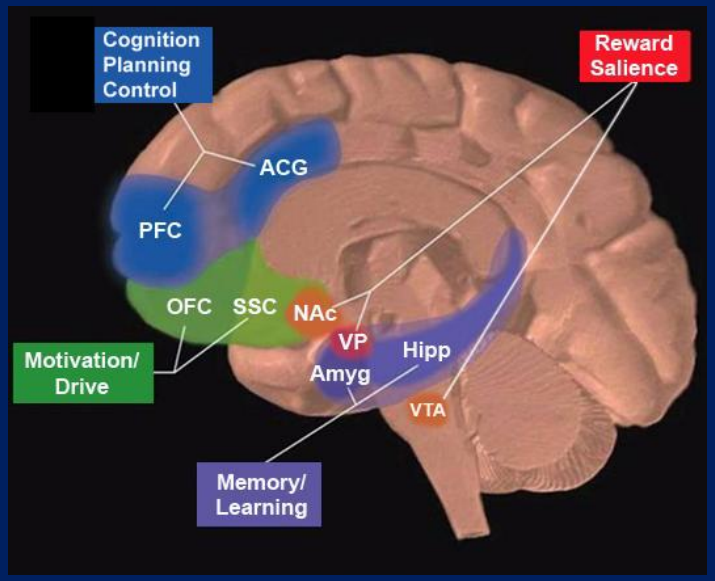
London et al, 1990; Galynker et al, 2000; Ersche et al, 2006; Volkow et al, 2007, (Goldstein and Volkow, 2002, Phan et al.,2002,Saxena et al., 2002) Source: Macmillan Publishers Ltd.: "Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective," by Antoine Bechara, 2005, *Nature Neuroscience, 8, p. 1459 ©2005 by Nature* Publishing Group.

Is Addiction a Brain Disease?

If Addiction is a Brain Disease…

- **Why do some people get addicted and others do not?**
- **Why do some people recover and others do not?**
- **Is drug use voluntary or involuntary behavior?**
- **Should addiction be punished or treated as a disease?**
- **How can a disease be treated by "talking' and not by medications?**

Behavioral Treatments are Effective



Interfere with Drug Reward	Contingency Management
Improve Inhibitory Control	Cognitive Therapy
Strengthen Cortical/ Limbic Connections	Motivational Therapy
Interfere conditioned memories/craving	Neurofeedback Desensitization
Promote new learning	Conditioning
Counteract stress responses to prevent relapse	Relaxation Behavioral Therapy

Courtesy: **NIDA**

II. Public Policy

1. Do Drug Consequences Justify Legal Control?

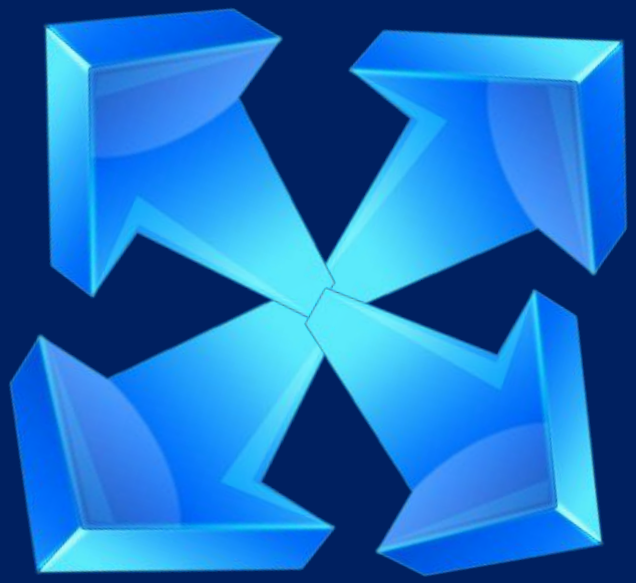
2. Should Brain Disease Model Affect Drug Policy?

3. Effective Action Plans?

Do Drug Consequences Justify Legal Control?

MEDICAL
- Accidents
- Psychiatric
- Other systems

SAFETY, SOCIAL
- **Drugged driving**
- **Violence**
- **Child neglect**



ECONOMIC
- Education
- Workplace
- Healthcare

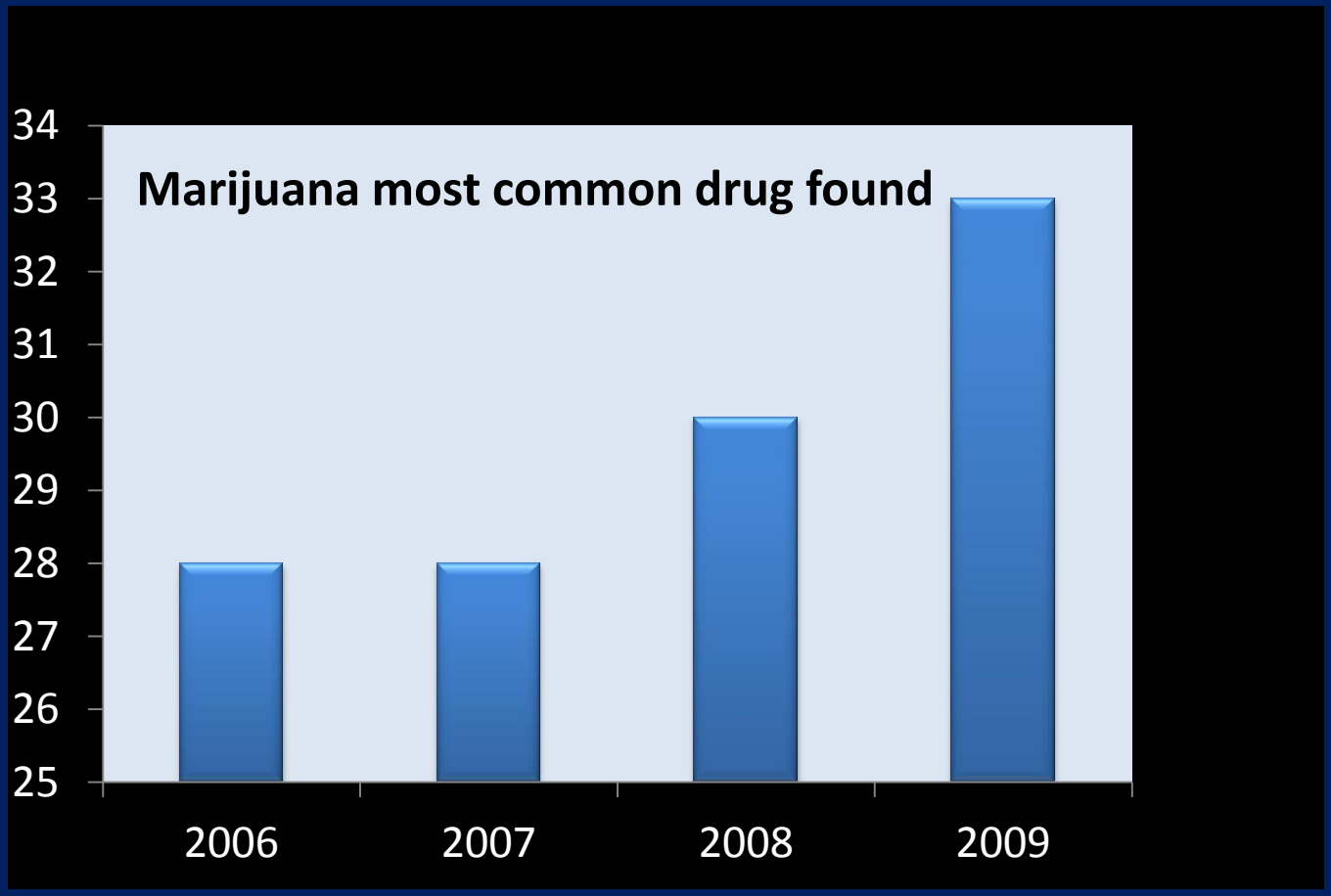
ADDICTION

1. Do Drug Consequences Justify Legal Control?

Drugged driving
Workplace
Crime under the Influence
Emergency rooms
Medical diseases
Overdose Deaths

Drugged Driving Fatalities Increasing

% fatally injured drivers testing Positive for drugs



http://www.nhtsa.gov/PR/NHTSA-16-10; ONDCP

Drugs Affect Workplace

Users are 2-5 times more likely to have:

- **3+ jobs in past year**
- **unexcused, longer absence**
- **been fired in past year**
- **early dismissal, time off**
- **late for work**
- **in workplace accident**
- **file a workers' compensation claim**

1/3 less productive

Drugs Produce Medical Diseases

- Brain
- Lungs
- Heart, blood vessels
- Hormones
- Liver, digestive tract
- Reproduction
- Developing fetus

Strokes in Young People

Subarachnoidal hemorrhage

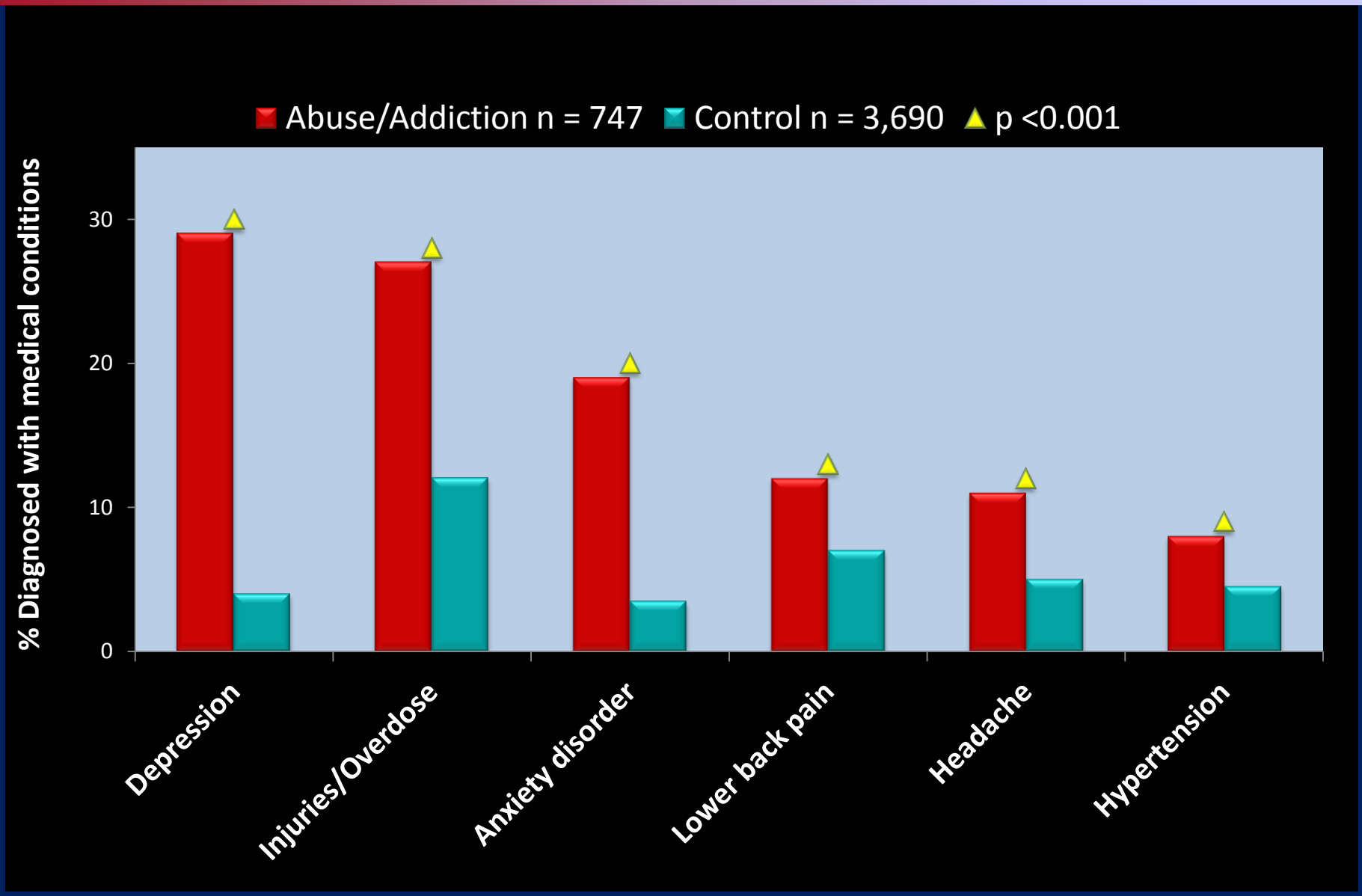
Strokes in young people

Most common cause are:

1. **Cocaine**
2. **Amphetamine**
3. **Methamphetamine**

Source: Reproduced from Buttner ; The Neuropathology of Drug Abuse,
In The Effects of Drugs in the Human Nervous System", 2012, Madras and Kuhar, Editors

Medical Conditions Higher in Addicted Patients



Mertens J et al 2007

Death Rates 3-5 Times Higher in Patients with a Substance Use Disorder

- Drug-related mortality associated with a substance use disorder was assessed in patients hospitalized in California from 1990-2005 with an ICD-9 diagnosis of a primary addiction to methamphetamine (N = 74,139), alcohol (N = 582,771), opioiods (N = 67,104)), marijuana (n = 46,548), or cocaine-related disorders (n = 48,927).
- Groups were followed for up to 16 years and age-, sex-, and race-adjusted standardized mortality rates (SMRs) were generated.
- The opioid cohort had the highest mortality rate (5.71), followed by methamphetamine (4.67), marijuana (3.85), alcohol (3.83), cocaine (2.96).
- Standard mortality rates differed on the basis of sex and race.

(adapted from: Callaghan RC, Cunningham JK, Verdichevski M, Sykes, J, Jaffer SR, Kish SJ. (2012) All-cause mortality among individuals with disorders related to the use of methamphetamine: A comparative cohort study. Drug Alcohol Depend. doi:10.1016/j.drugalcdep.2012.03.004)

2. Should Brain Disease Model Affect Drug Policy?

Public Safety (*Punishment) or *Public Health(Disease to be treated)

- **The purpose of government is to enable the people of a nation to live in safety and happiness.**
- **Government exists for the interests of the governed, not for the governors."**
- **In each of drug consequences, government policy bears some responsibility and oversight.**

2. Should the Brain Disease Model Shape Drug Policy?

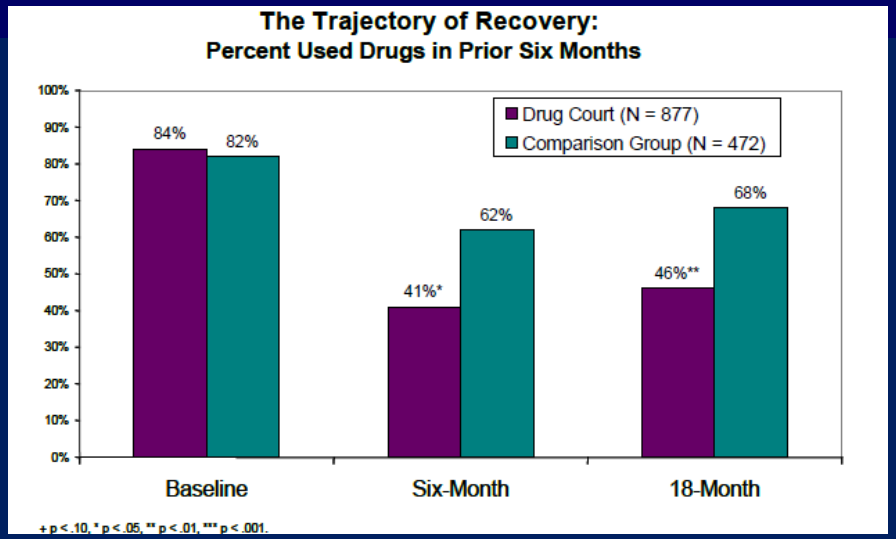
Science Says

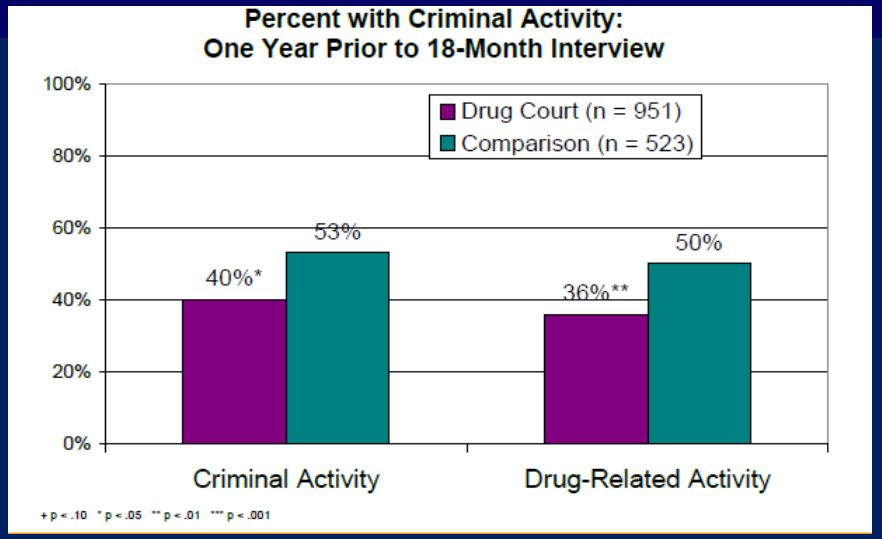
- Drugs induce brain, behavioral changes – disease state.
- Users', addicts' consequences can be severe for self, others.
- Imprisoned addicts, without treatment, have a limited chance of recovery.
- All diseases should be treated.
- Treatment is effective

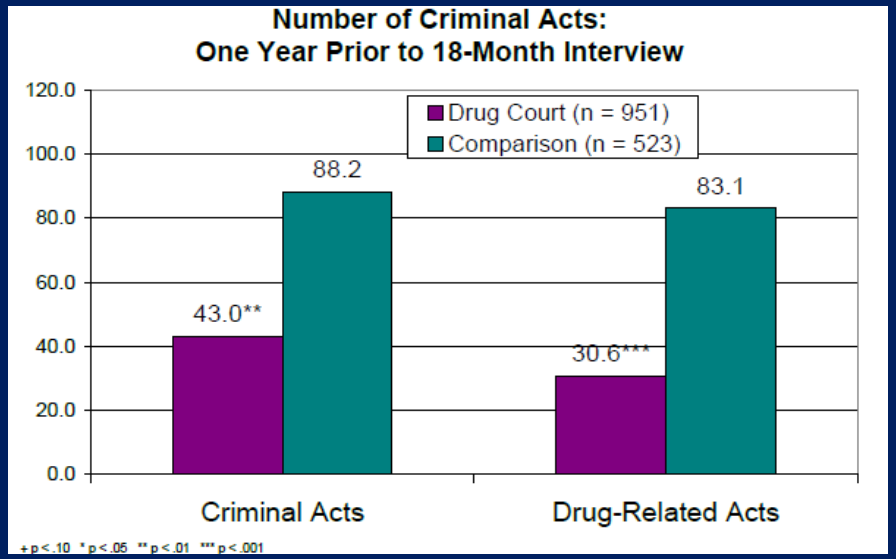
Some People Say

- Some users/addicts want to be left alone.
- Free choice versus common good?
- If some people age out of addiction, let nature prevail.

Drug Courts (Coercive Treatment) is Effective







- **Greatest Cost** = Drug Treatment
- **Greatest Benefit** = Reduced Crime and Victimization
- **Results for the Criminal Justice System** = Up-front costs but eventual savings through reductions in future arrests and incarceration
- **Targeting Lesson:** Benefits driven by a reduction in more serious crimes among a small number of high risk individuals

http://www.urban.org/uploadedpdf/500240-Findings-and-Implications-of-NIJ.pdf

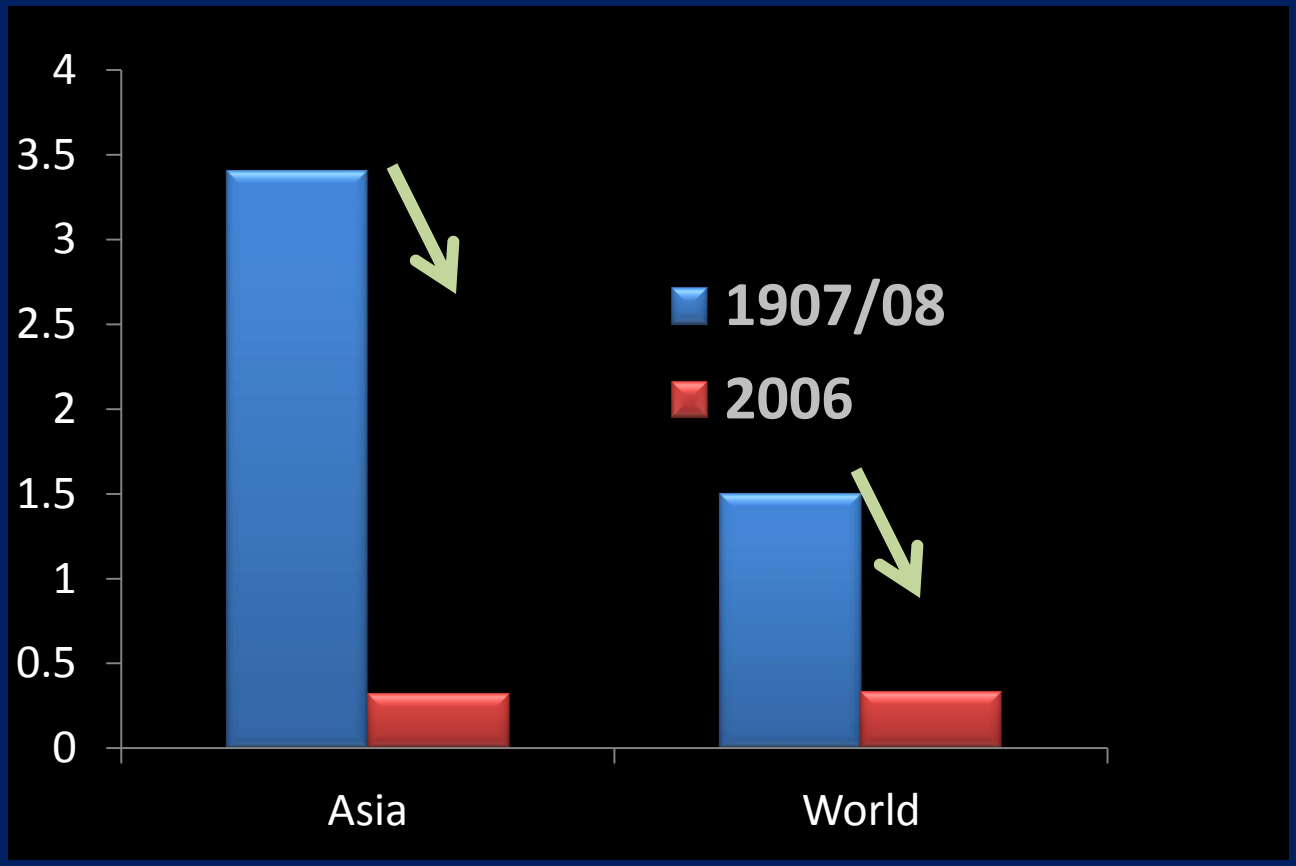
Brain Disease and Policy

- The brain changes after repeated exposure to drugs.
- Addiction evolves into a disconnect between reward and judgment of the reward.
- Treatment and coercive treatment are effective.
- In view of costs to society, legal constraints on drugs are warranted.

3. Action Plans

1. Legal Restrictions on Drugs

International Conventions Reduced Opioid Use dramatically from 1907/08 to 2006



Source: UN Office on Drugs and Crime, 2008 Report

2. Demand reduction
Prevention, Intervention, Treatment

A. Educate Parents, Youth: Science-based information

Reduce number of users

B. SBIRT: Medically intervene with at risk users

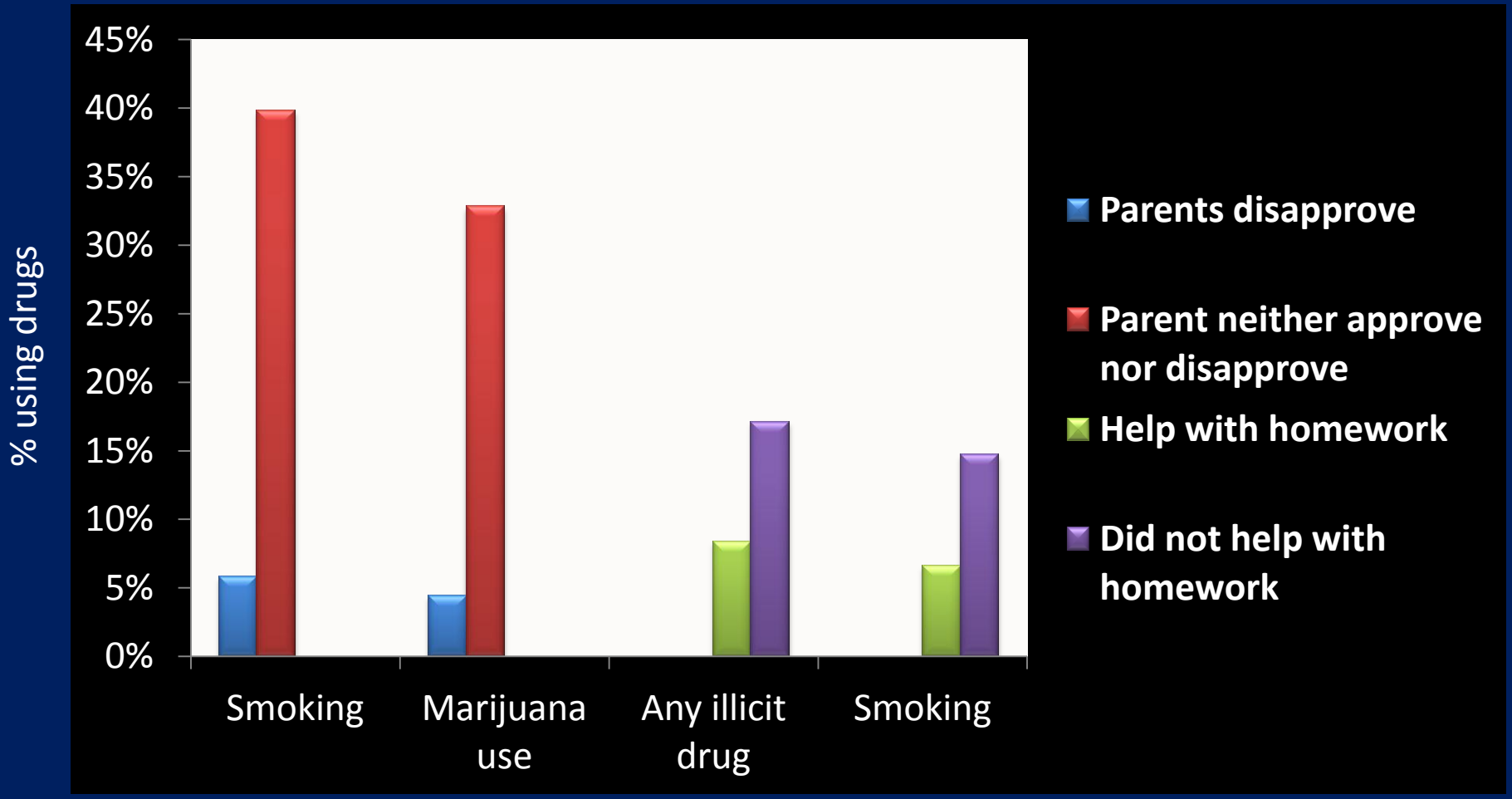
Reduce risky problematic use of alcohol, reduce illicit drug use

C. Provide effective treatment, recovery support to addicted

Reduce number of treatment seekers and addicts

D. Ongoing statistical evaluation of effectiveness

A. Educate Parents: Parents are a key to reducing drug use among children



Source: NSDUH, 2010 published Sept 2011; http://www.samhsa.gov/data/NSDUH/2k10NSDUH/2k10Results.htm

B. Medically intervene with at-risk users

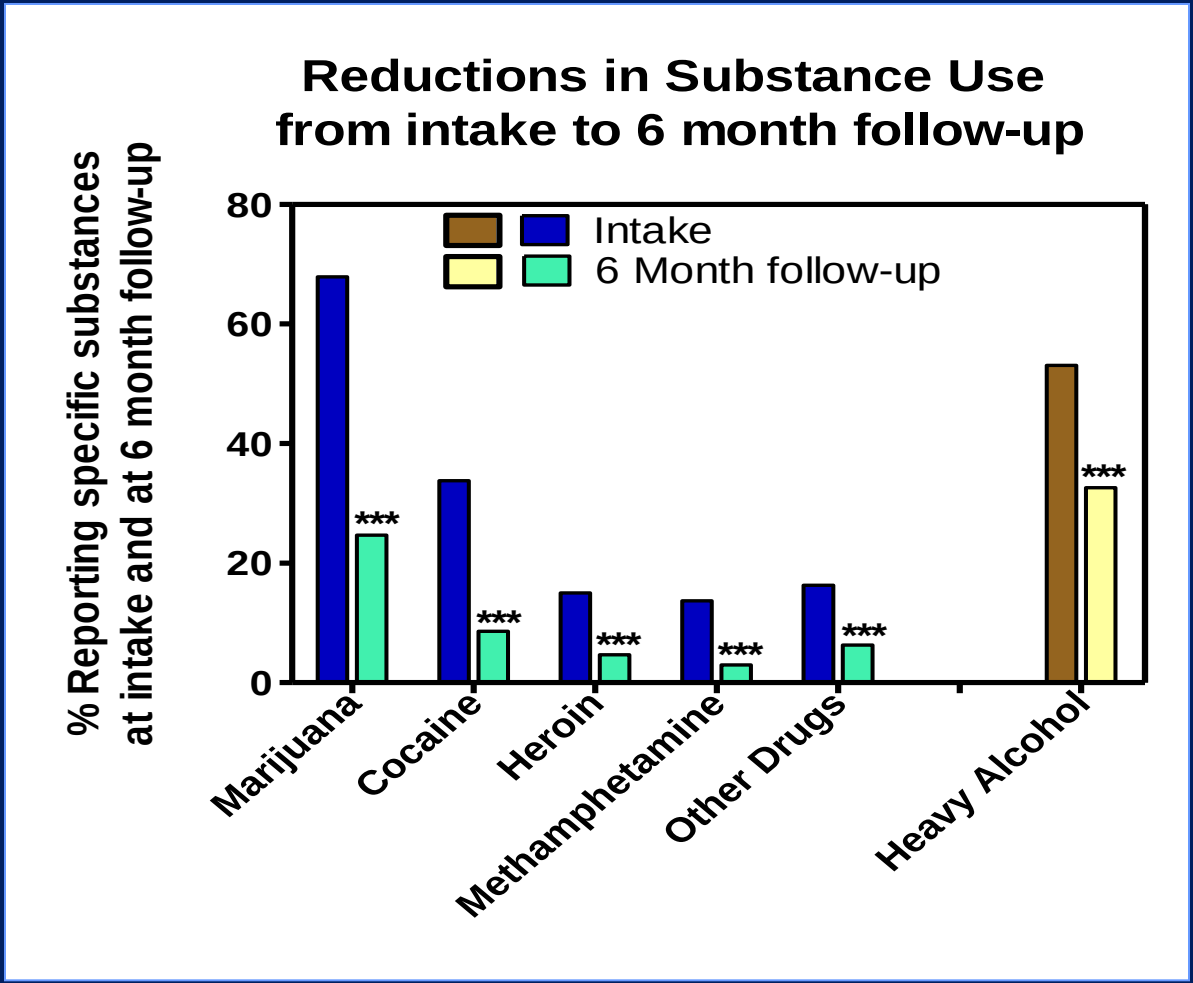
Screening, Brief Intervention, Referral to Treatment (SBIRT) is a Public Health Priority

Hazardous alcohol and substance use has significant medical, social, and financial consequences

Traditional emphasis is either universal prevention or specialist treatment

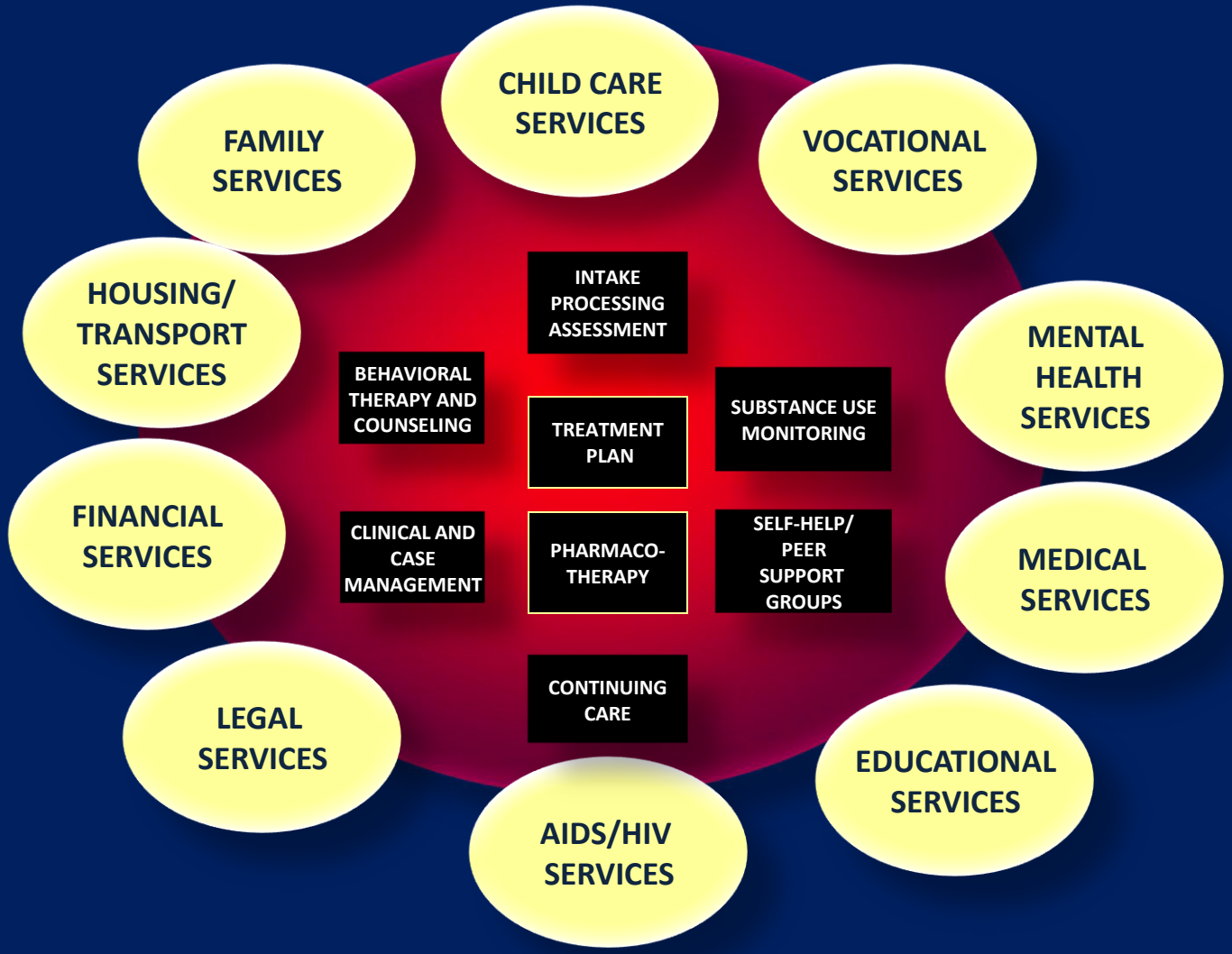
Little attention has been given to individuals who use alcohol, drugs but are not, or not yet, dependent.

SBIRT Effectiveness:
6-Month Follow-up Among Positive Screen For Drugs



Source: Madras et al. Drug and Alcohol Dependence 99: 280-295, 2009

C. Provide Effective Treatment, Recovery Support to Addicted: Attend to Multiple Needs



Source: NIDA

History of Pro-Drug Responses

- **Early in cycle:** Social tolerance prevails
- **Addiction and personal disaster:** Viewed as aberration, exception, belief in invulnerability
- **Casualties:** accumulate gradually; public relatively unaware
- **Addiction exceptions:** Some lifetime addicts remain productive
- **During greatest exposure:** Faith in drugs reigns for 15-25 years

David Musto

History of Anti-drug Movement

- **Resistance to drugs:** takes years to permeate society
- **Perceived risk:** increases over time and reverses
- **Drug problems:** increase at work, family, schools, neighborhood ,shifts perception, shakes invulnerability
- **Drugs previously perceived as "extension of "natural potential":** increasingly viewed as "reducing our potential
- **Non performing addicts:** become miserable and terrifying to families, legal other consequences

David Musto

“This is not a war on drugs!

It is a defense of our brains!”

… BK Madras