

The Science of Addiction: *Prescription Opioid Abuse*



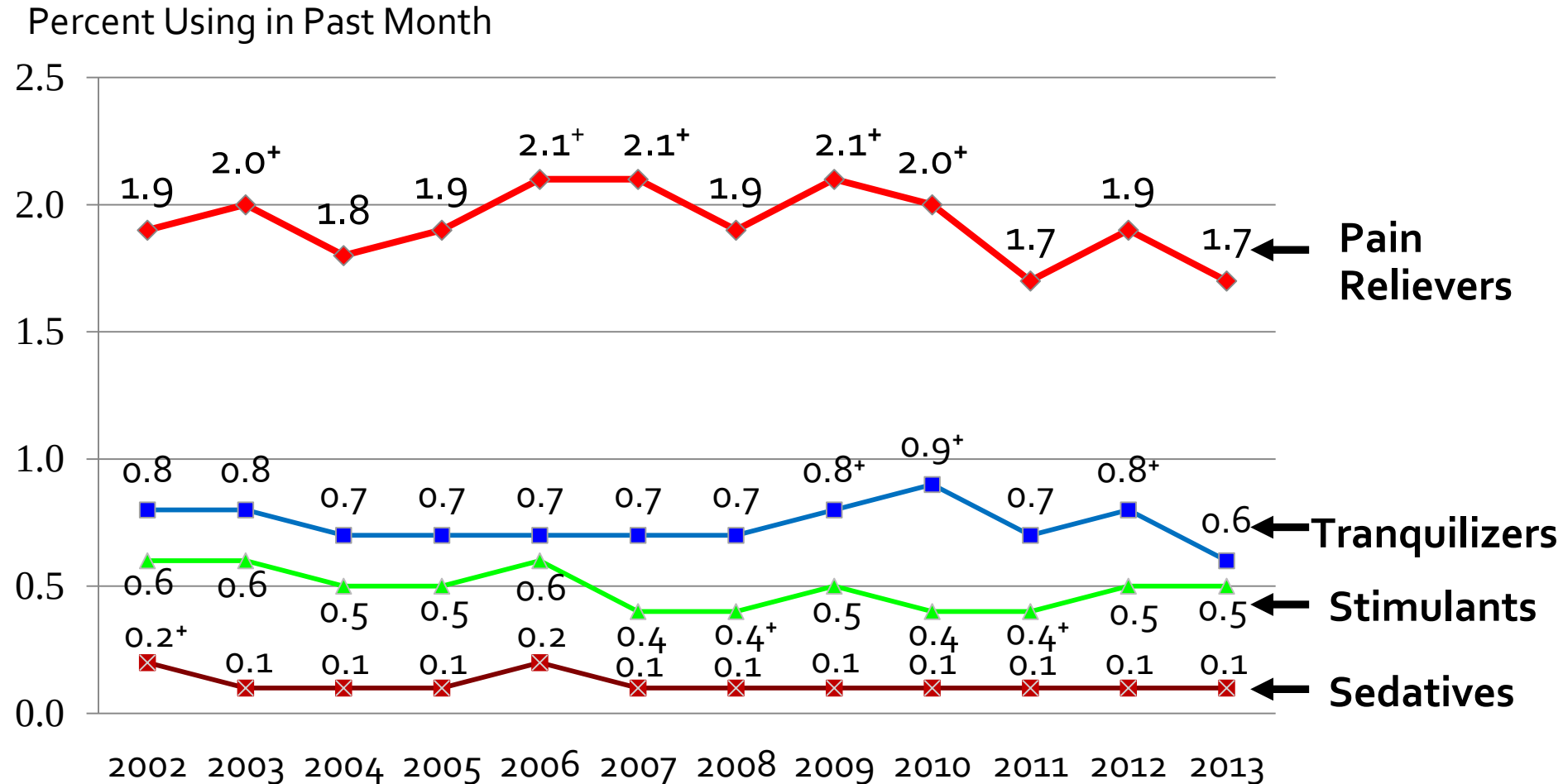
Wilson M. Compton, M.D., M.P.E.
Deputy Director, National Institute on Drug Abuse

Key Points:

- 1. Prescription opioid abuse is a major problem in USA and is related to recent increases in heroin***
- 2. Behavioral and pharmacokinetic factors differentiate Rx use from abuse, but***
- 3. Addiction issues transcend the differences between Rx and related illicit substances***
- 4. Interventions can be effective--both primary prevention and targeting overdose or addiction***

High Rates of Rx Abuse, especially Analgesics:

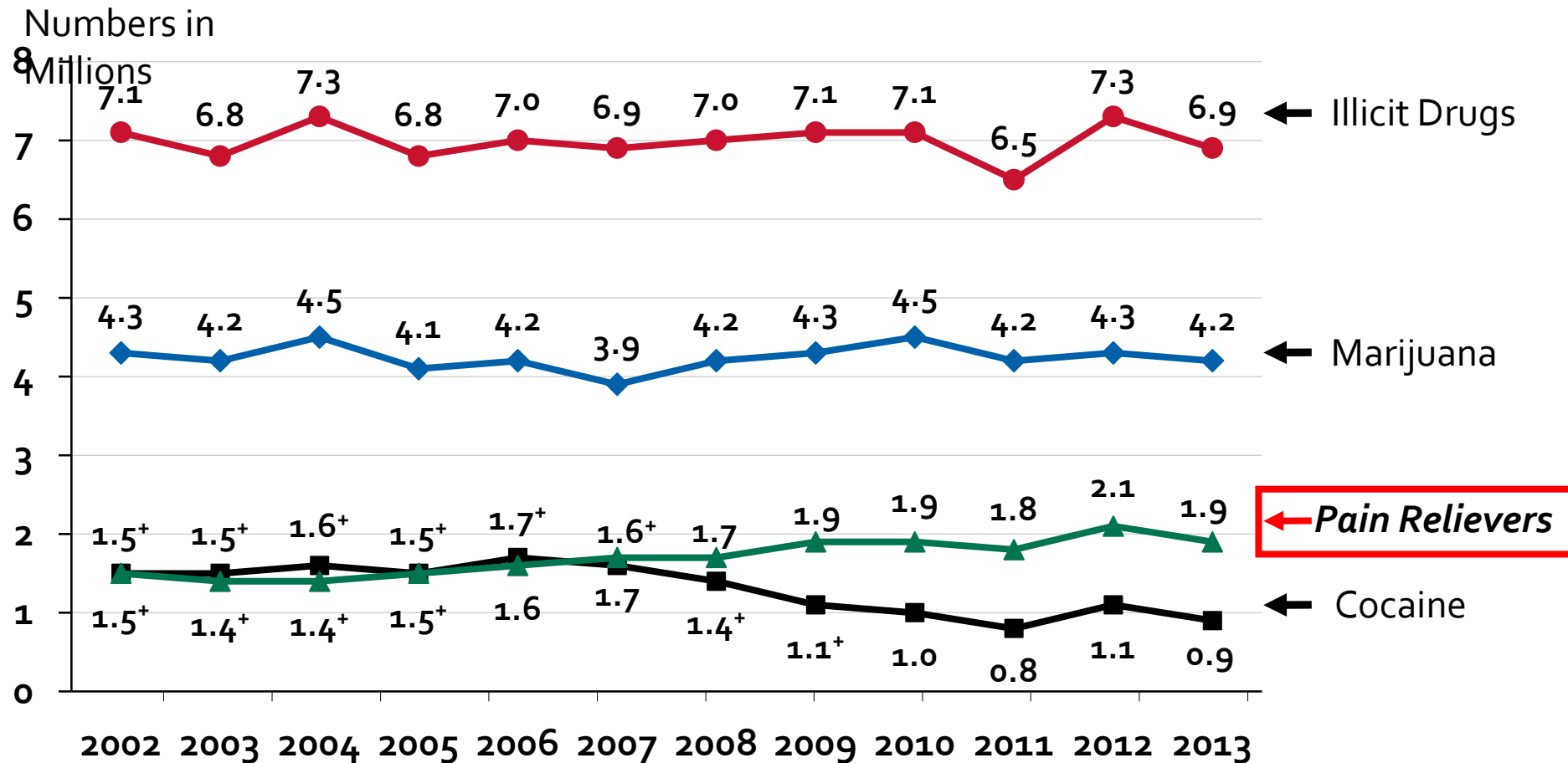
Past Month Psychotherapeutic Misuse, Ages 12+, 2002-2013



+ Difference between this estimate and the 2013 estimate statistically significant at the .05 level.

Source: SAMHSA, 2013 National Survey on Drug Use and Health, released September

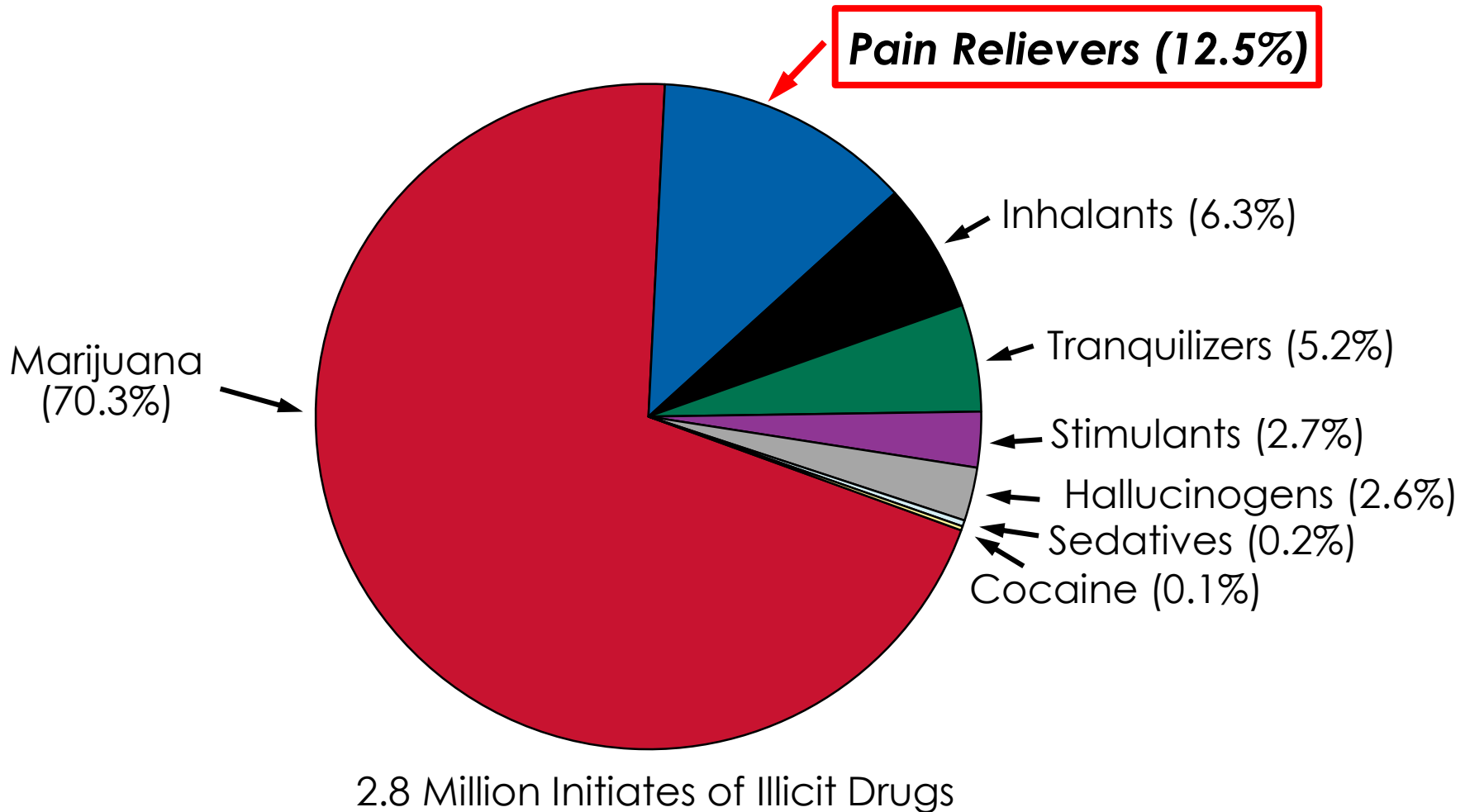
Increasing Drug Dependence or Abuse on Analgesics in the Past Year, Ages 12+, 2002-2013



+ Difference from the 2012 estimate is statistically significant at the .05 level.

Source: SAMHSA, 2013 National Survey on Drug Use and Health, released September 2014

Analgesics Often First Illicit Drug Initiated: **Past Year Initiator, Ages 12+, 2013, USA**

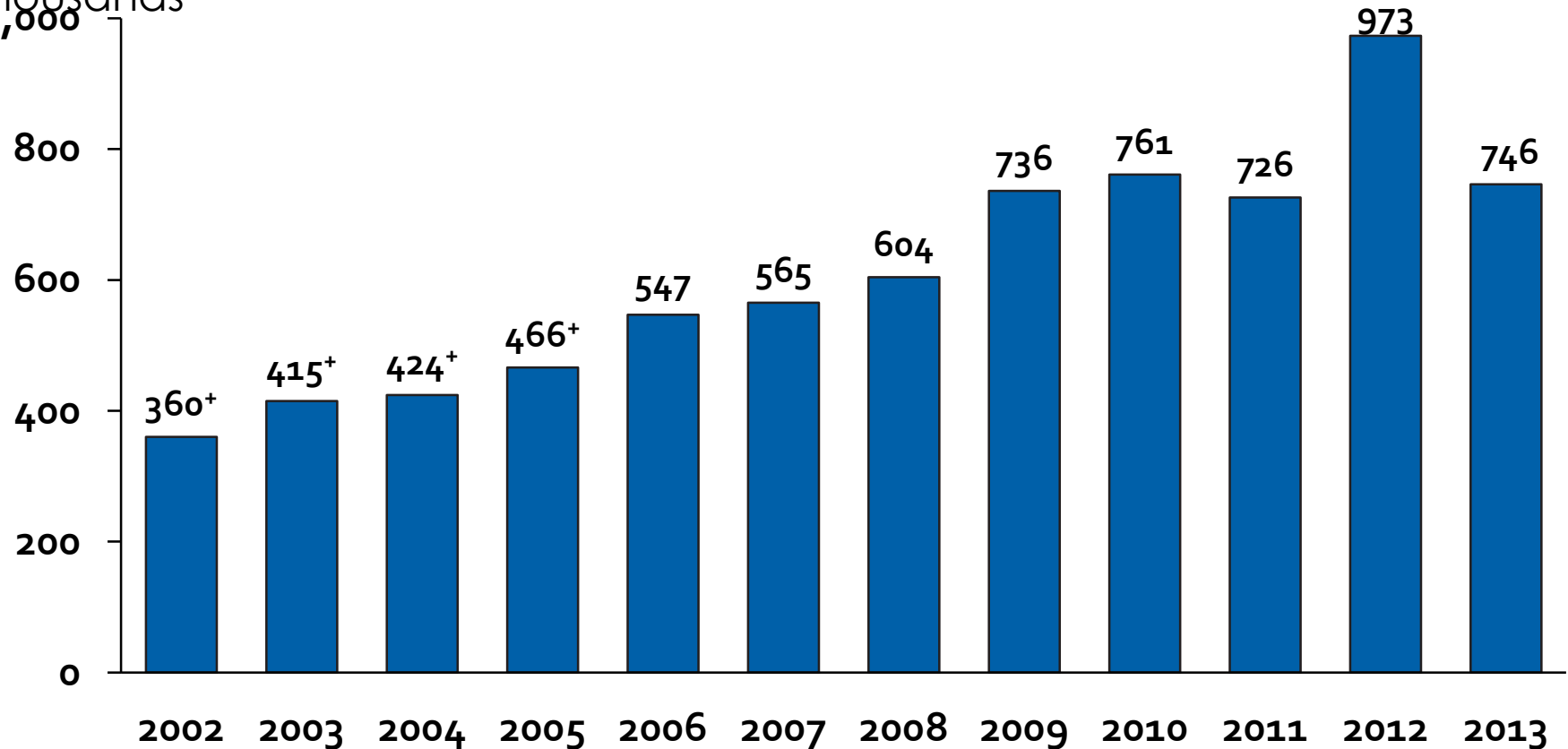


Note: The percentages do not add to 100 percent due to rounding or because small number of respondents initiated multiple drugs on the same day. The first specific drug refers to the one that was used on the occasion of first-time use of any illicit drug.

Source: SAMHSA, 2013 National Survey on Drug Use and Health, released September 2014

Doubling of Treatment for Analgesic Use 2002 - 2013:
***Most Recent Treatment in the Past Year for the Use of Pain Relievers
among USA Persons Aged 12 or Older***

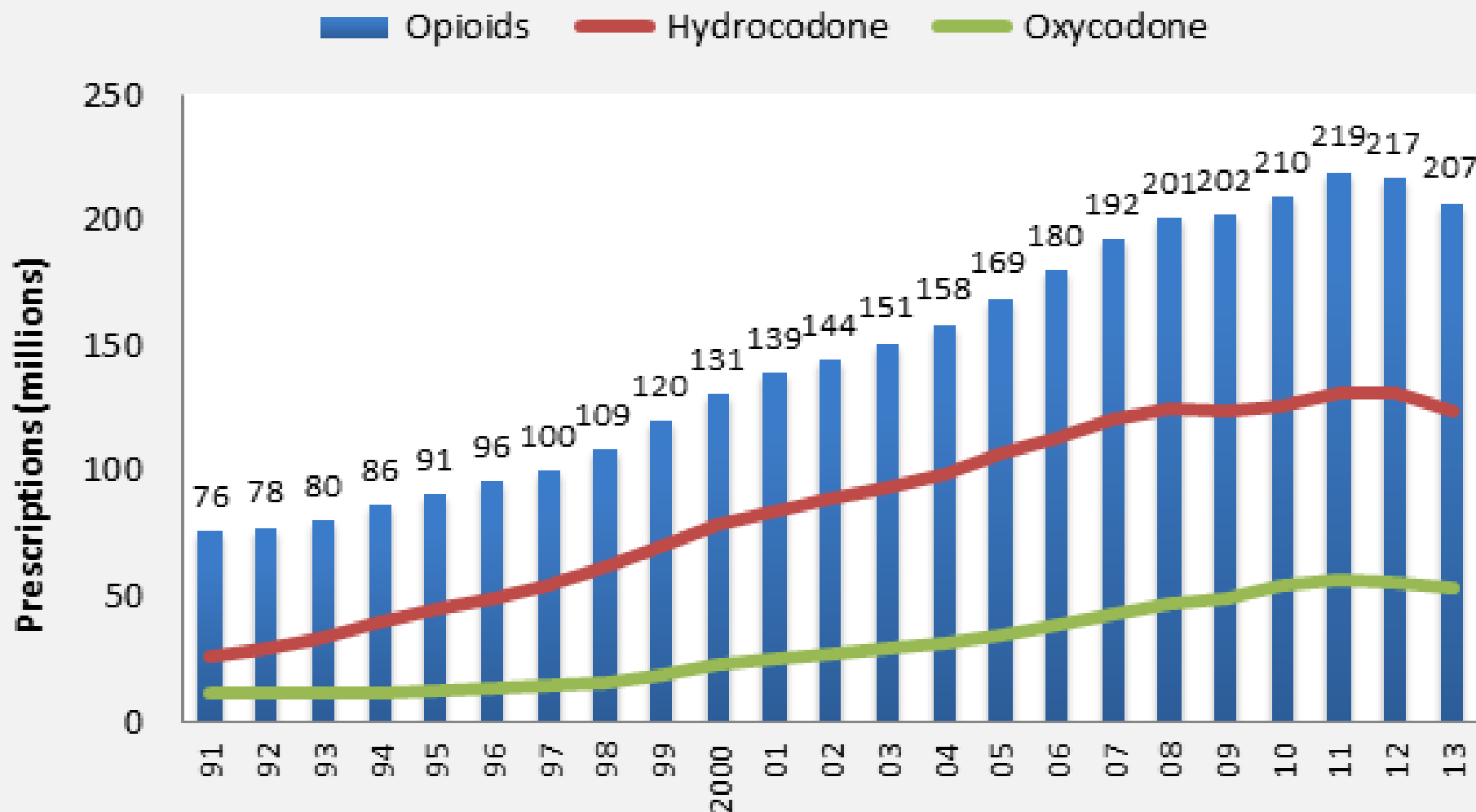
Numbers in
Thousands



⁺ Difference from the 2013 estimate is statistically significant at the .05 level.

Source: SAMHSA, 2013 National Survey on Drug Use and Health, released September

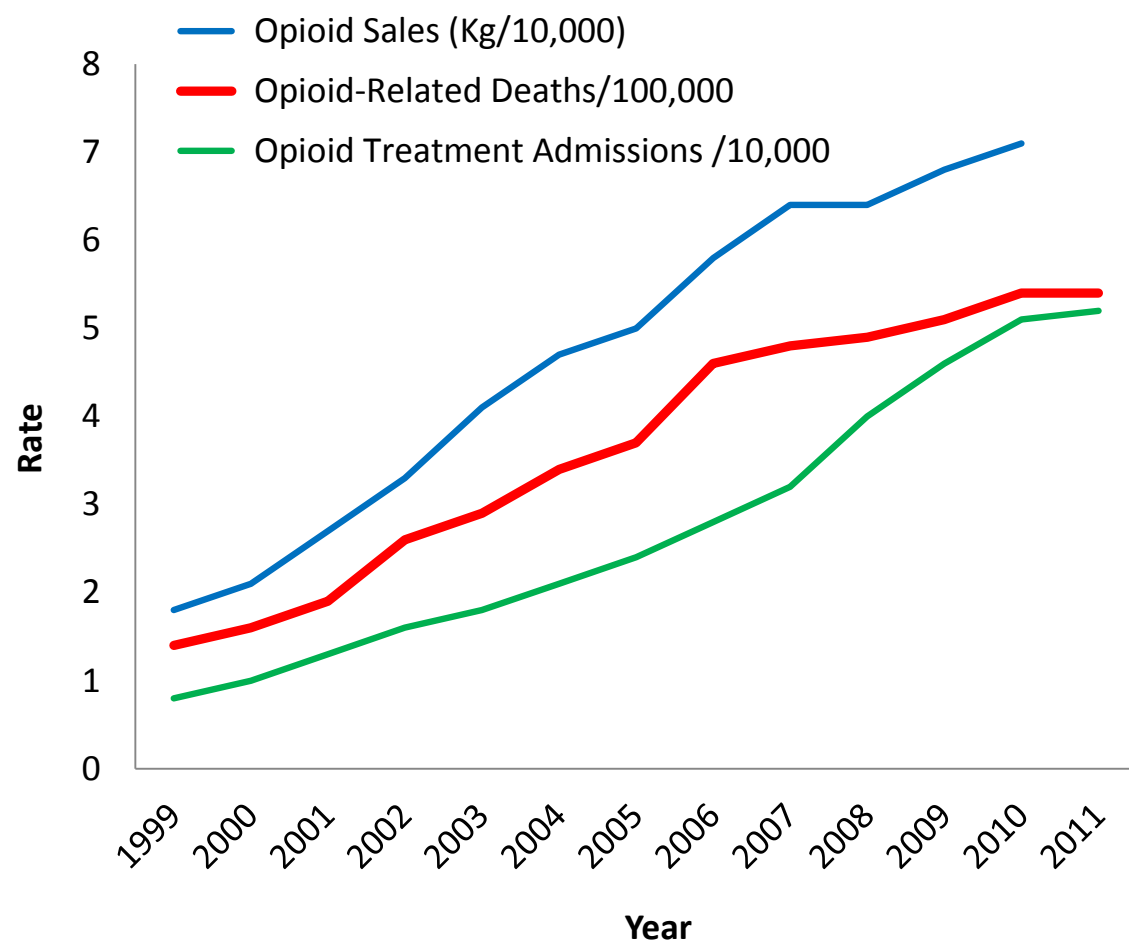
Near Tripling of Opioid Prescriptions Dispensed by U.S. Retail Pharmacies, Years 1991-2013



IMS Health, Vector One®: National, Years 1991-2011, Data Extracted 2012

IMS Health, National Prescription Audit, Years 2012-2013, Data Extracted 2014

Marked Increases in Opioid-related Deaths (parallel to opioid sales and Rx opioid treatment admits), USA



2013 OD Deaths:

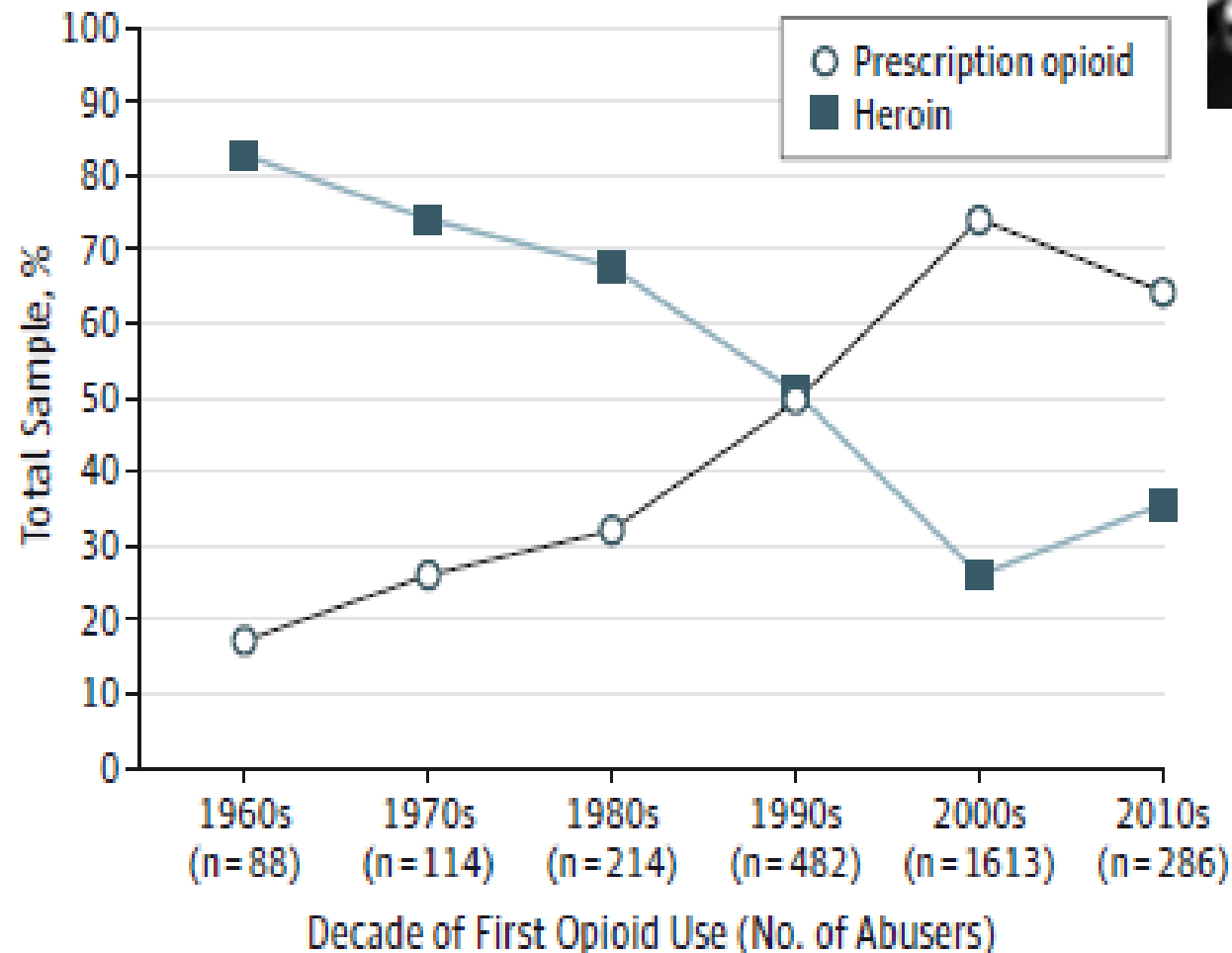
- **43,982 Any Drug**
- **16,235 Rx opioid**
- **8,257 Heroin**

Sources: National Vital Statistics System, DEA Automation of Reports and Consolidated Orders System, SAMHSA TEDS

Which Drug is the First Opioid Used in Addicts?

Shifting Pattern of Heroin vs. Prescription Opioid First

Percentage of Heroin-Addicted Treatment Admissions that Used Heroin or Prescription Opioid as First Opioid



1960s: more than 80% started with heroin.

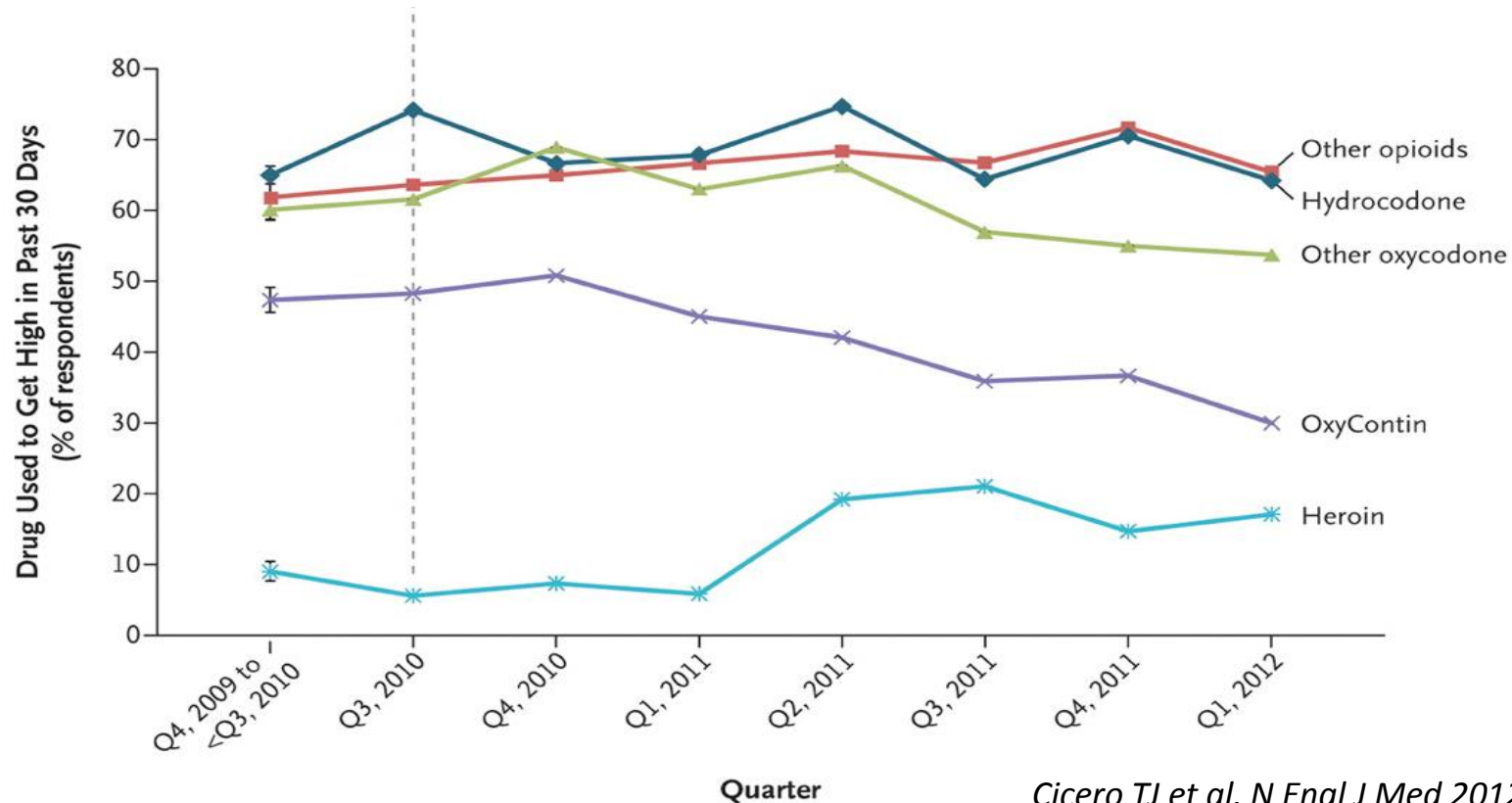
2000s: 75% started with prescription opioids.

2010-2013:
Increasing initiation with heroin

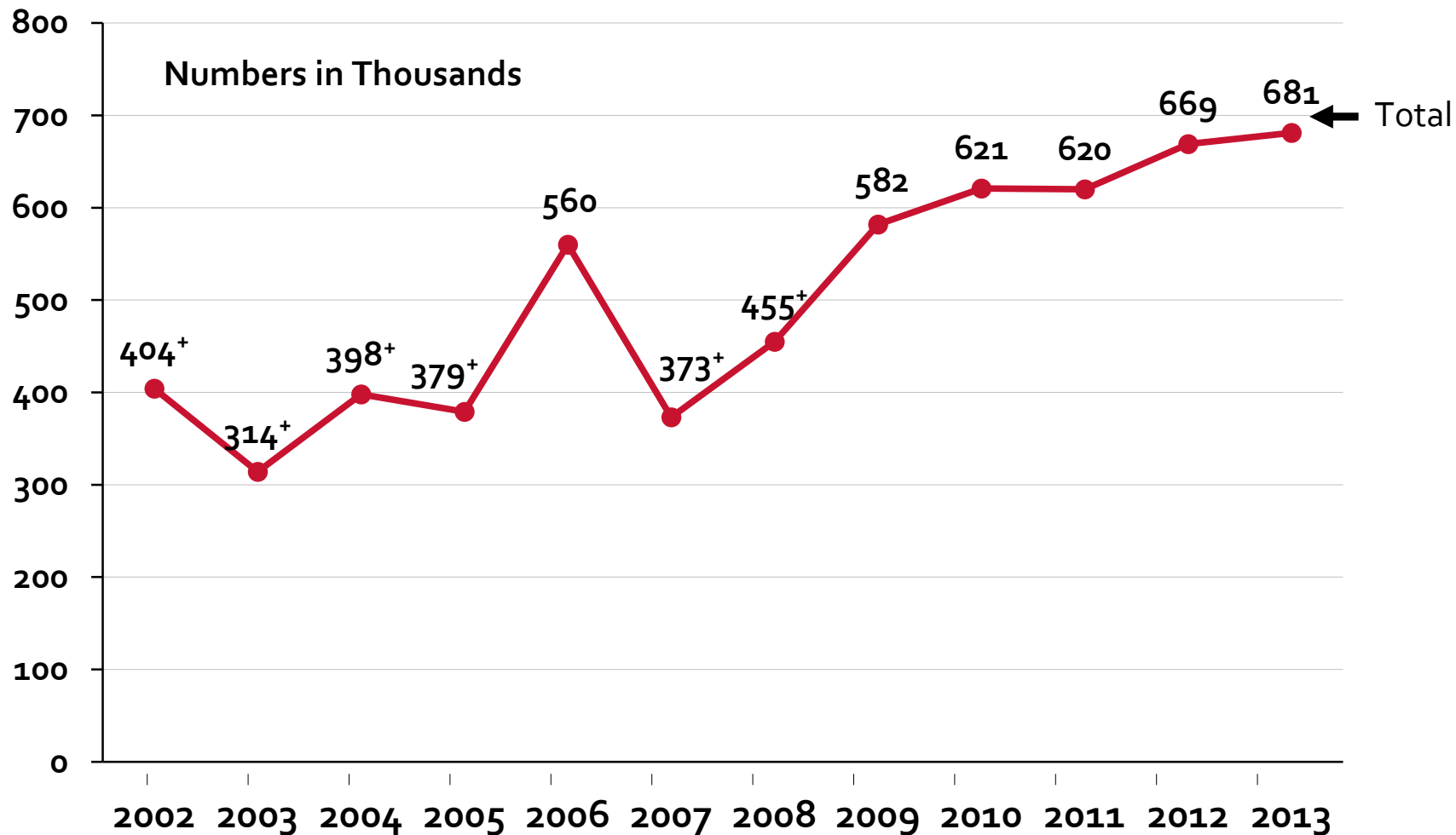
A Shift From Abuse of Prescription Pain Relievers to Heroin

Growing evidence suggests a shift to heroin: *Recent increase in heroin use accompanied a downward trend in OxyContin abuse following introduction of abuse-deterrent formulation.*

B



Past Year Heroin Use among Persons Aged 12 or Older, 2002-2013

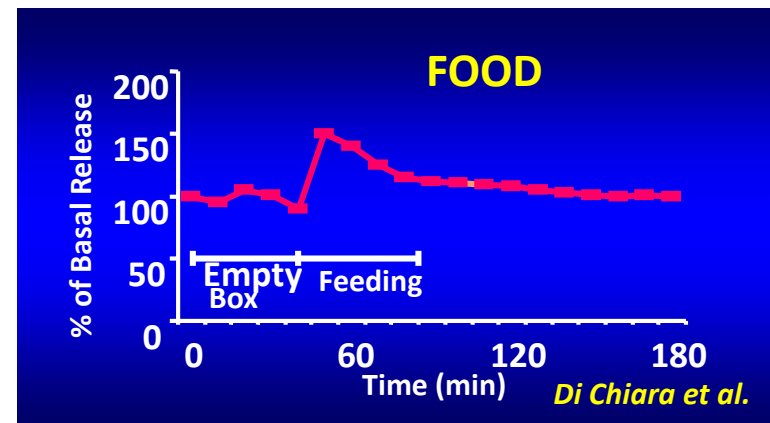
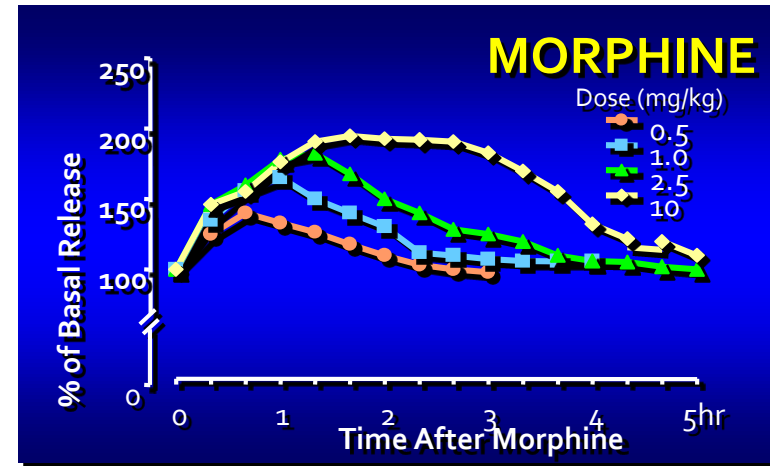
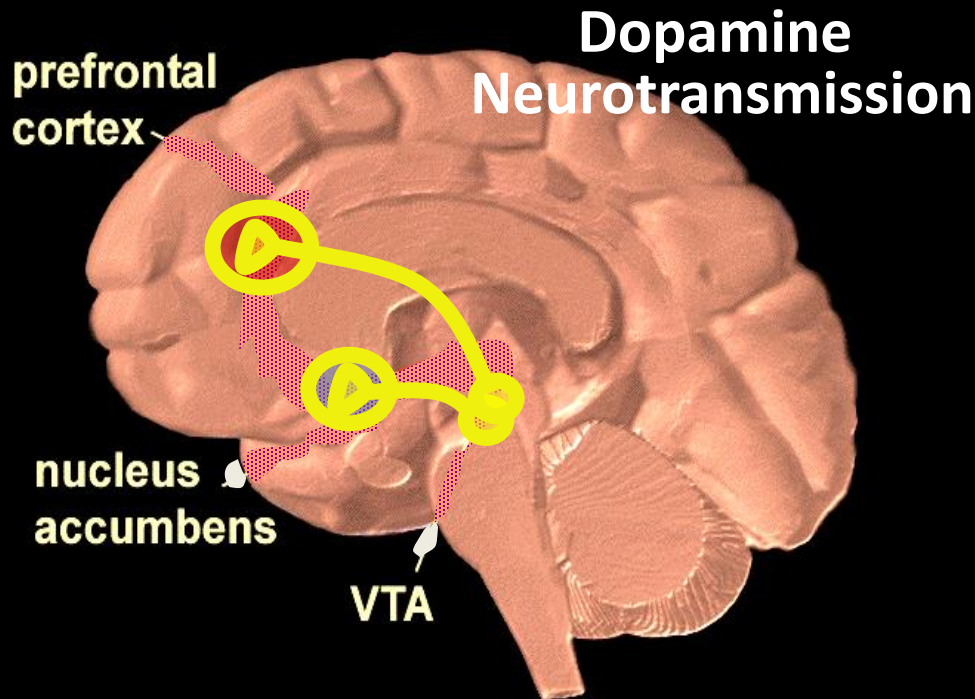


⁺ Difference between this estimate and the 2013 estimate is statistically significant at the .05 level. Note: Estimated numbers for the age groups may not sum to the total due to rounding.

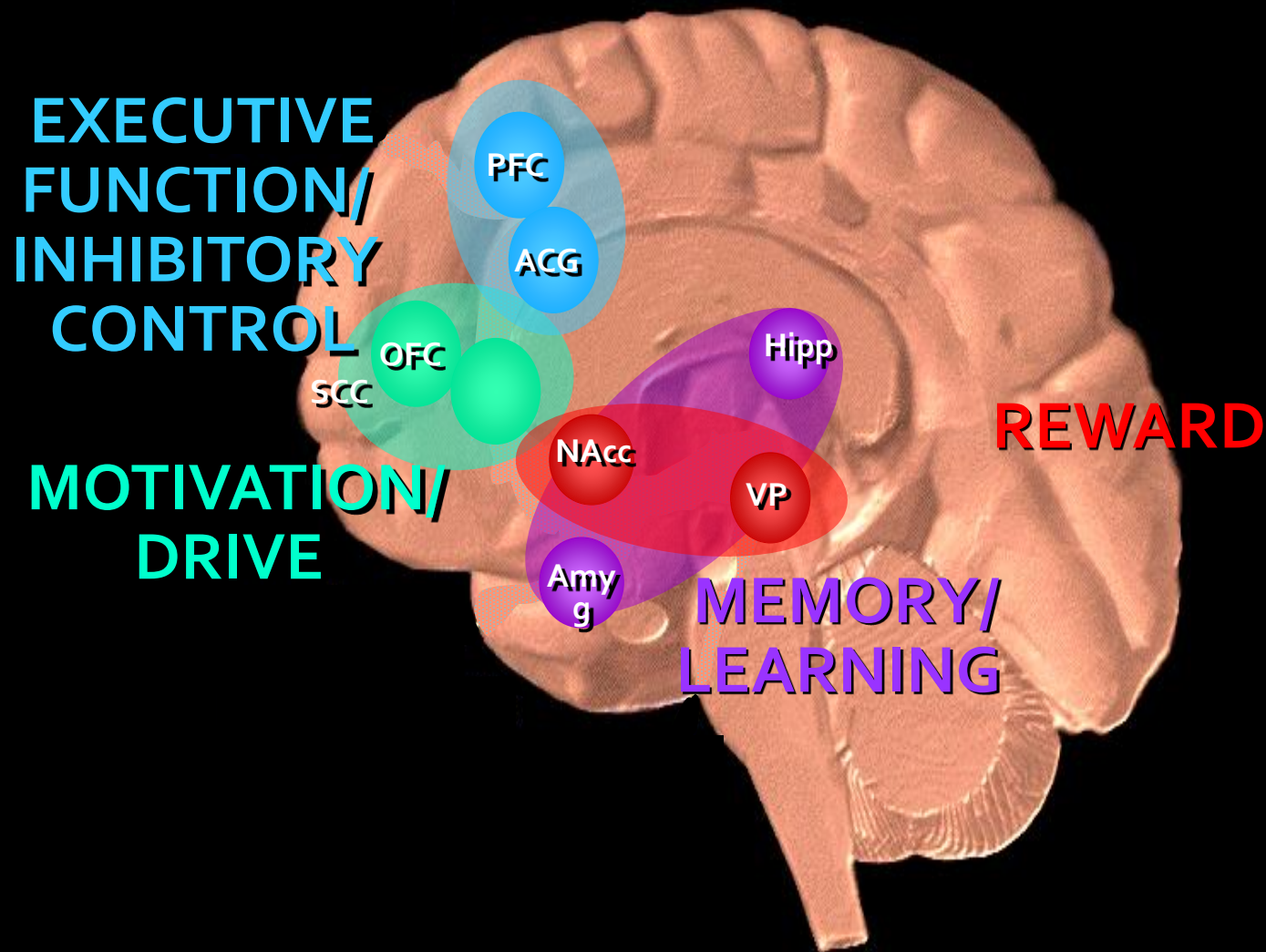
Source: SAMHSA, 2013 National Survey on Drug Use and Health, 2014.

Why Do People Abuse Prescription Drugs?

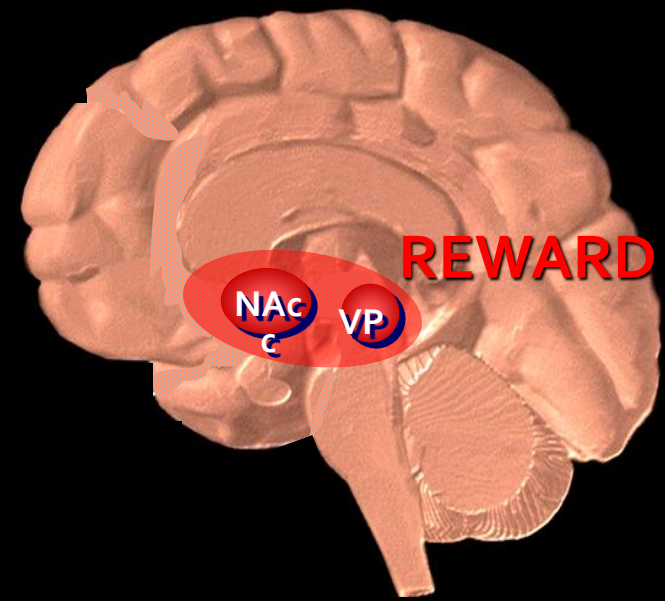
Opioid prescription drugs, like other drugs of abuse (cocaine, heroin, marijuana) raise brain dopamine levels



Circuits Involved In Drug Abuse and Addiction

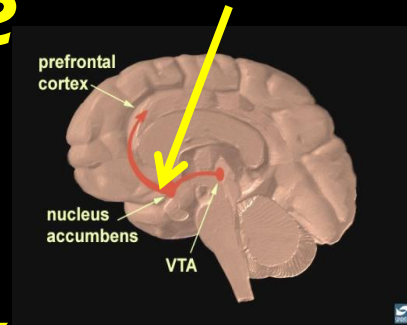


1. Reward Circuit

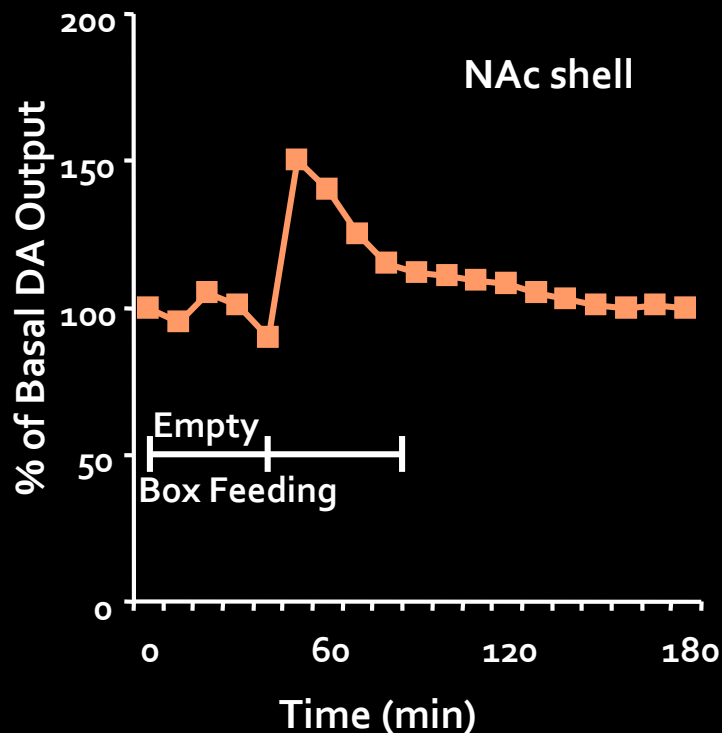


Drugs of Abuse
Engage
Systems in the
*Motivation
Pathways*
of the Brain

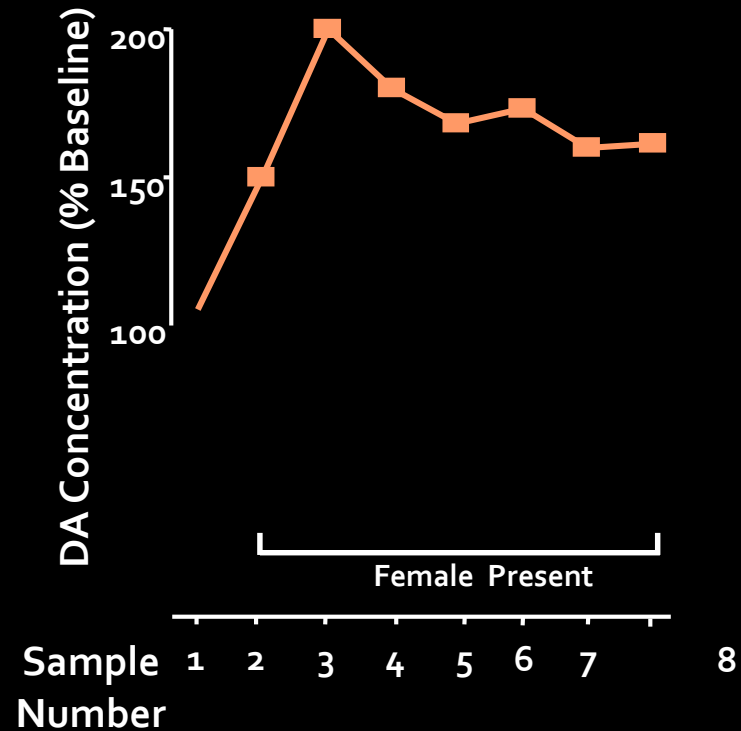
Natural Rewards Elevate Dopamine Levels



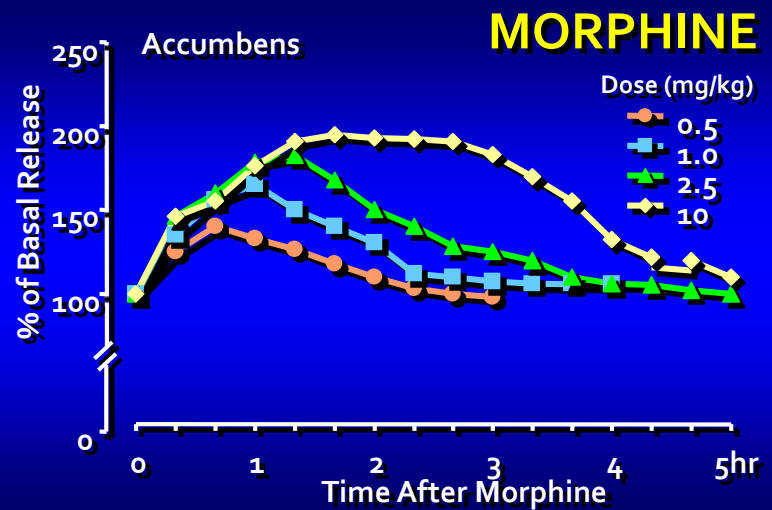
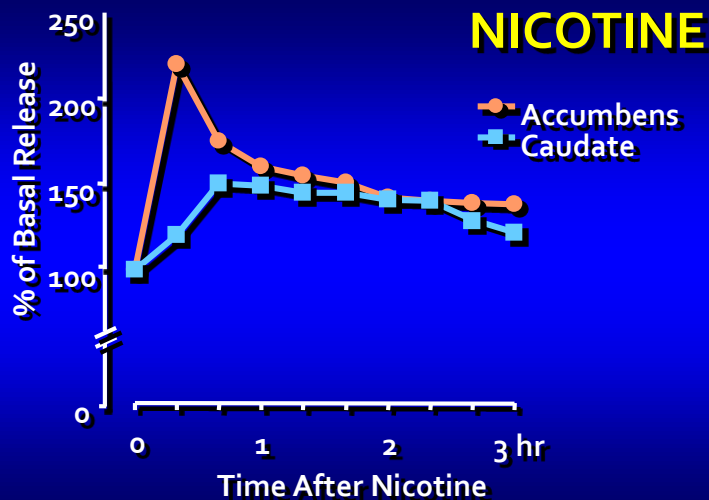
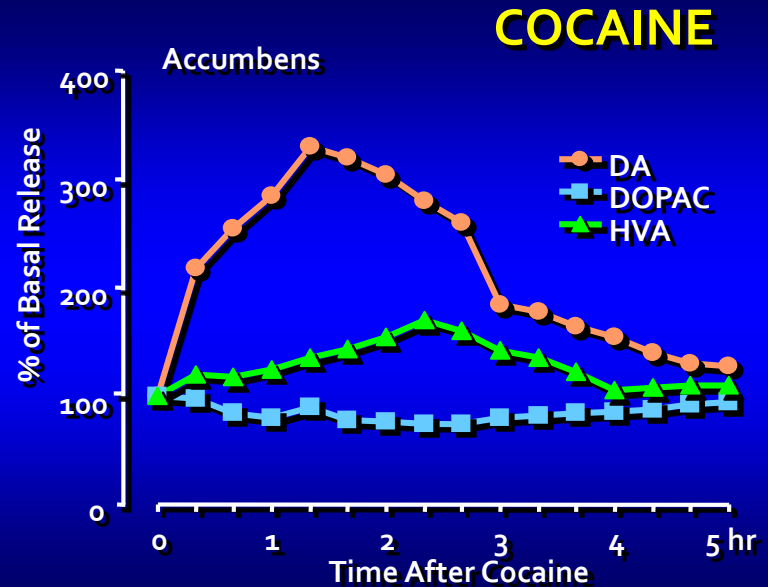
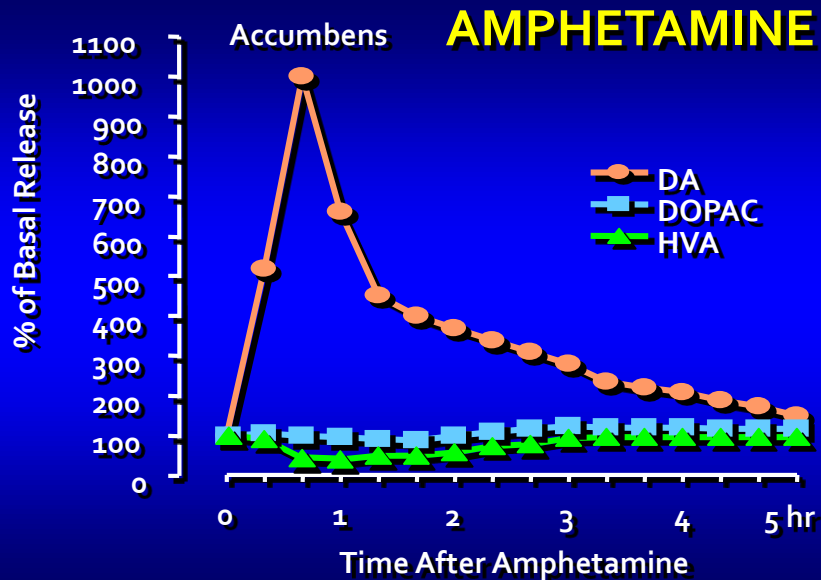
Food



Sex

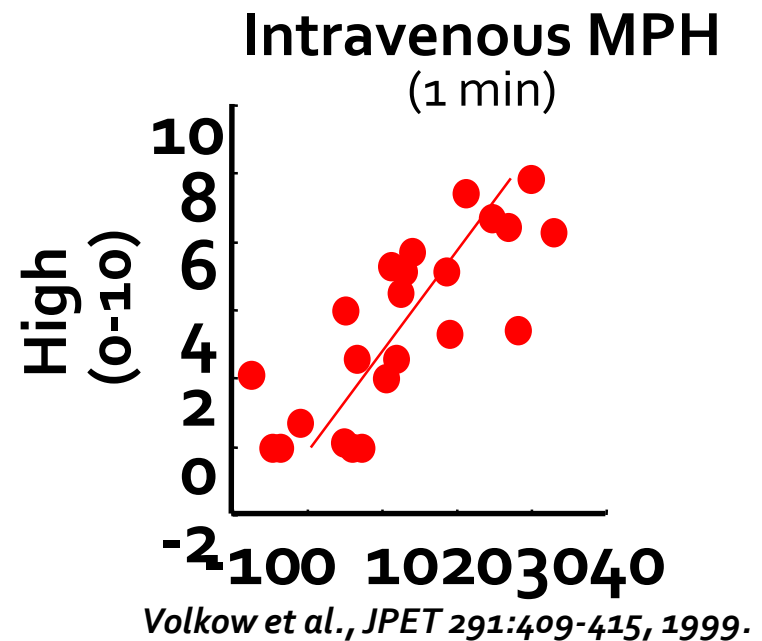
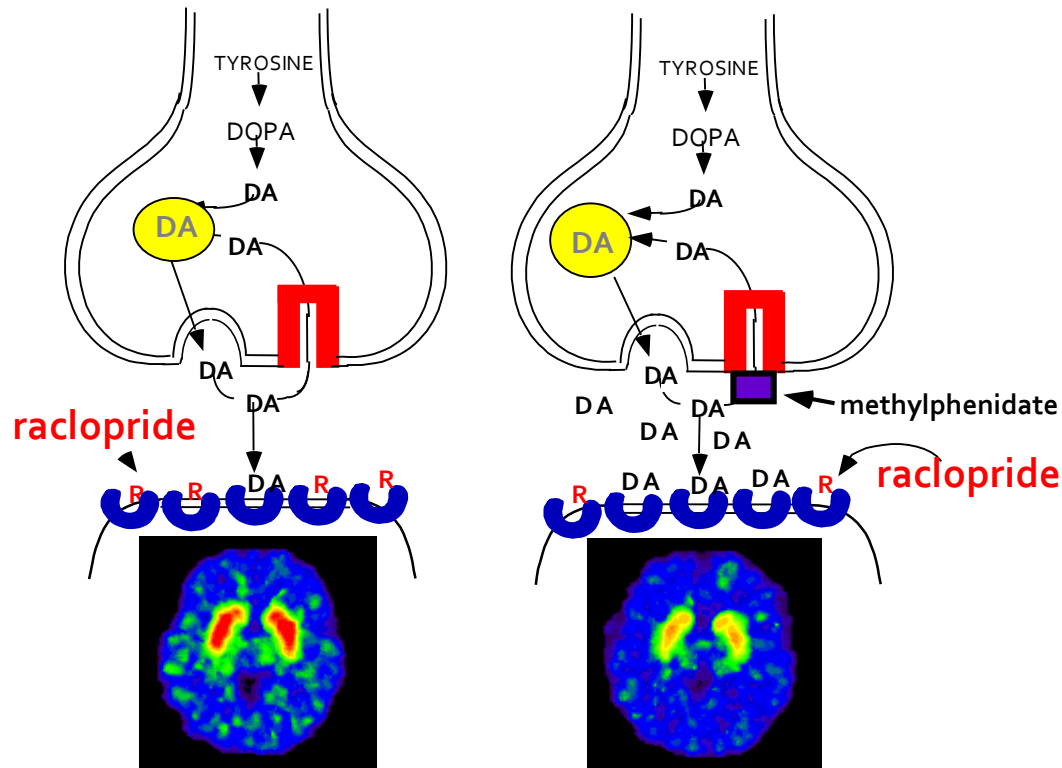


Drugs of Abuse Also Cause Dopamine Release

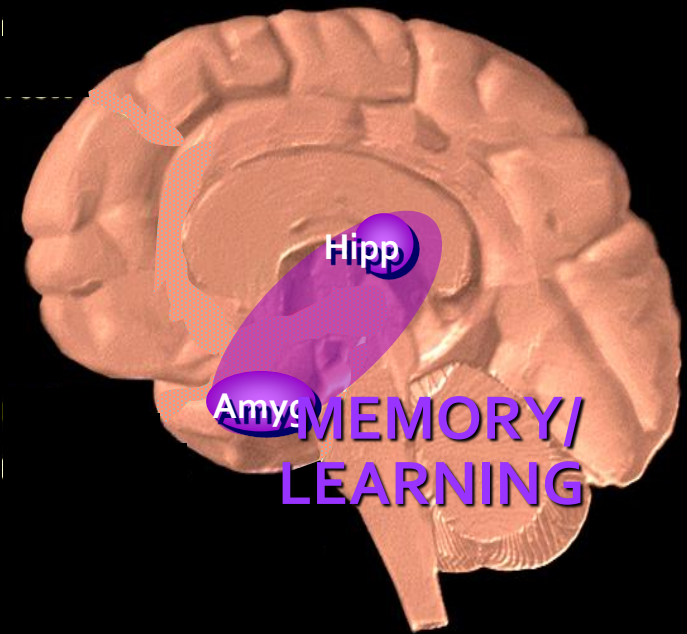


Source: Di Chiara and Imperato

DA and the **Rewarding** Effects of Drugs in Humans

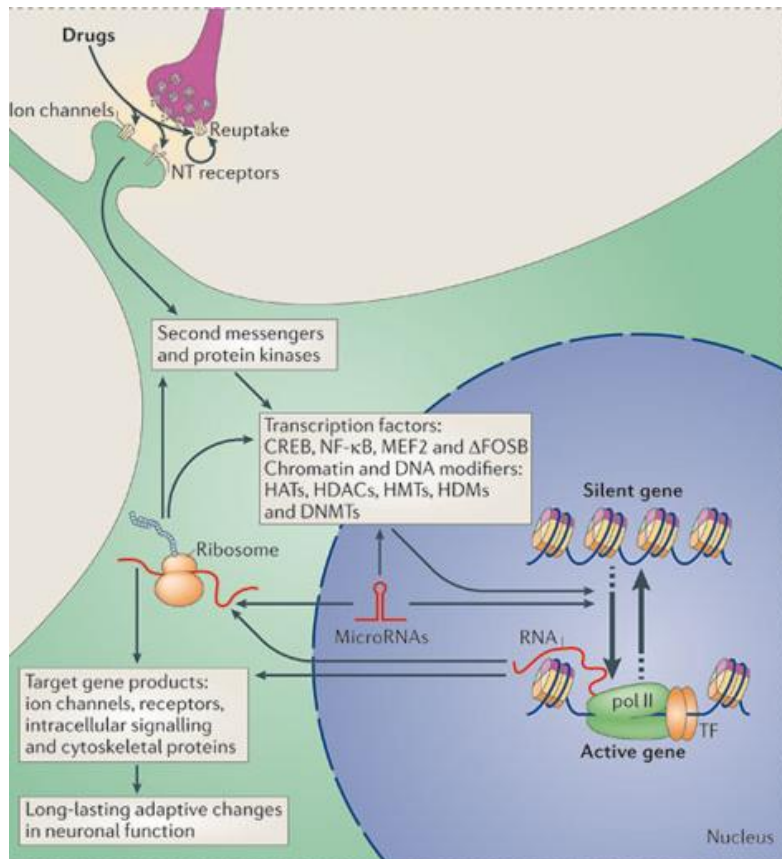


2. Memory circuit



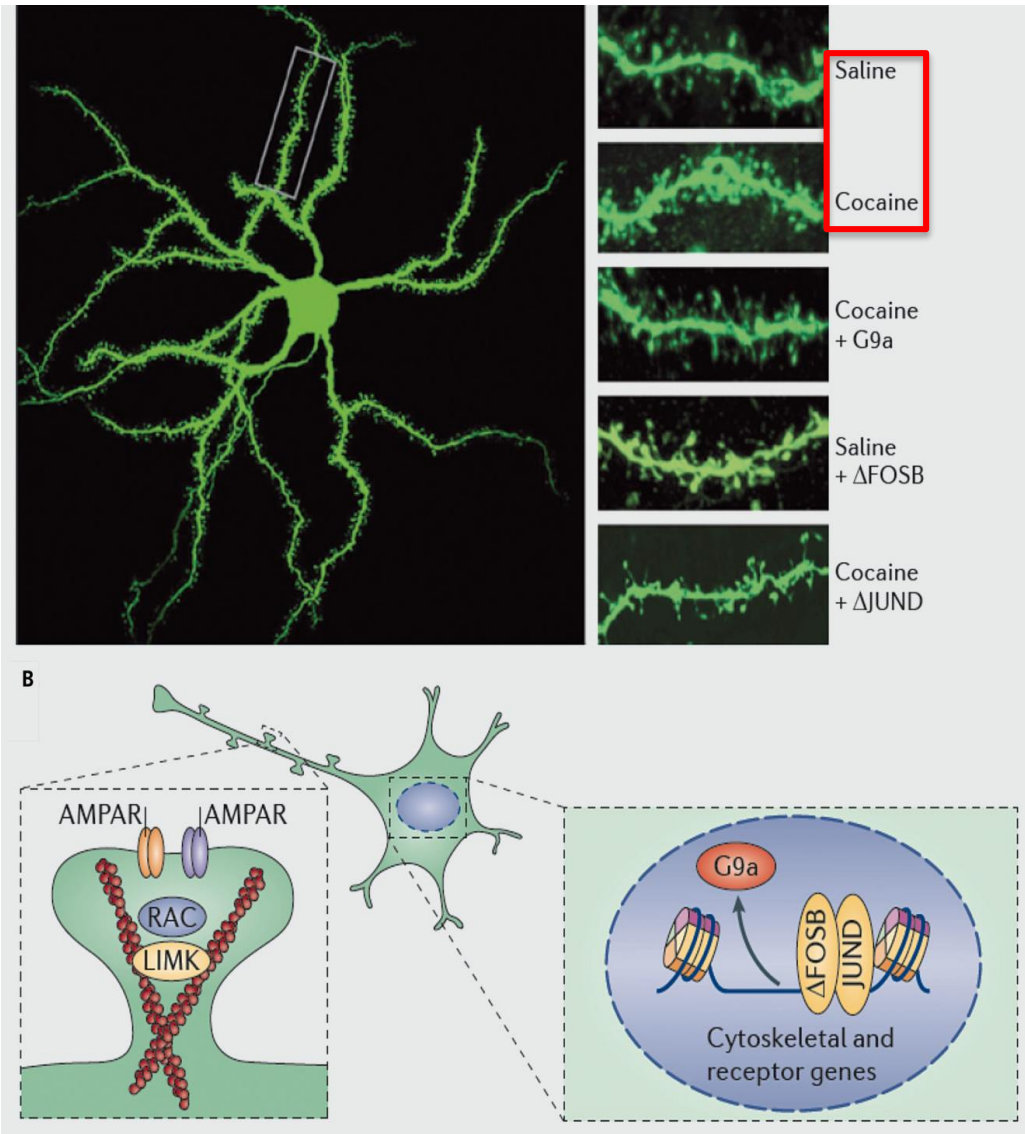
*"People, Place
and Things..."*

Drugs Trigger changes in Gene Expression that Either Strengthen or Weaken Synapses thus Creating a MEMORY



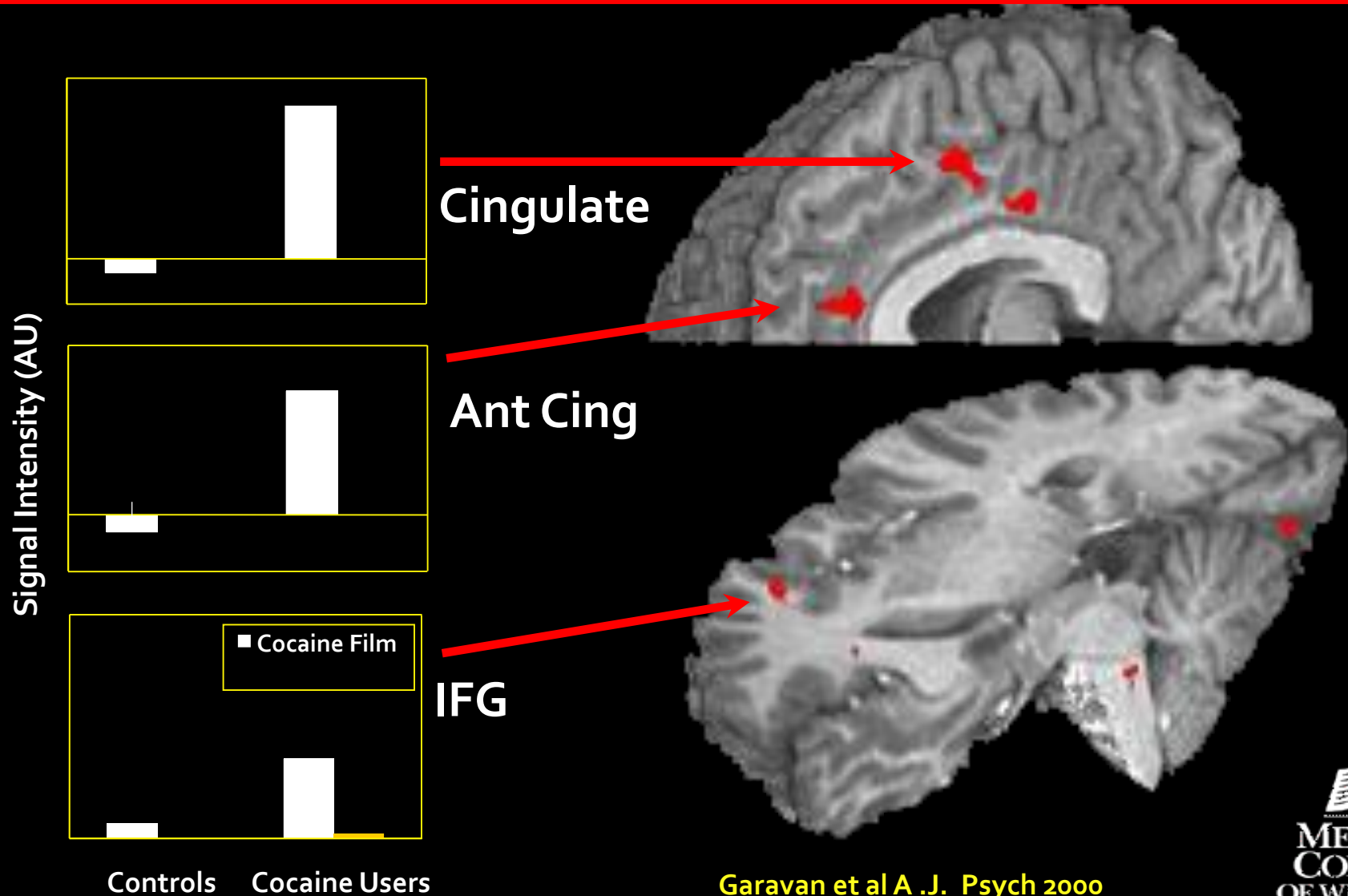
Nature Reviews | Neuroscience

Robison and Nestler 2011



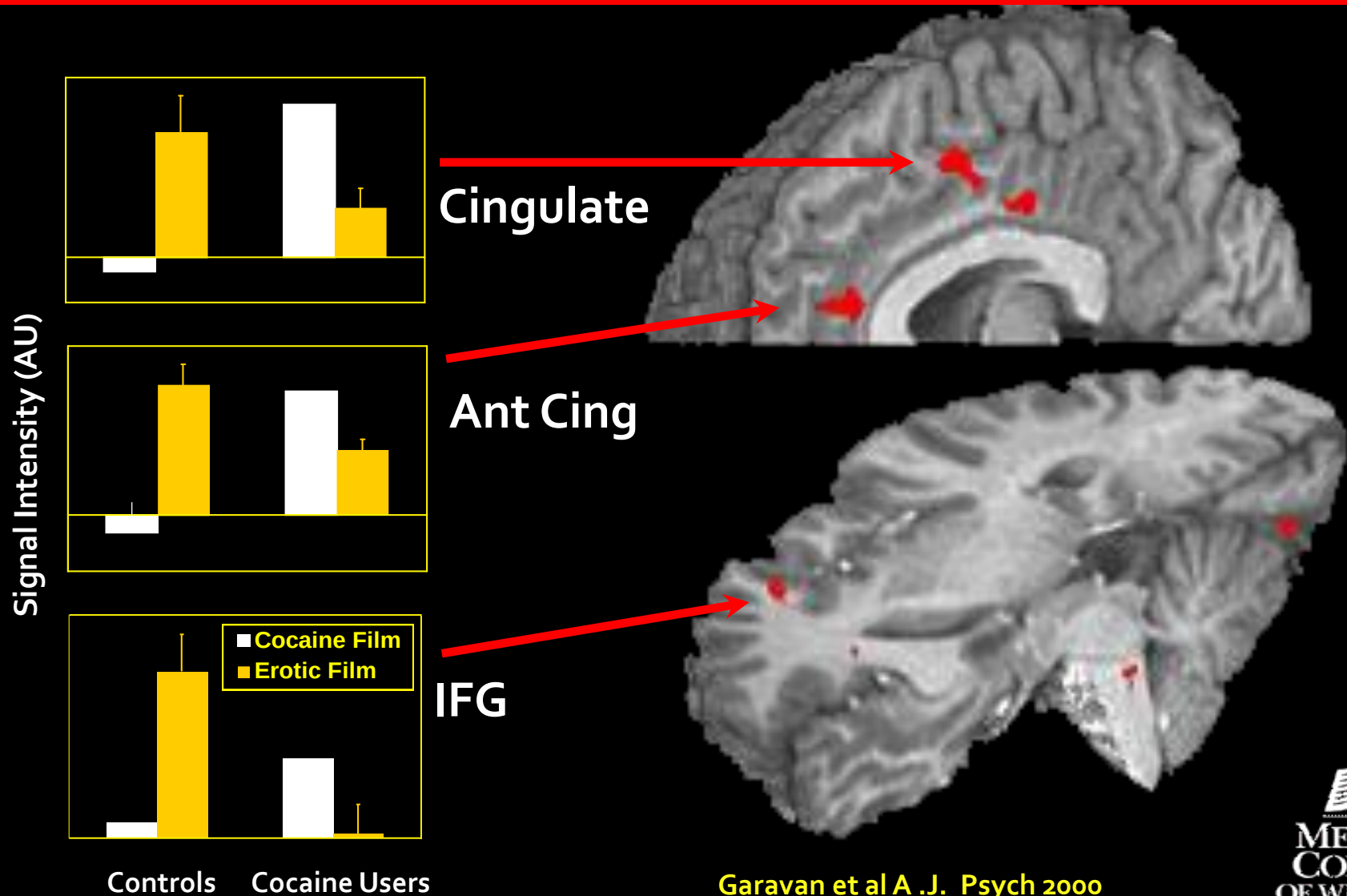
Cocaine Craving:

Population (Cocaine Users, Controls) x Film (cocaine)

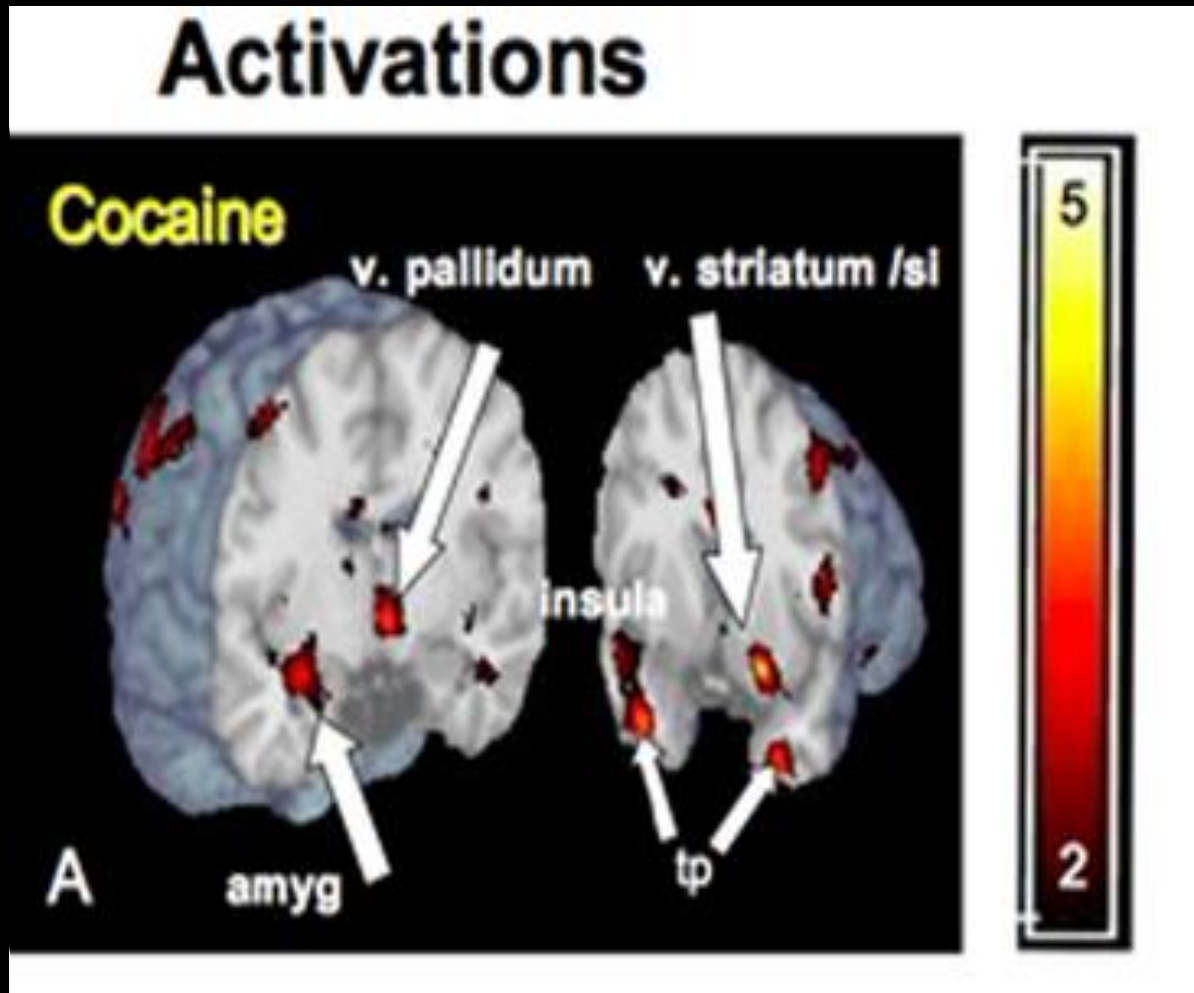


Cocaine Craving:

Population (Cocaine Users, Controls) x Film (cocaine, erotic)



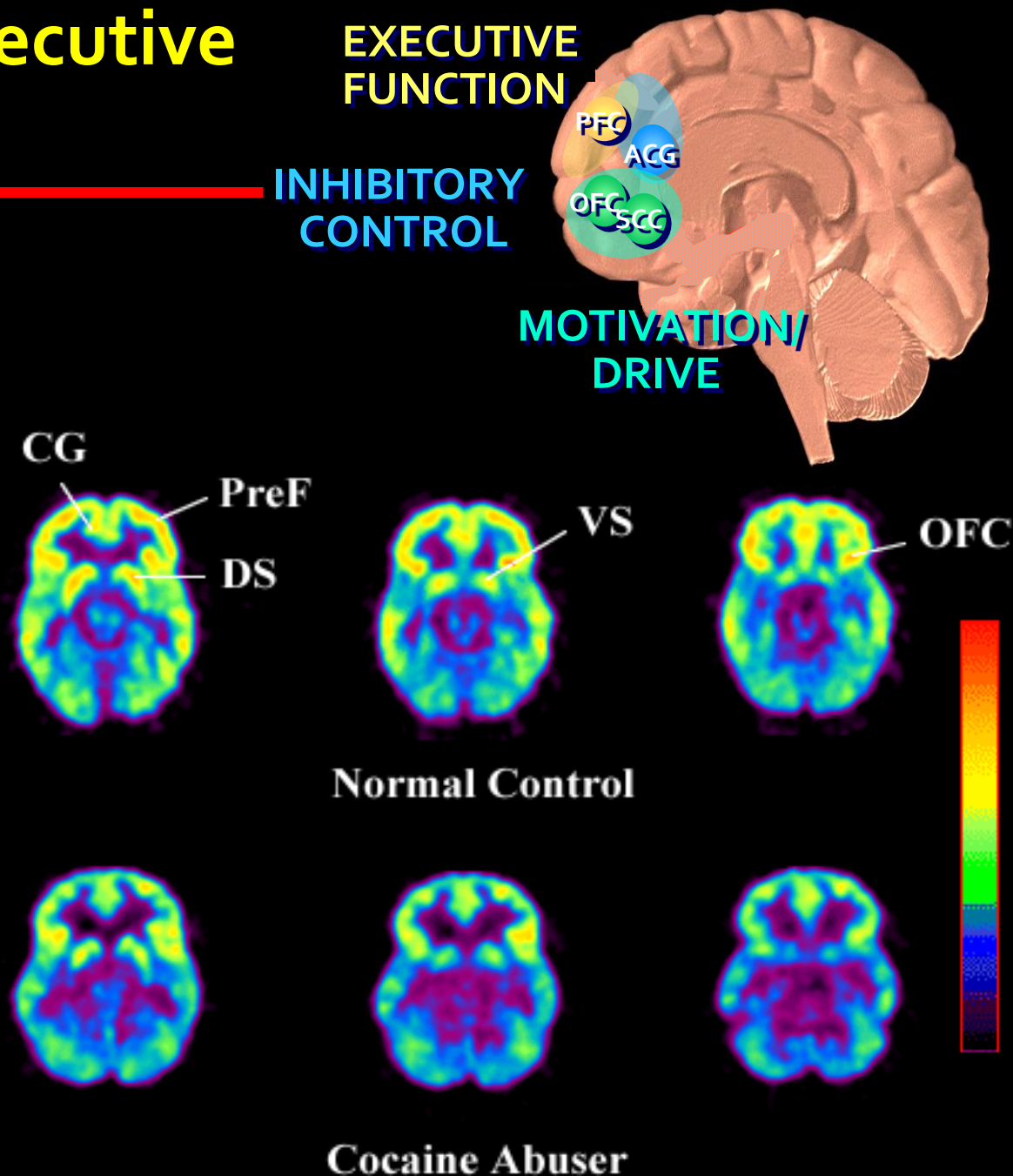
Even Unconscious Cues Can Elicit Brain Responses



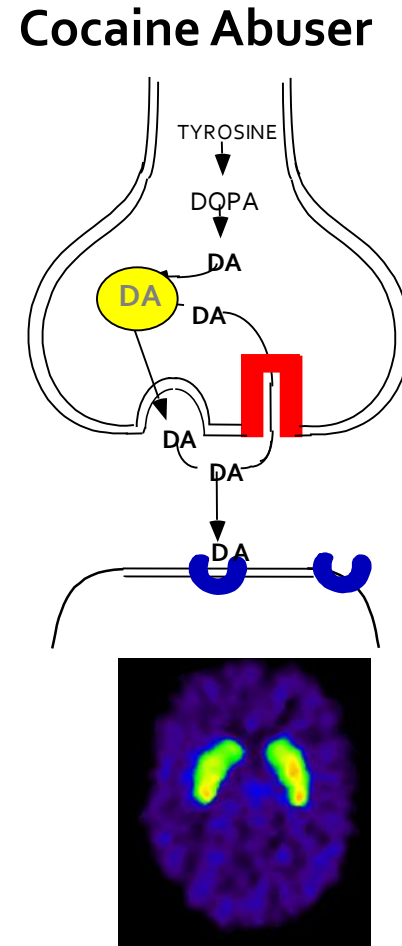
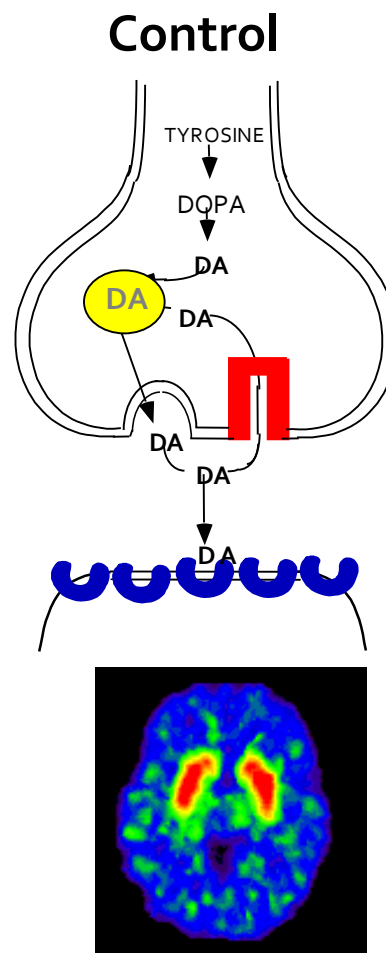
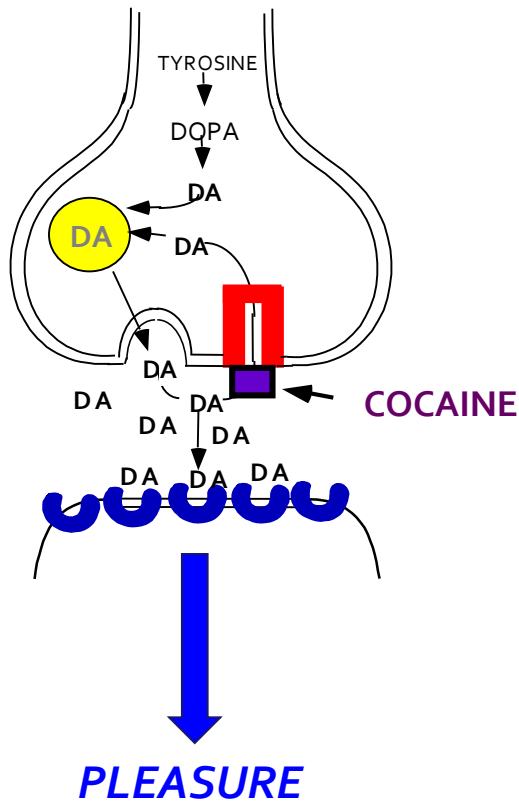
Brain Regions
Activated by 33
millisecond
Cocaine Cues
(*too fast for
conscious
recognition*)

3. Motivation & Executive Control Circuits

Dopamine is also associated with motivation and executive function via regulation of frontal activity.

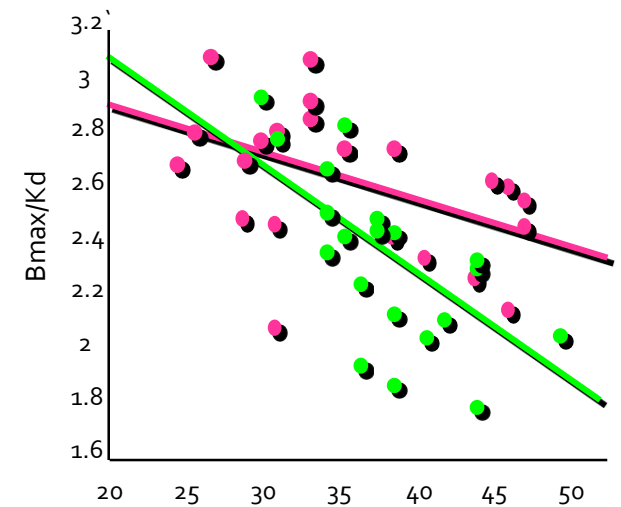
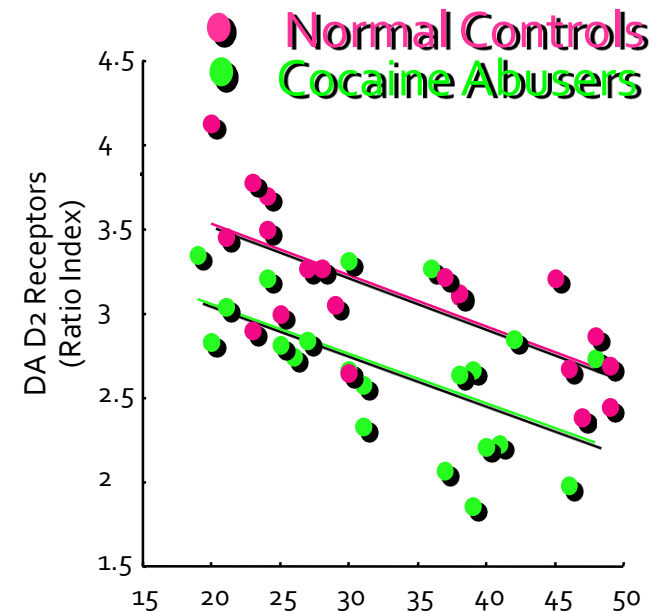
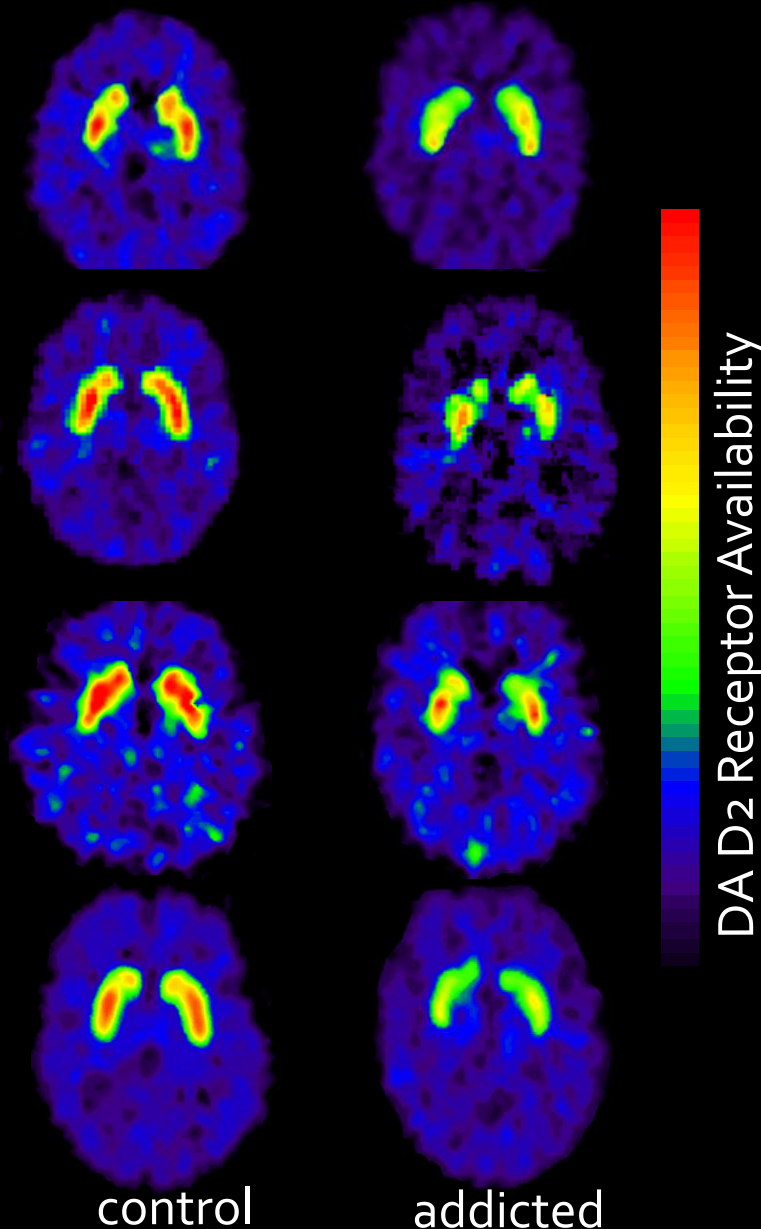
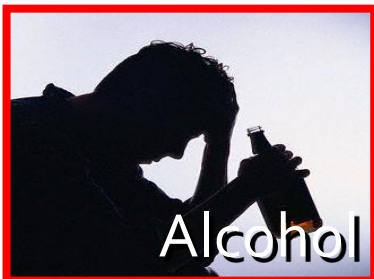


Repeated Drug Use **Changes the Brain** *Weakens the Brain Dopamine System*



**REPEATED USE OF COCAINE OR OTHER DRUGS REDUCES
LEVELS OF DOPAMINE D₂ RECEPTORS**

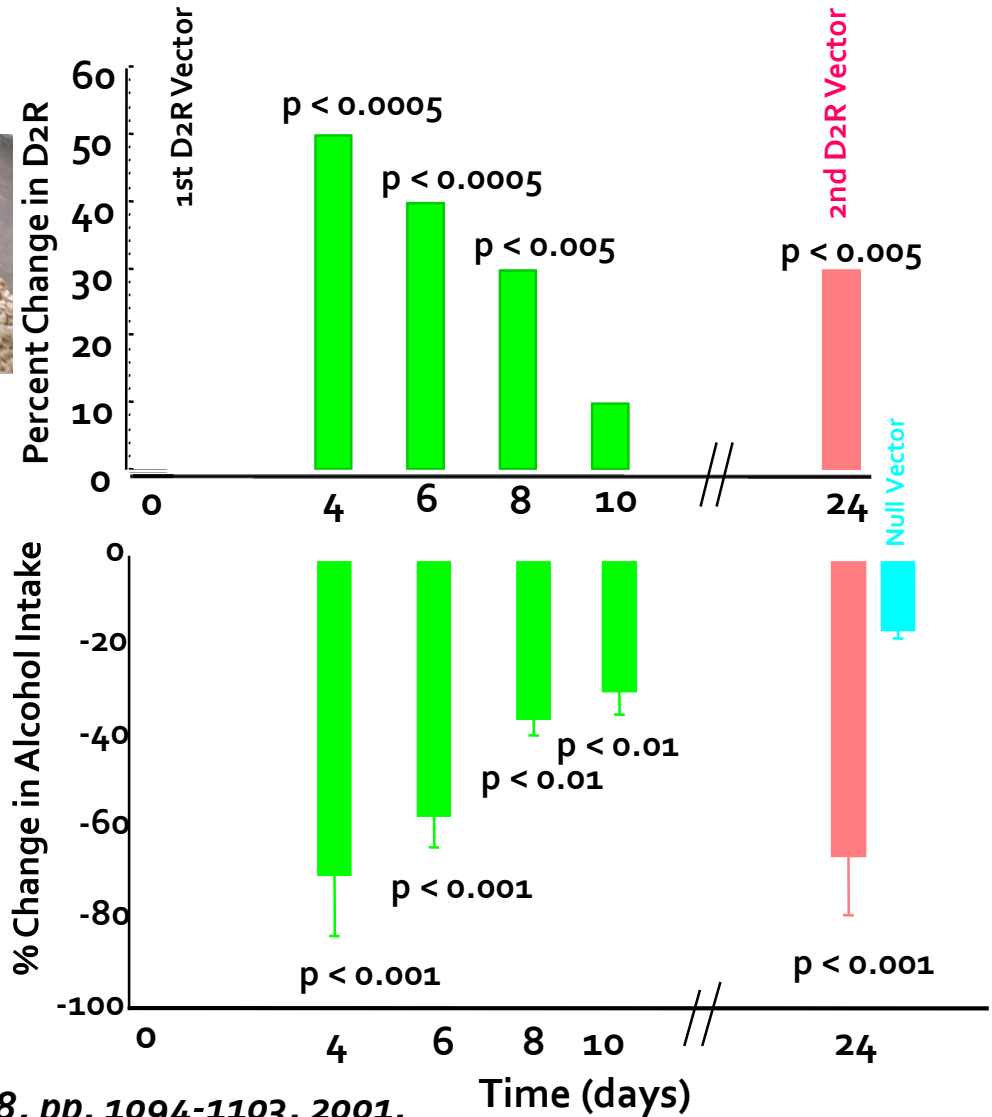
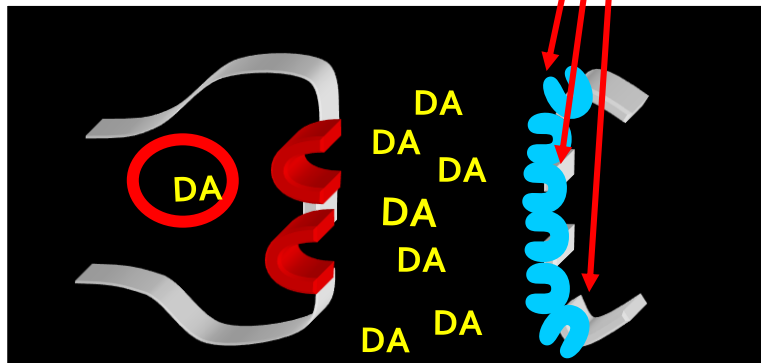
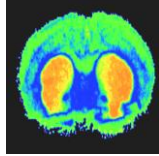
Dopamine D2 Receptors are Lower in Addiction



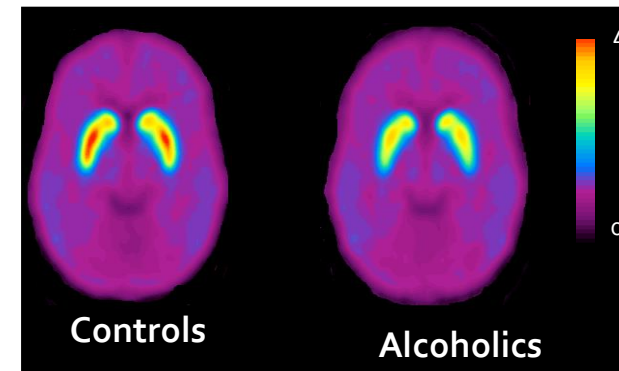
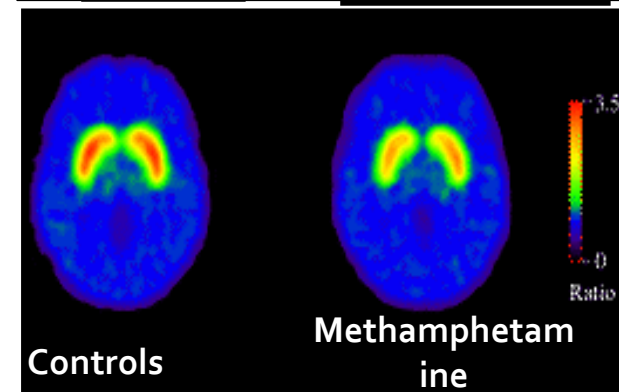
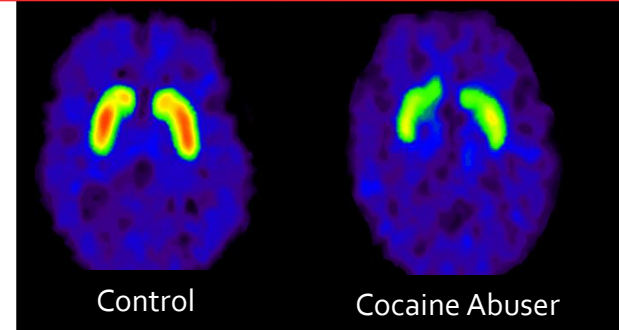
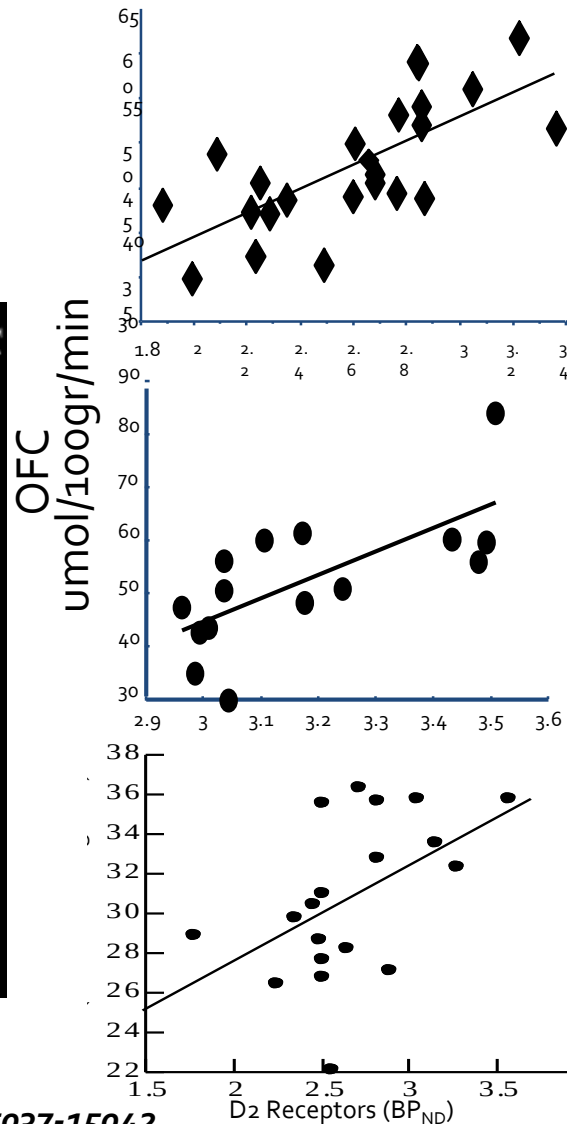
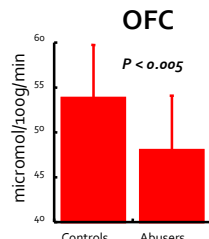
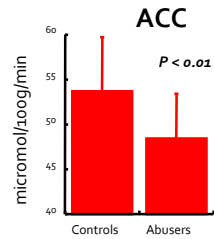
Volkow et al., *Neuro Learn Mem* 2002.

Effects of Tx with an Adenovirus Carrying a DA D2 Receptor Gene into NAc in DA D2 Receptors

Overexpression of DA D2 receptors reduces alcohol self-administration

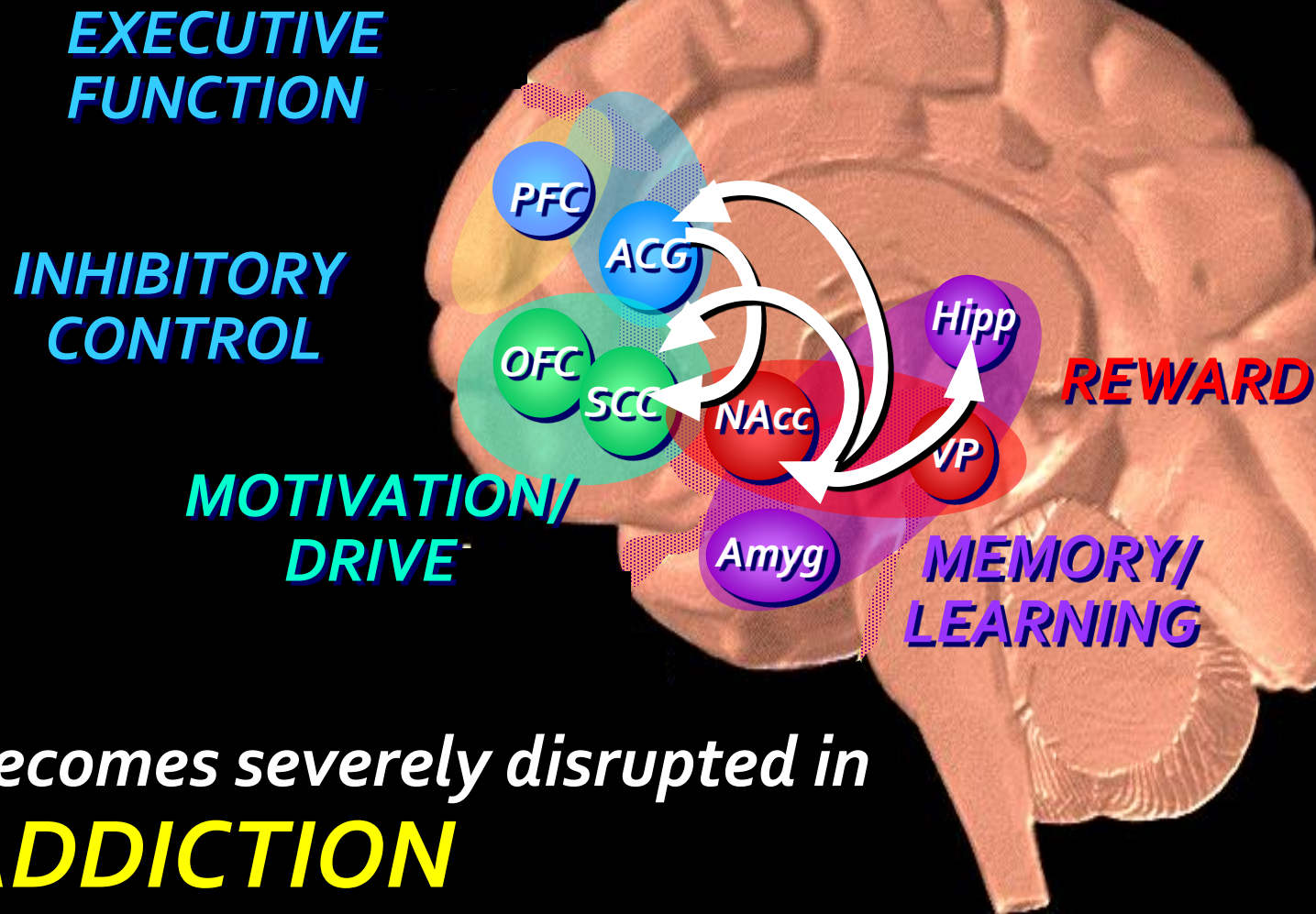


Relationship Between Brain Glucose Metabolism and Striatal D2 Receptors



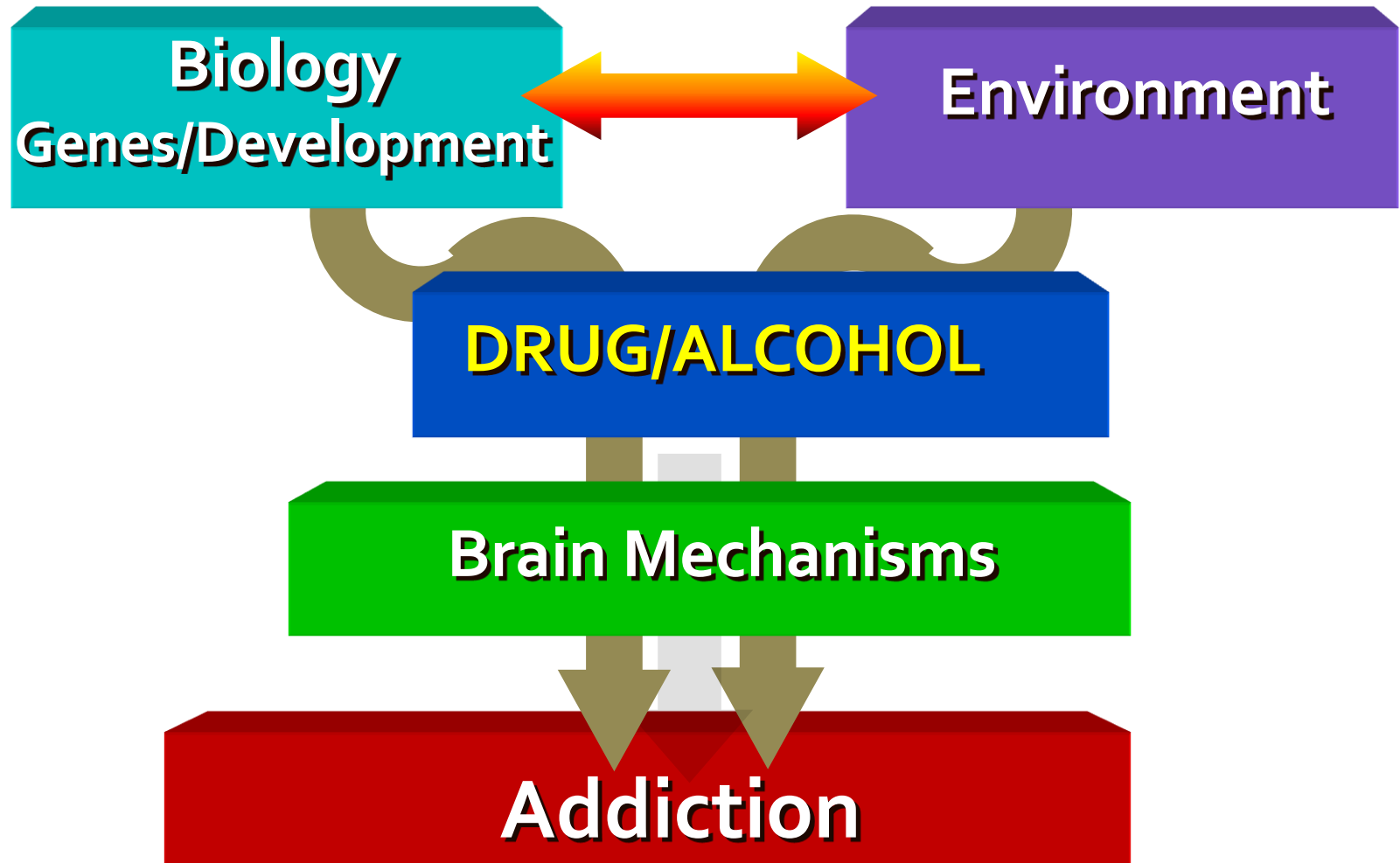
Volkow et al., PNAS 2011 108(37): 15037-15042.

The fine balance in connections that normally exists between brain areas active in reward, motivation, learning and memory, and inhibitory control

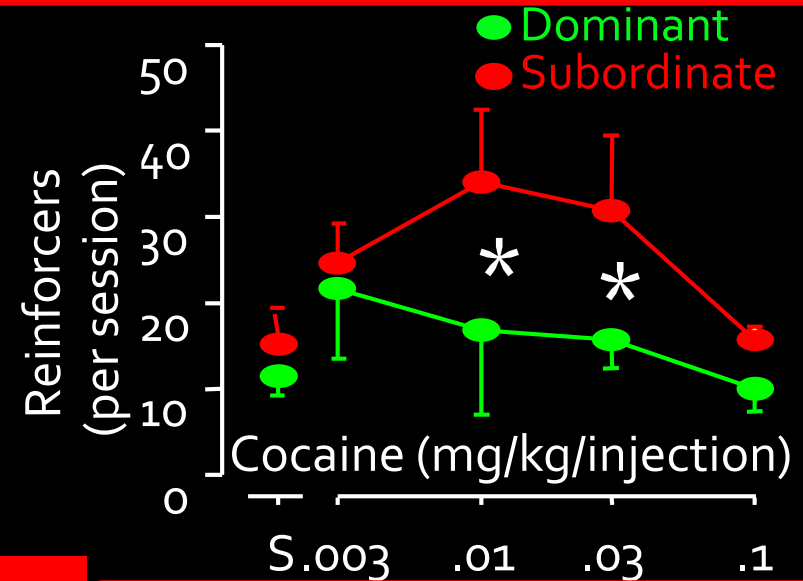
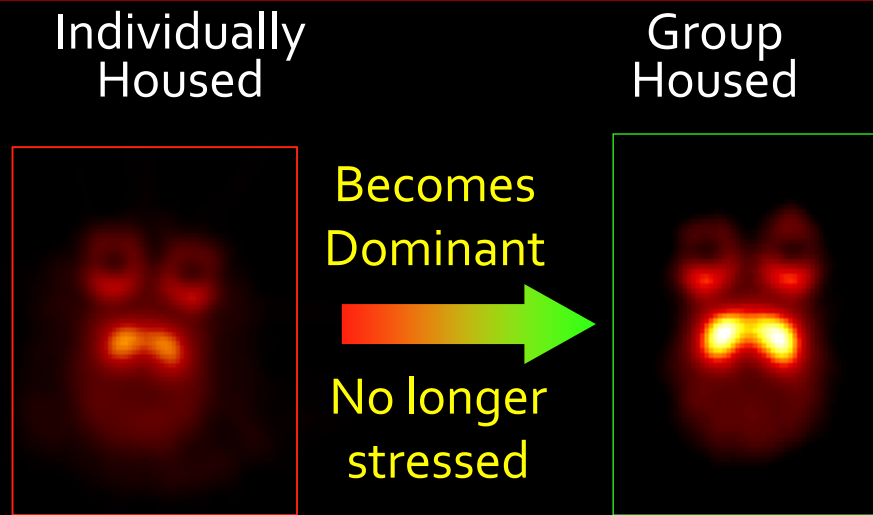


ADDICTIONS as diseases of *Gene-Environment-Development*

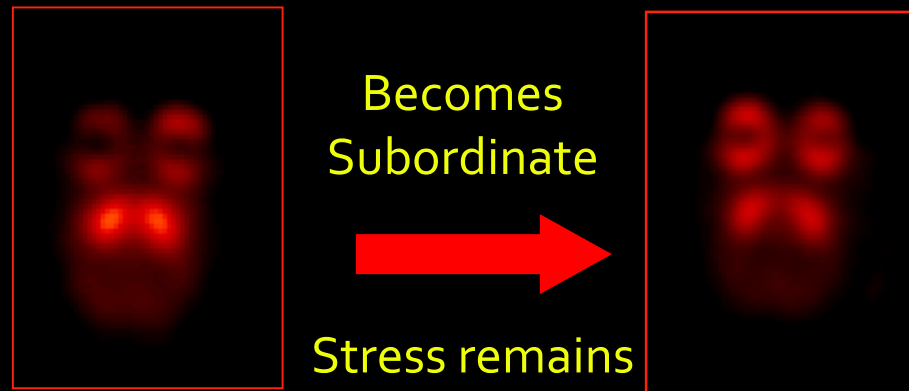
Addictions are common, developmental brain diseases expressed as compulsive behavior through continued use of a drug despite negative consequences: Onset depends on many intrinsic and extrinsic factors.



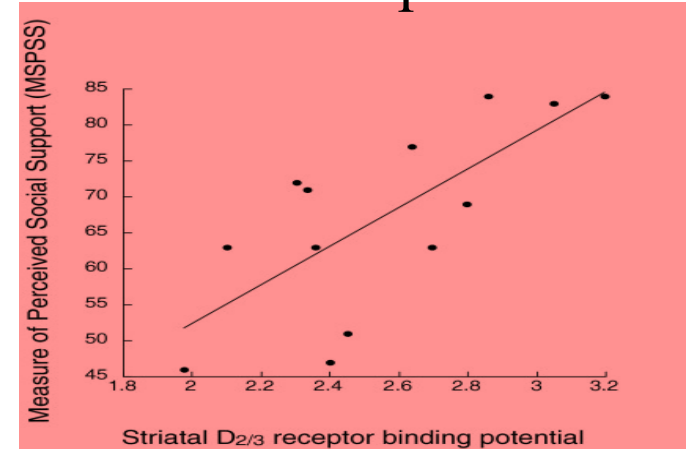
Effects of a Social Stressor on Brain Dopamine D2 Receptors and Propensity to Administer Drugs



Social Setting Can Change Neurobiology

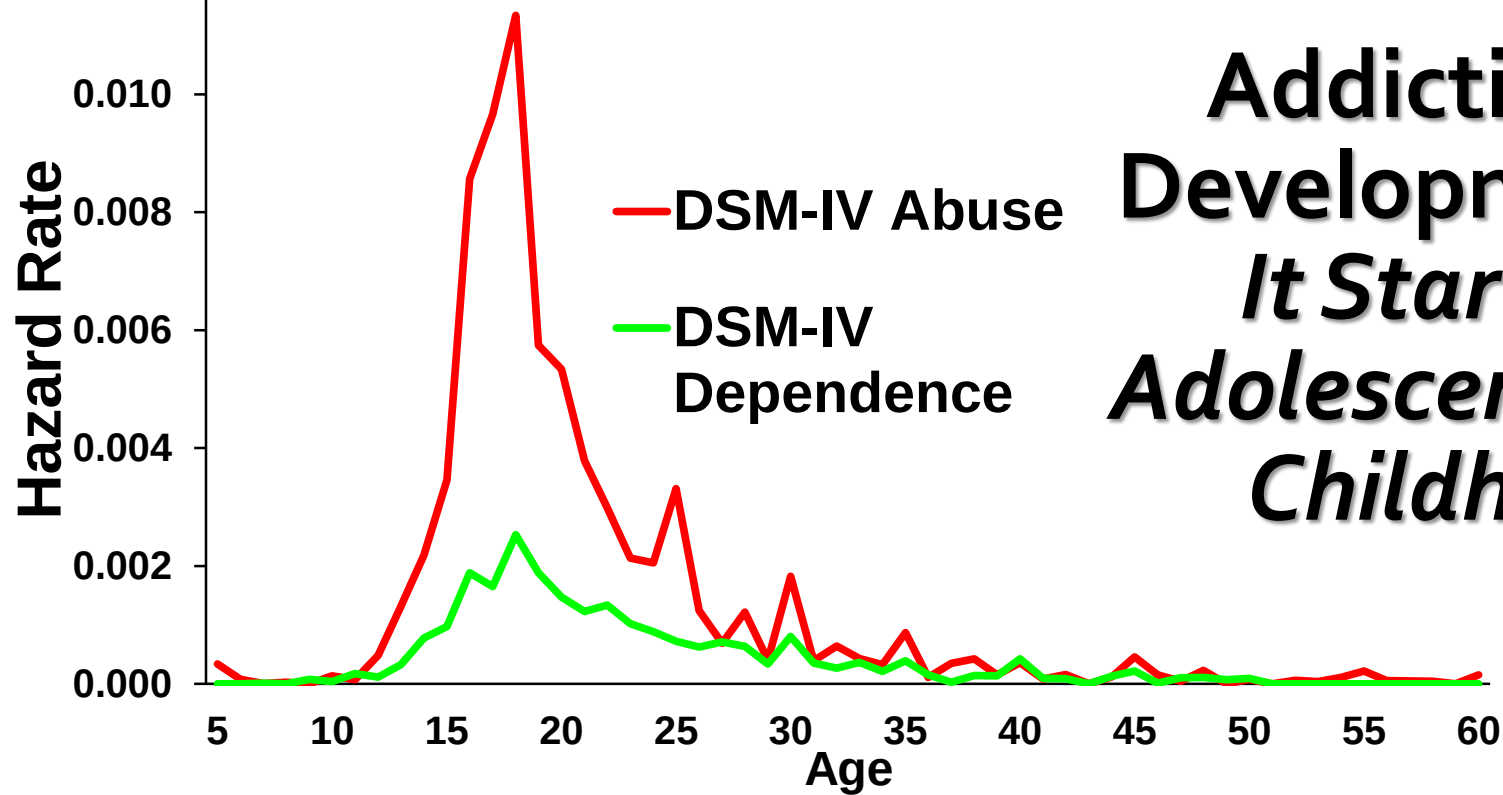


Social Support Is Correlated with D2/3 Receptor Binding



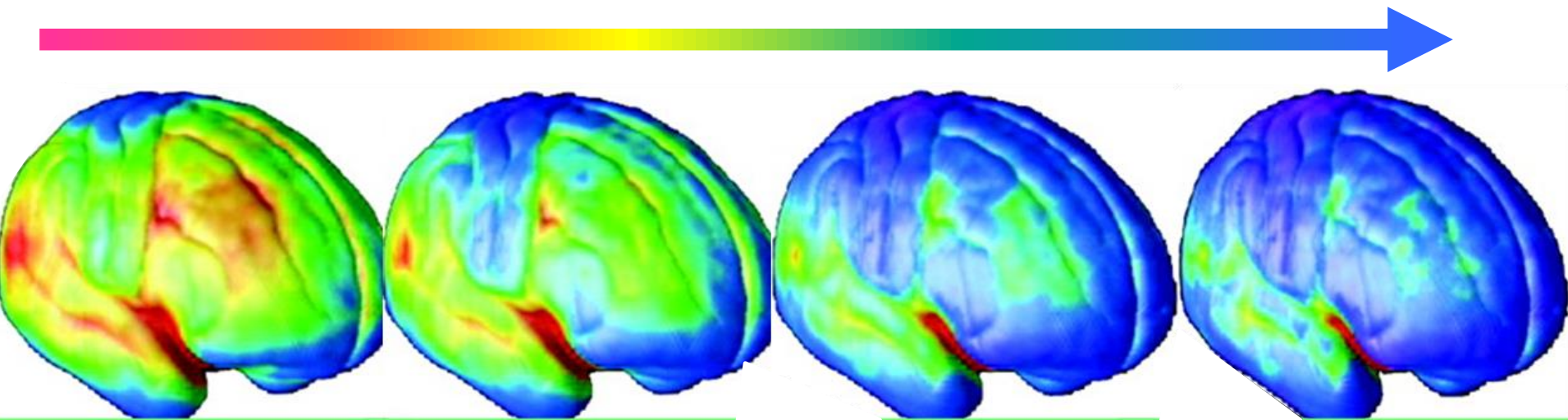
Morgan, D. et al. Nature Neuroscience, 2002.

Martinez D. et al., Bio Psychiatry 2010.



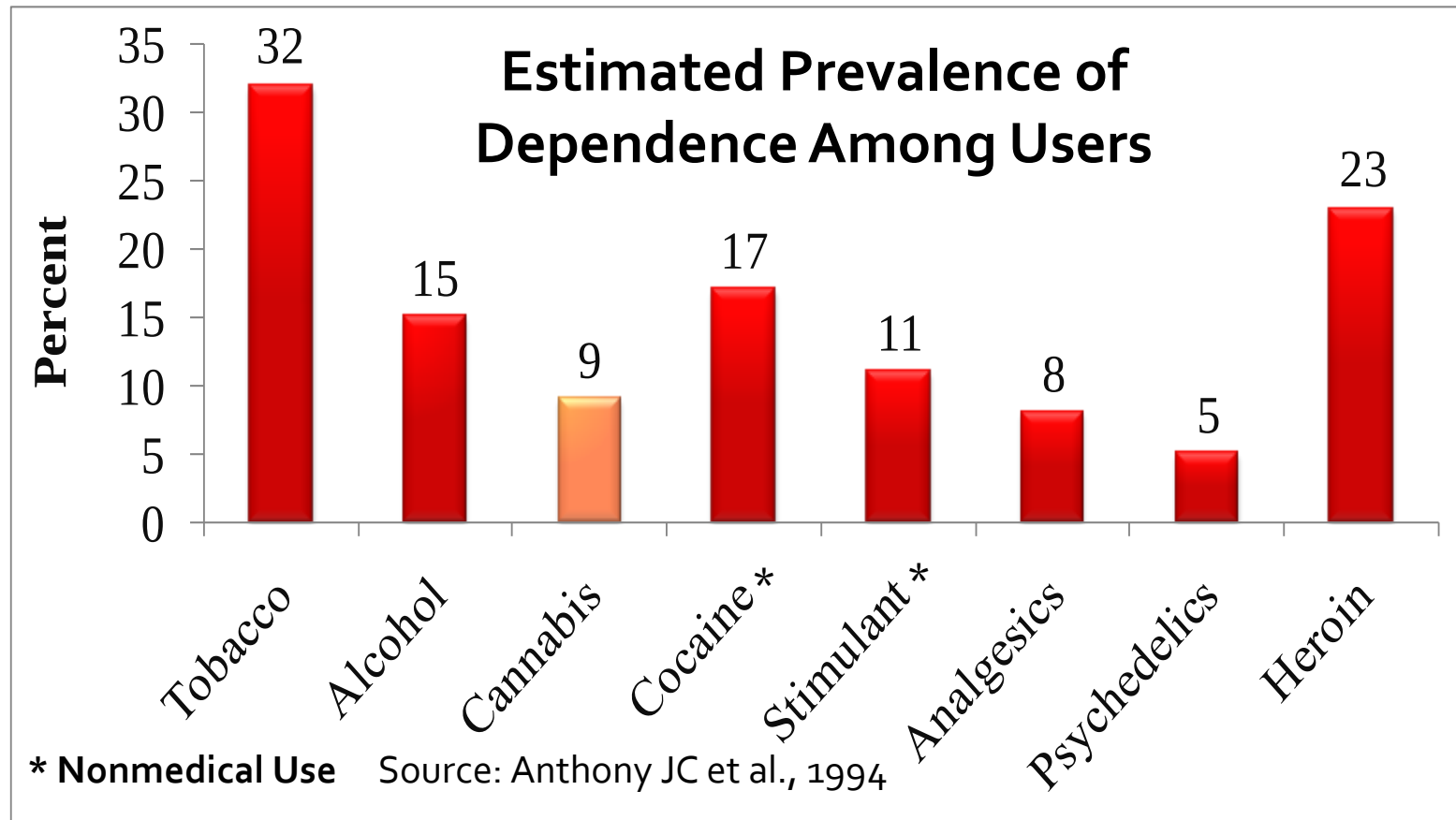
Age of Onset of Drug Abuse and Dependence

Source: Compton, et al. *Archives of General Psychiatry* 2007. NESARC Study.

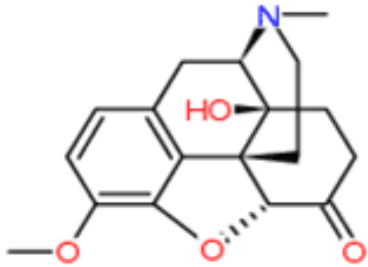


Key Question: *Do All Users Become Addicted?*

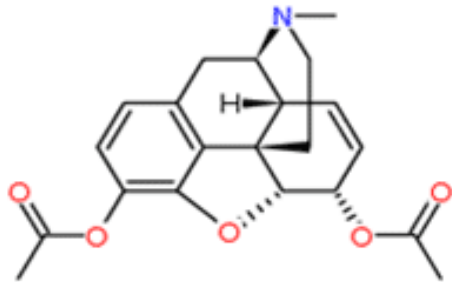
Use is NOT the Same as Addiction but Heavy Use and Early Use (i.e. early teens) increases risk



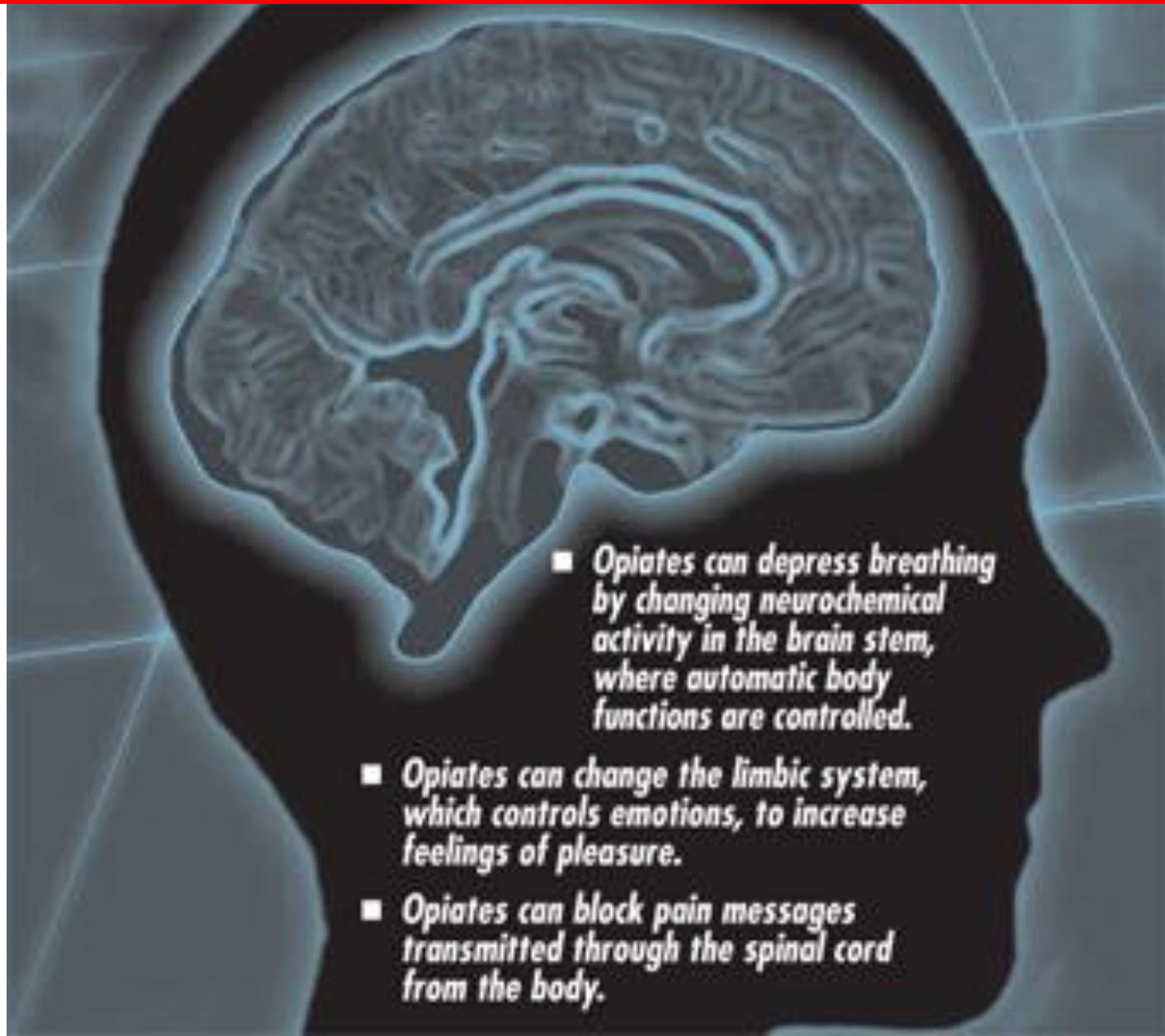
Similarities of Illicit & Prescription Drugs: Opioids



OXYCONTIN (OXYCODONE)



HEROIN



- Opiates can depress breathing by changing neurochemical activity in the brain stem, where automatic body functions are controlled.
- Opiates can change the limbic system, which controls emotions, to increase feelings of pleasure.
- Opiates can block pain messages transmitted through the spinal cord from the body.

What is the Difference Between *Therapeutic Use* and *Abuse*?

- **Dose and Frequency of Dosing**

Lower, fixed regimes vs higher, escalating use

- **Route of Administration**

Oral vs injection, smoking, snorting

- **Expectation of Drug Effects**

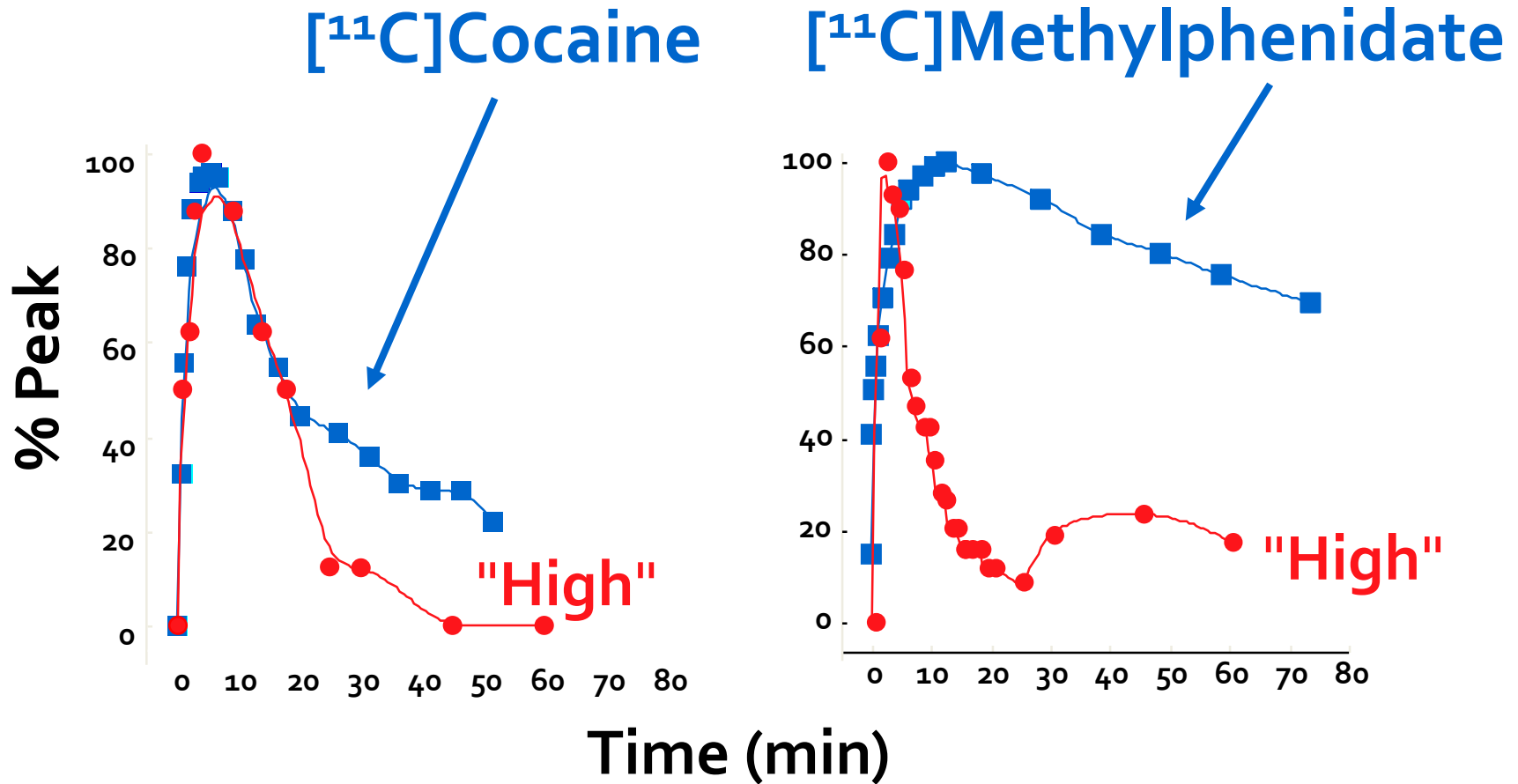
Expectation of clinical benefits vs euphoria “high”

- **Context of Administration**

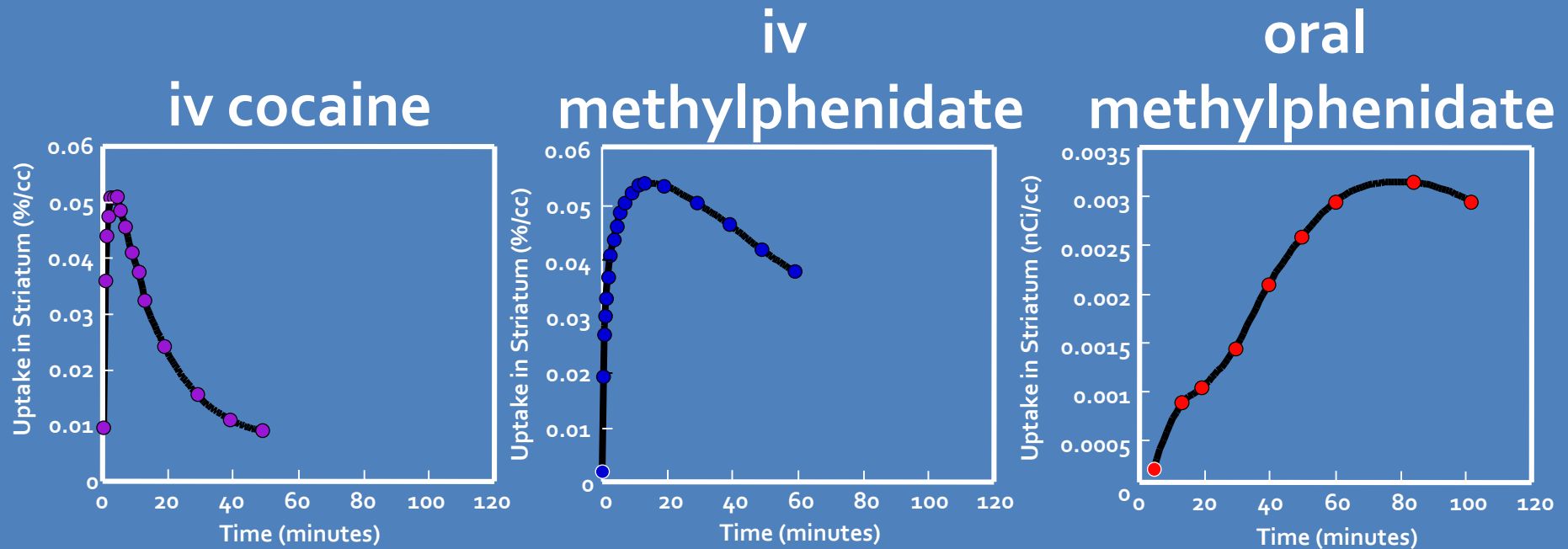
School, clinic, home vs bar, party



Rewarding Effects Depend on How Fast the Drug Gets into the Brain

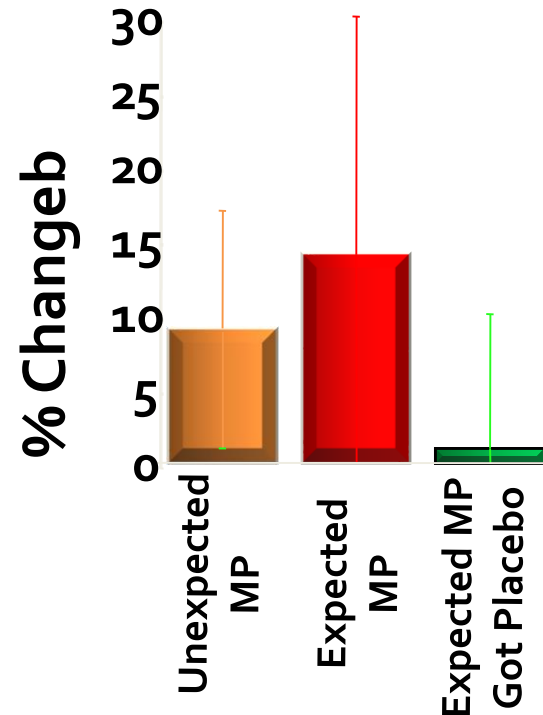
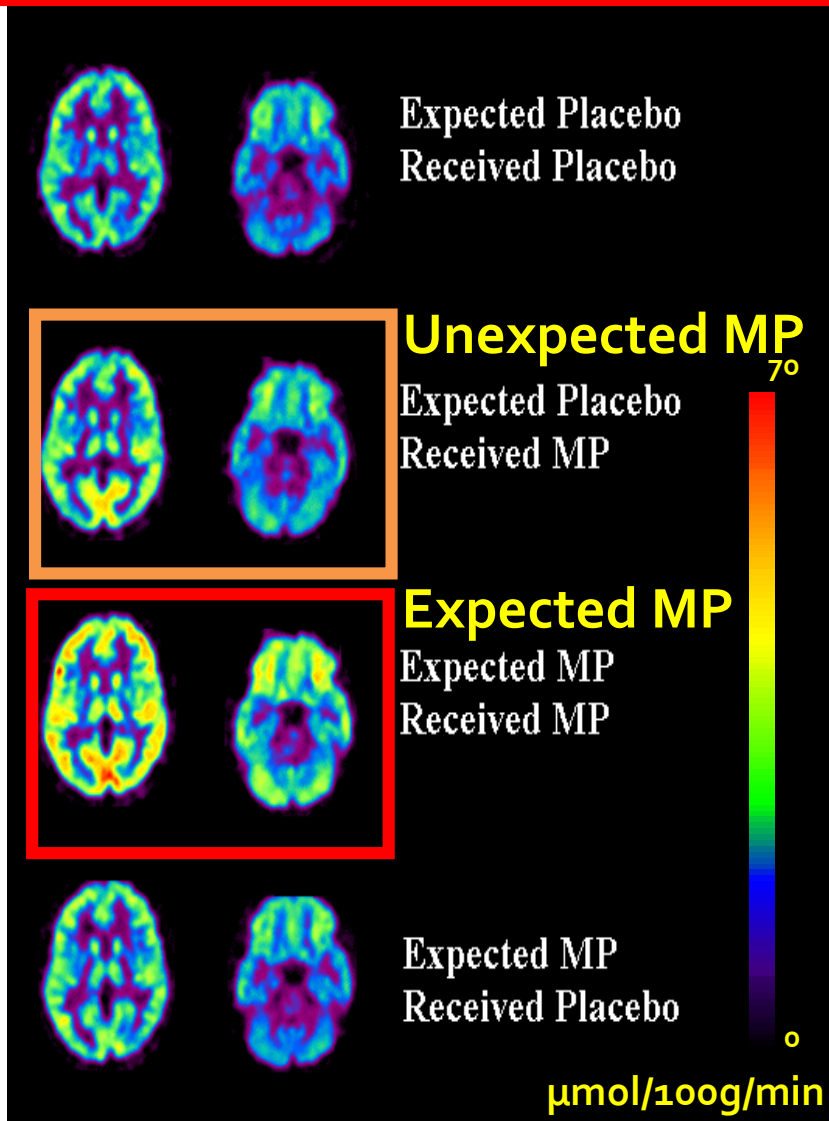


Rate of Drug Uptake Into the Brain



*Slower uptake of oral Ritalin
permits effective treatment with less intrinsic
reward (perceived "high")*

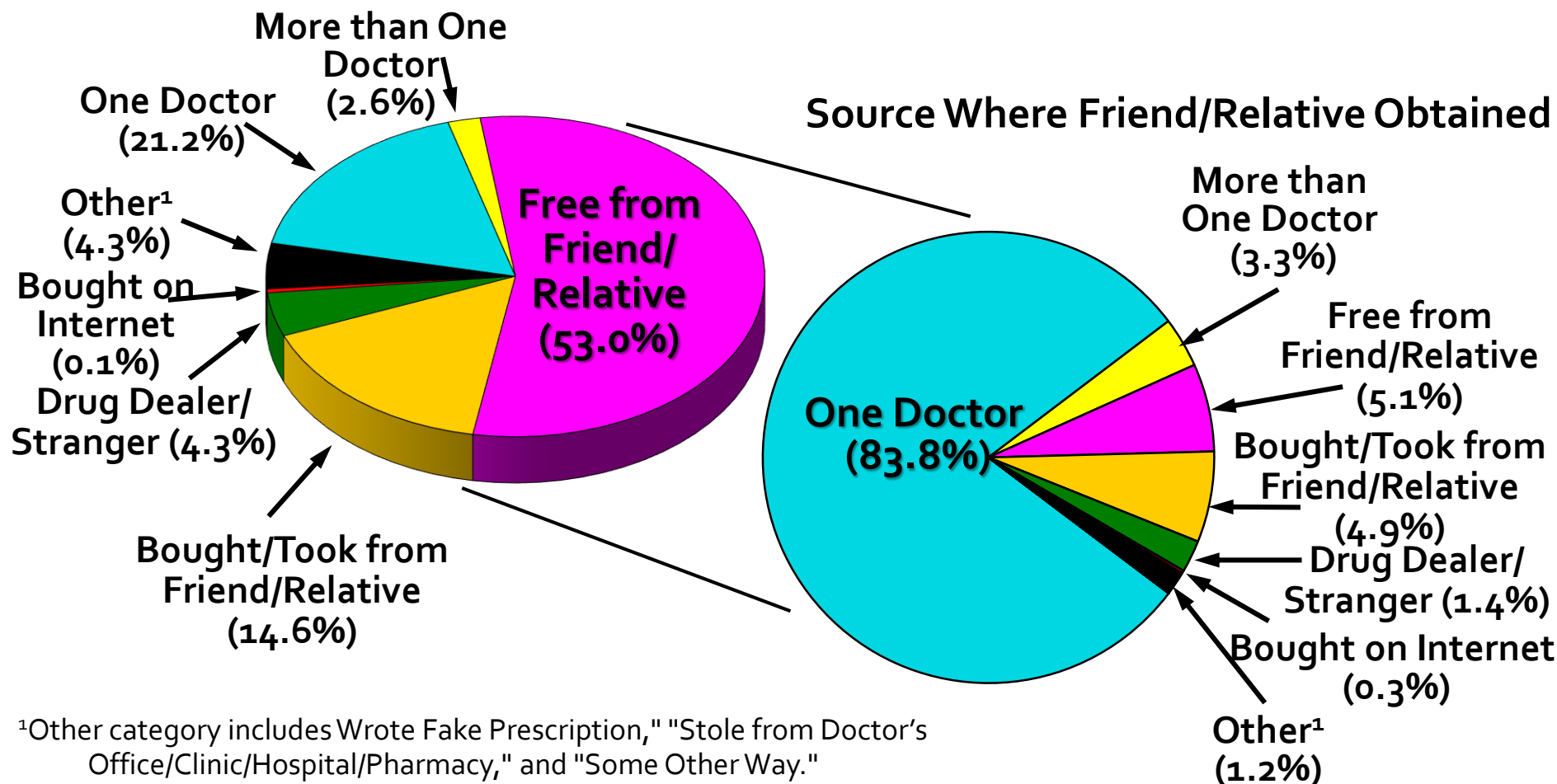
Glucose Metabolism Was Greatly Increased By the *Expectation* of the Drug



Increases in Metabolism Were About 50%
Larger When MP Was Expected Than
Unexpected

People Abusing Analgesics **DIRECTLY & INDIRECTLY** Obtain Them by Prescription: Most Recent Pill Source

Source Where Respondent Age 12+ Obtained Analgesics:



Source: SAMHSA, 2012 and 2013 National Survey on Drug Use and Health

Prescription Drug Abuse:

What can be done?





EXAMPLES OF RISK AND PROTECTIVE FACTORS

Risk Factors	Domain	Protective Factors
Early Aggressive Behavior	Individual	Self-Control
Poor Social Skills	Individual	Positive Relationships
Lack of Parental Supervision	Family	Parental Monitoring and Support
Substance Abuse	Peer	Academic Competence
Drug Availability	School	Anti-Drug Use Policies
Poverty	Community	Strong Neighborhood Attachment

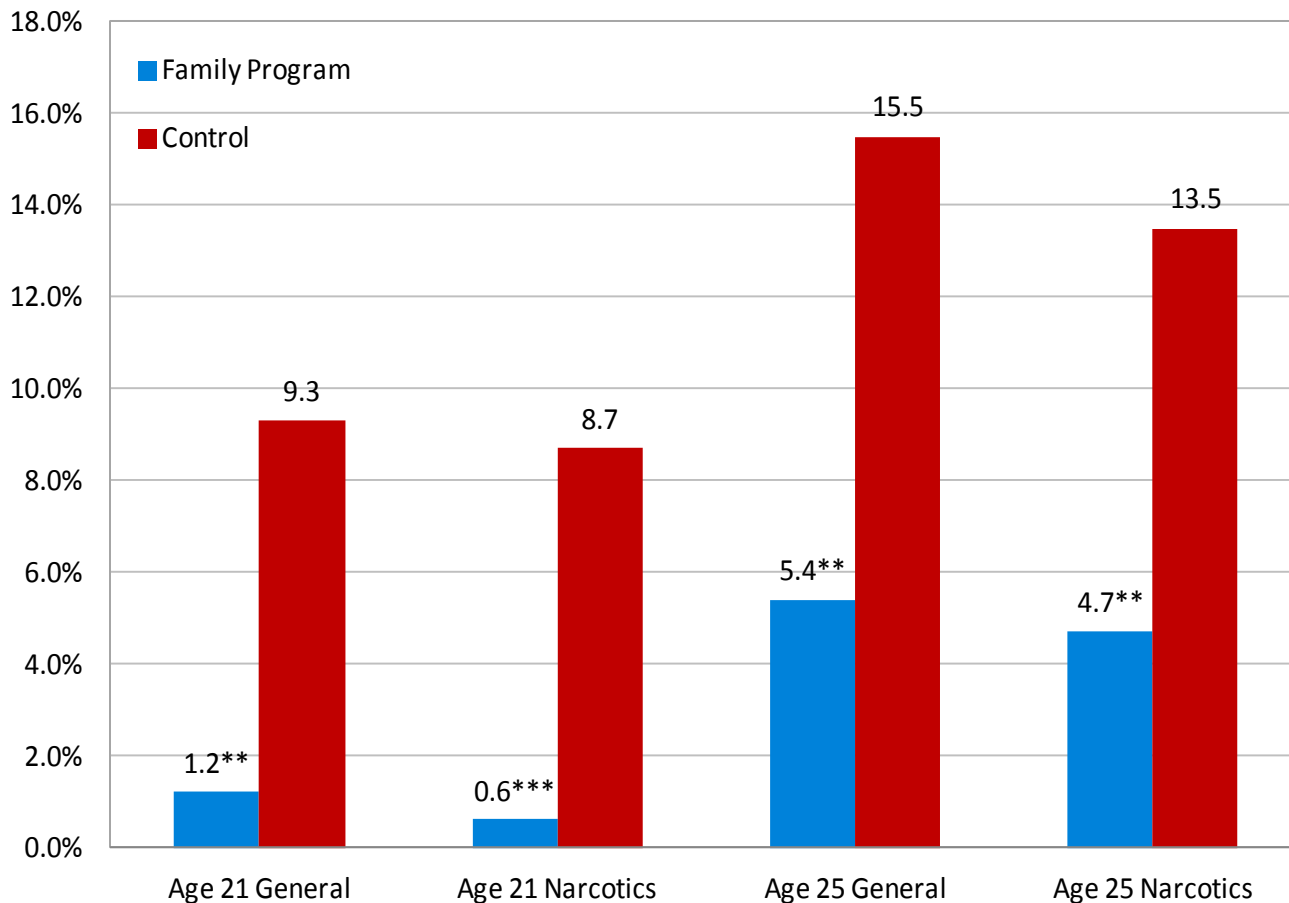
Reduce these

Elevate these

Prevention Programs Should
Enhance Protective Factors & Reduce Risk Factors

Universal Drug Abuse Prevention

Reduces Prescription Drug Misuse



** $p < .01$; *** $p < .001$; Relative Reduction Rates (RRRs)= 65-93%

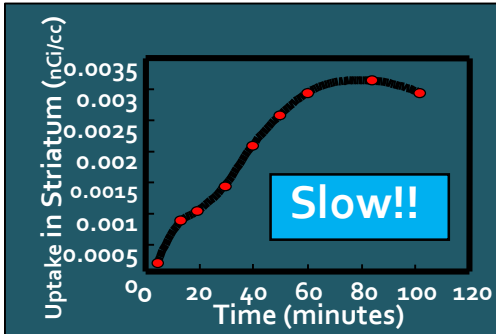
Notes: General=Misuse of narcotics or CNS depressants or stimulants.

Source: R Spoth et al. *American Journal of Public Health* 2013

In this study, for 100 young adults in general population starting Rx abuse, only 35 young adults from an intervention community started.

Overall, three studies now suggest the impact of universal prevention on prescription drug abuse.

Prevention: Need for New Medications

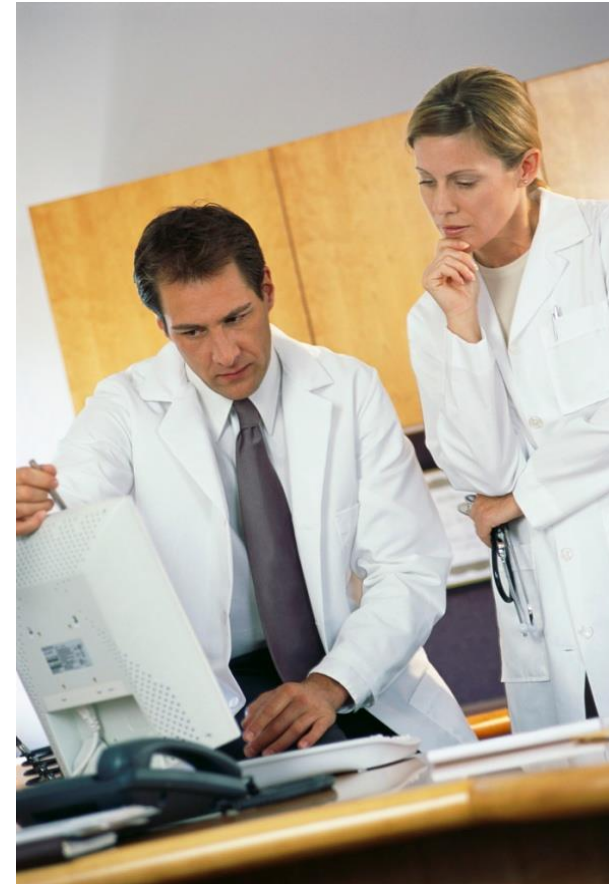


- Develop medications with **lower abuse potential** including drugs that don't cross the *Blood-Brain-Barrier* (*i.e.*, CbR2 agonist)
- Develop **slow release formulations** (low dose and long duration)
- Develop novel formulations to **reduce abuse liability** including mixture formulations (e.g., naloxone and buprenorphine)

Prevention: Clinicians Need to Know What Prescriptions Have Been Given to Their Patients By Other Practitioners

This information should be:

- 1) included in the patients' electronic health care records**
- 2) accessible through a Prescription Drug Monitoring Program (PDMP) that provides immediate information**



Overdose Intervention

- **Naloxone Distribution** for opioid overdose victims. The *potential* for direct intervention to save lives.
 - *Note the April 3, 2014 FDA approval of the naloxone auto-injector (called "Evzio")*
- **Naloxone Nasal Spray Development**
Needle-free, unit-dose, ready-to-use opioid overdose antidote.
 - *NIDA STTR Grantee – AntiOp, Inc., Daniel Wermeling, CEO*
 - *NIDA clinical study with Lightlake Therapeutics, Inc.*



Enacted
Legislation

- Controlled Substance/Paraphernalia Possession Protections (23†)
- Lay Administration Criminal Liability Protections (24)
- Lay Administration Civil Liability Protections (21)
- Prescriber Criminal Liability Protections (14)
- Prescriber Civil Liability Protections (13)
- Allows Third Party Prescriptions (23)

MIDWEST

WEST

SOUTHWEST

SOUTHEAST

State Naloxone and Good Samaritan Legislation

as of July 15, 2014

(Please check the individual statute
as the language is nuanced and
varies from state to state.)

*Only if person has received training.

†Only applies to 1st responders.

‡In Utah and Indiana, evidence of providing assistance to someone experiencing an overdose can be presented as a mitigating factor at sentencing to a conviction for possession of a controlled substance and/or paraphernalia. Utah allows evidence of providing assistance to someone experiencing an overdose to be used as an affirmative defense to an allegation of possession of a controlled substance and/or paraphernalia.

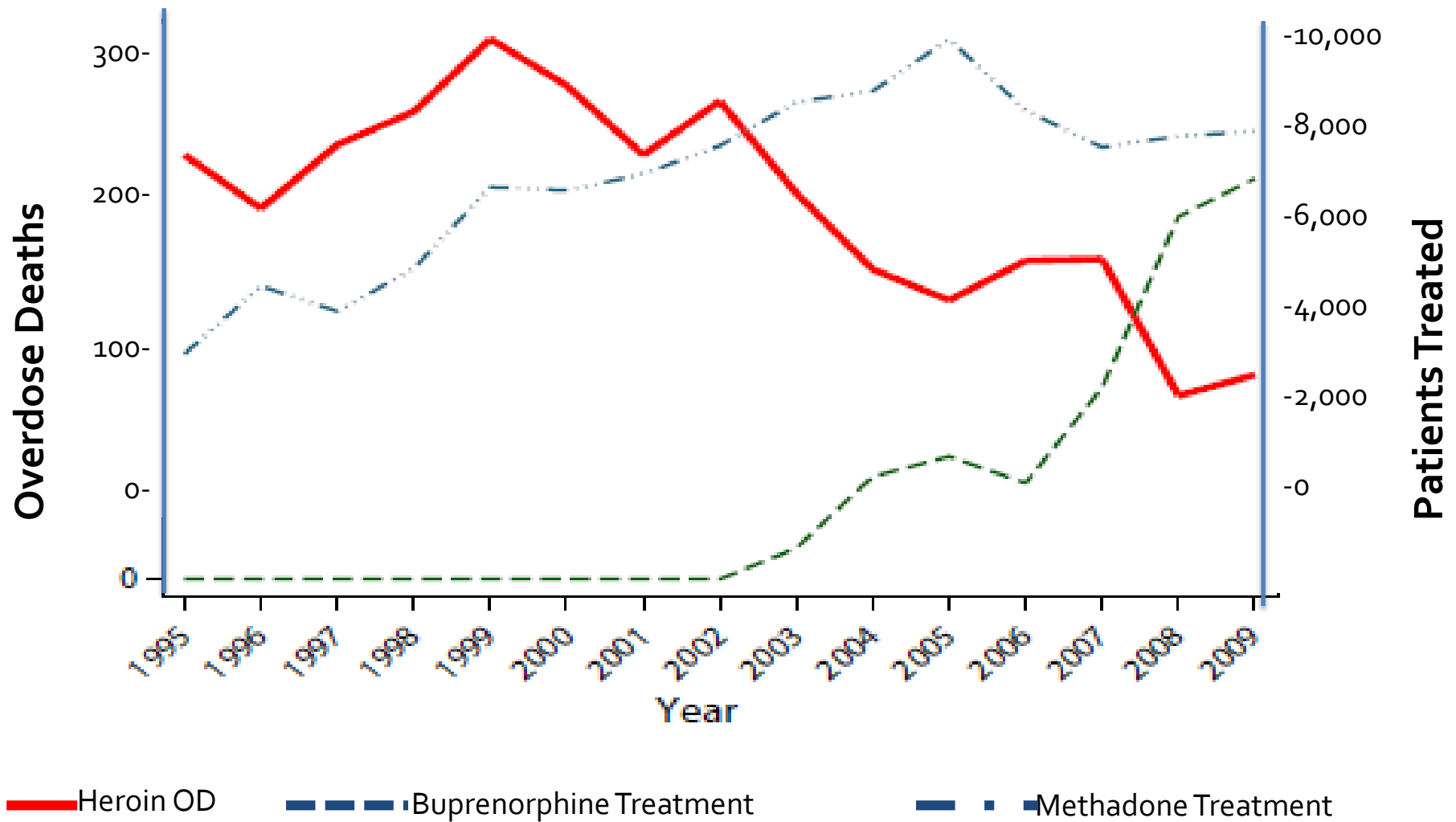
Source: Office of National Drug Control Policy (ONDCP) searches of state legislative information from the following online databases yielded the information on the chart, and were current as of July 15, 2014:

<https://advance.lexis.com>
<http://www.cqstatetrack.com/>
<http://openstates.org/>

Created by ONDCP: July 29, 2014

NORTHEAST

Medical Treatment May Reduce Deaths



R Schwartz et al. *American Journal of Public Health* 2013

Additional Challenge...

Lack of uptake of medication-assisted treatment

<i>Addiction Specialty Programs Offering Services</i>	<i>As % of all programs surveyed (N=345)</i>	<i>Within adopting programs, % of eligible patients receiving Rx</i>
TOO FEW ARE TREATED		
<u>Opioid Tx Med:</u>		
Methadone	7.8	41.3
Buprenorphine	20.9	37.3
Tablet naltrexone	22.0	10.9
<i>Knudsen et al, 2011, J Addict Med; 5:21-27.</i>		

Education for Healthcare Providers

CME Courses developed by NIDA & Medscape Education, funded by ONDCP

Safe Prescribing for Pain

Skills and tools clinicians can use to screen for and prevent opioid medication abuse in patients with pain.



Managing Pain Patients Who Abuse Rx Drugs

Learn opioid addiction symptoms in patients with chronic pain, and how to screen for, prevent, and treat such conditions.



NIDAMED 

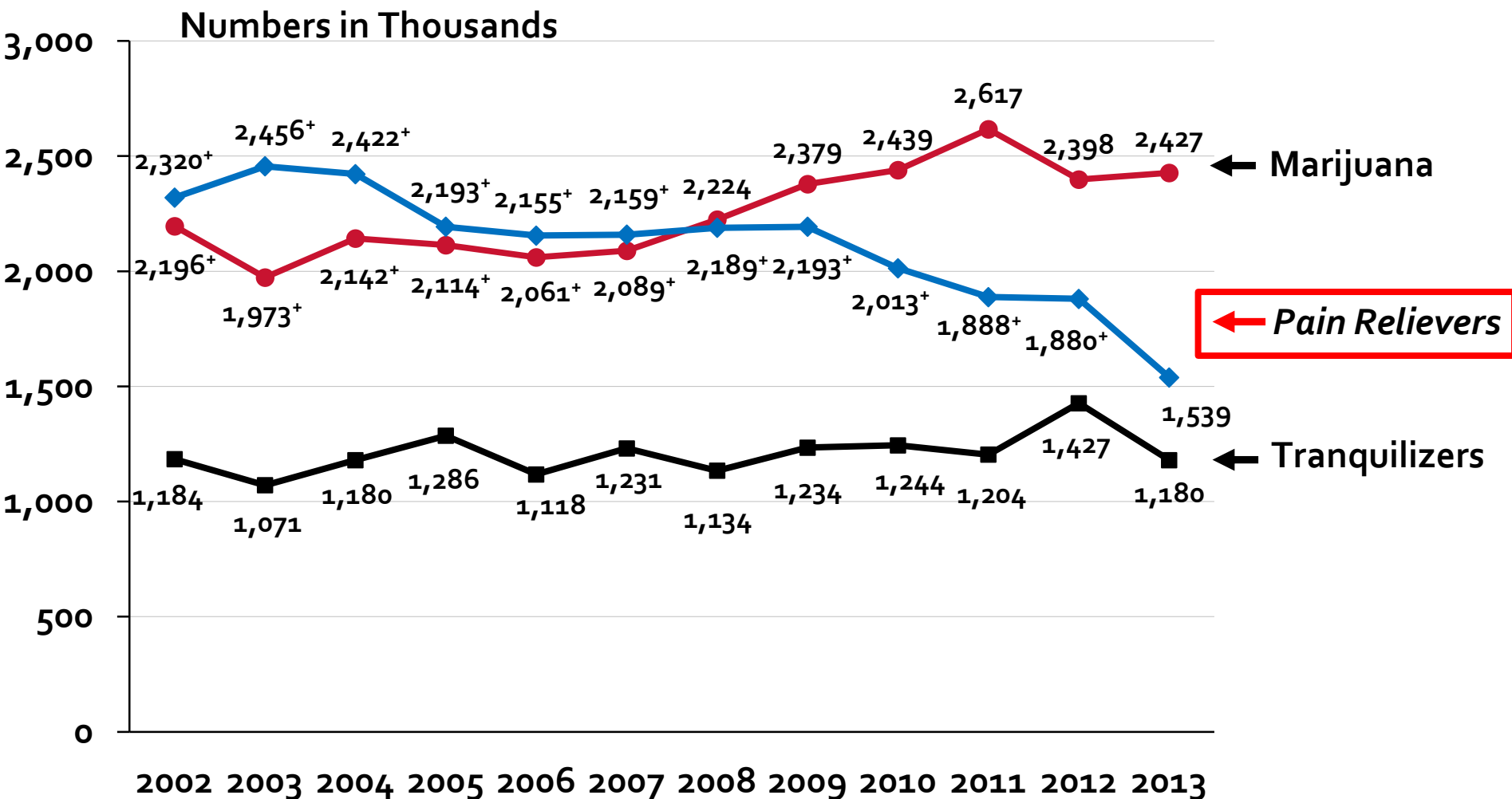
Prescription Drug Abuse:

What can be done?

- Primary Prevention
- Less abusable analgesics
- Overdose Intervention
- Better Access to Effective Addiction Treatments
(especially medications for opioid addiction)
- Public and Clinician Education



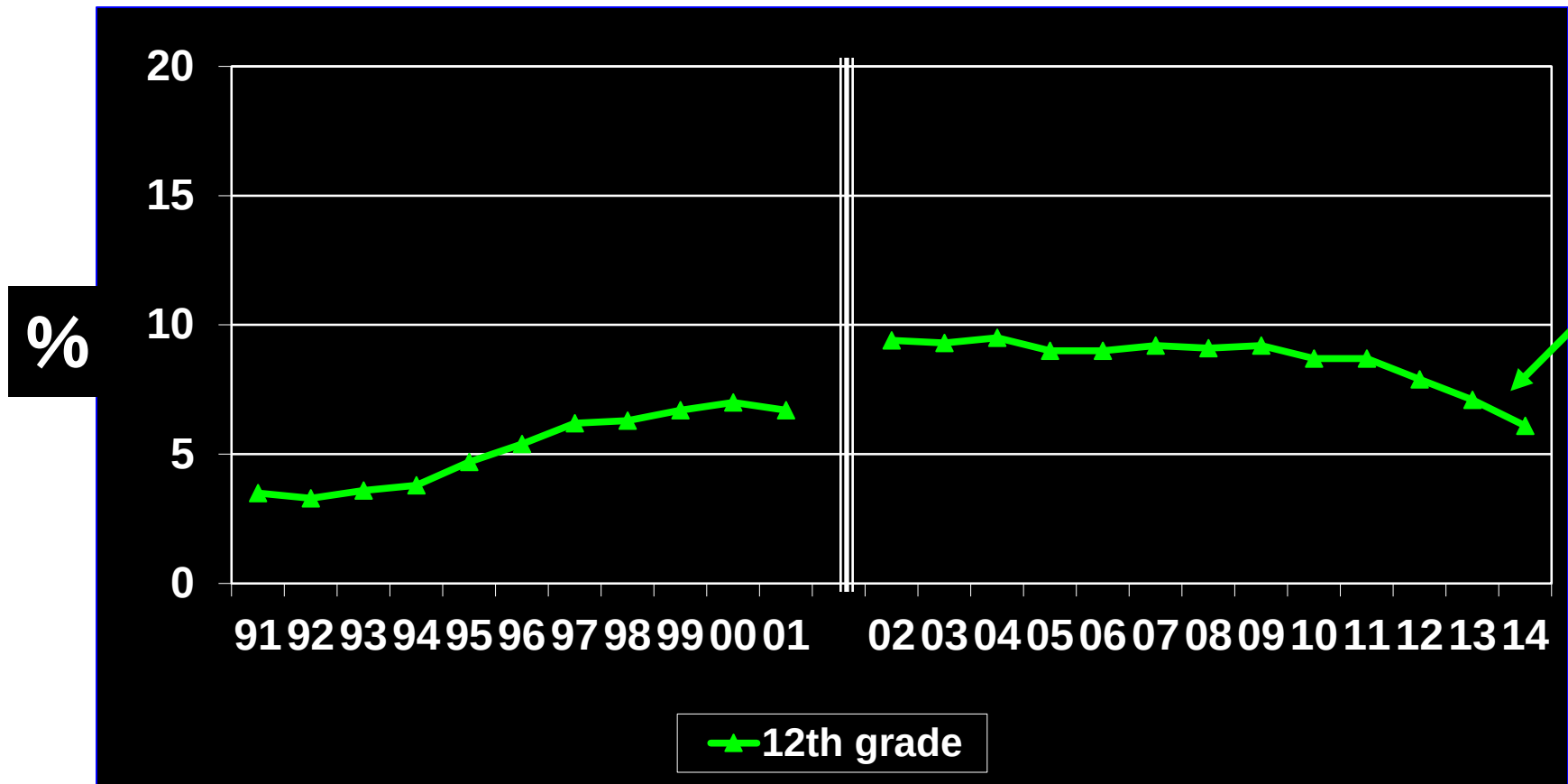
Reduced Numbers of Analgesic Misuse Initiators: Past Year Drug Initiates, Ages 12+, 2002-2013



⁺ Difference between this estimate and the 2012 estimate is statistically significant at the .05 level.

Source: SAMHSA, 2013 National Survey on Drug Use and Health, released September

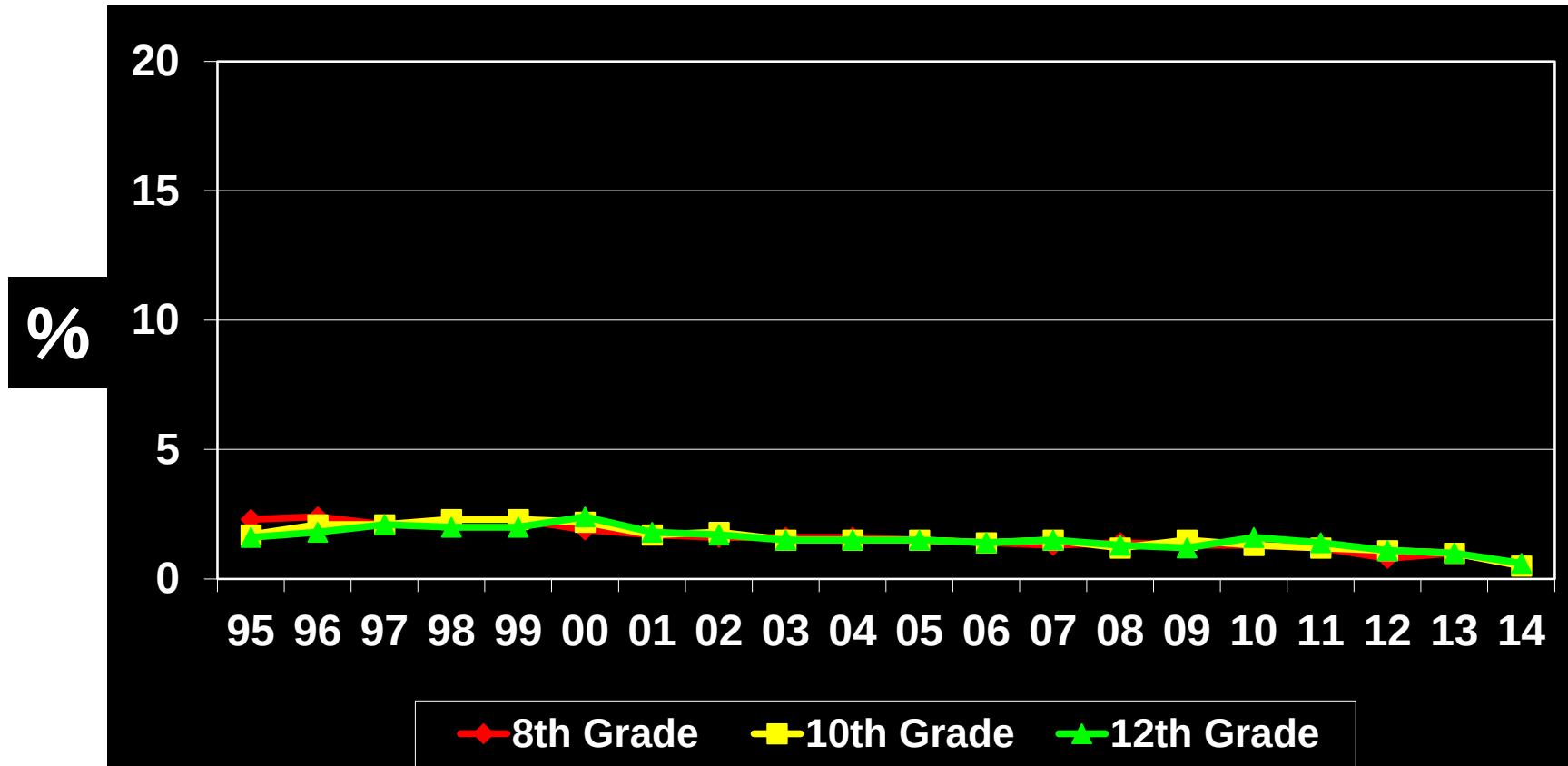
Fewer High School Seniors Reporting Use of Narcotics Other than Heroin, in USA



Denotes significant difference
between 2013 and 2014

SOURCE: University of Michigan, 2012 Monitoring the Future Study

Few Students Reporting Use of Heroin in Past Year, in USA



SOURCE: University of Michigan, 2014 Monitoring the Future Study

Recent Slight Reductions in Rx Opioid-Related Deaths but *Marked Increases in Heroin*

2013 OD Deaths:

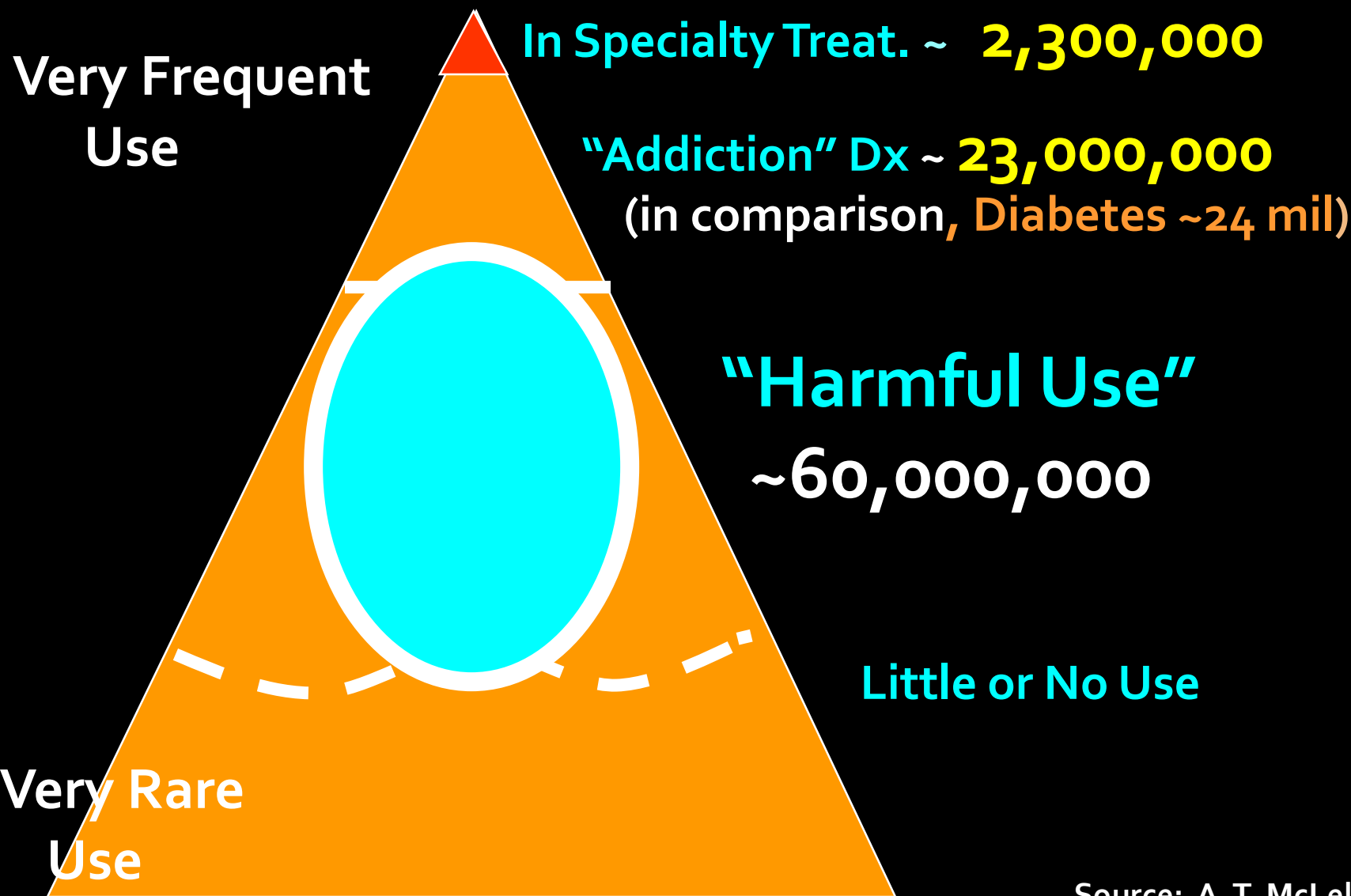
- 16,235 Rx opioid
 - (16,007 in 2012 and 16,917 in 2011) 
- 8,257 Heroin
 - (5,927 in 2012 and 4,397 in 2011) 

Conclusions

- Addictions are examples of gene x environment x development conditions
- Prevention and treatment can be effective (when actually applied)
- Physicians play a key role....

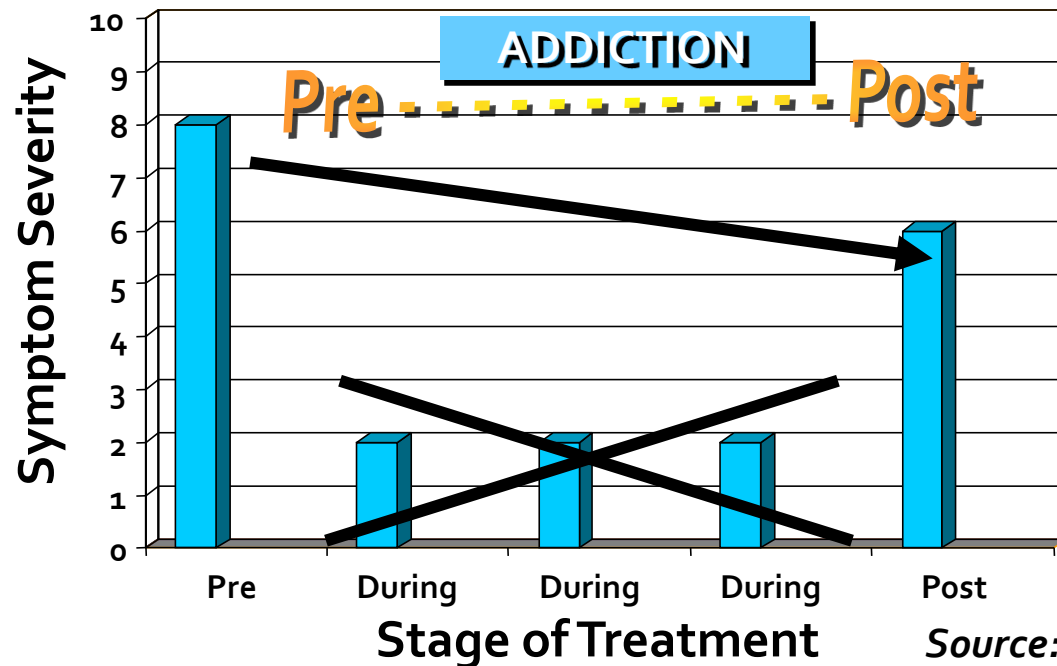
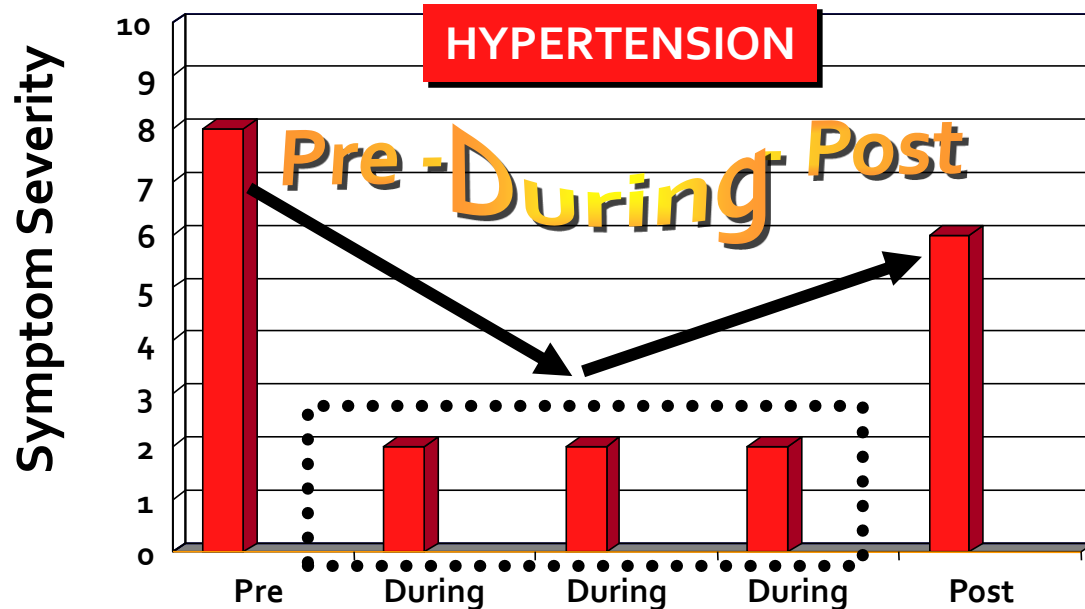
Scope of Substance Use in the US

Alcohol, Illicit & non-prescribed drugs



Source: A. T. McLellan, 2011

Evaluation of A Hypothetical Treatment

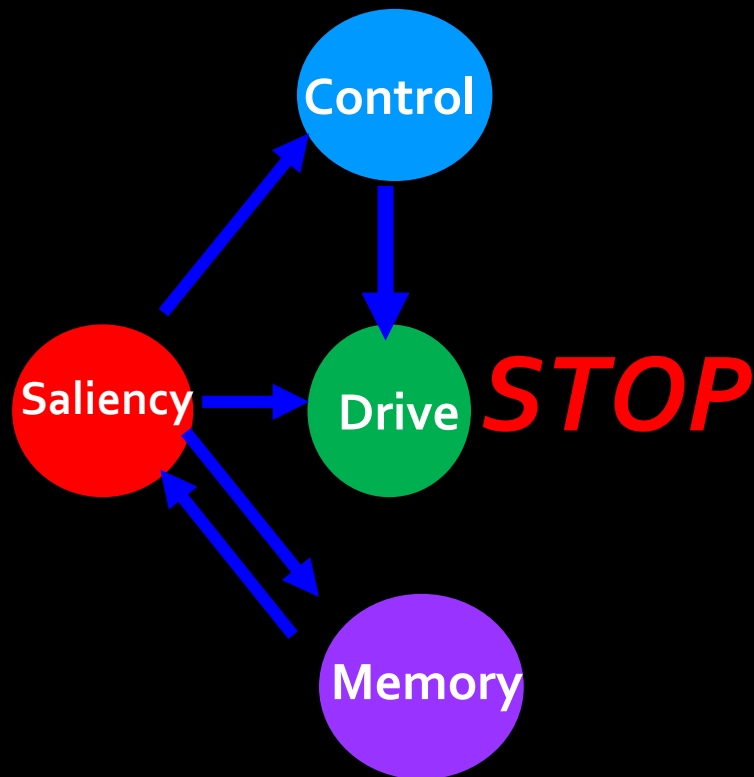


*Just Like
Hypertension,
Addiction Is A
Chronic Disease
That
Requires Continued
Care*

Source: McLellan, AT, *Addiction* 97, 249-252, 2002.

Medications for Relapse Prevention

Treated/Non-Addicted
Brain



Interfere with
drug's reinforcing
effects

Vaccines
Enzyme degradation
Naltrexone
DA D₃ antagonists
CB₁ antagonists

Executive function/
Inhibitory control

Biofeedback
Modafinil
Bupropion
Stimulants

Strengthen prefrontal-
striatal communication

Adenosine
A₂ antagonists
DA D₃ antagonists

Interfere with
conditioned memories

Antiepileptic GVG
N-acetylcysteine

Teach new memories

Cycloserine

Counteract stress
responses that lead to
relapse

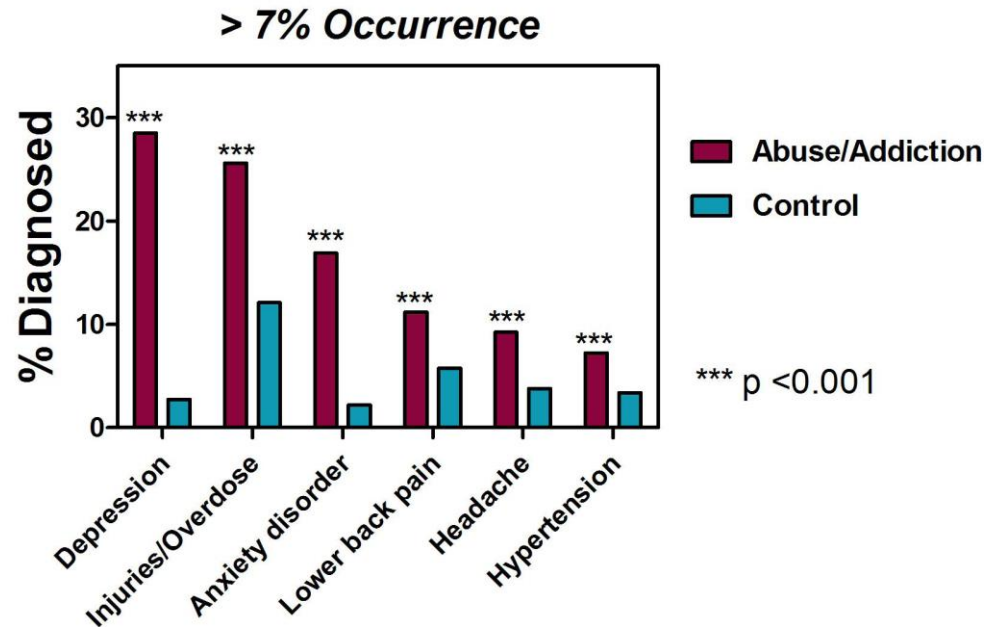
CRF antagonists
Orexin antagonists

Why focus on drug use in medical settings?

Drug use has wide ranging health , social consequences.

- Cardiovascular disease, stroke, cancer, HIV/AIDS, anxiety, depression, sleep problems, as well as financial difficulties and legal, work, and family problems can all result from or be exacerbated by drug use.

Occurrence of Medical Conditions in Diagnosed Substance Abusers



Source: Mertens JR et al, Arch Intern Med 163: 2511-2517, 2003

Why focus on drug use in medical settings?

Health Care Reforms are shifting the emphasis to integrated care based in general medical settings.

- 2009 Enhanced parity of coverage of mental illnesses and substance use disorders (compared to coverage of other medical conditions)
- 2010 Health care reform to reduce the number of uninsured persons

WE NEED YOUR HELP!

- **Medical expertise is needed in practice
AND RESEARCH**

Emergency Department–Initiated Buprenorphine/Naloxone Treatment for Opioid Dependence

	Referral	Brief Intervention	Buprenorphine	<i>P</i> Value ^b
Days of Self-reported Illicit Opioid Use in the Past 7 Days, Mean (95% CI)				
Baseline	5.4 (5.1-5.7)	5.6 (5.3-5.9)	5.4 (5.1-5.7)	<.001, Treatment effect <.001, Time effect .02, Interaction effect
30 d	2.3 (1.7-3.0)	2.4 (1.8-3.0)	0.9 (0.5-1.3)	
Outpatient Addiction Treatment in the Past 30 Days, Mean (95% CI) ^c				
No. of outpatient visits				
Baseline	0.38 (0.0-1.0)	1.16 (0.6-1.7)	0.20 (0.0-0.8)	.07, Treatment effect <.001, Time effect .63, Interaction effect
30 d	4.99 (3.1-6.8)	5.67 (4.0-7.4)	3.71 (2.1-5.3)	
ED-Based Addiction Treatment in the Past 30 Days, No./Total (%)				
Any addiction-related ED visit				
Baseline	8/104 (7.7)	6/111 (5.4)	5/114 (4.4)	.57
30 d	15/69 (21.7)	12/82 (14.6)	18/93 (19.4)	.51
Inpatient Addiction Treatment in the Past 30 Days, No./Total (%) ^d				
Any inpatient addiction treatment				
Baseline	10/104 (9.6)	7/111 (6.3)	7/114 (6.1)	.55
30 d	31/84 (36.9)	32/91 (35.2)	11/100 (11.0)	<.001

D’Onofrio, et al. JAMA. April 28, 2015;313(16):1636-1644.

www.drugabuse.gov

Now NIDA resources are with you wherever you go!

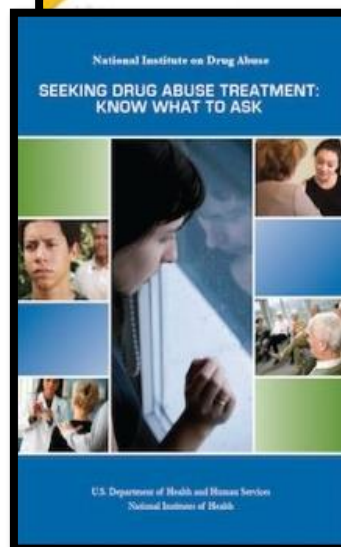
We're connecting communities with a new mobile Web site that gives you drug-related information by topic, audience, and format—when you need it, where you need it.

The new mobile site (m.drugabuse.gov) provides:

- ✓ Easy access to NIDA's resources through iPhone, Android, iPad, and other smartphones and tablets.
- ✓ A convenient way to find, view, request, and share publications—right in the palm of your hand.
- ✓ E-books of all publications to allow offline reading on all major e-readers, including Kindle and NOOK.
- ✓ New Spanish-language content on drugs of abuse and related topics.



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