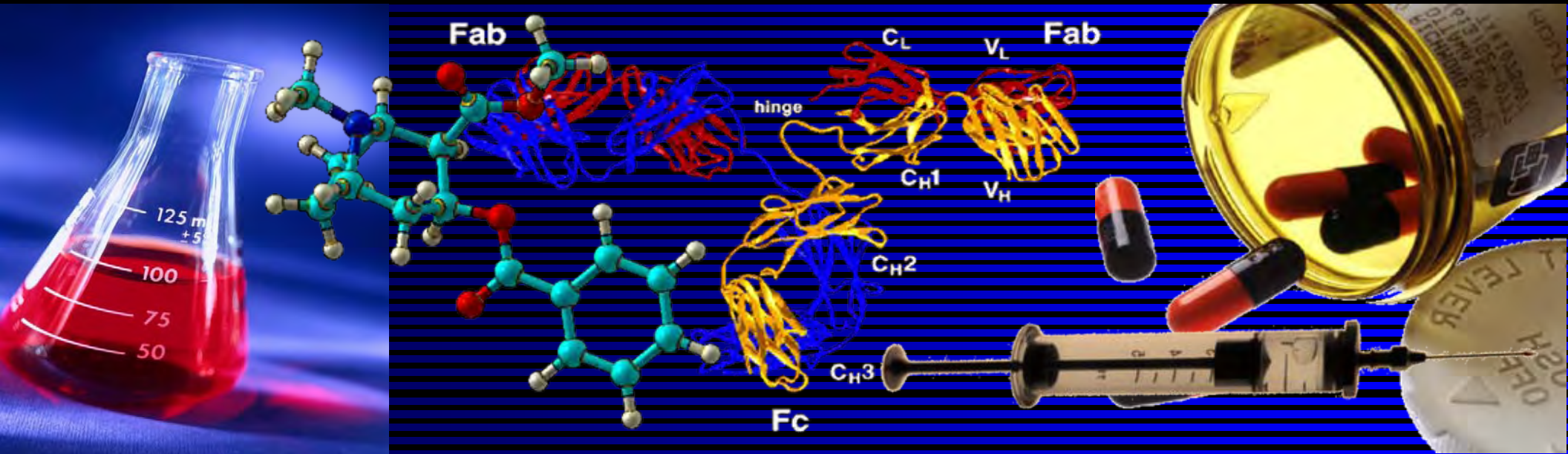


Developing Medications to Treat Addiction: *Implications for Policy and Practice*



Nora D. Volkow, M.D.
Director



National Institute on Drug Abuse

Medications Currently Available

For Nicotine Addiction

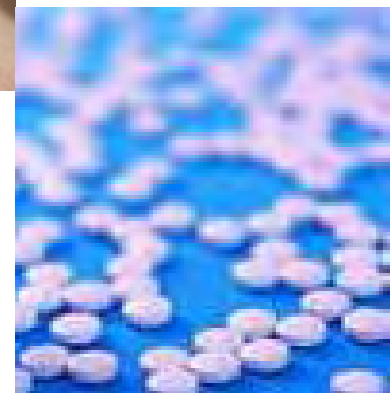
- **Nicotine Replacement Therapies (NRT)**
- **Bupropion**
- **Varenicline**

For Alcoholism

- **Disulfiram**
- **Naltrexone**
- **Acamprosate**

For Opiate Addiction

- **Methadone**
- **Naltrexone**
- **Buprenorphine**
- **Buprenorphine/Naloxone**



There is Still Enormous Need For Medications to Treat Addiction

Currently there are *no approved medications* to treat...

● Cocaine Addiction>



● Methamphetamine Addiction>

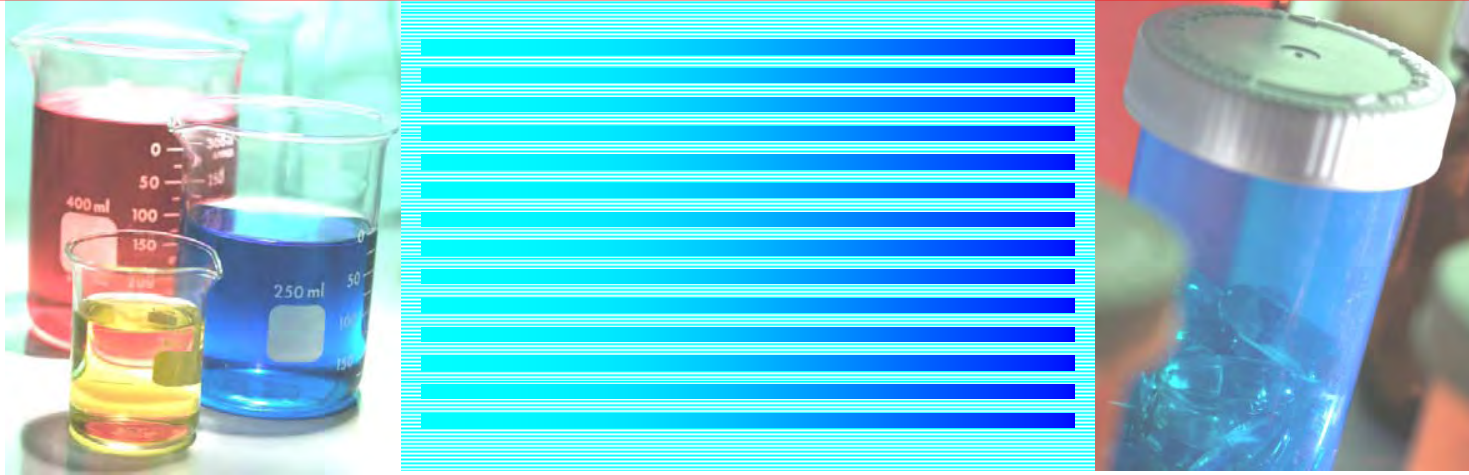


● Marijuana Addiction>



...and the efficacy of existing treatments is, on average, only about 30%

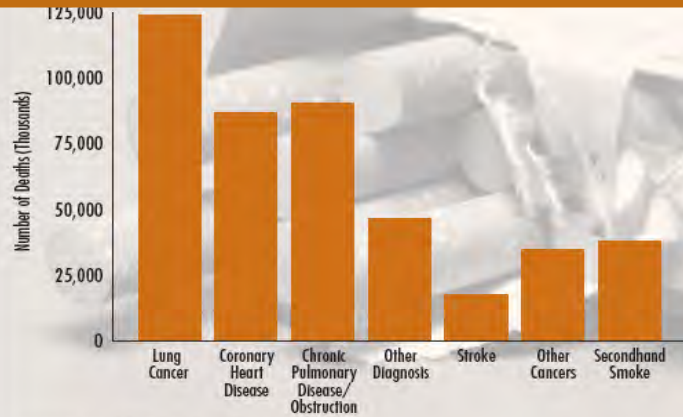
Challenges Involved in Developing Medications to Treat Addiction



- **STIGMA of addiction**
- **Lack of pharmaceutical industry involvement**
- **Prohibitive cost: \$2.3 B to bring medication to clinic**
- **Length of drug discovery process: 7-13 years**
- **Regulatory issues surrounding controlled substances**

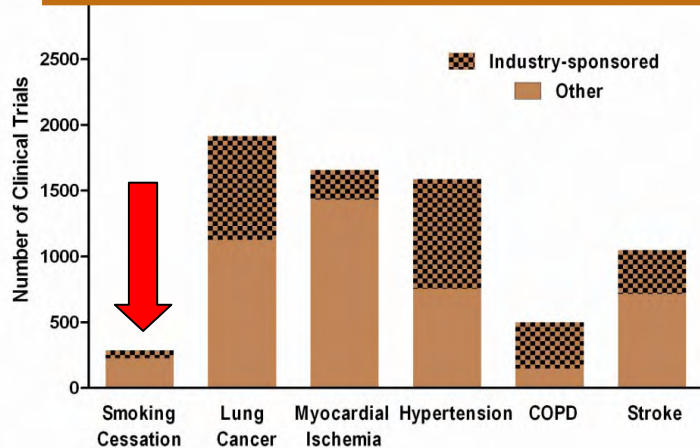
ROADBLOCK #1: Lack of Pharmaceutical Industry Interest in Conducting Clinical Trials for Addiction/Alcoholism

440,000 Annual Deaths from Smoking



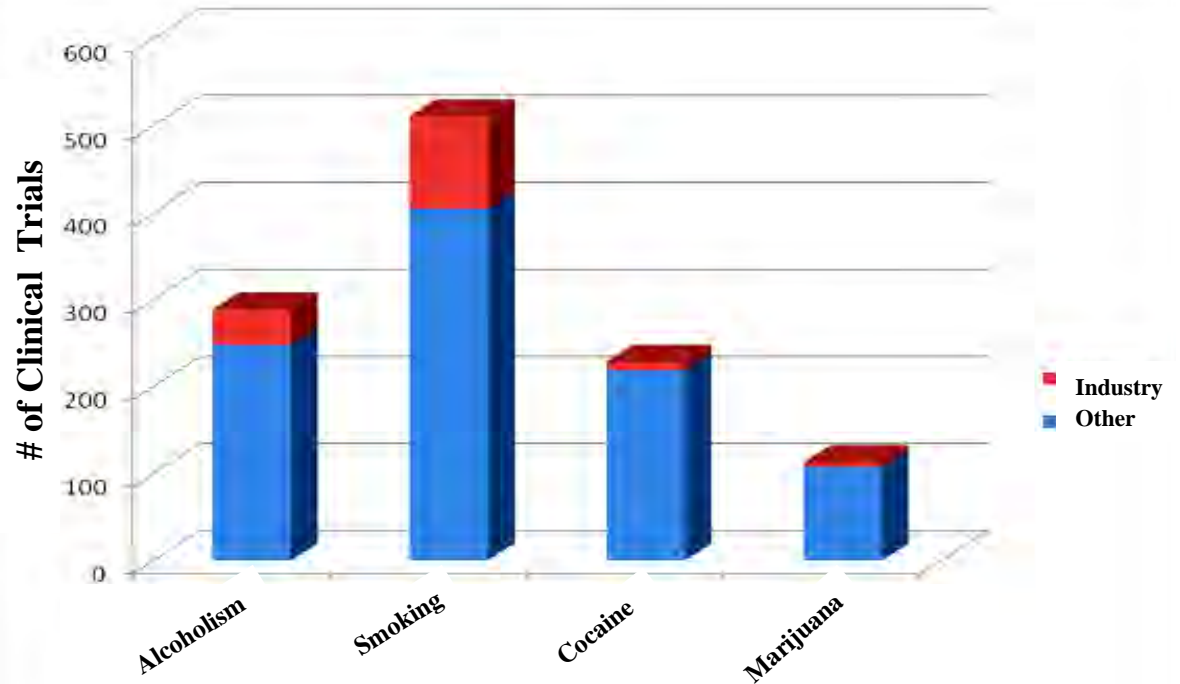
Source: CDC, *MMWR* 2005, 54(25):625-628

170 Pharmacotherapy Trials Smoking Cessation Conducted



Source: *Clinicaltrials.gov*, October 2008

Current Pharmaceutical Investment in Substance Abuse Treatment

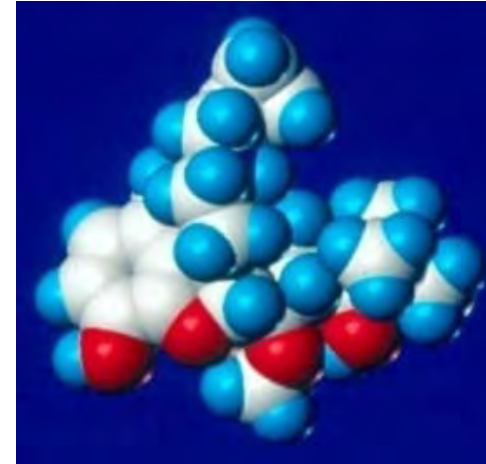


Source: *Clinicaltrials.gov*

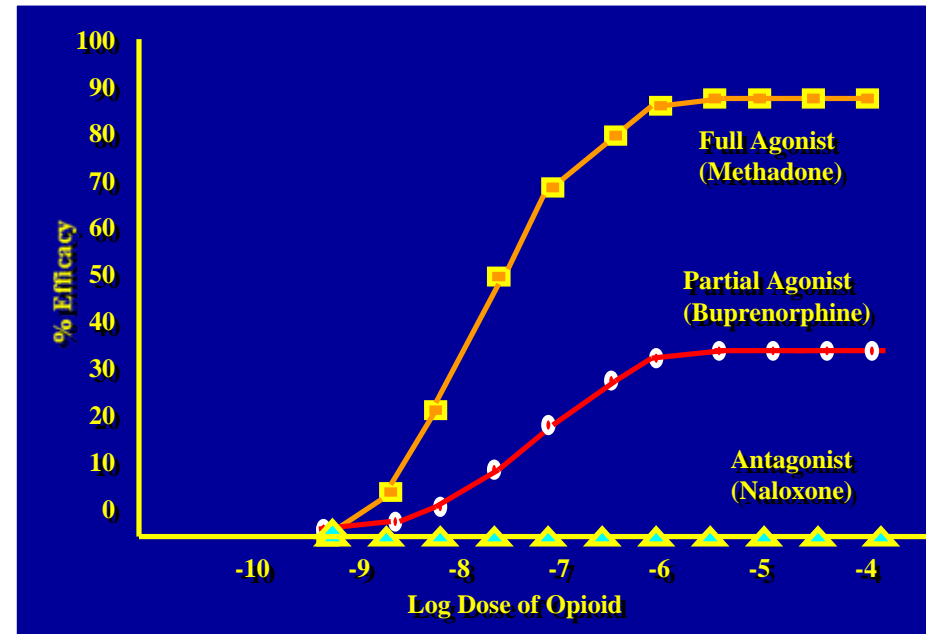
In 2002 Buprenorphine and Buprenorphine/Naloxone were approved for prescribing by qualified physicians

Subutex® -- Monotherapy product
Suboxone® -- Buprenorphine/Naloxone

Currently 19,000 physicians
are certified to prescribe buprenorphine
(Source: CSAT Buprenorphine Information Center)

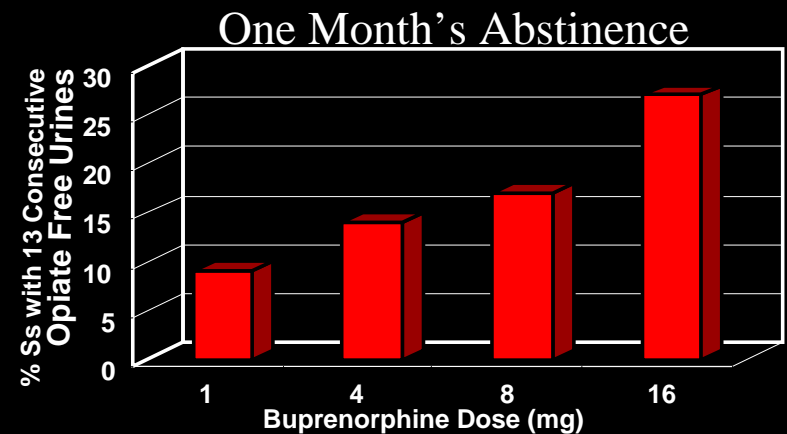
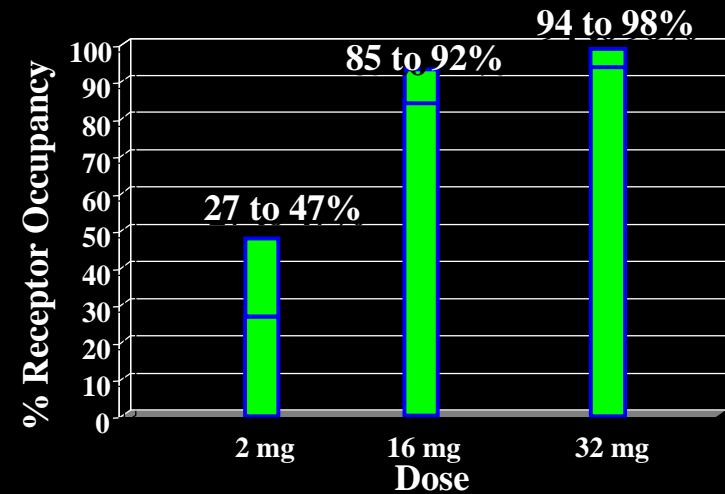
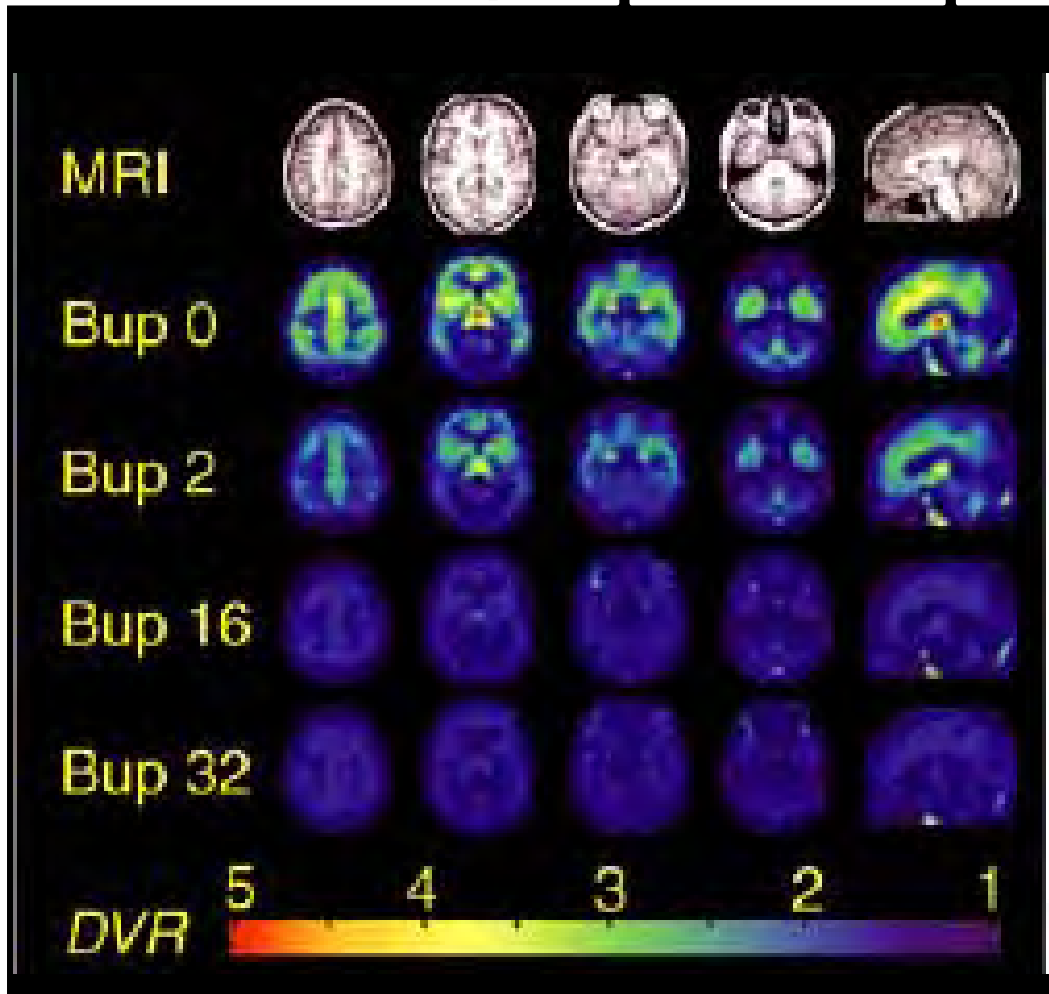


- ✓ Related to morphine (**partial agonist**)
- ✓ Uses **same receptors** as morphine but **does not produce the same high**
- ✓ Can be abused, but **combining with naloxone decreases abuse potential**
- ✓ **Long-lasting**, less likely to cause respiratory depression



Medications to Treat Addiction

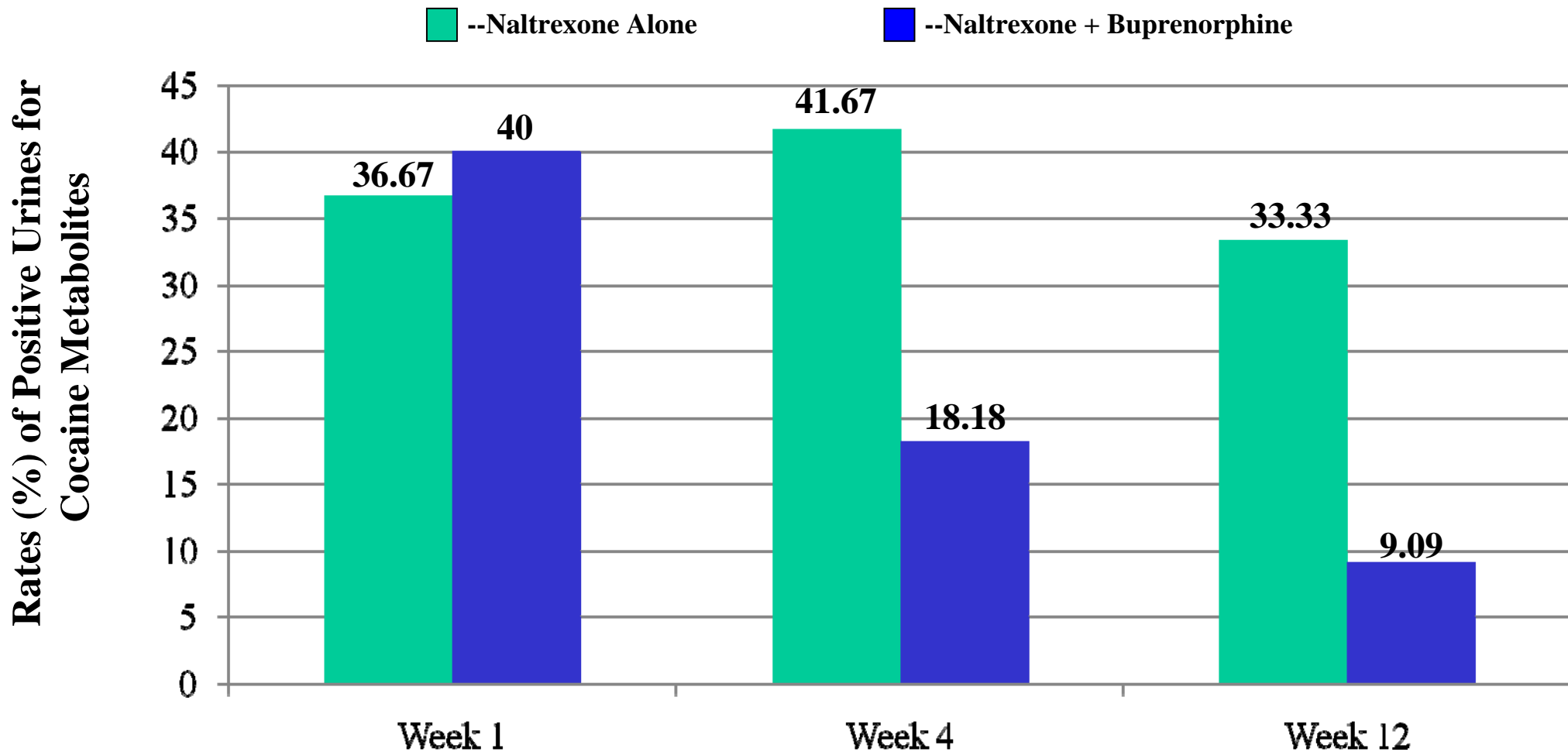
Effects of Buprenorphine Maintenance Dose on μ -Opioid Receptor Availability



Ling et al., *Addiction* 1998.

Source: Greenwald, MK et al., *Neuropsychopharmacology* 28, 2000-2009, 2003.

Naltrexone & Buprenorphine in the Treatment of Cocaine Dependence

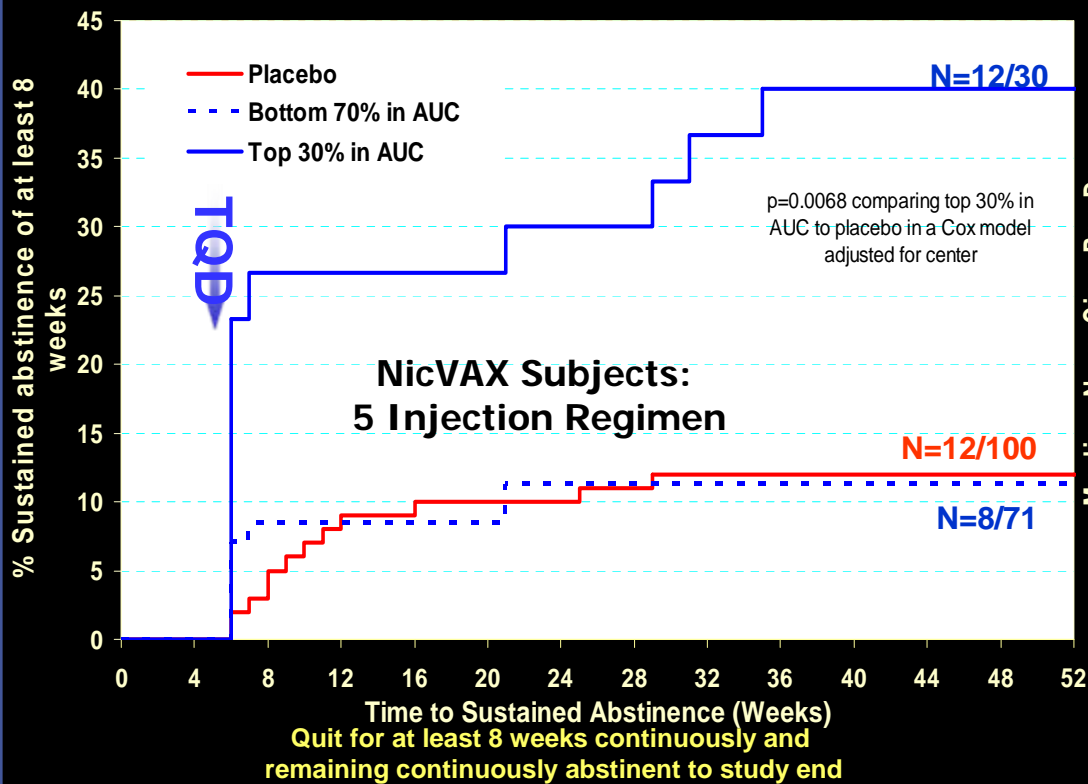


Gerra G et al., J Psychopharmacol Online First January 9, 2006.

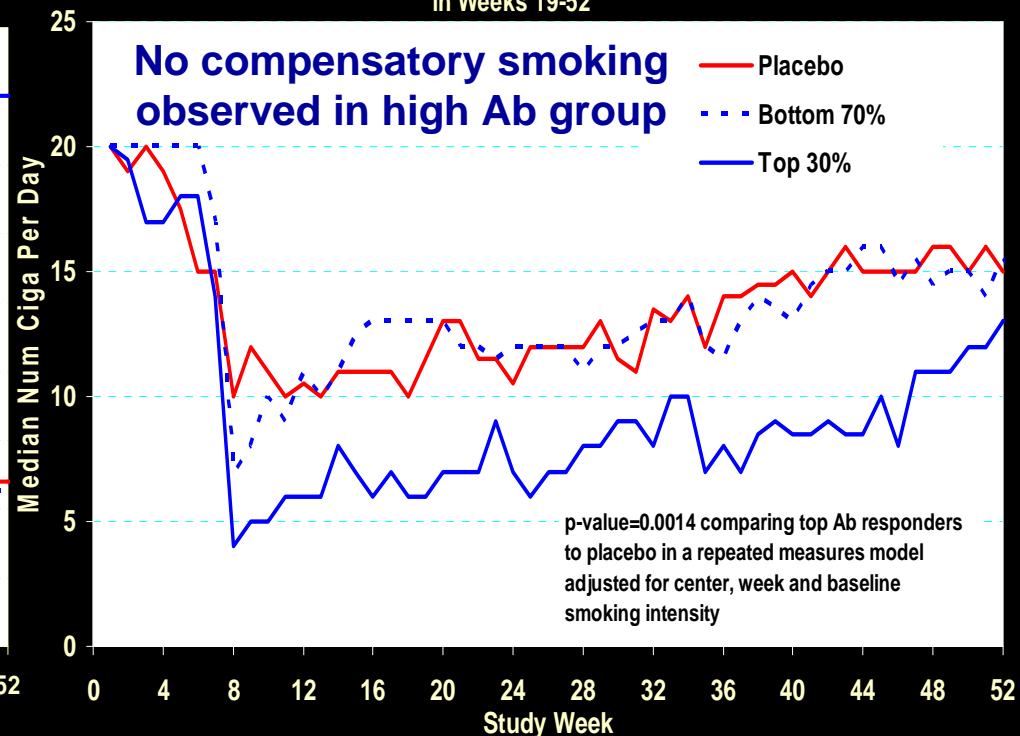
High Antibody Levels Support Sustained Quit in 5 Injection Regimen



Antibody-Dependent Reduction in Cigarette Consumption in Non-Abstainers



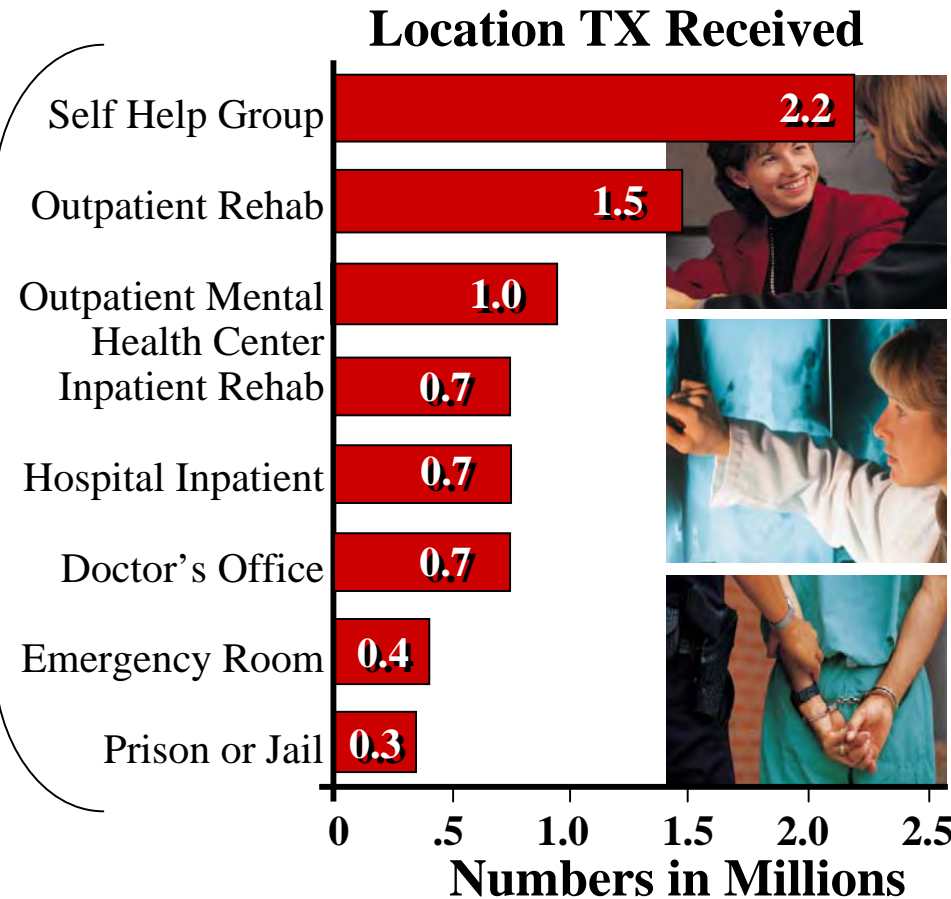
Median Number of Cigarettes per Day by AUC: Subjects Who Did not Abstain in Weeks 19-52



ROADBLOCK #2: Although Treatments For Substance Abuse Are Available, They Are Not Being Widely Used By Those Who Need Them

In 2008 An Estimated 22.2 Million Americans Were Dependent On or Abused Any Illicit Drugs or Alcohol

But...Only 4.0 Million (18%) of These Individuals Had Received Some Type of Treatment In the Past Year



Source: 2008 NSDUH, National Findings, SAMHSA, OAS, 2009.

Patients Receiving ORT in US Prisons

- **In any given year over 200,000 heroin addicts pass through prison**

- **An estimated 1,614 - 1,817 prisoners receive methadone in state and federal prisons**

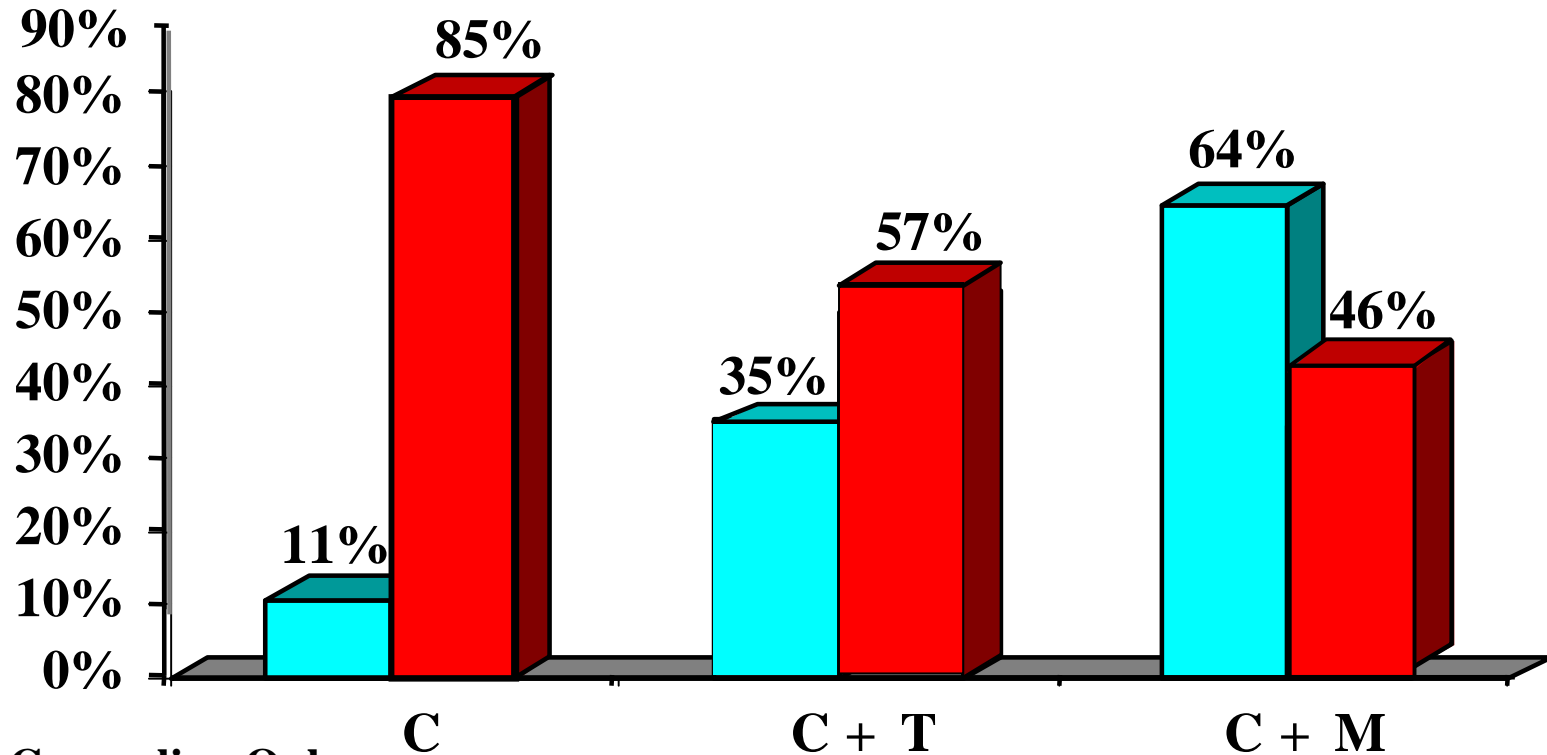
- **An estimated 57-150 prisoners receive buprenorphine in state and federal prisons**

- **Most common use: pregnant women, acute opiate withdrawal, chronic pain management**



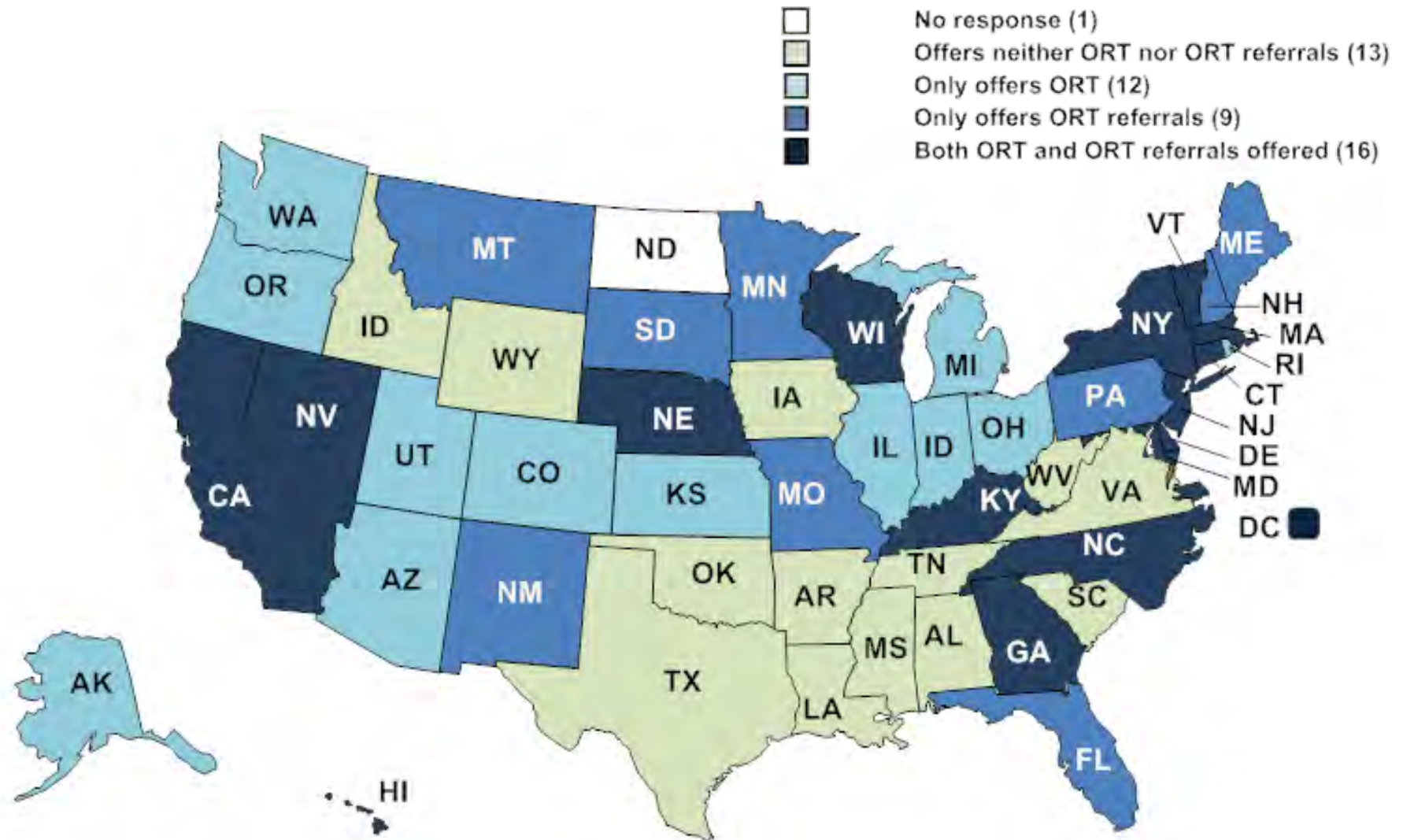
Treatment Linkage & Days Used Heroin 6 Months Post-release

 % of the 180 days post-release spent in treatment  % of the 180 days post-release used heroin



C = Counseling Only
C+T = Counseling & Treatment Referral
C+M = Counseling & Methadone Started in Prison

State Prisons Offering Opiate Replacement Tx

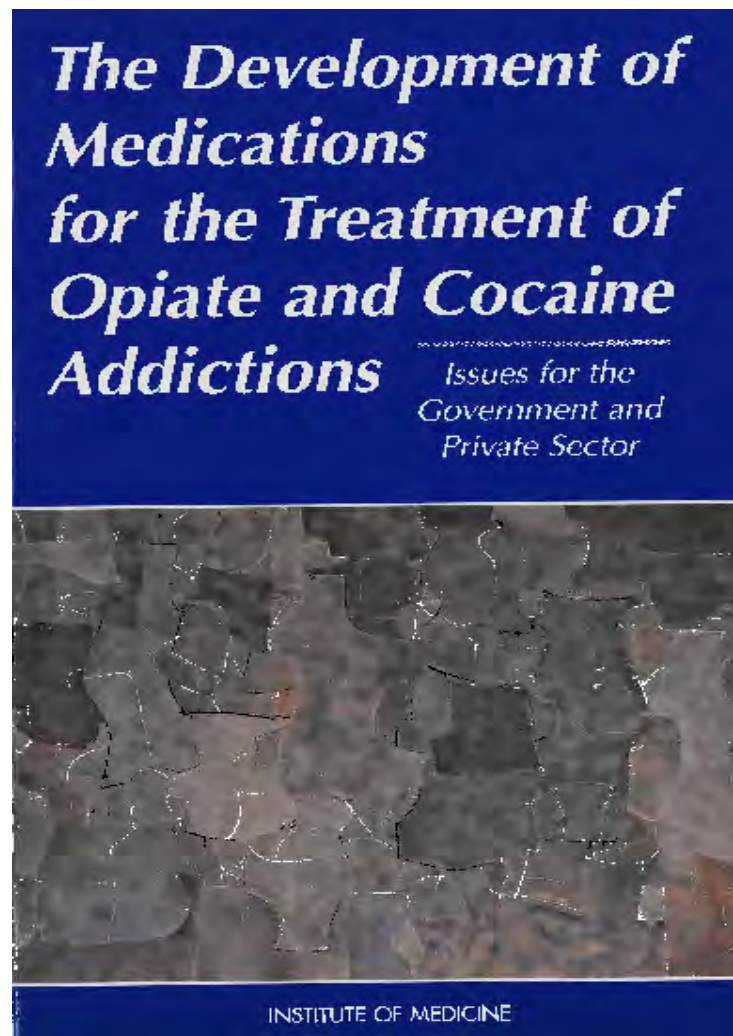


ALTERNATIVES TO ORT

Depot Naltrexone

- **Can be administered once a month**
- **Can be used in the prison system and the criminal justice system...ensuring adherence to treatment**
- **Can be “exported” to countries that have opiate abuse problems but don’t allow agonist therapy-
Russia, Egypt**
- **May help to reduce HIV incidence resulting from
i.v. drug abuse**

In 1992, the Congress stipulated in the Alcohol, Drug Abuse and Mental Health Administration (ADAMHA) Reorganization Act (P.L. 102-321) that DHHS contract with the National Academy of Sciences to establish a committee in the Institute of Medicine (IOM) to **examine the current conditions for the development of anti-addiction medications**



Source: IOM, Development of Medications for the Treatment of Opiate and Cocaine Addictions, 1995.

Perceived Market Barriers in 1995 IOM Report

- Uncertain market environment
- *Limited number of researchers focusing on drug abuse*
- *Lack of well-characterized animal models of cocaine addiction*
- *Limited basic science knowledge of addiction, craving and relapse*
- DEA regulations
- Complications of concomitant illness and polydrug abuse
- Patient populations perceived as difficult to study
- Efficacy outcomes difficult to define or measure
- Few clinical investigators
- **Length of FDA approval process**
- State rescheduling
- Varied State/local regulations
- Lack of traditional marketing to physicians
- Pricing clause in DHHS CRADAs
- Small foreign market
- Limited number of narcotic treatment programs
- **Stigma of drug abuse**
- Bias of some treatment providers against pharmacologic treatments
- Varied State/local treatment regulations and financing mechanisms
- **Uncertain treatment financing**

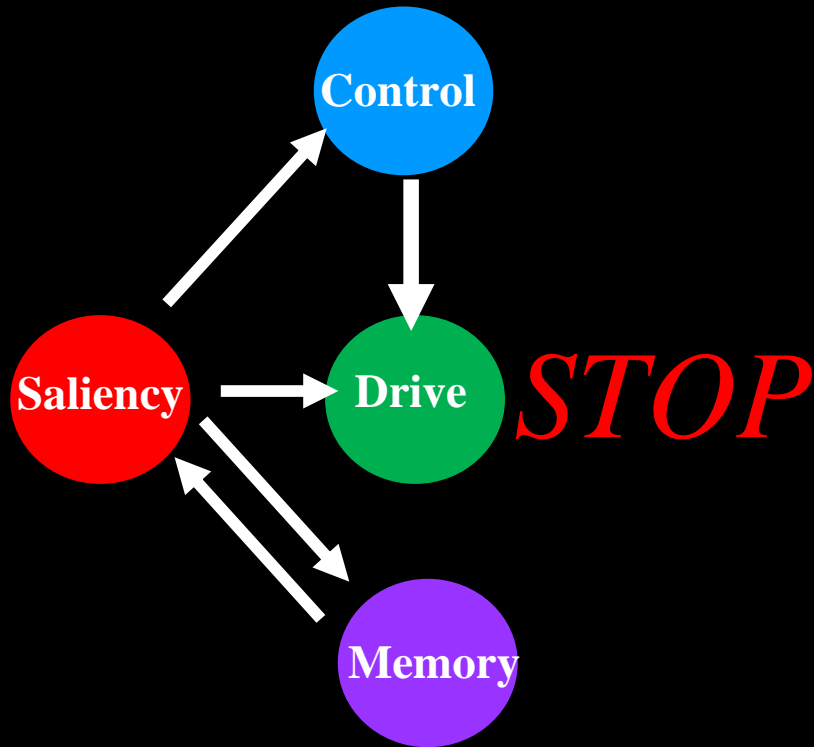
Source: IOM, Development of Medications for the Treatment of Opiate and Cocaine Addictions, 1995.

IOM Recommendations: Overcome Critical Market Barriers

- **Government Funding of New Drug Development**
- **Expansion and Enhancement of Substance Abuse Treatment System**
- **Extended Market Exclusivity**

Examples of Medications Strategies for Addiction

Non-Addicted Brain



Interfere with drug's reinforcing effects

Vaccines

Executive function/
Inhibitory control

*Bupropion
Modafinil*

Strengthen prefrontal-striatal communication

*Adenosine
A2 antagonists
DA D3 antagonists*

Interfere with conditioned memories (craving)

N-acetylcysteine

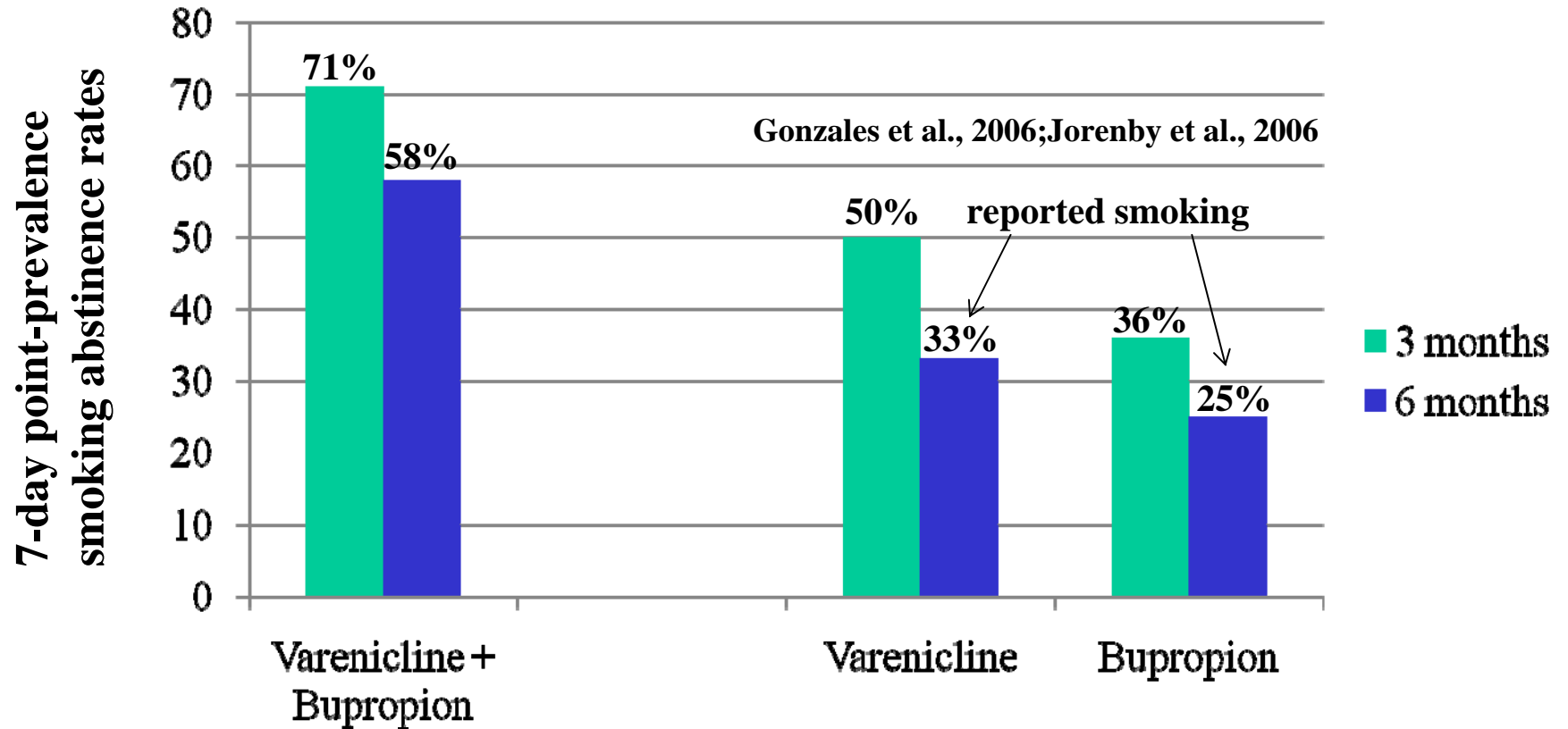
Teach new memories

Cycloserine

Counteract stress responses that lead to relapse

Orexin antagonists

Varenicline & Bupropion SR Combination Therapy for Smoking Cessation



Ebbert JO et al. Nic Tobacco Research 2009;11(3):234-239.

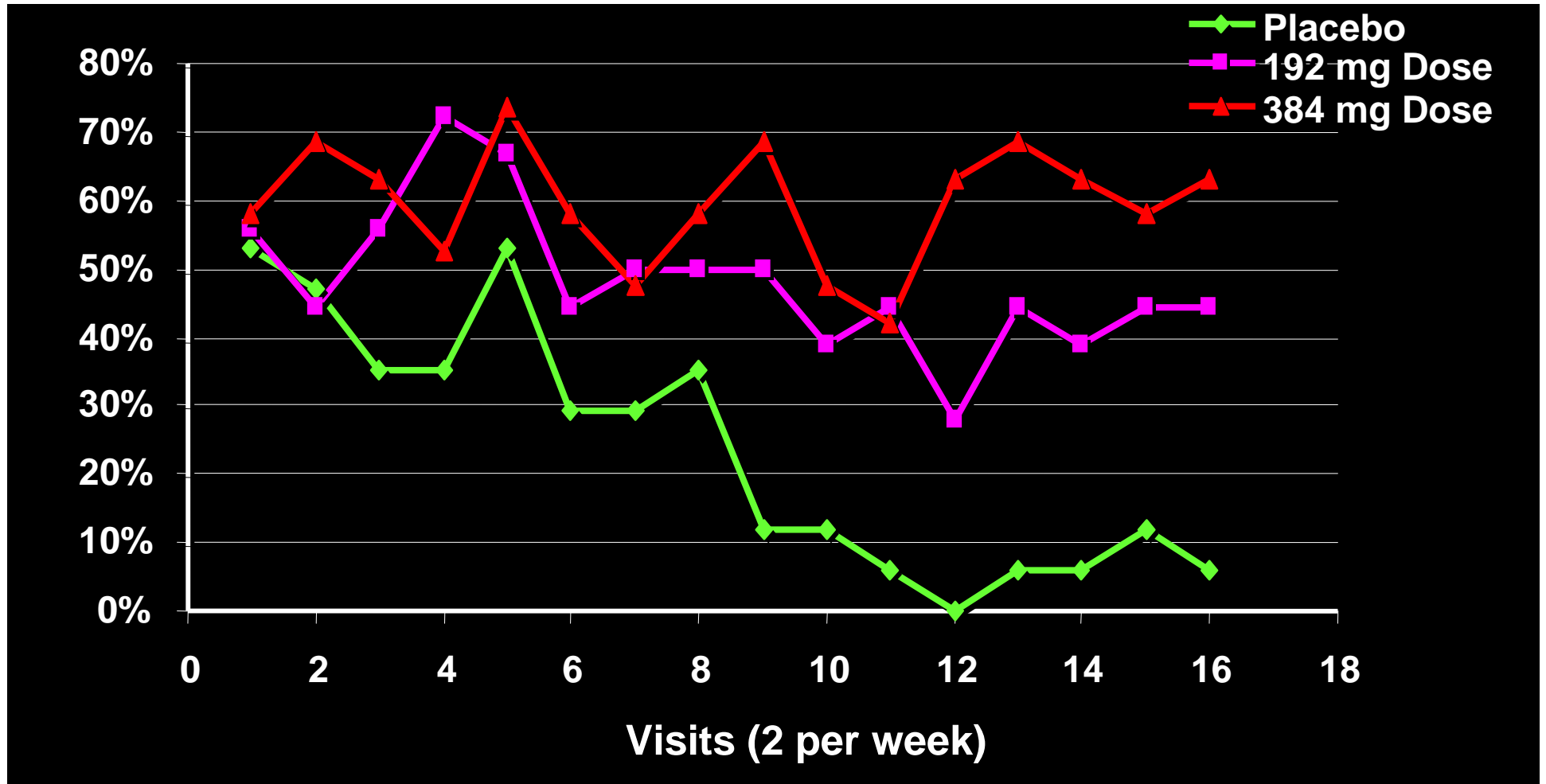
Availability of Opiate Replacement Therapy in US Prisons

	NE N (%)	South N (%)	MW N (%)	West N (%)	Federal	Total N (%)
Methadone Offered in Prison						
Yes	6(67)	6(35)	7(64)	8(62)	1	28(55)
No	3(33)	11(65)	4(36)	5(38)	0	23(45)
Buprenorphine Offered in Prison						
Yes	3(33)	2(12)	1(9)	1(8)	0	7(14)
No	6(67)	15(88)	10(91)	12(92)	1	44(86)
Referral to Community-Based Methadone						
Yes	7(78)	7(41)	5(45)	4(31)	0	23(45)
No	2(22)	10(59)	6(55)	9(69)	1	28(55)
Referral to Community-Based Buprenorphine						
Yes	6(67)	4(24)	2(18)	3(23)	0	15(29)
No	3(33)	13(76)	9(82)	10(77)	1	36(71)

Geographic region defined by CDC

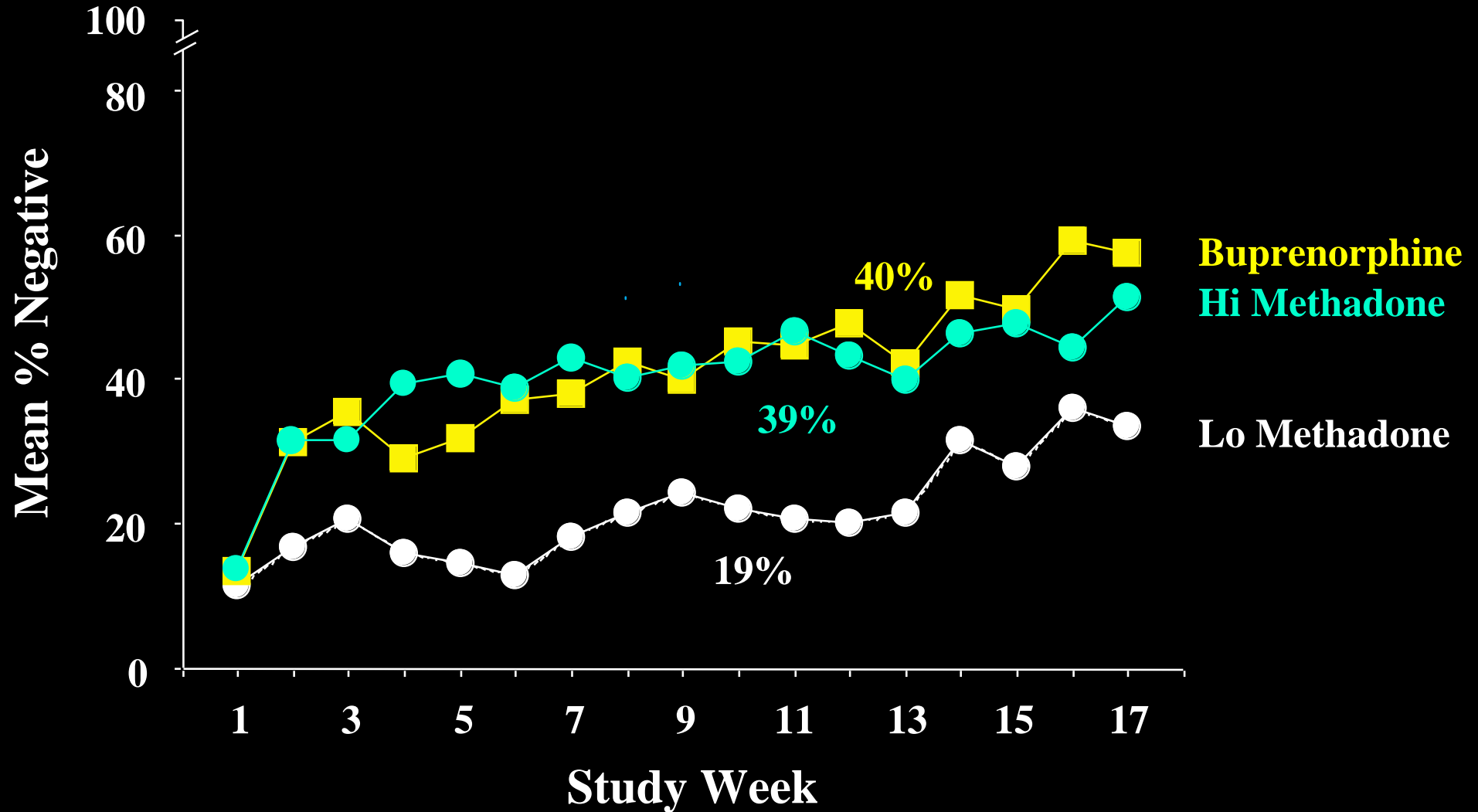
Nunn et al., Drug and Alcohol Dependence 2009;105:83-88.

Outpatient Study: Percent of Negative Urines After Depot Naltrexone Administration



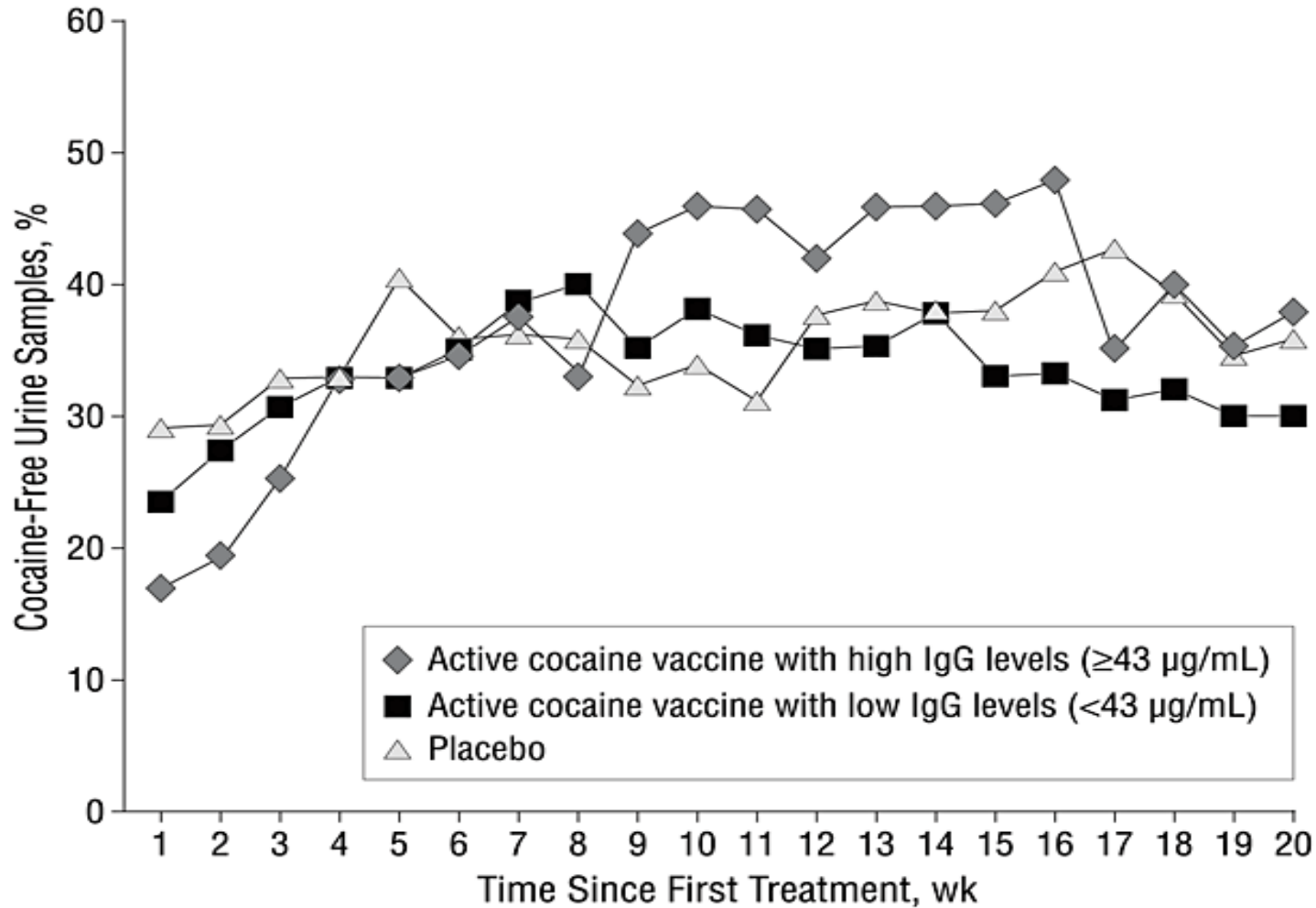
Comer, S. D., Sullivan, M. A., Yu, E., Rothenberg, J. L., Kleber, H. D., Kampman, K. et al.
Arch.Gen.Psychiatry, 63, 210-218, 2006.

Opioid Urine Results for Buprenorphine and Methadone



Adapted from Johnson, et al., 2000

Mean Weekly Cocaine-Free Urine Samples by Medication Condition for Weeks 1 to 20



Martell, BA et al., Arch Gen Psychiatry 2009; 66: 1116-1123.