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COMISION INTERAMERICANA PARA EL CONTROL DEL ABUSO DE DROGAS

C I C A D

Secretaría de Seguridad Multidimensional

CUADRAGÉSIMO SEXTO PERIODO ORDINARIO DE SESIONES
Del 18 al 20 de noviembre de 2009
Miami, Florida

OEA/Ser.L/XIV.2.46
CICAD/doc.1760/09
17 noviembre 2009
Original: Español

AVANCES EN LA INVESTIGACION DE MEDICAMENTOS Y VACUNA PARA EL TRATAMIENTO DE LA DEPENDENCIA DE DROGAS

IVAN MONTOYA

Avances en la Investigación de Medicamentos y Vacunas para el Tratamiento de la Dependencia de Drogas

Iván D. Montoya, M.D., M.P.H.
Subdirector (e), División de Farmacoterapias y Consecuencias Médicas del Abuso de Drogas

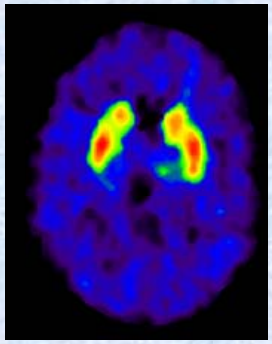
NIDA

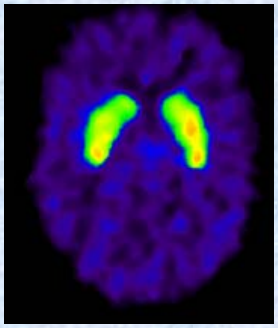
Adicción

- Enfermedad crónica
- Conducta compulsiva en consumo de drogas
- Cambios cerebrales
- Factor de riesgo genético/ambiental
- Consecuencias médicas, psicológicas, sociales
- Prevenible
- Tratable
- Acompañada de recaídas

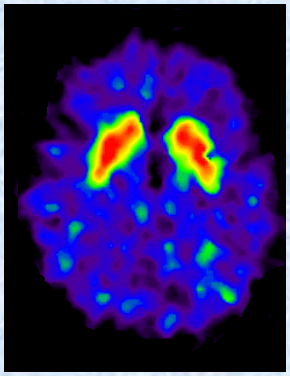
Disminución de Receptores Dopamina D2 en Adictos

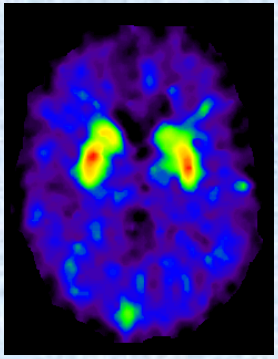
Cocaína



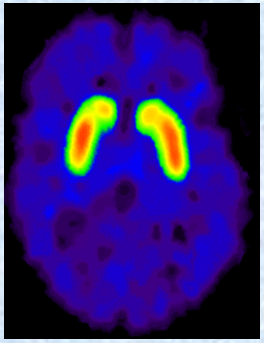


Alcohol





Heroína



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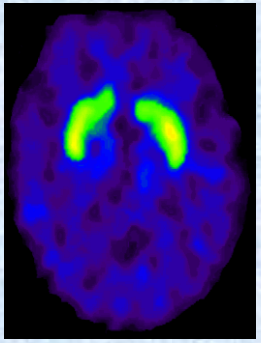
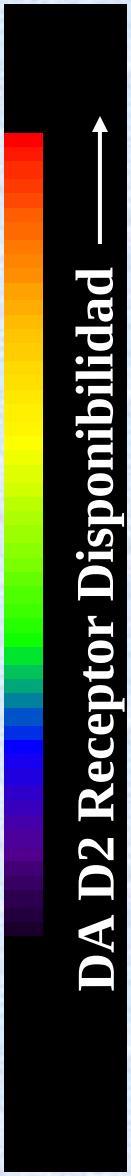


Adicto



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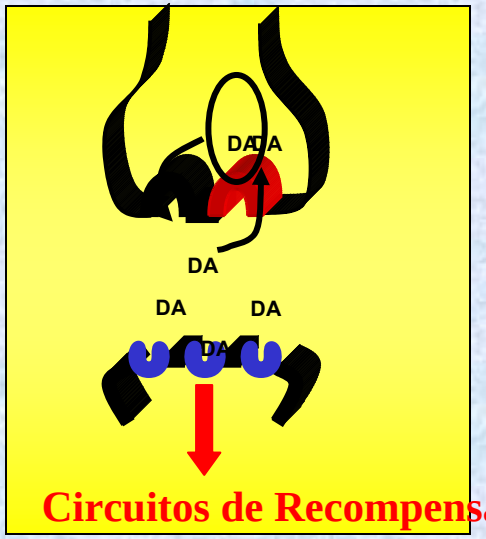
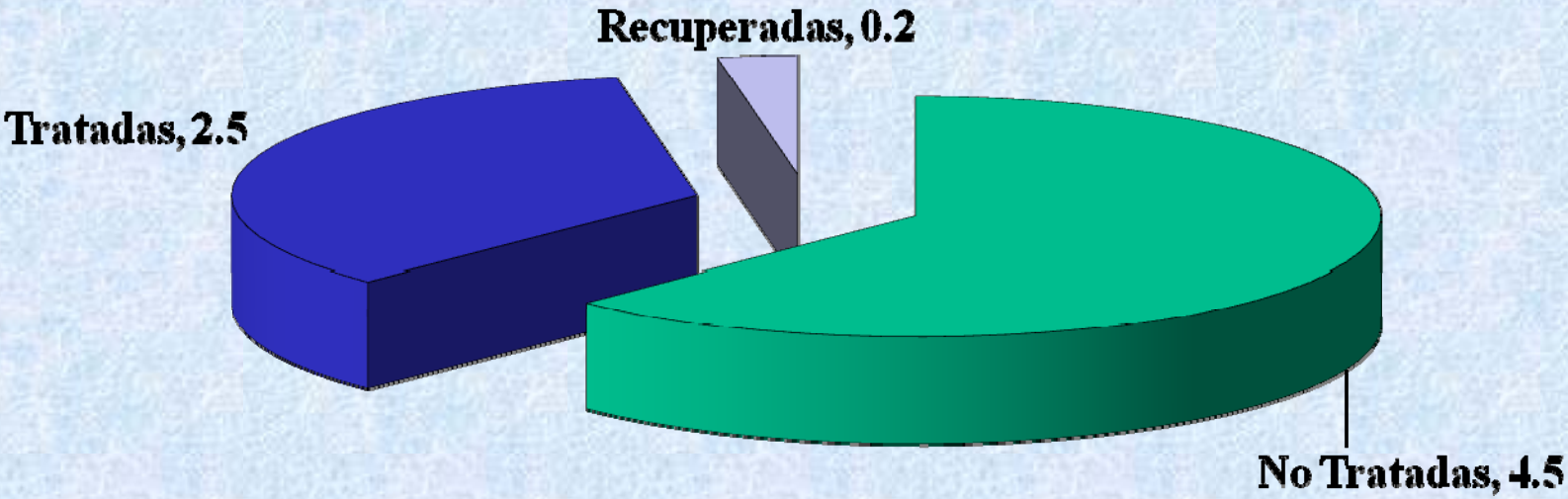


Adicto

Adicción a Drogas Ilícitas



Millones de Personas

NSDUH, 2006

Razones para Investigar Medicamentos y Vacunas

- Problemas de salud pública
- Psicoterapias tienen eficacia limitada
- Avances del conocimiento sobre efectos de drogas y fisiopatología de adicciones
- Nuevos objetivos farmacológicos
- Avances en marcadores biológicos
- Farmacogenética
- Nuevas moléculas, medicamentos y vacunas

Programa de Investigación de Medicamentos de NIDA

Mandato del Congreso a NIDA

Marzo, 1990

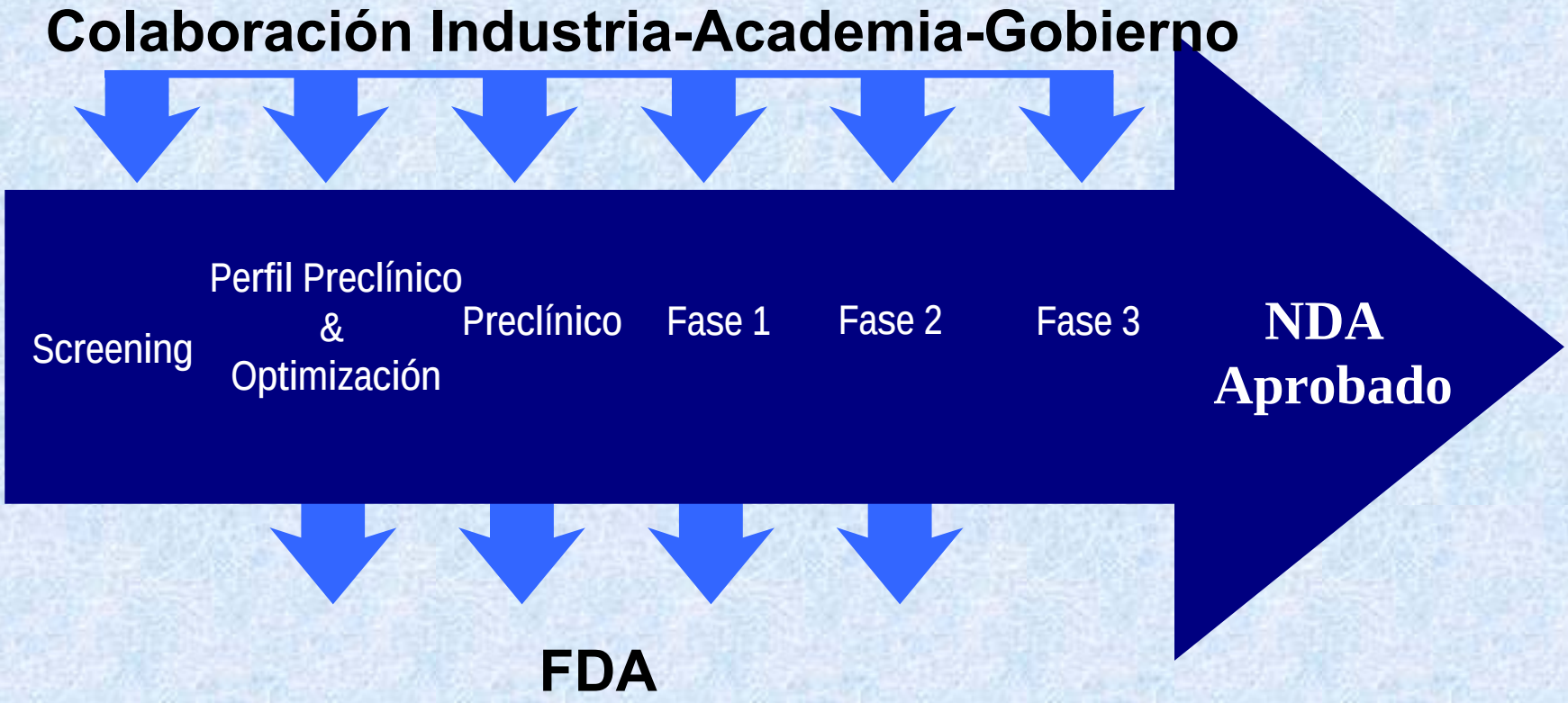
Establecer un programa nacional de investigación de tratamiento para la adicción a la cocaína y heroína

Colaborar en forma estrecha con la industria farmacéutica

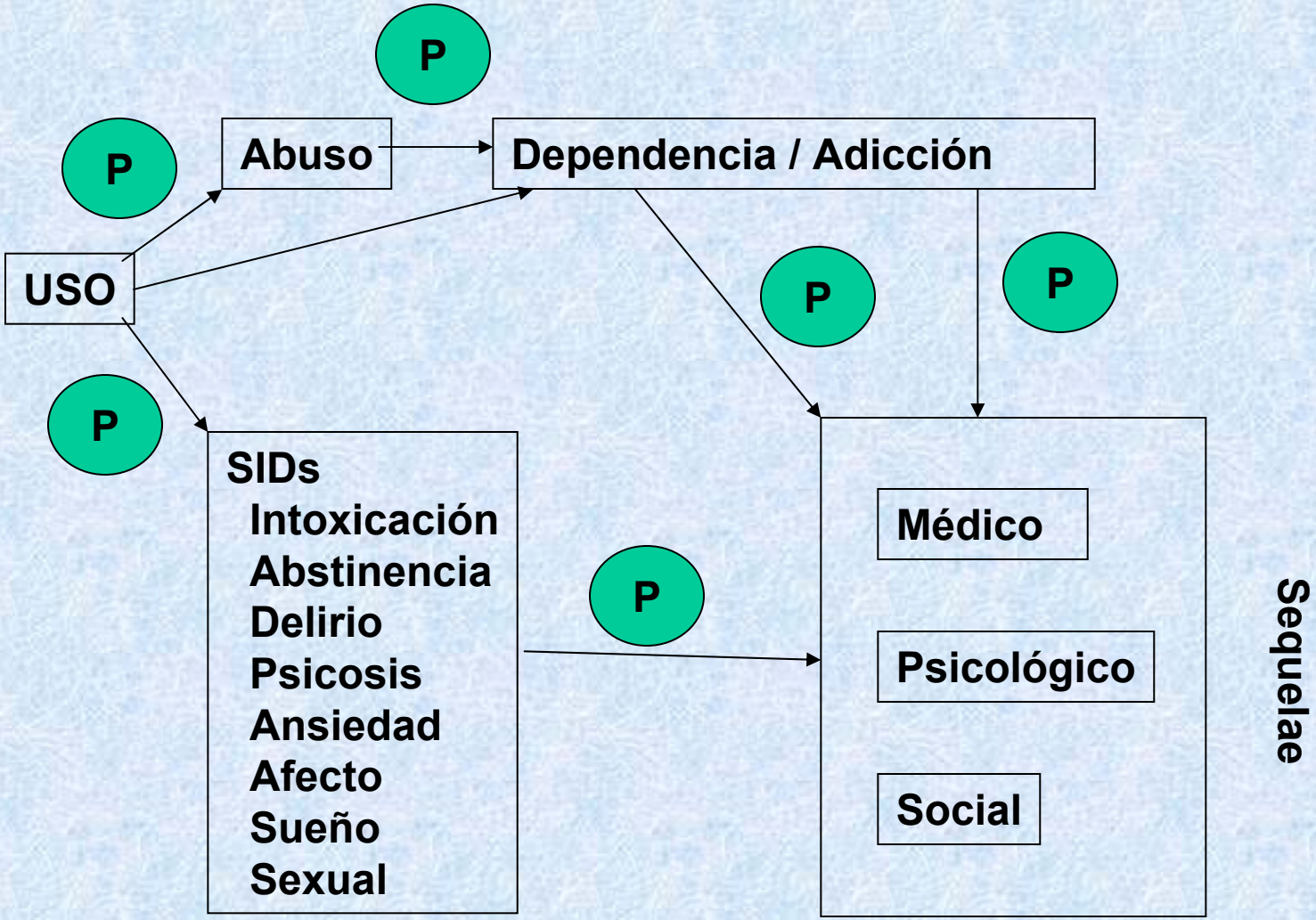
Facilitar la investigación necesaria para cumplir los requisitos de aprobacion por la FDA

Colaborar con la FDA para que los medicamentos con eficacia demostrada sean evaluados y aprobados en forma expedita.

Programa de Desarrollo de Medicamentos del NIDA



Enfoques Farmacológicos



Medicamentos

FDA aprobados :

- **Levo-Alfa Acetil Metadol (LAAM)**
- **Buprenorfina**
- **Buprenorfina/naloxona**
- **Naltrexona**

En fase avanzada de desarrollo:

- **Lofexidina**
- **Vacuna anti-nicotina**

Adicción a Opioides

- Metadona
- Buprenorfina
- Naltrexona
- LAAM
- Clonidina
- Lofexidina

Metadona y Buprenorfina

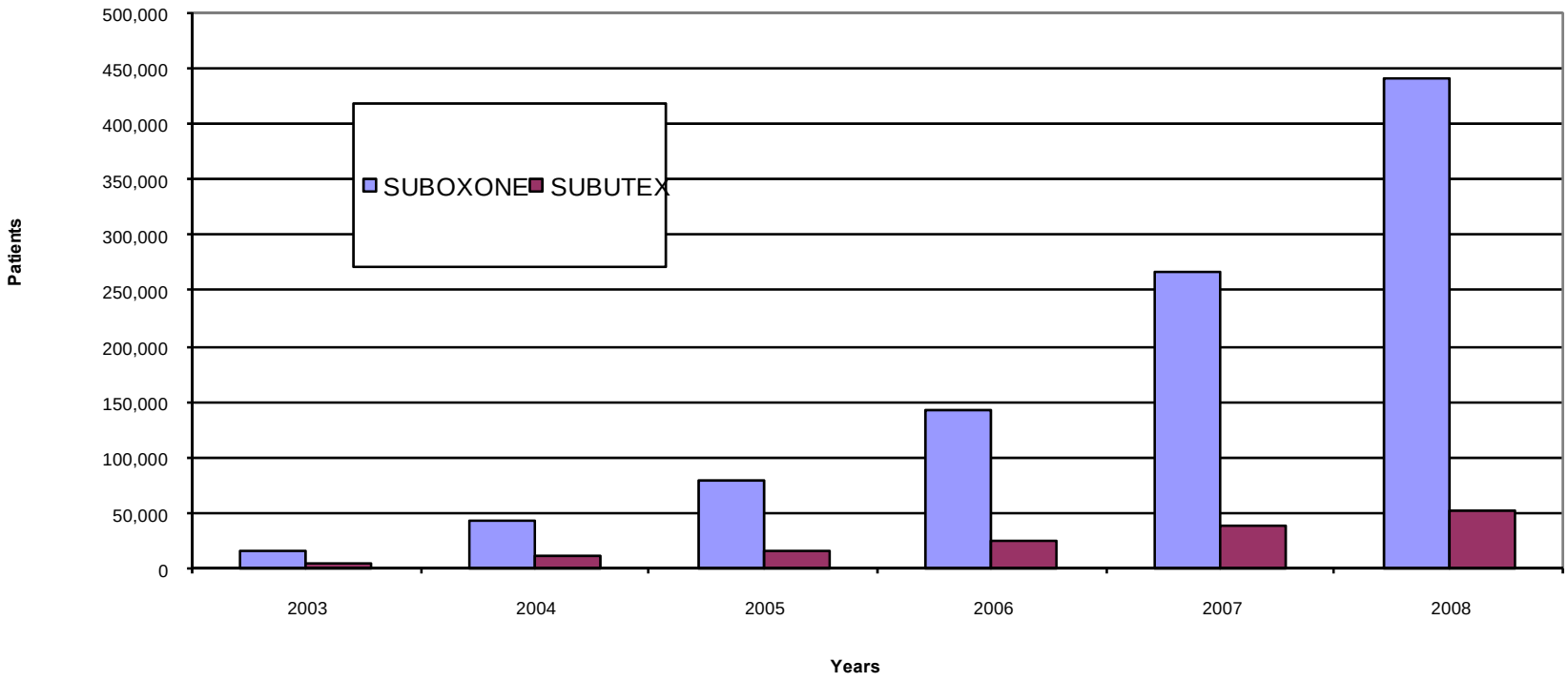
Comparando con adictos a heroína que no reciben tratamiento:

- **↓ Índice de mortalidad**
- **↓ Actividad criminal / encarcelamiento**
- **↑ Empleo**
- **↓ Compartir jeringas**
- **↓ Infección VIH**

Buprenorfina :

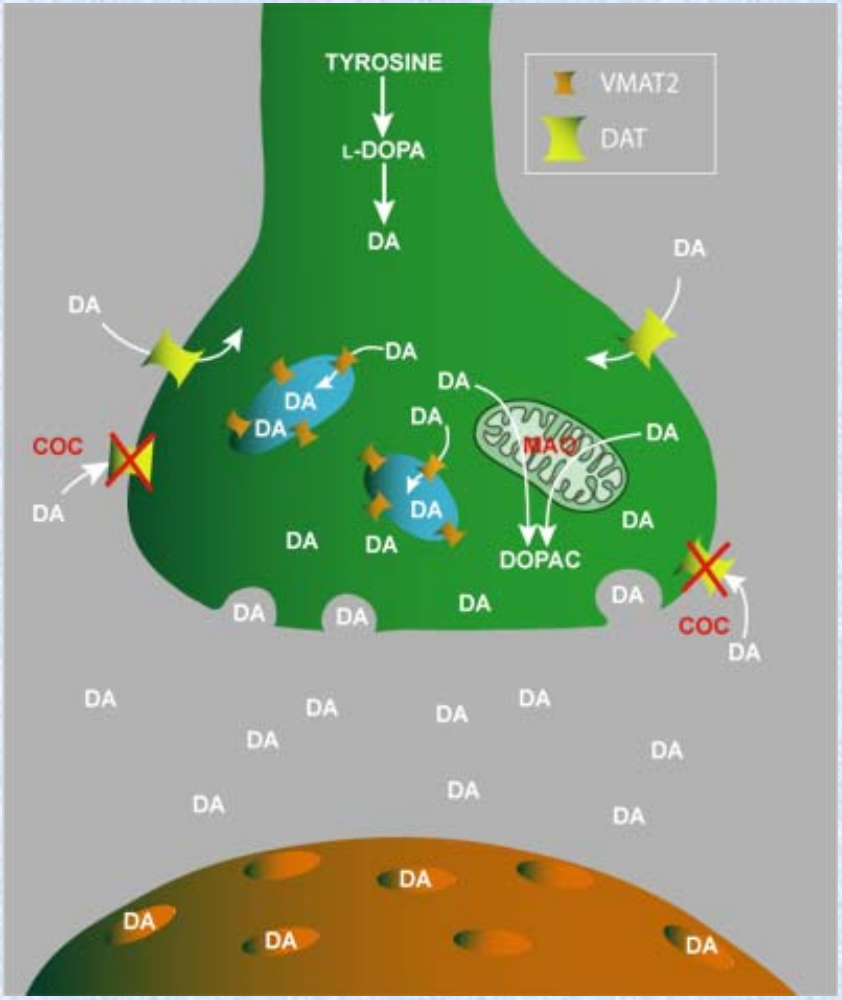
- **Segura en sobredosis**

Número total de pacientes que recibieron una receta para Subutex o Suboxone en farmacias de EE.UU. , Años 2003 - 2008



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

Cocaína



Cocaína - Medicamentos Evaluados

Fase I

Cyclazocine
Tolcapone
Modafinil
Metyrapone

Fase II Screen

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

Fase II

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

Fase 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.

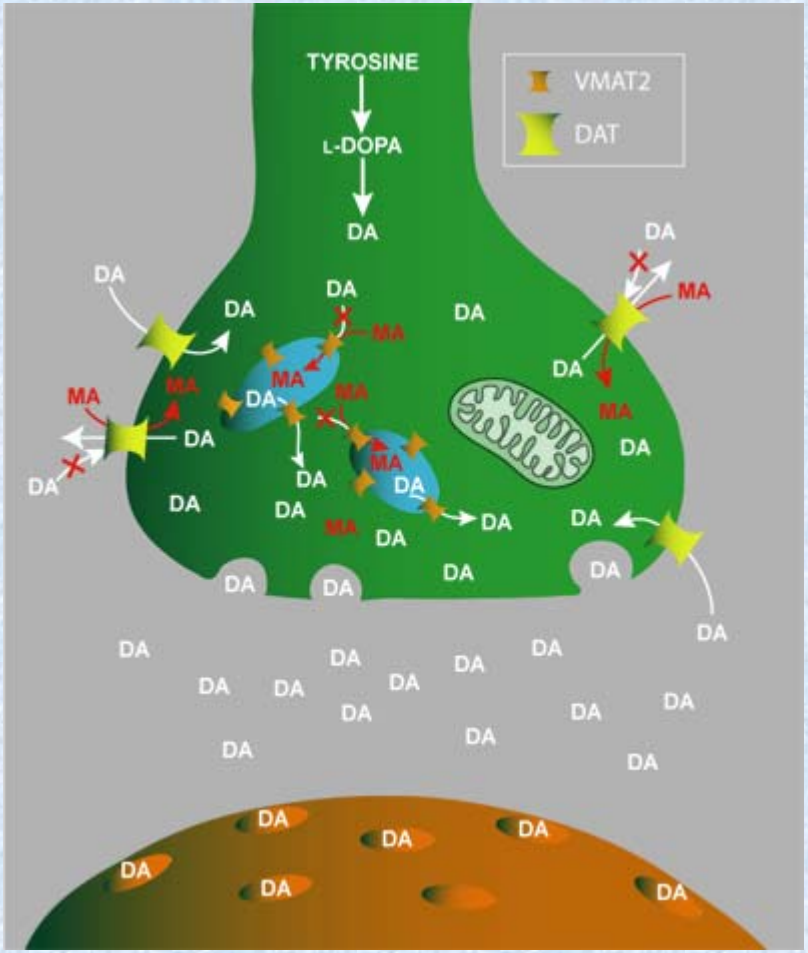
(Am J Psychiatry Brodie et al.; AiA:1–9)

Vigabatrin para Adicción a Cocaína

	Abstinencia durante últimas 3 semanas de Tto	
	Fracasos	Exitos
Placebo	49 (92.5%)	4 (7.5%)
Vigabatrin	36 (72%)	14 (28%)

P = 0.009 (Chi-square test)

Metanfetamina



Bupropion para la Adicción a Metanfetamina

	Abstinencia Durante últimas 3 Semanas de Tto	
	Fracasos	Exitos
Placebo	68 (94.4%)	4 (5.56%)
Bupropion	65 (82.3%)	14 (17.7%)

P = 0.02 (Chi-square test)

Inmunoterapias

Vacunas

Anticuerpos

Programa de Desarrollo de Inmunoterapias

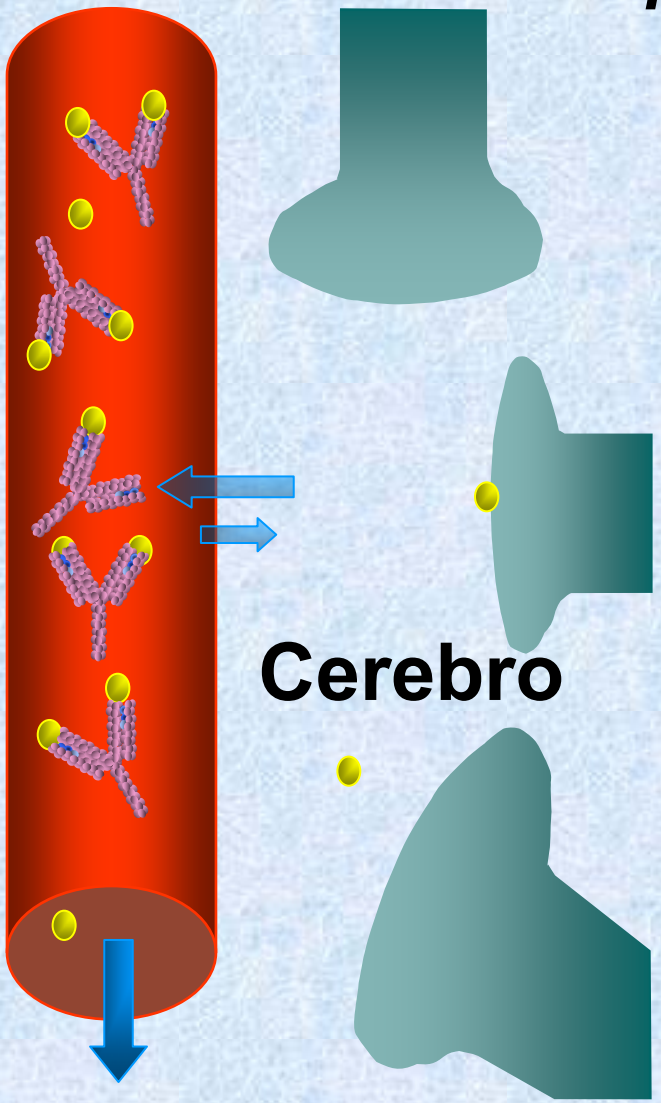
Estudios Preclínicos

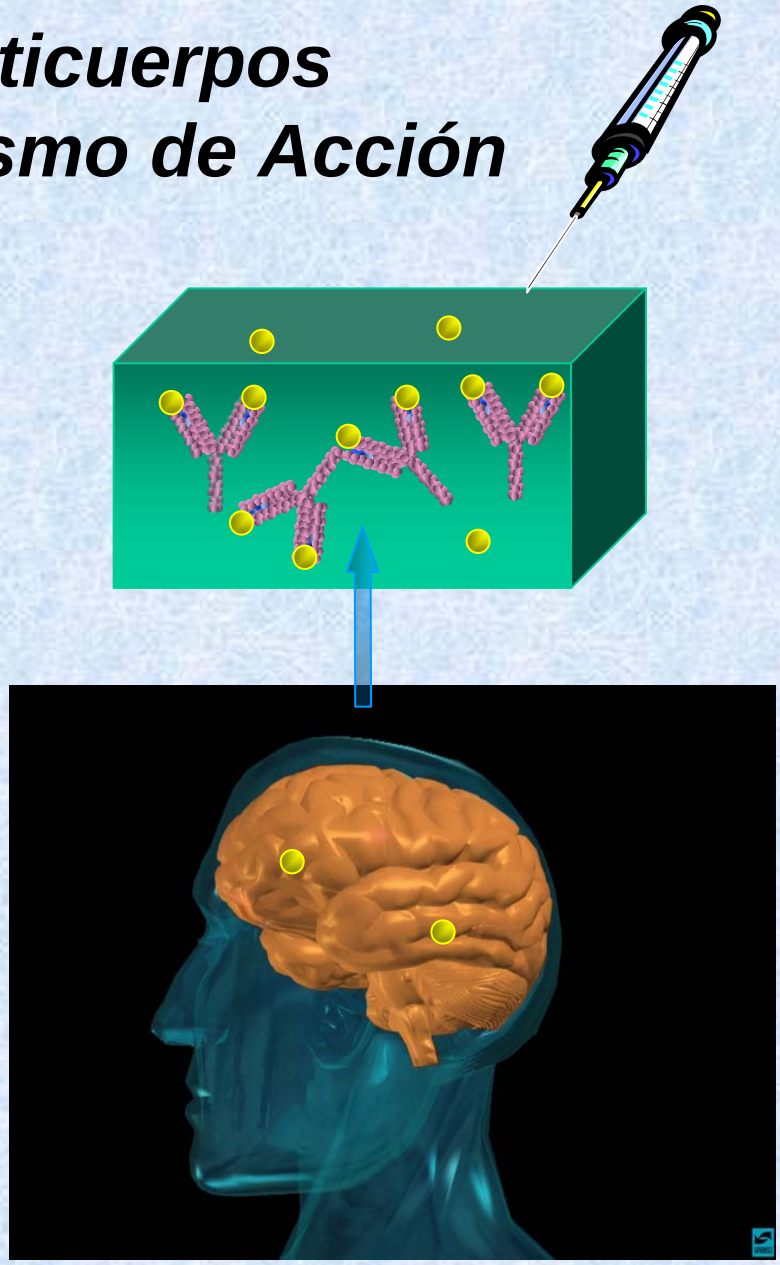
- **anti-PCP mAb**
- **anti-Metamfetamina mAb**
- **anti-MDMA mAb**
- **anti-cocaína mAb**
- **anti-heroína mAb (Mexico)**

Estudios Clínicos

- **Vacuna anti-Nicotina**
- **Vacuna anti-Cocaína**

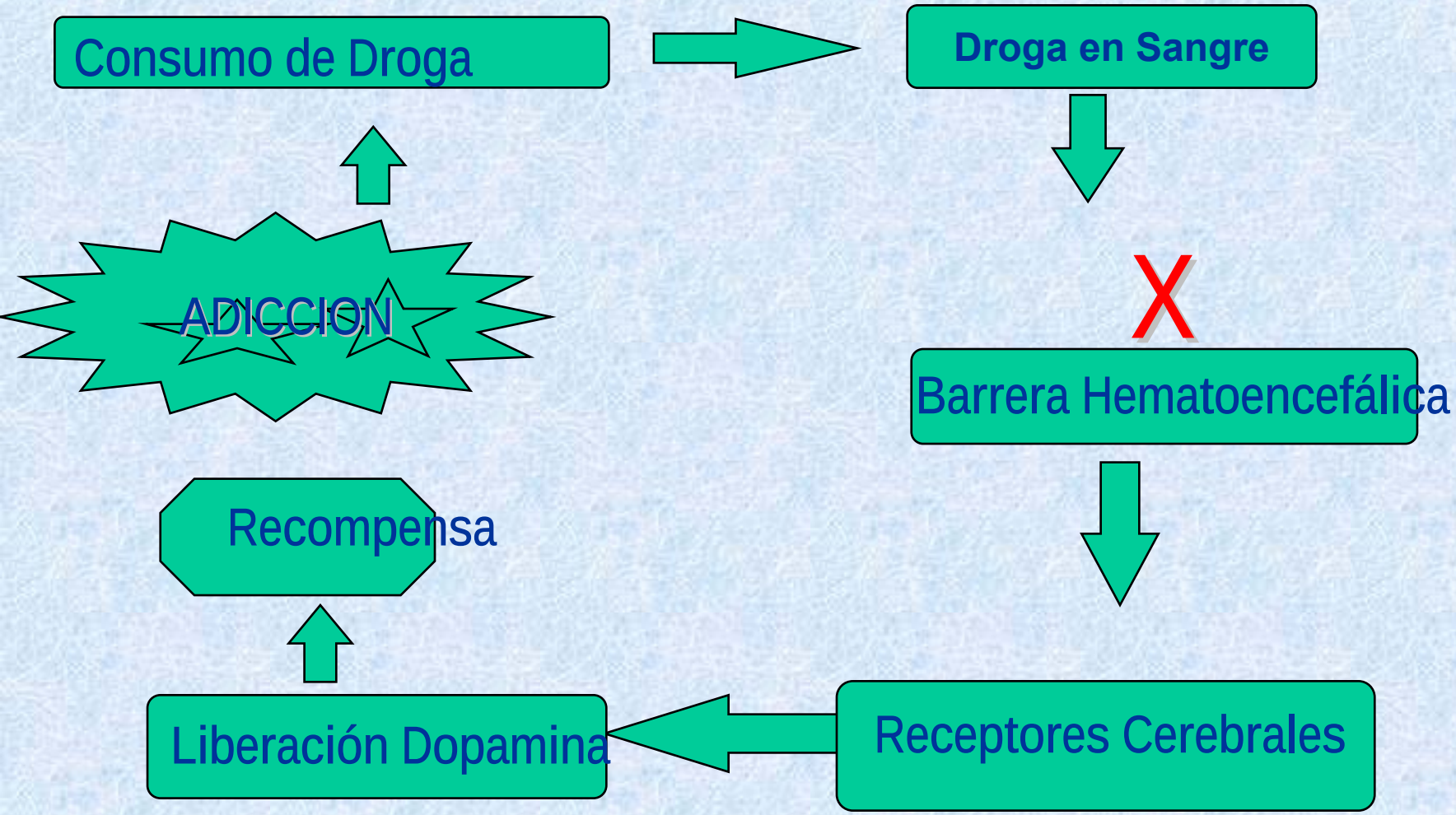
Anticuerpos
Mecanismo de Acción



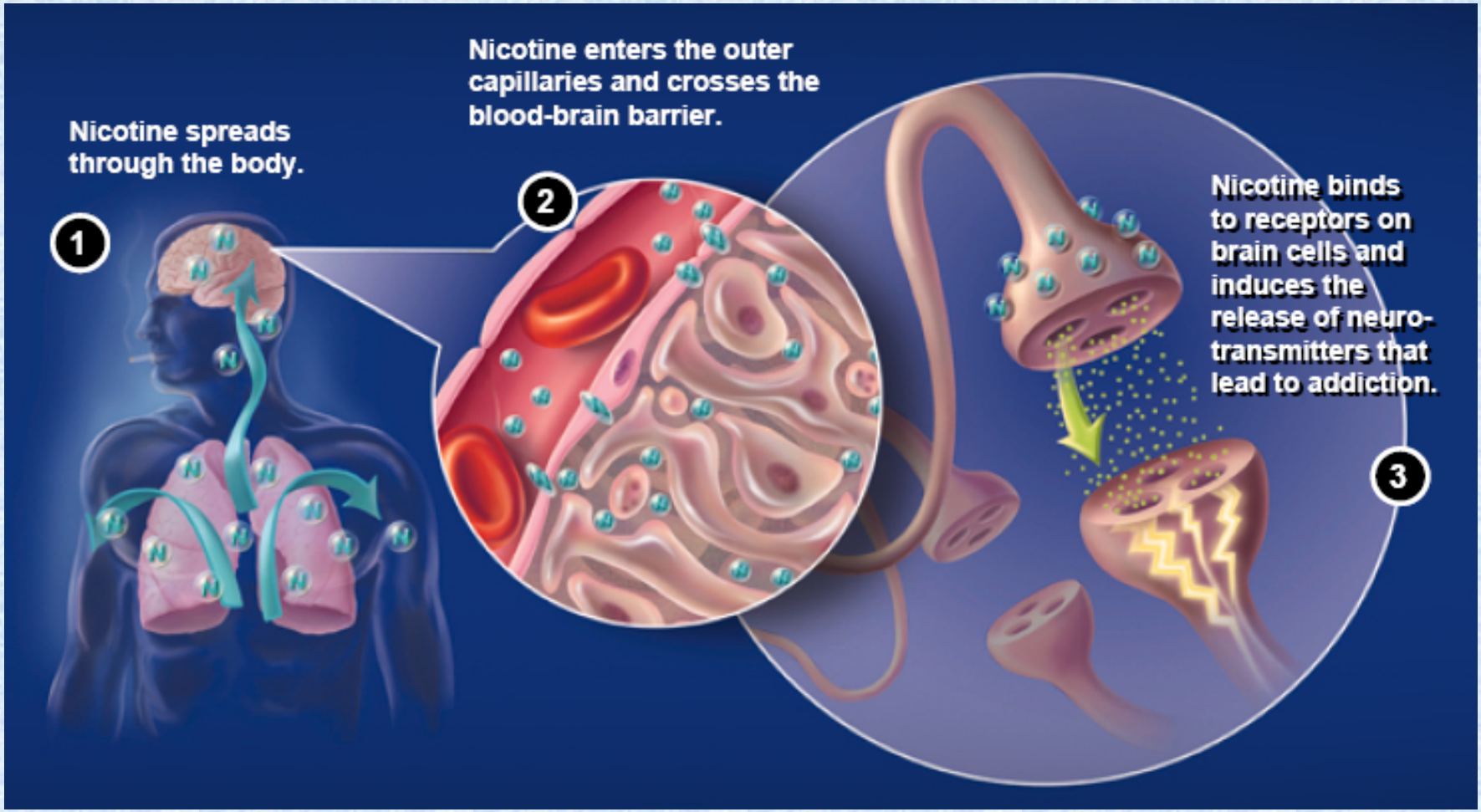


(Owens & Gentry 2002)

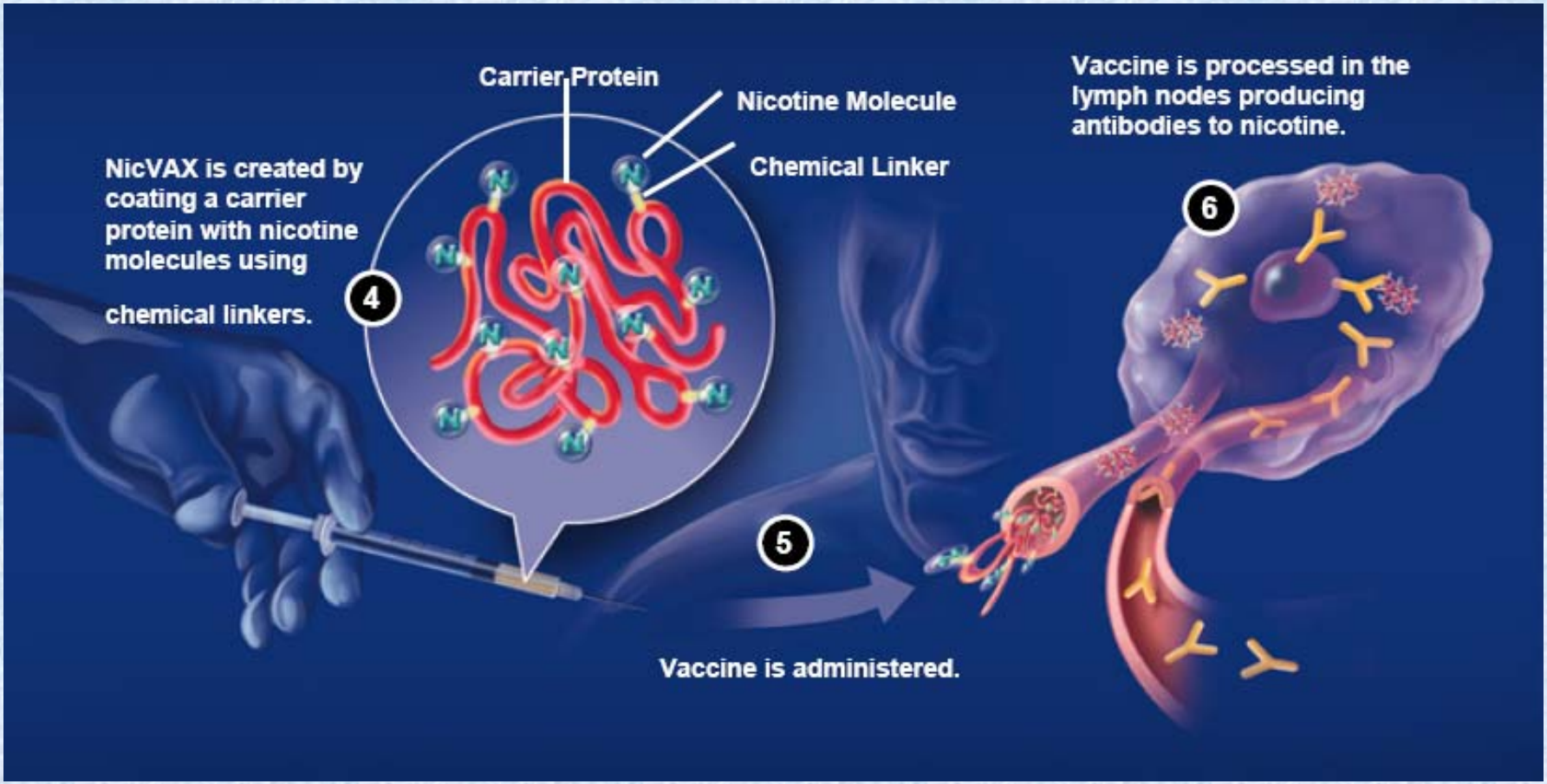
Mecanismo de Acción de Inmunoterapias para Adicciones



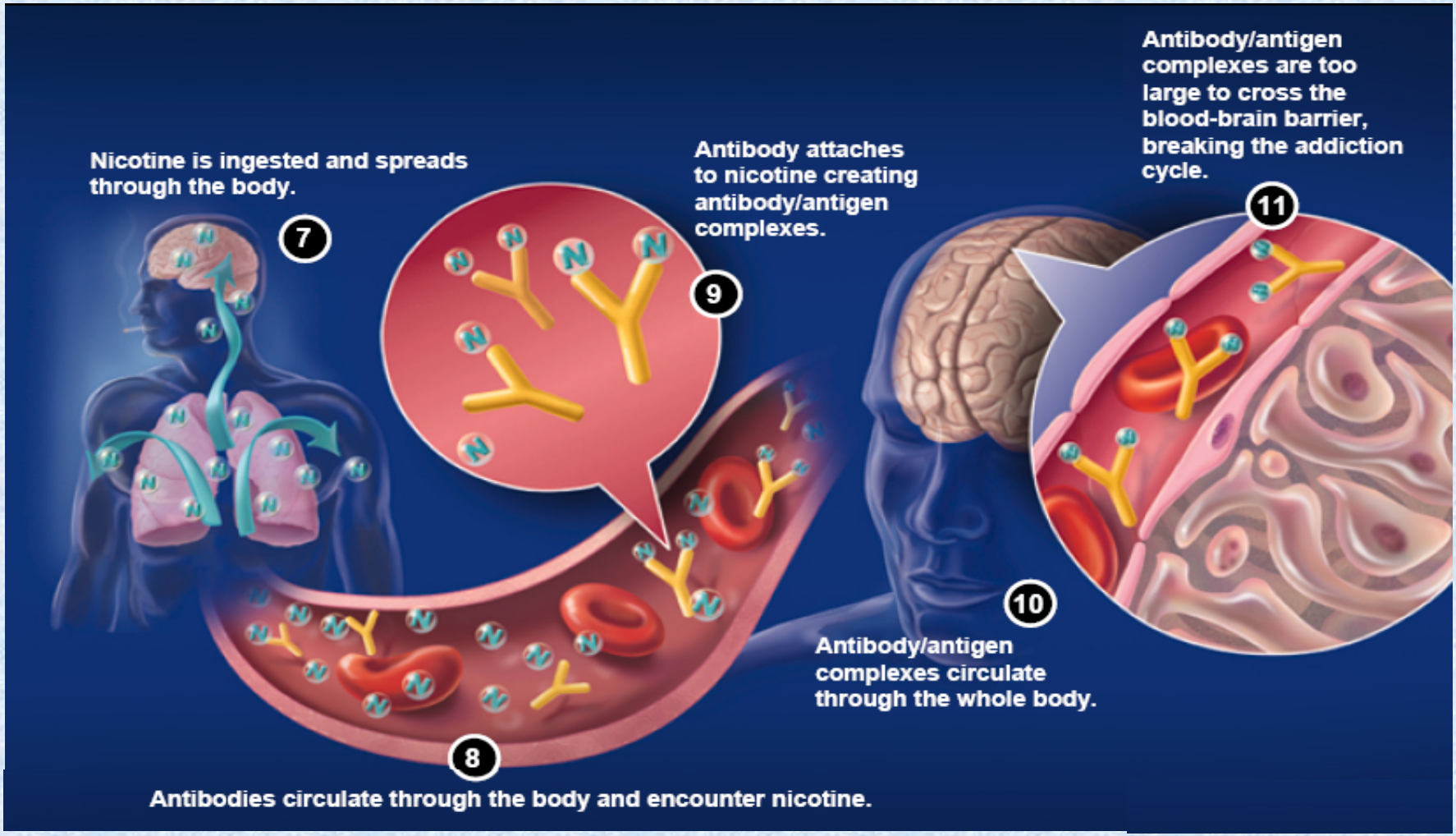
Adicción a Nicotina



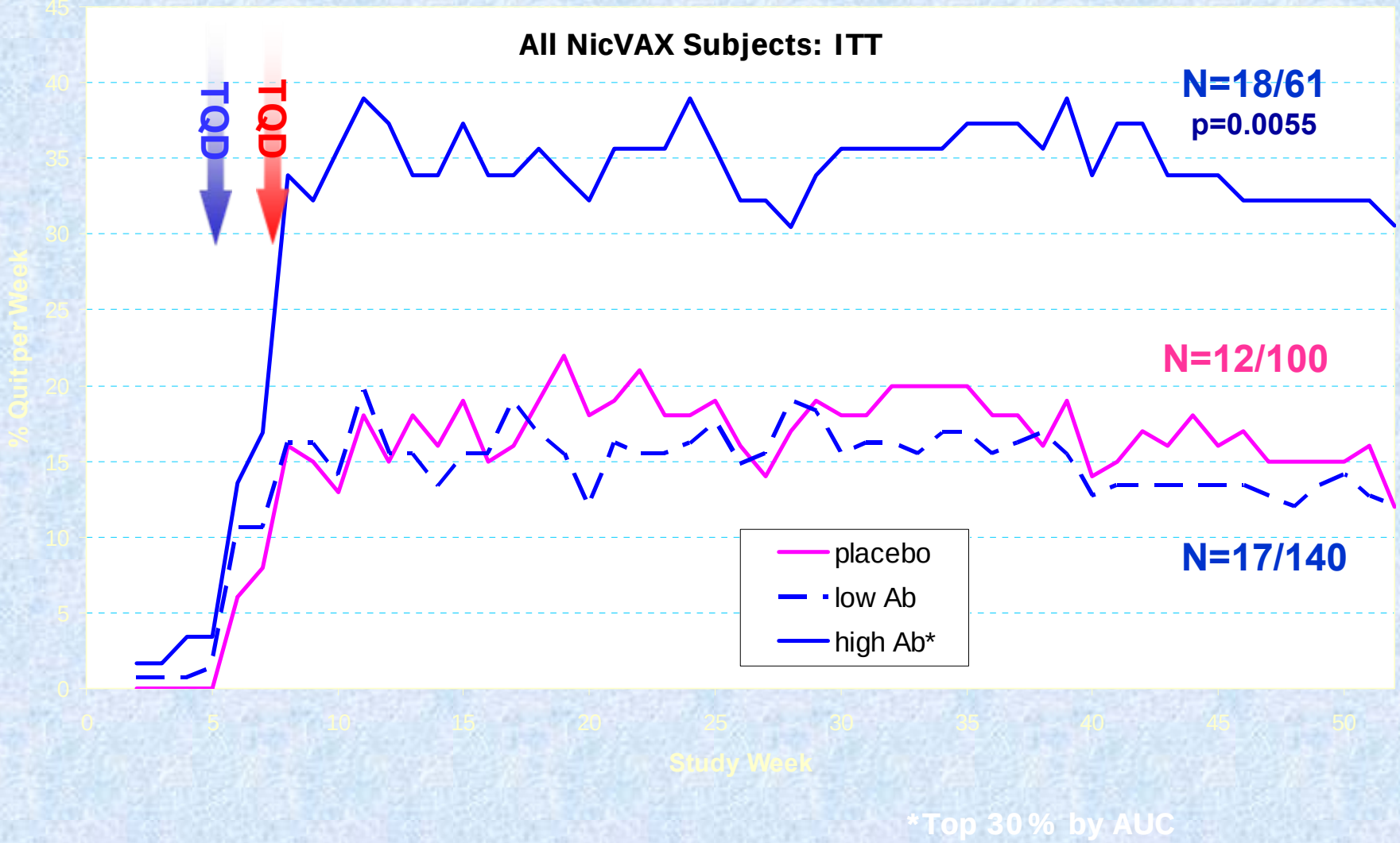
Vacuna Anti-nicotina



Rompiendo el Ciclo de Adicción



Proporción de sujetos que dejaron de fumar Según nivel de anticuerpos



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.

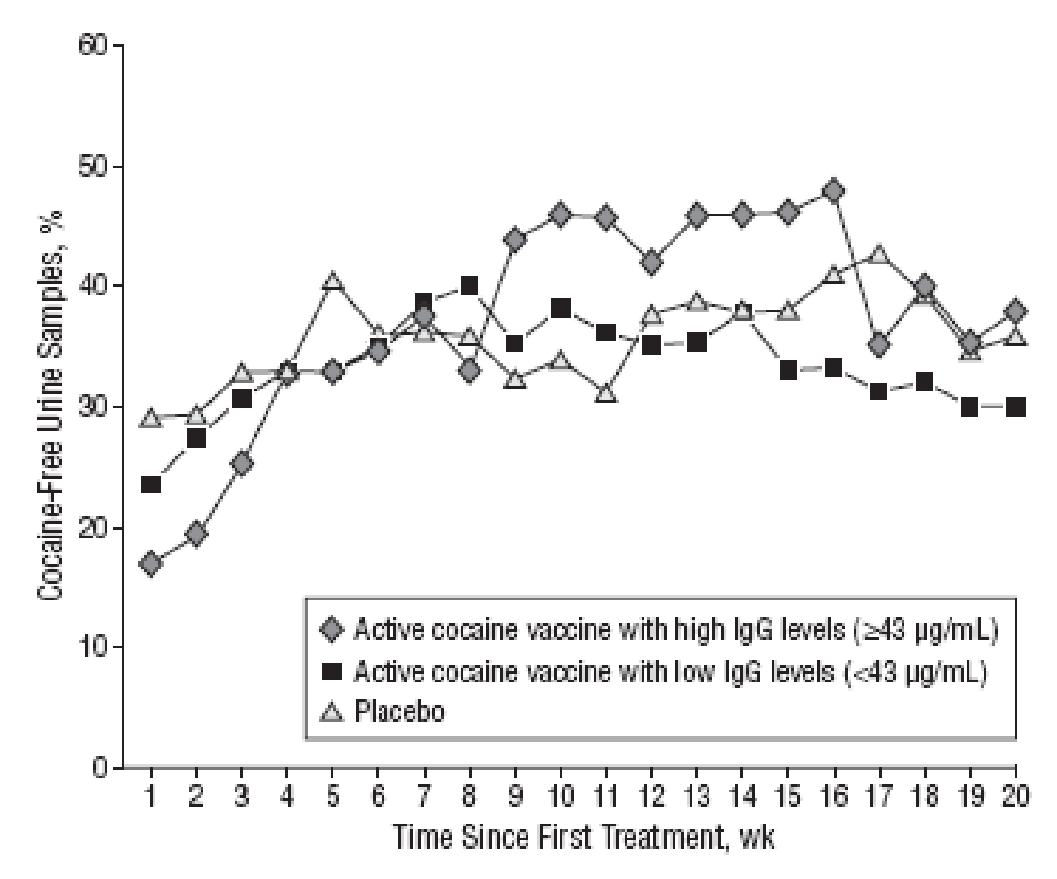
Results: The 21 vaccinated subjects (38%) who attained serum IgG anticocaine antibody levels of 43 µg/mL or higher (ie, high IgG level) had significantly more cocaine-free urine samples than those with levels less than 43 µg/mL (ie, low IgG level) and the placebo-receiving subjects during weeks 9 to 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

Vacuna anti-cocaína



Potenciales Aplicaciones Clínicas

- Anticuerpos
  - Sobredosis
  - Prevenir toxicidad cerebral
- Vacunas
  - Ayuda para dejar de consumir drogas
  - Prevenir recaídas
  - Prevenir daño cerebral
  - Prevenir progreso de uso a adicción

Resumen

- Medicamentos aprobados por la FDA para adicciones a opioides (heroína) (metadona, buprenorfina, naltrexona)
- Medicamentos en investigación para la adicción a cocaína, metanfetamina y canabis
- Inmunoterapia (vacunas o anticuerpos) enfoque prometedor
- Vacunas antinicotina y anticocaína en ensayos clínicos fase III