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INTER-AMERICAN DRUG ABUSE CONTROL COMMISSION

C I C A D

Secretariat for Multidimensional Security

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PROGRESS IN DEVELOPING MEDICATIONS AND VACCINES FOR DRUG ADDICTION TREATMENT

DR. IVAN MONTOYA

Progress in Developing Medications and Vaccines for Drug Addiction Treatment

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NIDA

Addiction

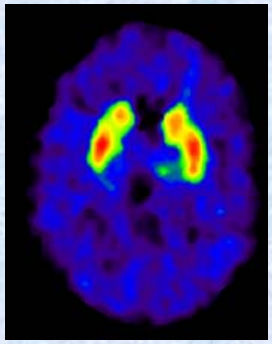
- Chronic disease
- Compulsive behavior of drug use
- Brain changes
- Genetic/environmental risk factors
- Medical, psychological and social consequences
- Prevetable
- Treatable
- Frequently with relapses

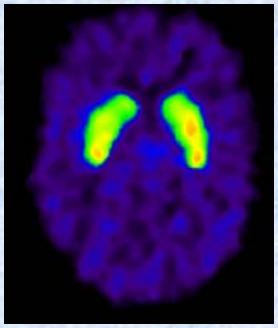
Dopamine D2 Receptors are Lower in Addiction

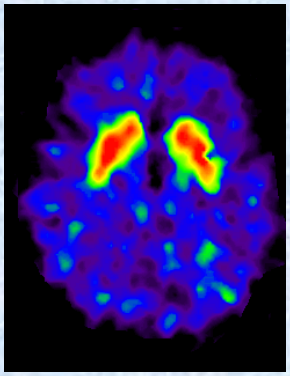
Cocaine

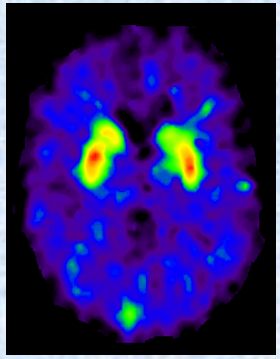
Alcohol

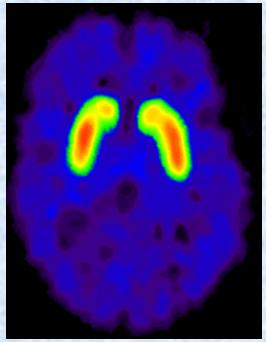
Heroin

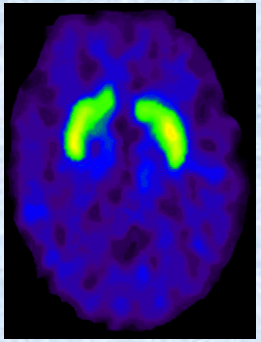






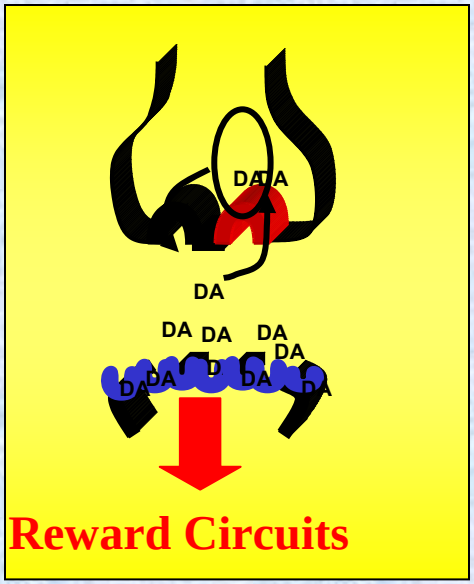




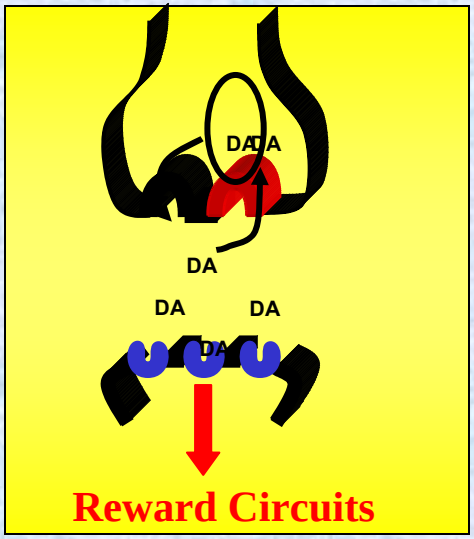


Control

Addicted

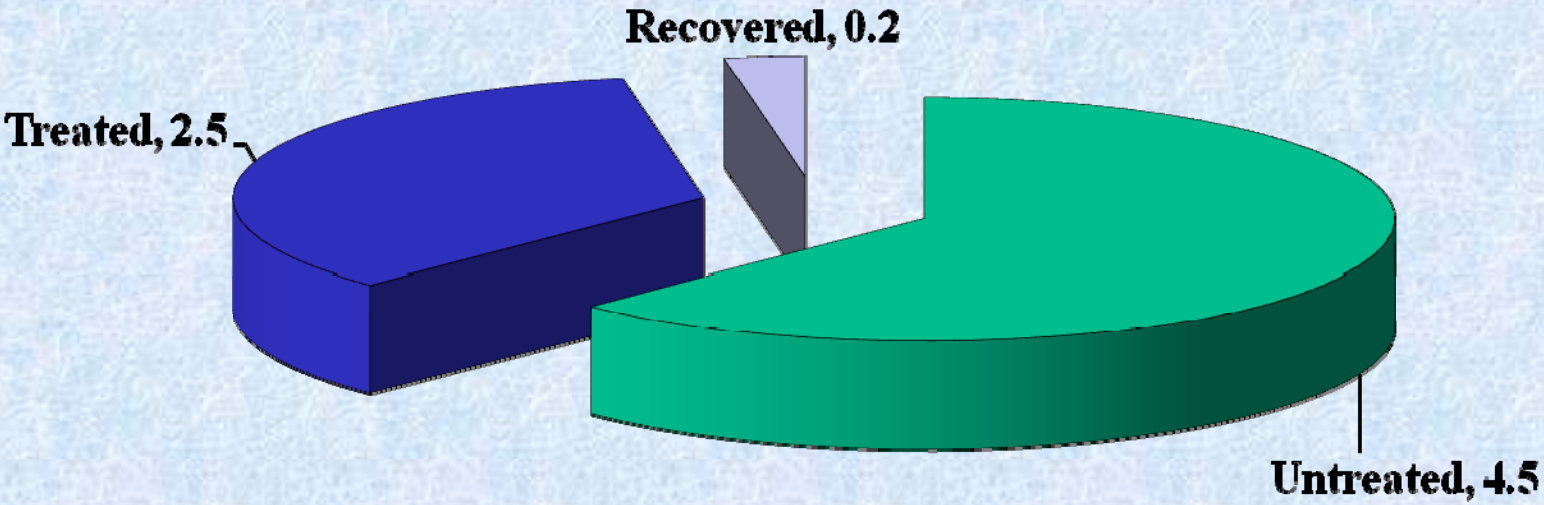


Non-Drug Abuser



Drug Abuser

Illicit Drug Addiction



Millions of People

NSDUH, 2006

Rationale for Medications and Vaccine Research

- Public health problems
- Limited efficacy of psychotherapies
- New knowledge about the effects of illicit drugs and pathophysiology of addictions
- New pharmacological targets
- New biomarkers
- Pharmacogenetics
- New molecules, medications and vaccines

The NIDA Medications Development Program

Congressional Mandate to NIDA

March, 1990

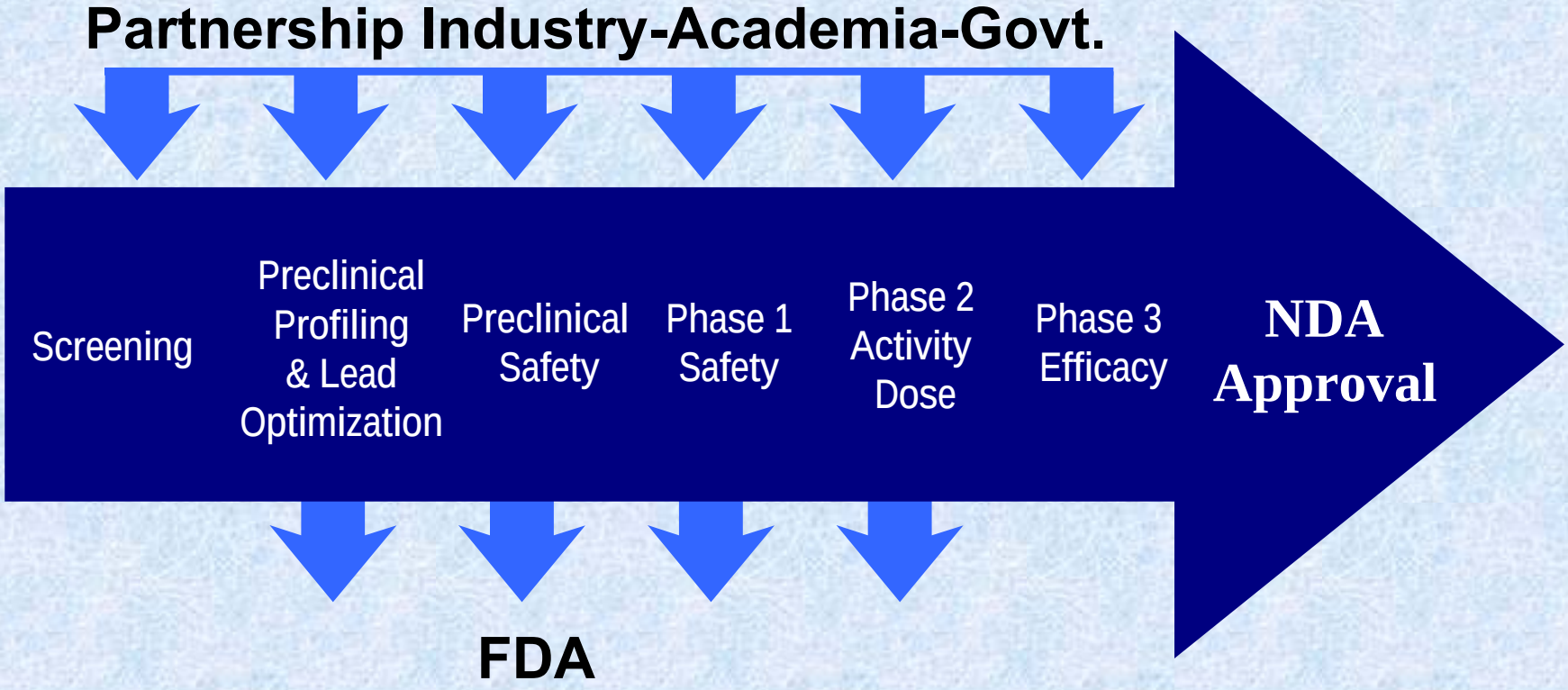
Establish a national program on biological and pharmacological approaches to heroin and cocaine addiction treatment.

Develop a close working relationship with the pharmaceutical industry.

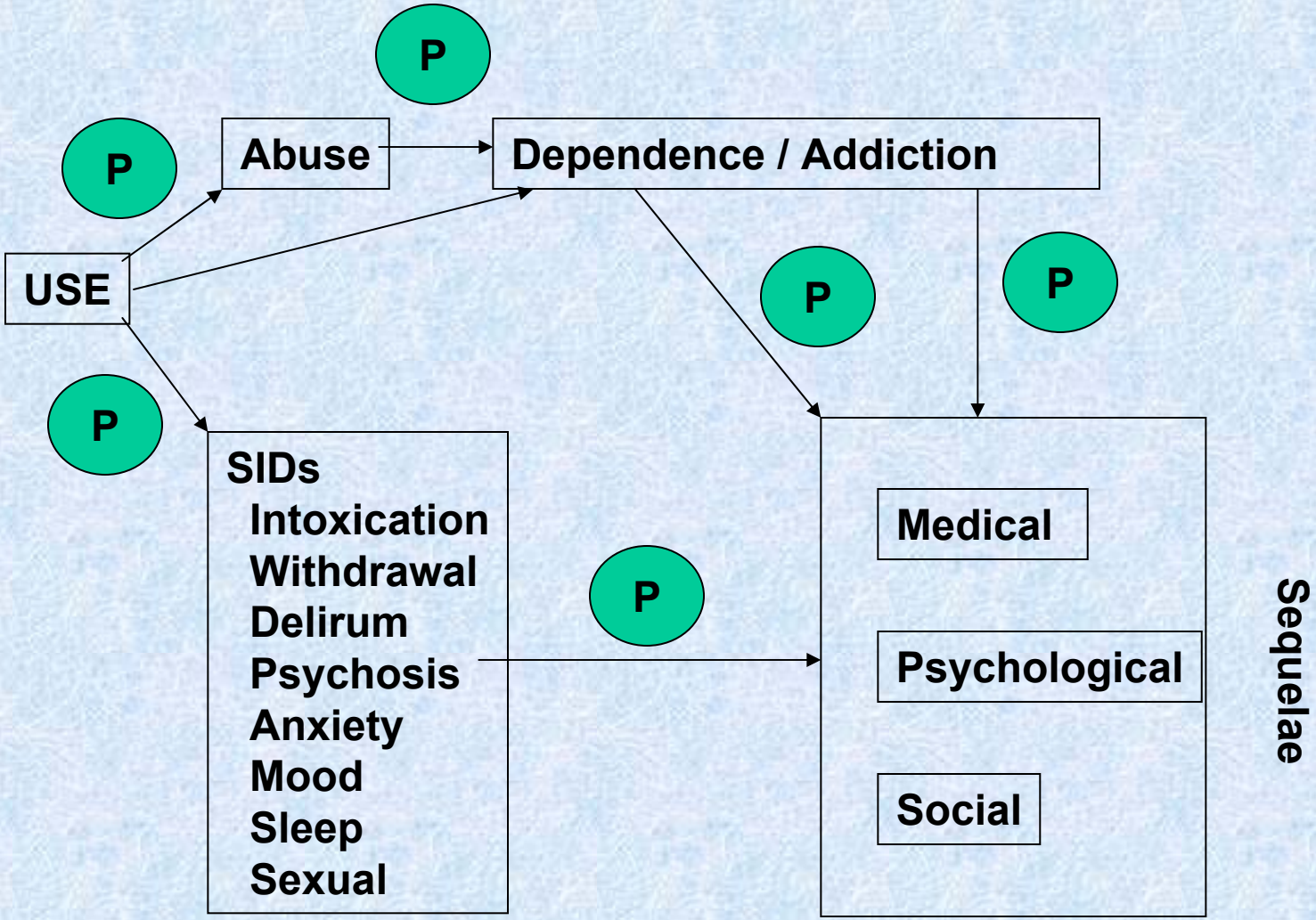
Conduct studies to gain approval of new medications for addiction treatment.

Work with FDA to assure that efficacy of compounds is expeditiously evaluated and approved.

The NIDA Medications Development Program



Pharmacotherapy Approaches



The NIDA Medications Development Program

Four NDA approvals:

- **Levo-Alpha Acetyl Methadol (LAAM)**
- **Buprenorphine**
- **Buprenorphine/naloxone**
- **Naltrexone**

In late-stage development:

- **Lofexidine**
- **Nicotine vaccine**

Opioid Addiction

- Methadone
- Buprenorphine
- Naltrexone
- LAAM
- Clonidine
- Lofexidine

Methadone or Buprenorphine

Compared to heroin users who are not in treatment, patients in treatment show:

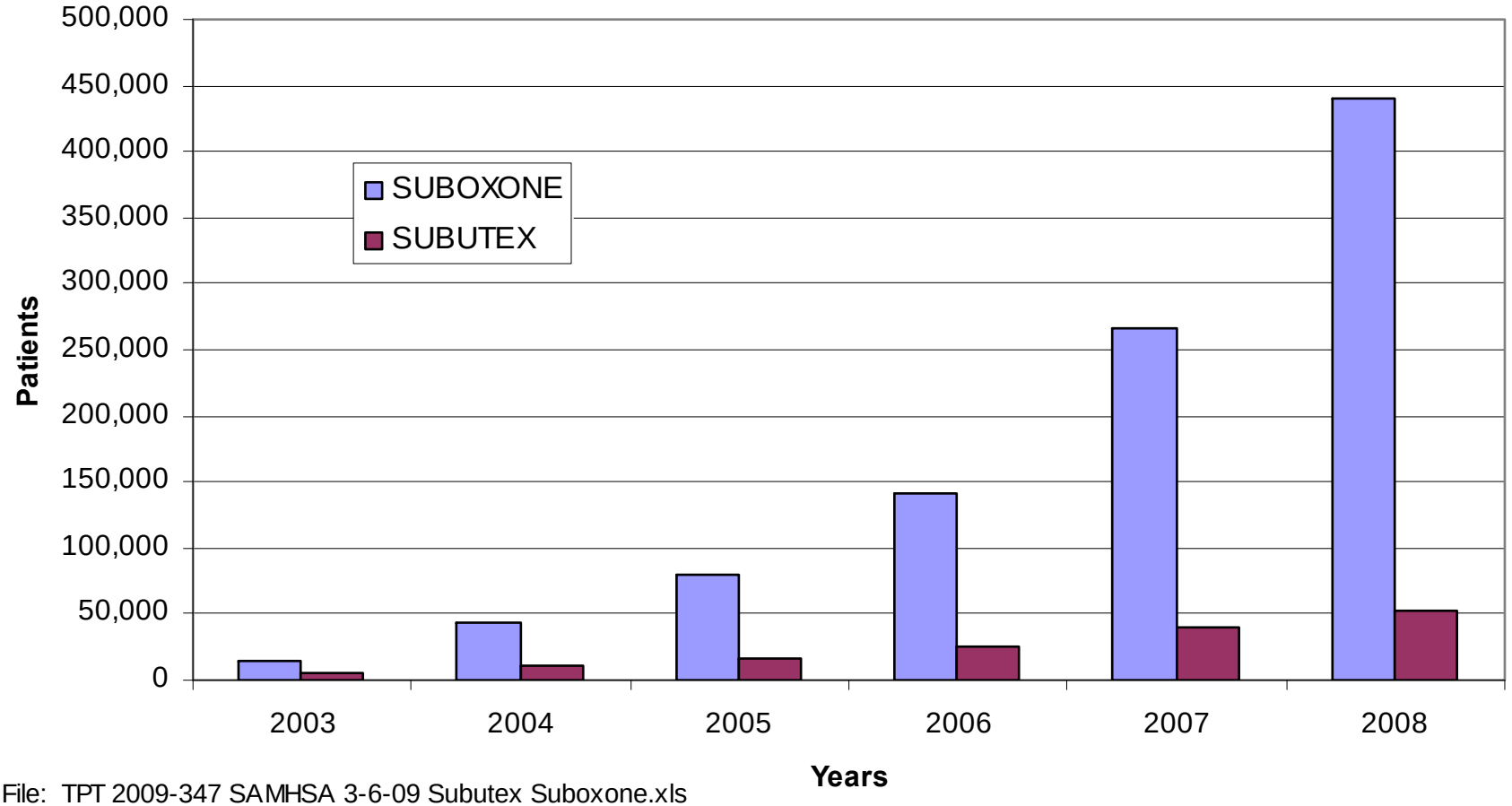
- ↓ death rates
- ↓ criminal activity / incarceration
- ↑ employment
- ↓ needle sharing
- ↓ HIV infection rates

Advantage of buprenorphine:

- Safer in overdose situations (due to “partial agonist” activity)

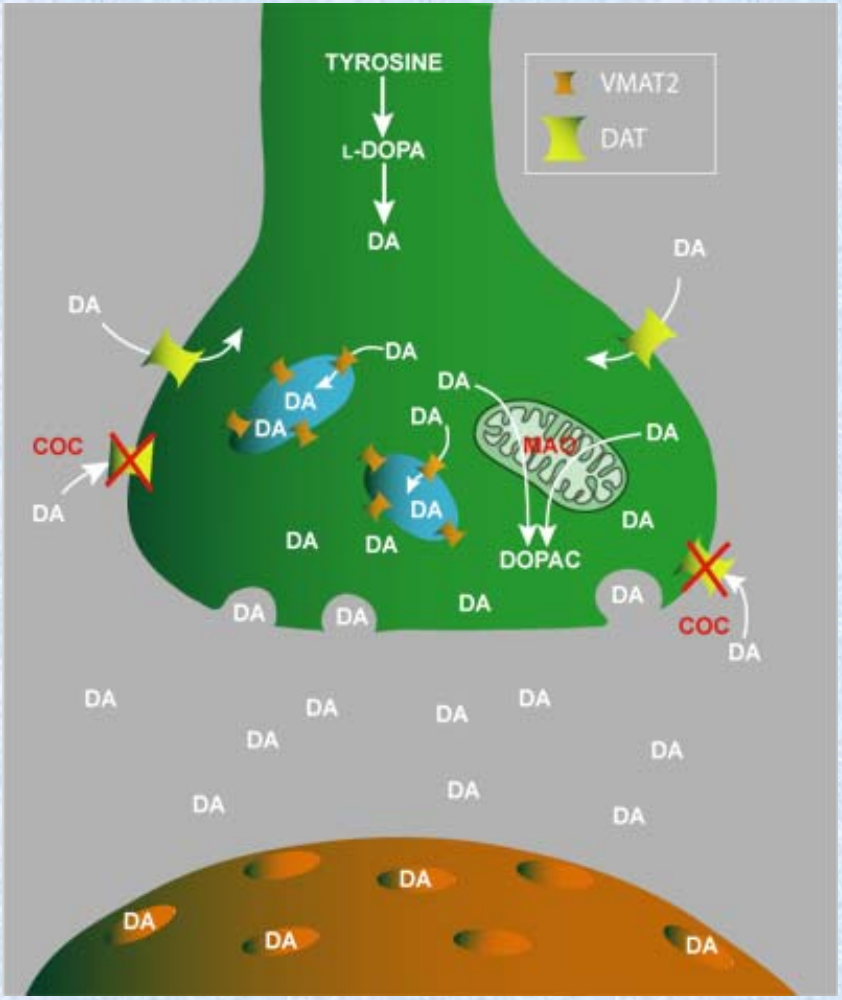
Total number of patients receiving a prescription for Subutex or Suboxone from U.S. outpatient retail pharmacies, Years 2003 - 2008

SDI Total Patient Tracker, Extracted 3/09



File: TPT 2009-347 SAMHSA 3-6-09 Subutex Suboxone.xls

Cocaine



Cocaine – Medications Evaluated

Phase I

Cyclazocine
Tolcapone
Modafinil
Metyrapone

Phase II Screen

Carnitine/CoQ
Cocaine Vaccine
Donepezil
Gabapentin
Gingko
Hypericum celebrex
Lamotrigine
Levodopa/Carbidopa
Olanzapine
Ondansetron
Paroxetine
Pentoxifylline
Piracetam
Pramipexole
Riluzole
Sertraline
Tiagabine
Valproate

Phase II

Amantadine
Baclofen
Bupropion
Cabergoline
Desipramine
Dextroamphetamine
Disulfiram
Enadoline
Hydergine
Mazindol
Methylphenidate
Naltrexone
Pemoline
Pergolide
Phenytoin
Propranolol
Reserpine
Risperidone
Selegiline IR
Valproate

Phase III

Selegiline TS
Disulfiram
Modafinil
Baclofen
Naltrexone
Desipramine
Buprenorphine
Vaccine

AJP in Advance. Published August 3, 2009 (doi: 10.1176/appi.ajp.2009.08121811)

Article

Randomized, Double-Blind, Placebo-Controlled Trial of Vigabatrin for the Treatment of Cocaine Dependence in Mexican Parolees

Jonathan D. Brodie, M.D., Ph.D.

Brady G. Case, M.D.

Emilia Figueroa, M.D.

Stephen L. Dewey, Ph.D.

James A. Robinson, M.Ed.

Joseph A. Wanderling, M.A.

Eugene M. Laska, Ph.D.

Objective: Cocaine dependence is associated with severe medical, psychiatric, and social morbidity, but no pharmacotherapy is approved for its treatment in the United States. The atypical antiepileptic vigabatrin (γ-vinyl gamma-aminobutyric acid [GABA]) has shown promise in animal studies and open-label trials. The purpose of the present study was to assess the efficacy of vigabatrin for short-term cocaine abstinence in cocaine-dependent individuals.

Method: Participants were treatment seeking parolees who were actively using cocaine and had a history of cocaine dependence. Subjects were randomly assigned to a fixed titration of vigabatrin (N=50) or placebo (N=53) in a 9-week double-blind trial and 4-week follow-up assessment. Cocaine use was determined by directly observed urine toxicology testing twice weekly. The primary endpoint was full abstinence for the last 3 weeks of the trial.

Results: Full end-of-trial abstinence was achieved in 14 vigabatrin-treated subjects (28.0%) versus four subjects in the placebo arm (7.5%). Twelve subjects in the vigabatrin group and two subjects in the placebo group maintained abstinence through the follow-up period. The retention rate was 62.0% in the vigabatrin arm versus 41.5% in the placebo arm. Among subjects who reported prestudy alcohol use, vigabatrin, relative to placebo, was associated with superior self-reported full end-of-trial abstinence from alcohol (43.5% versus 6.3%). There were no differences between the two groups in drug craving, depressed mood, anxiety, or Clinical Global Impression scores, and no group differences in adverse effects emerged.

Conclusions: This first randomized, double-blind, placebo-controlled trial supports the safety and efficacy of short-term vigabatrin treatment of cocaine dependence.

(Am J Psychiatry Brodie et al.; AiA:1–9)

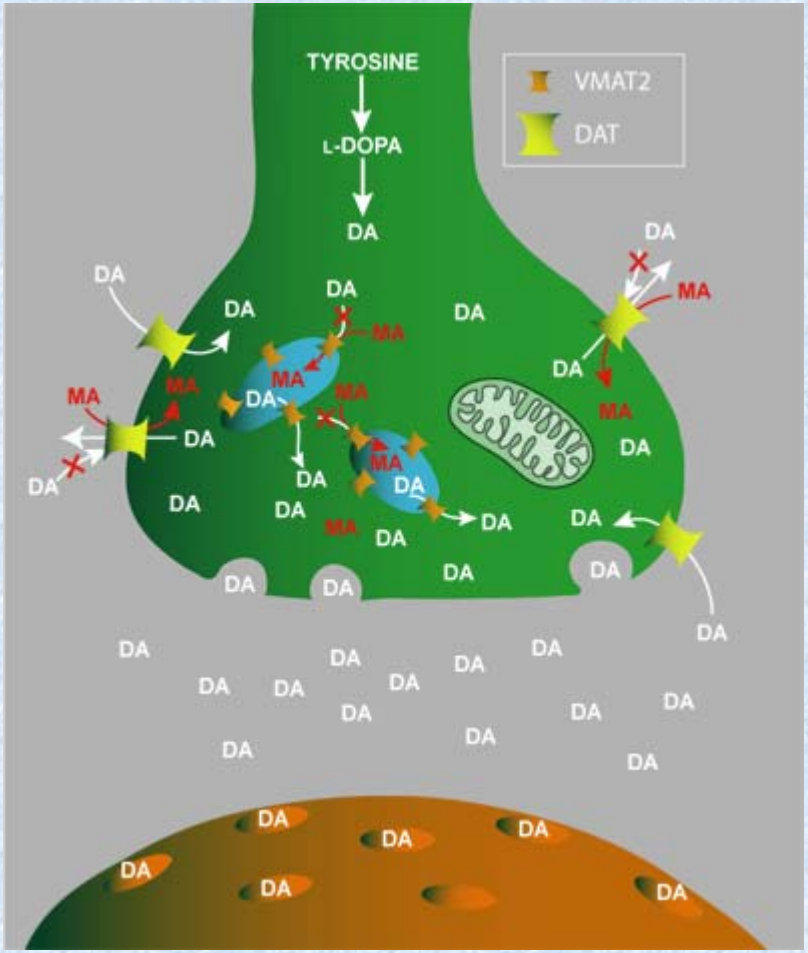
Vigabatrin for Cocaine Addiction

	Abstinence During Last 3 Weeks of Tx	
	Failures	Successes
Placebo	49 (92.5%)	4 (7.5%)
Vigabatrin	36 (72%)	14 (28%)

3.7 x

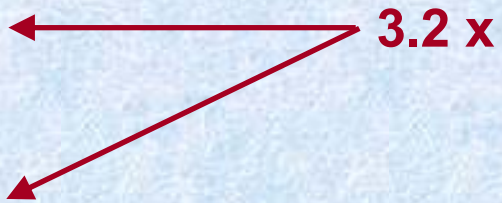
P = 0.009 (Chi-square test)

Methamphetamine



Bupropion for Methamphetamine Addiction

	Abstinence During Last 3 Weeks of Tx	
	Failures	Successes
Placebo	68 (94.4%)	4 (5.56%)
Bupropion	65 (82.3%)	14 (17.7%)



P = 0.02 (Chi-square test)

Immunotherapies

Vaccines

Antibodies

Immunotherapy Development Program

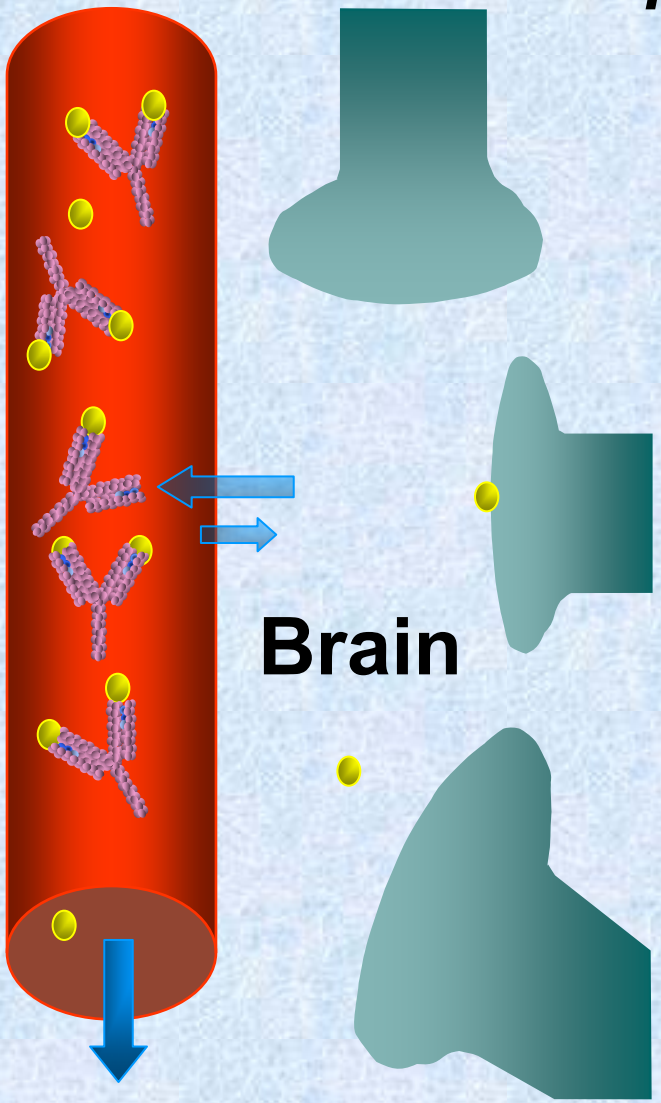
Preclinical Studies

- **anti-PCP mAb**
- **anti-Methamphetamine mAb**
- **anti-MDMA mAb**
- **anti-Cocaine mAb**

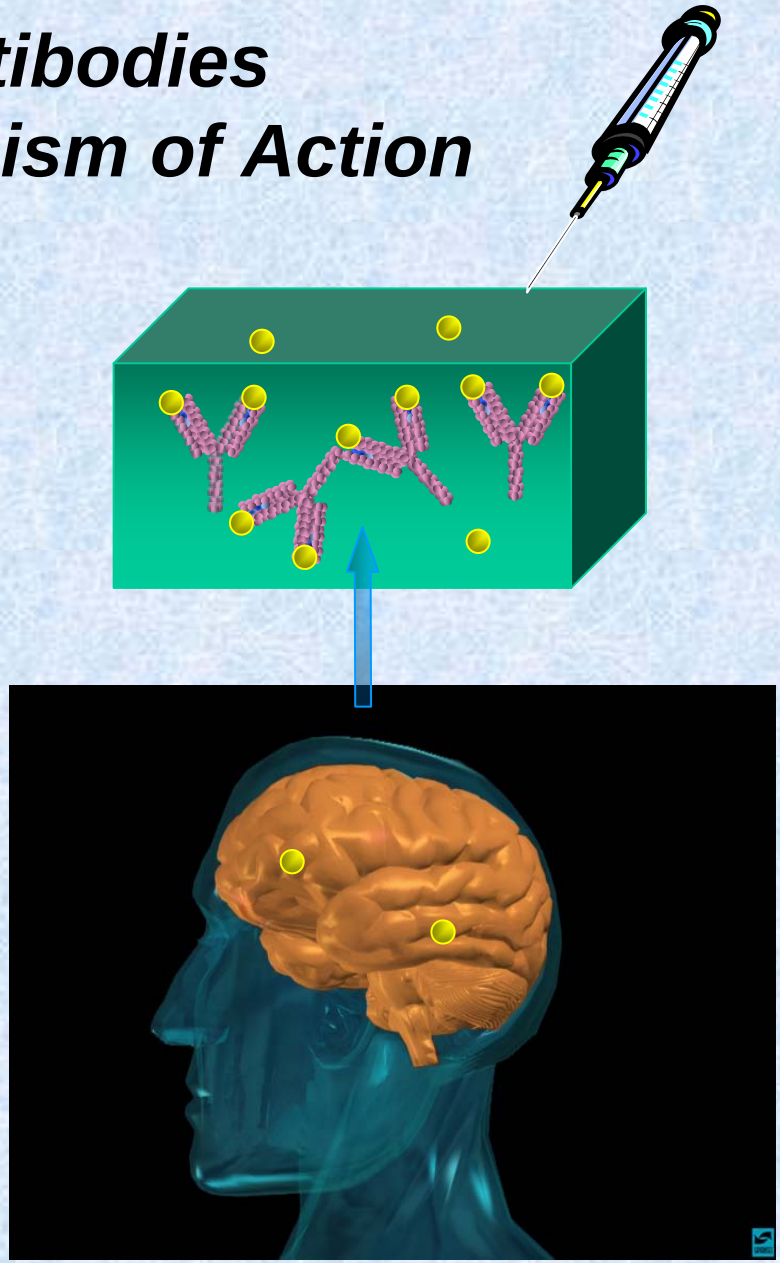
Clinical Studies

- **Anti-Nicotine vaccine**
- **Anti-Cocaine vaccine**

Capillary Blood Flow

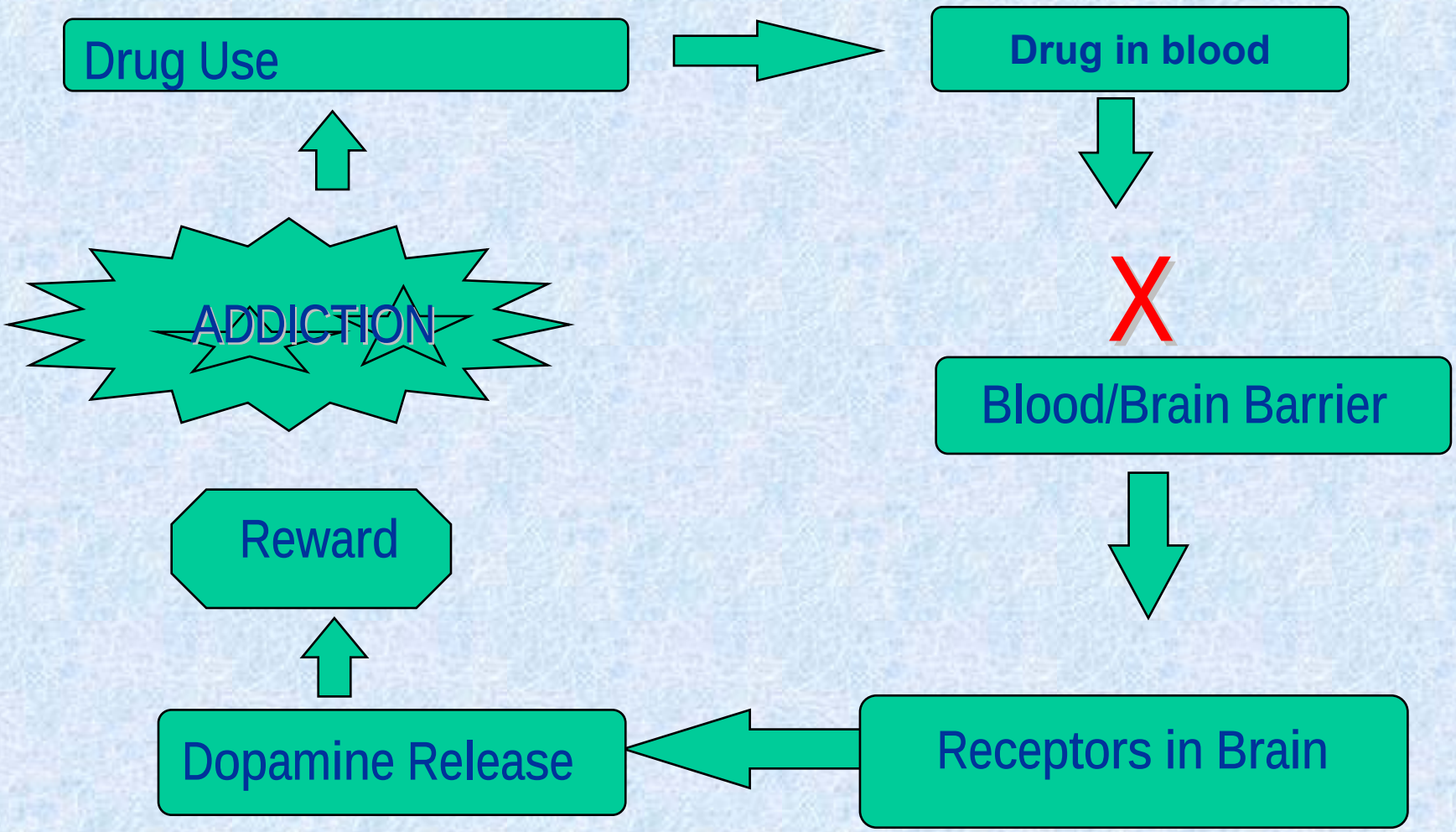


Antibodies Mechanism of Action

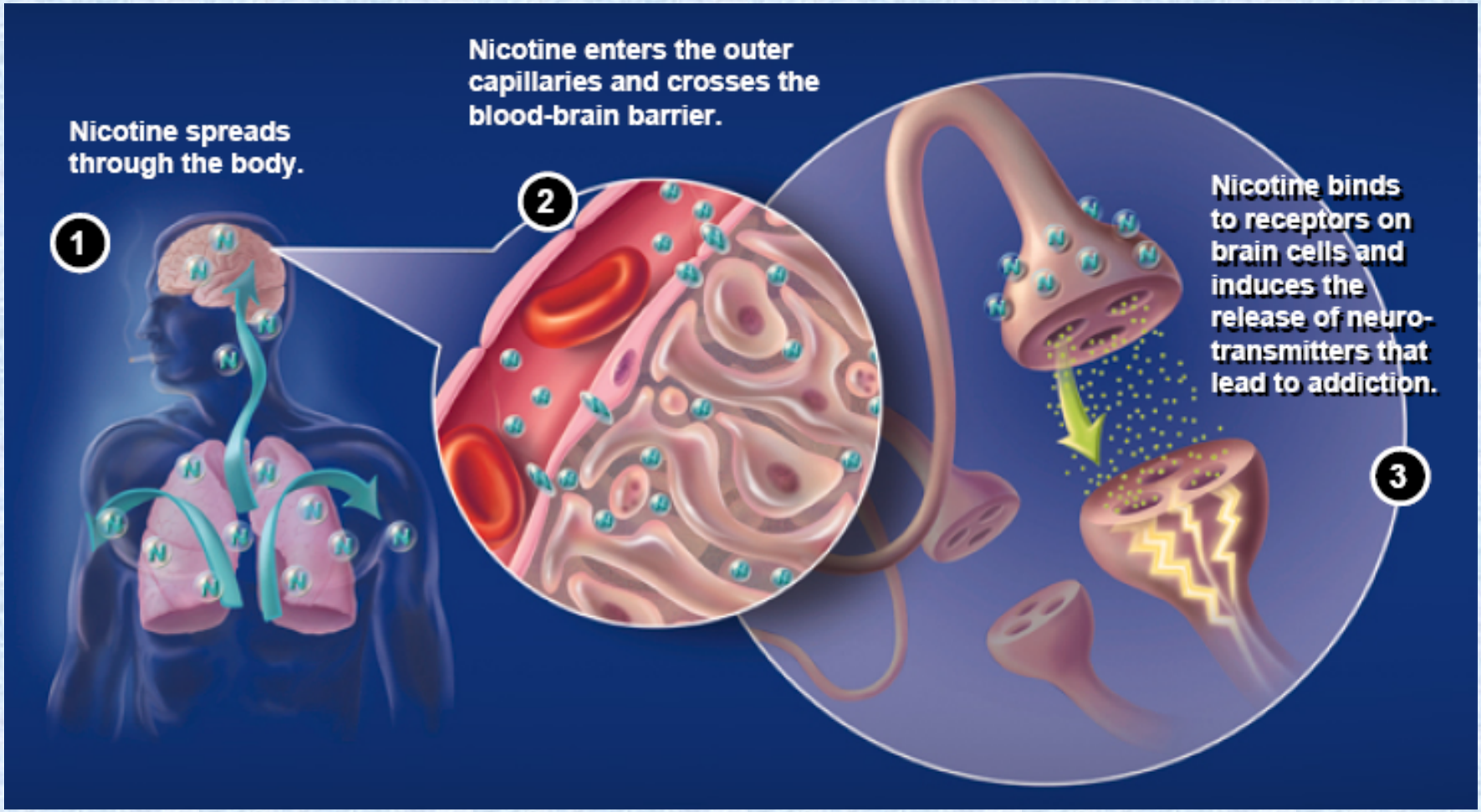


(Owens & Gentry 2002)

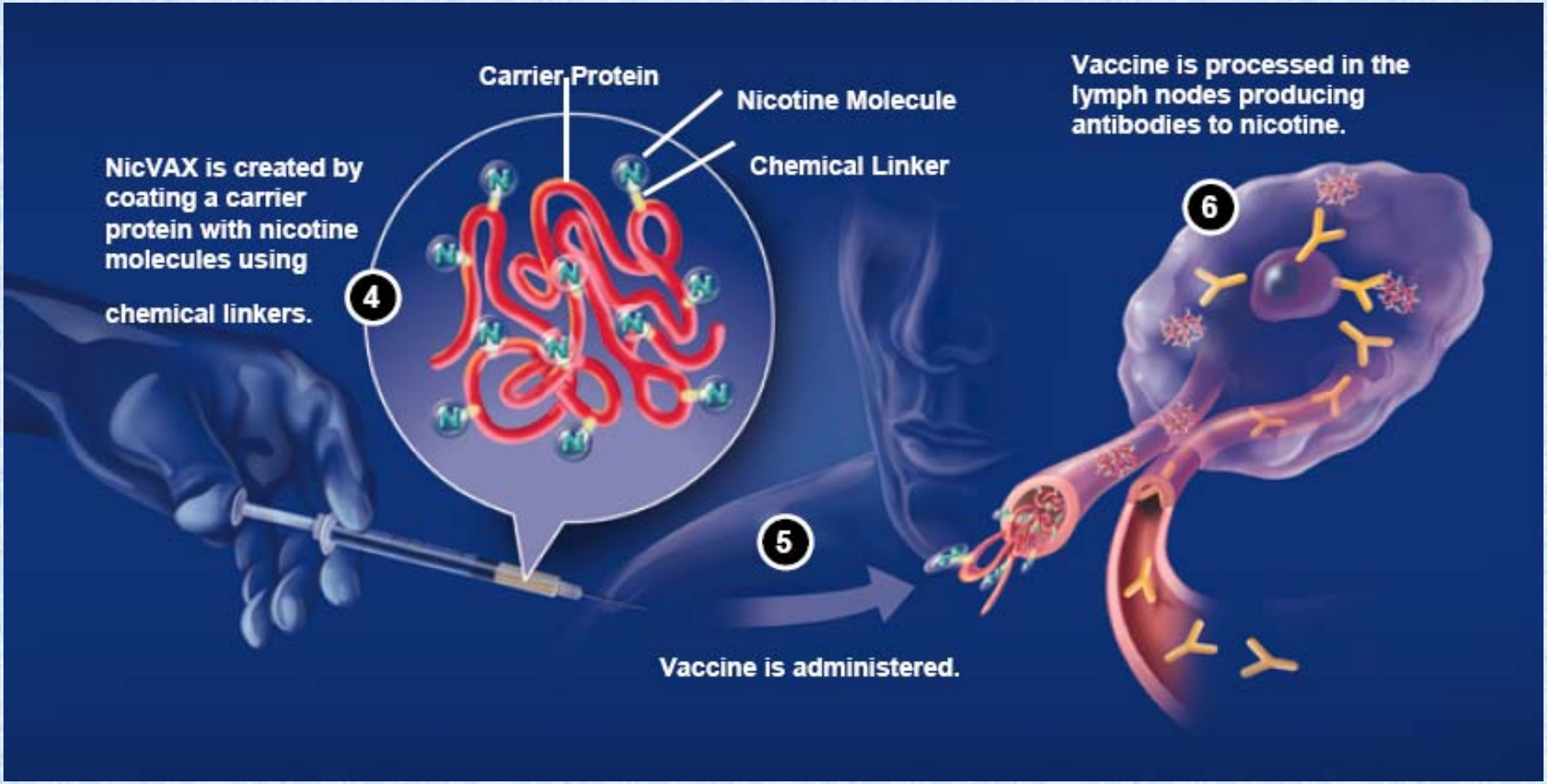
Rationale for Immunotherapy against Addictions



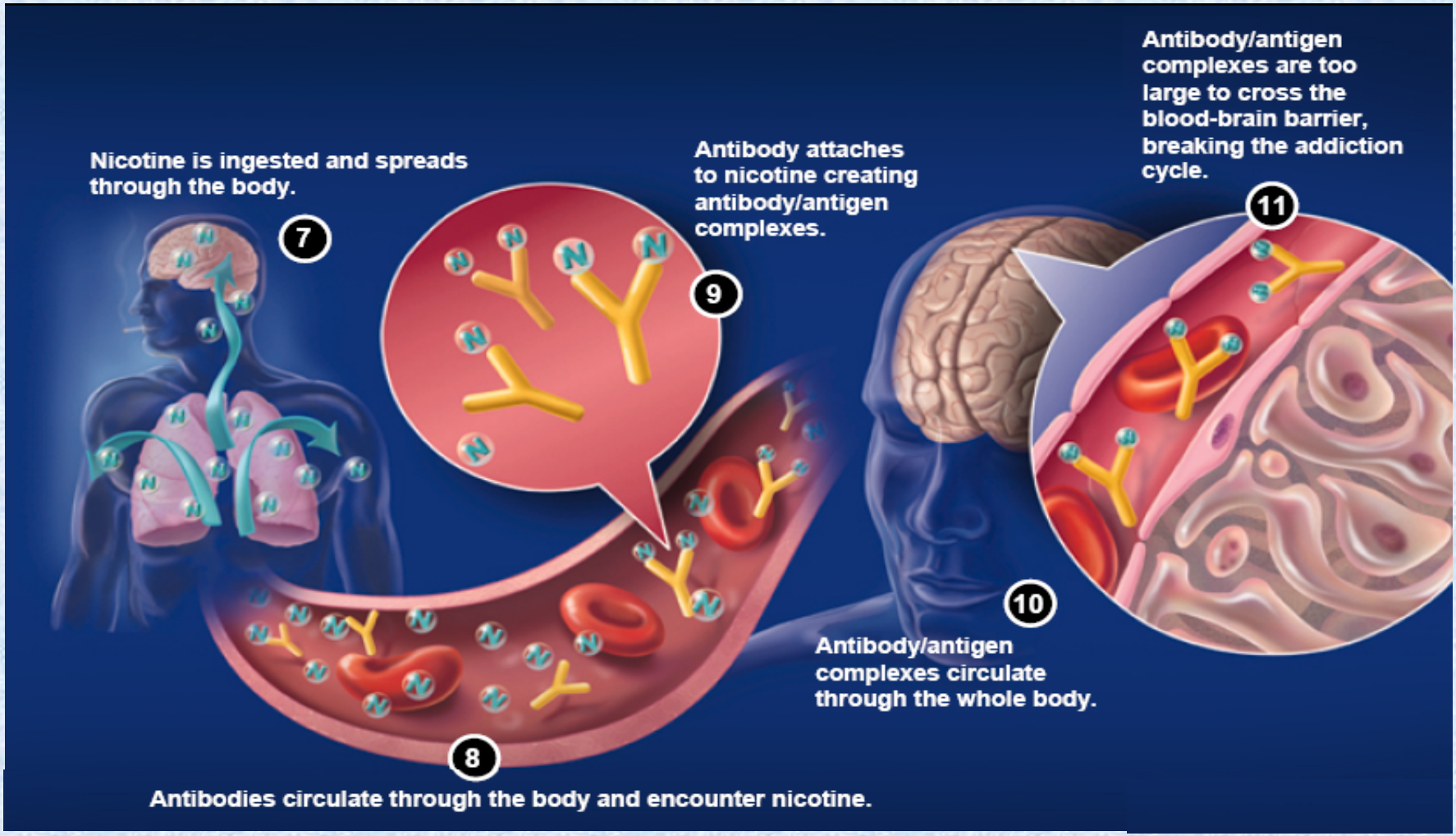
Nicotine Addiction



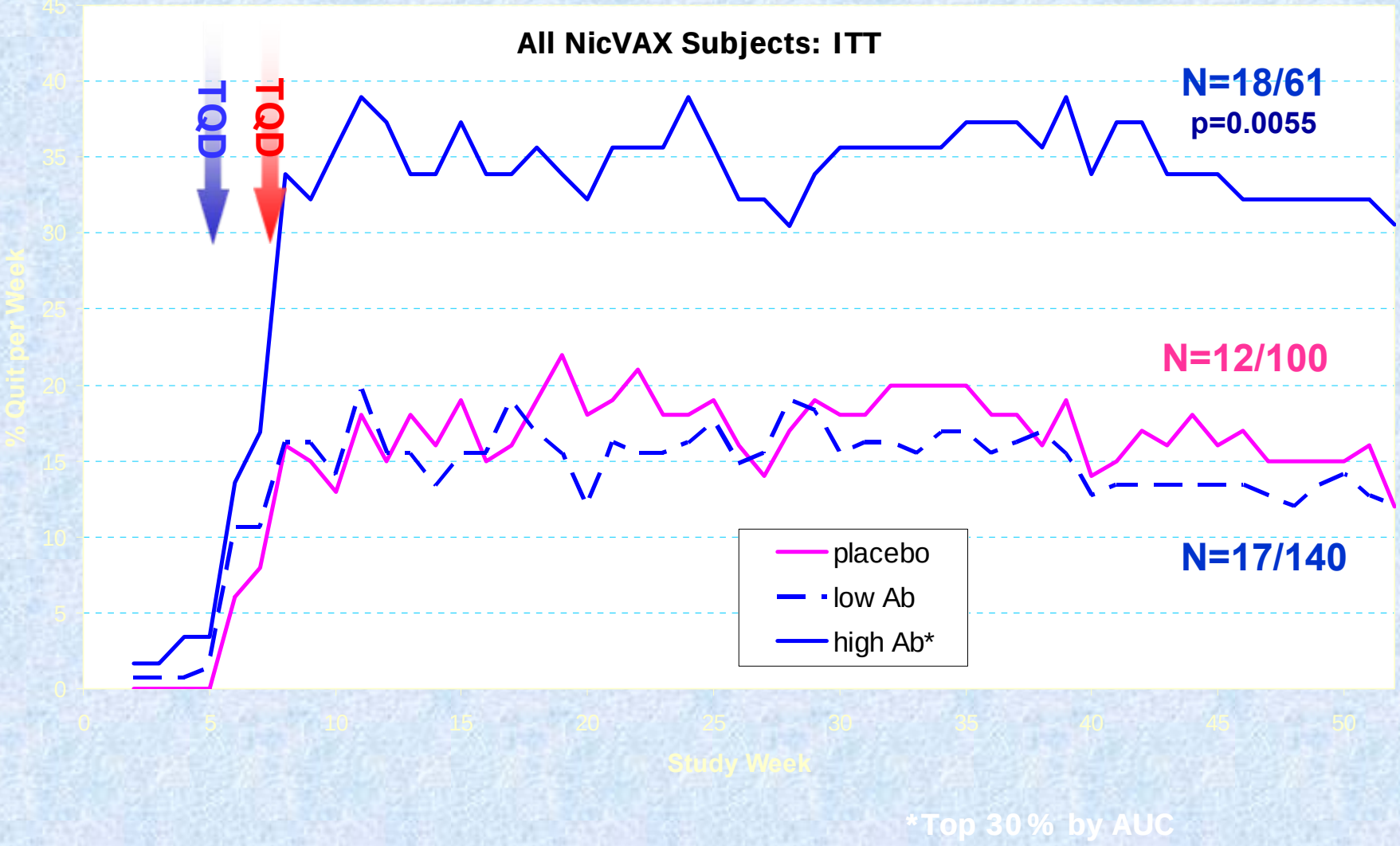
Nicotine Vaccine



Breaking the Addiction Cycle



Proportion of Subjects Quit Each Week: Point Prevalence Stratified by Antibody Levels



NIDA

ORIGINAL ARTICLE

Cocaine Vaccine for the Treatment of Cocaine Dependence in Methadone-Maintained Patients

A Randomized, Double-blind, Placebo-Controlled Efficacy Trial

Bridget A. Martell, MD, MA; Frank M. Orson, MD; James Poling, PhD; Ellen Mitchell, RN; Roger D. Rossen, MD; Tracie Gardner, PhD; Thomas R. Kosten, MD

Context: Cocaine dependence, which affects 2.5 million Americans annually, has no US Food and Drug Administration–approved pharmacotherapy.

Objectives: To evaluate the immunogenicity, safety, and efficacy of a novel cocaine vaccine to treat cocaine dependence.

Design: A 24-week, phase 2b, randomized, double-blind, placebo-controlled trial with efficacy assessed during weeks 8 to 20 and follow-up to week 24.

Setting: Cocaine- and opioid-dependent persons recruited from October 2003 to April 2005 from greater New Haven, Connecticut.

Participants: One hundred fifteen methadone-maintained subjects (67% male, 87% white, aged 18-46 years) were randomized to vaccine or placebo, and 94 subjects (82%) completed the trial. Most smoked crack cocaine along with using marijuana (18%), alcohol (10%), and nonprescription opioids (44%).

Intervention: Over 12 weeks, 109 of 115 subjects received 5 vaccinations of placebo or succinylnorcocaine linked to recombinant cholera toxin B-subunit protein.

Main Outcome Measure: Semiquantitative urinary cocaine metabolite levels measured thrice weekly with a positive cutoff of 300 ng/mL.

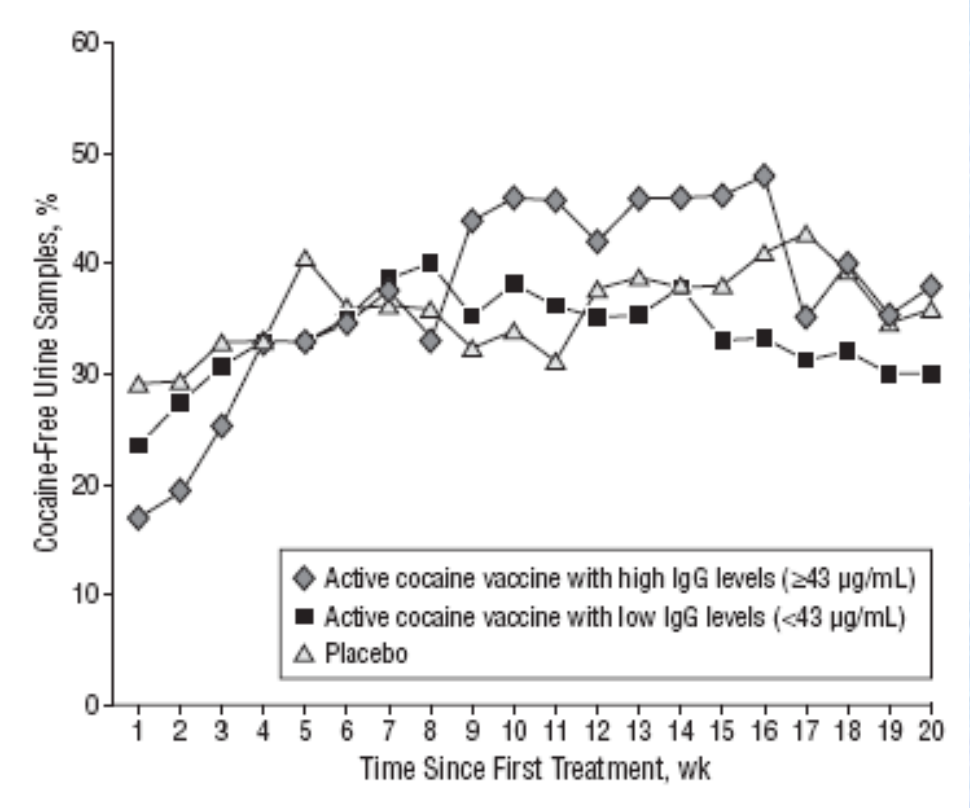
Results: The 21 vaccinated subjects (38%) who attained serum IgG anticocaine antibody levels of 43 µg/mL or higher (ie, high IgG level) had significantly more cocaine-free urine samples than those with levels less than 43 µg/mL (ie, low IgG level) and the placebo-receiving subjects during weeks 9 to 16 (45% vs 35% cocaine-free urine samples, respectively). The proportion of subjects having a 50% reduction in cocaine use was significantly greater in the subjects with a high IgG level than in subjects with a low IgG level (53% of subjects vs 23% of subjects, respectively) (P=.048). The most common adverse effects were injection site induration and tenderness. There were no treatment-related serious adverse events, withdrawals, or deaths.

Conclusions: Attaining high (≥43 µg/mL) IgG anticocaine antibody levels was associated with significantly reduced cocaine use, but only 38% of the vaccinated subjects attained these IgG levels and they had only 2 months of adequate cocaine blockade. Thus, we need improved vaccines and boosters.

Trial Registration: clinicaltrials.gov Identifier: NCT00142857

Arch Gen Psychiatry. 2009;66(10):1116-1123

Cocaine Vaccine



Potential Clinical Applications

- MAbs
  - Overdoses
  - Prevent brain toxicity
- Vaccines
  - Aid to quit use
  - Relapse prevention
  - Prevention of brain toxicity
  - Prevention of development of addiction

Summary

- Medications approved by the FDA for opioid (heroin) addiction (methadone, buprenorphine, naltrexone)
- Medications under research for cocaine, methamphetamine, and cannabis addiction
- Immunotherapy (vaccines or antibodies) is a promising approach
- Nicotine and cocaine vaccines phase III clinical trials in progress