

APA Presentation

Substance Abuse Pharmacotherapy: *From Antabuse to Zenova-vax*

Thomas Kosten MD

Waggoner Chair and Professor of Psychiatry &
Neuroscience, Baylor College of Medicine

President – College on Problems of Drug Dependence

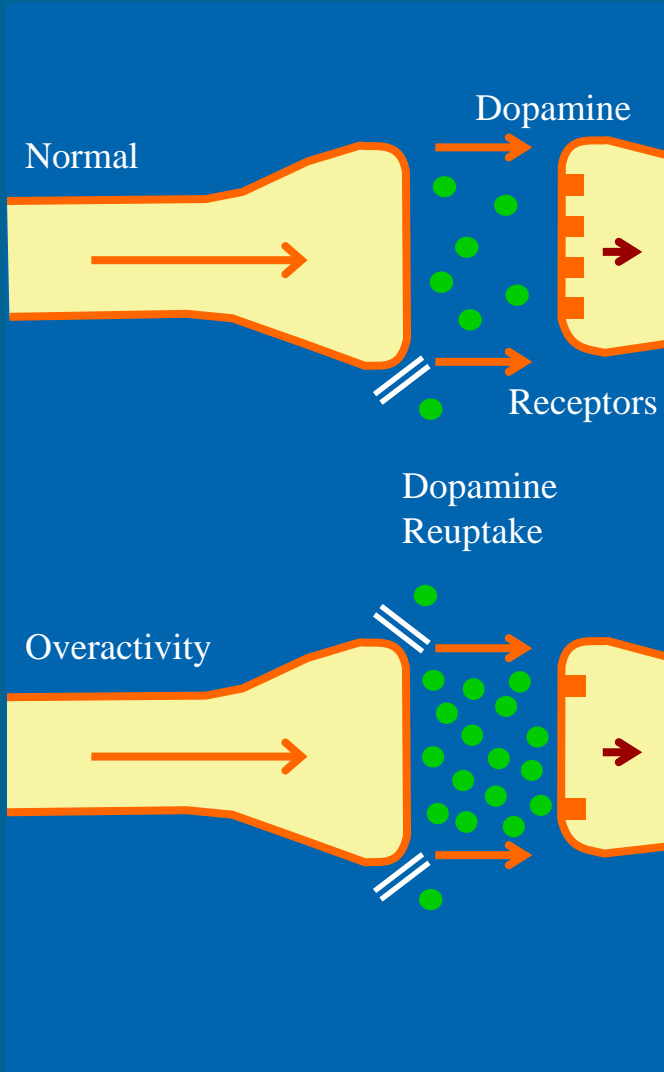
Past President – American Academy of Addiction Psychiatry

Outline of Presentation

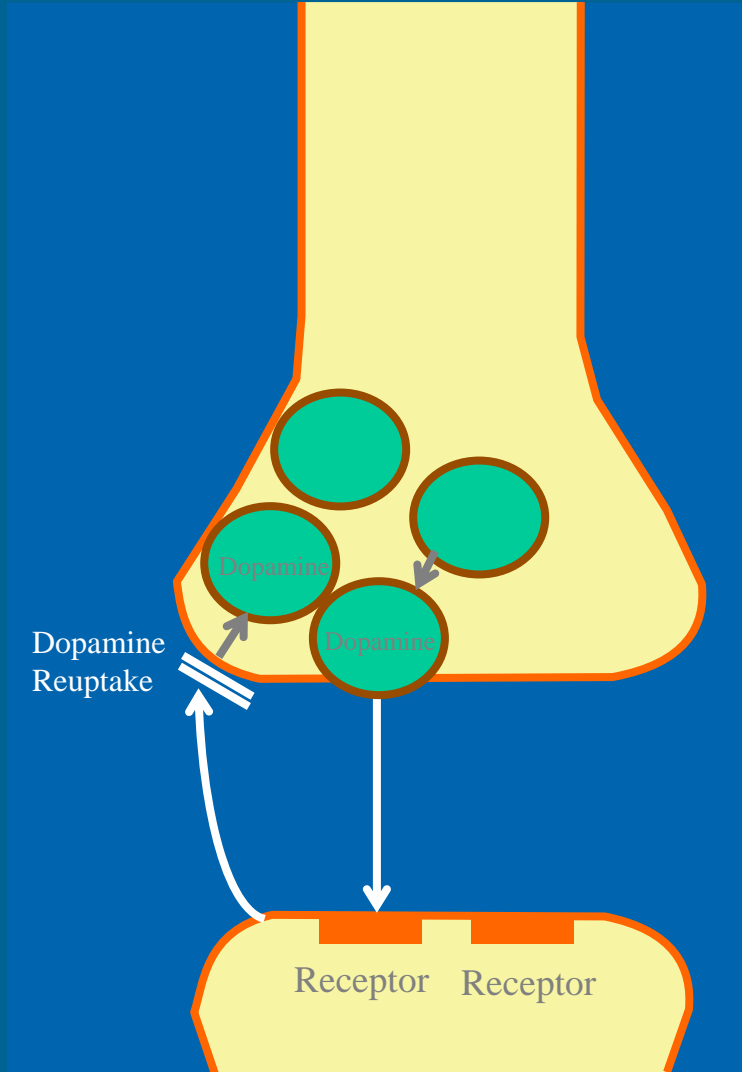
- ▶ **Focus on Stimulants**
- ▶ **Disulfiram (Antabuse)**
 - Dopamine & pharmacogenetics
- ▶ **Cocaine vaccine (Zenova-vax)**
 - Blocking cocaine entry into brain

How Cocaine Alters the Brain: Dopamine Damage & Parkinsonism

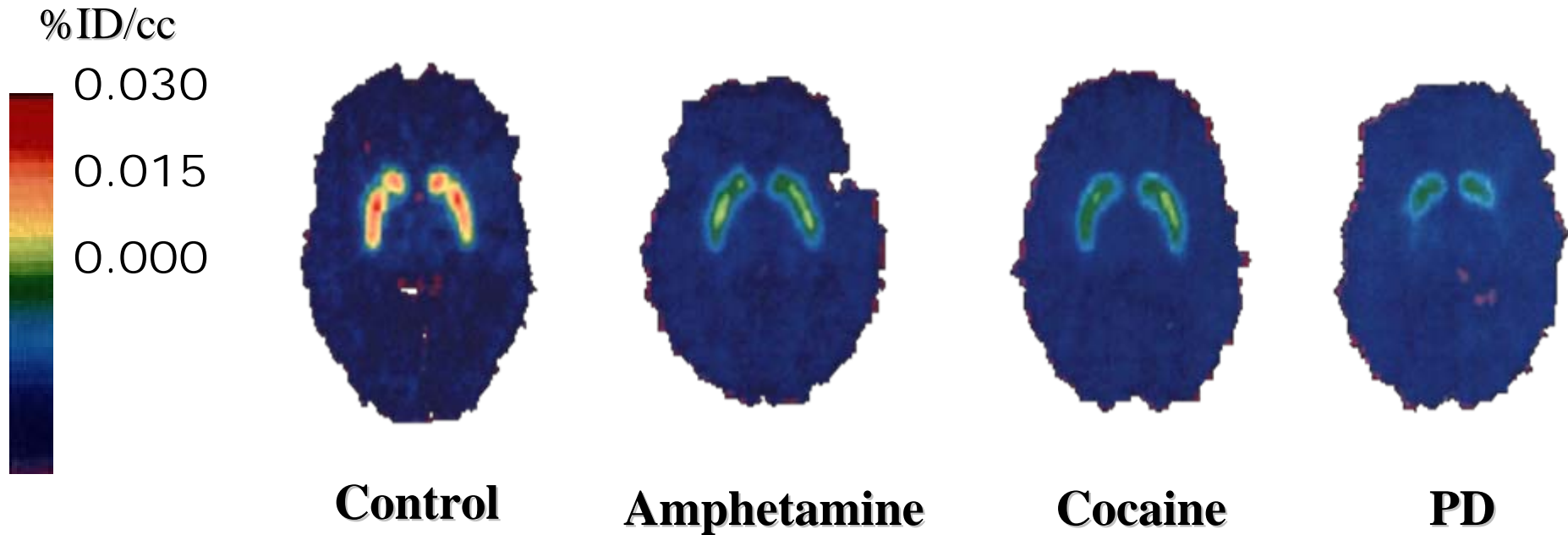
Receptor Sensitivity



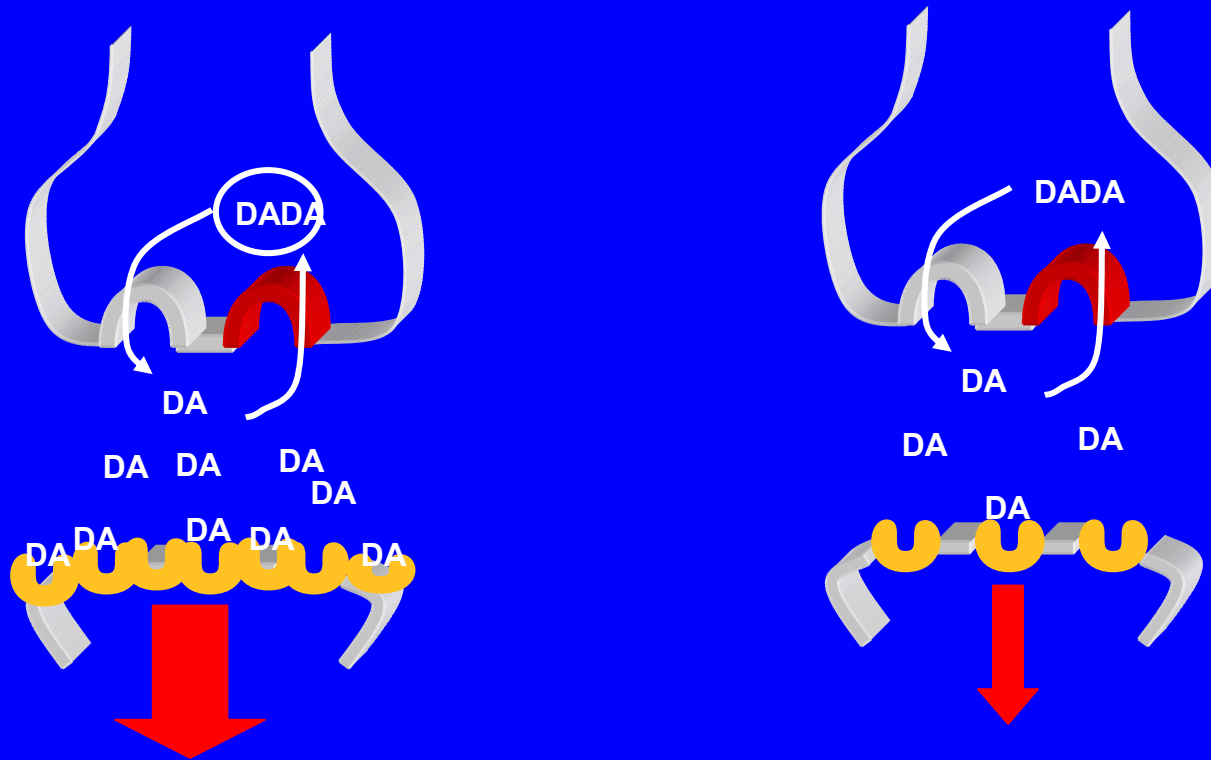
Sites of Drmcg Action at the Synapse



Parkinsonian (PD) Brain Abnormalities in Cocaine Abusers



Hypodopaminergic State In Drmcg Addiction



Reward Circuits

Reward Circuits

Non Drmcg Abuser

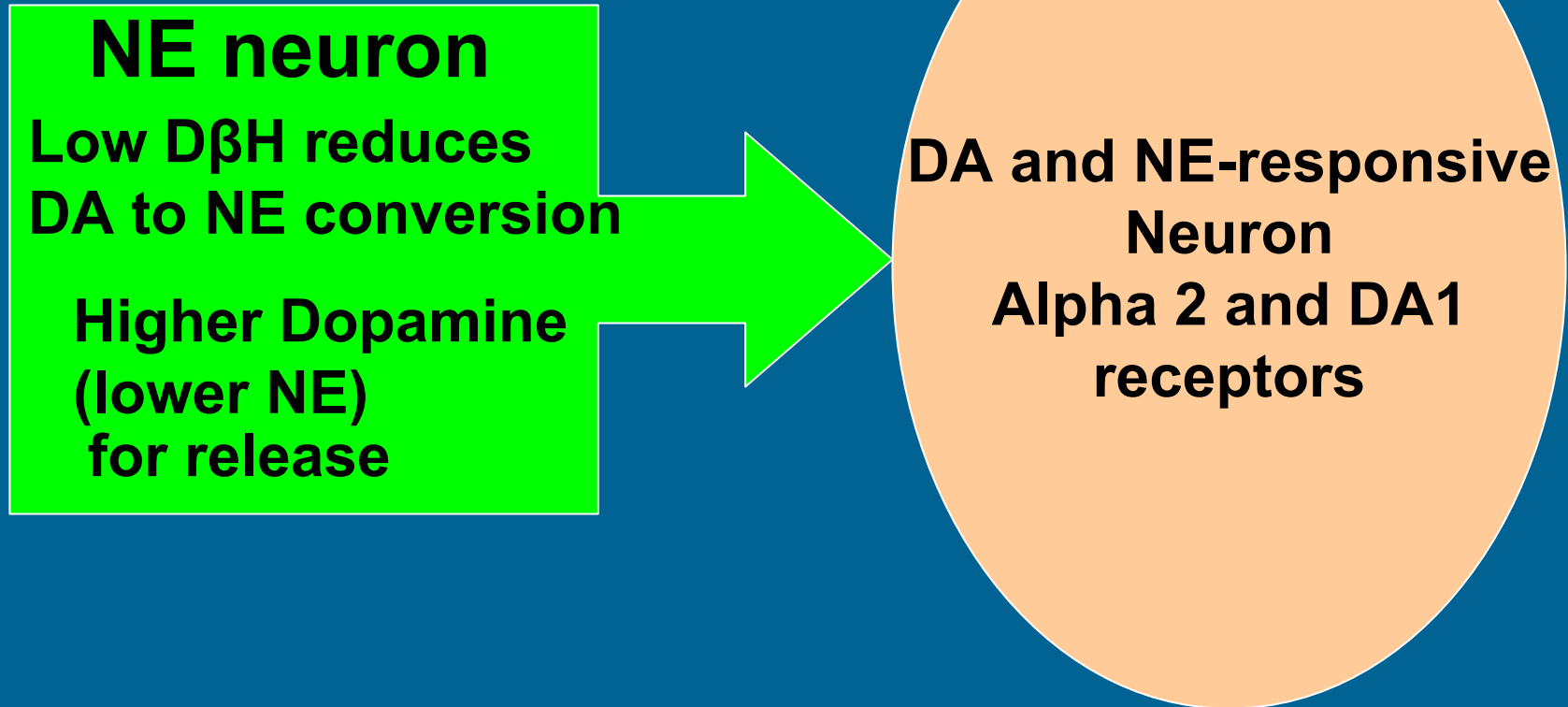
Addicted Subject

Dopamine Agonist Therapy

Reverse Craving and Attenuate Priming

- ▶ **Reverse stimulant induced dopamine deficiency – receptors down, transporters up**
- ▶ **D2 agonists not effective – bromocriptine**
- ▶ **Indirect agonists promising**
- ▶ **Disulfiram: inhibit dopamine beta hydroxylase conversion of dopamine to norepinephrine**

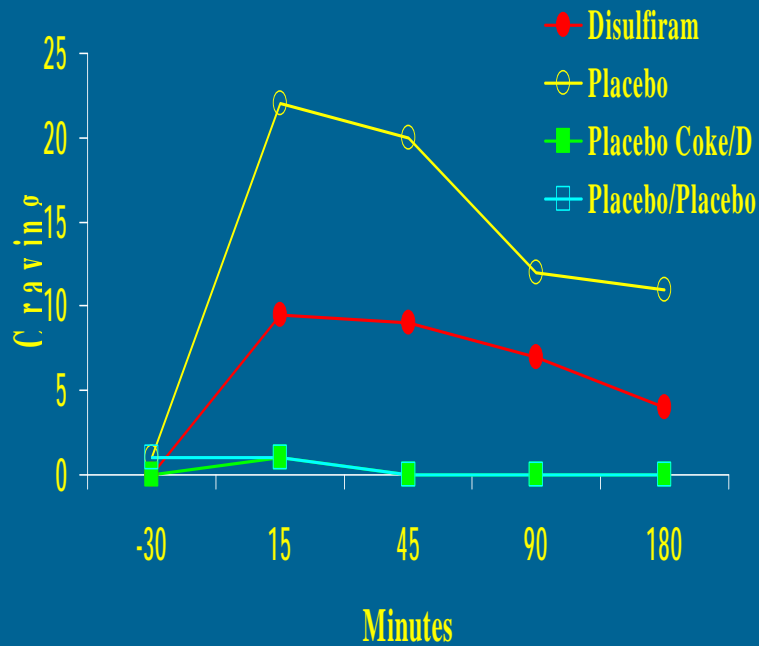
Disulfiram increases dopamine (DA) by inhibiting its conversion to norepinephrine (NE)



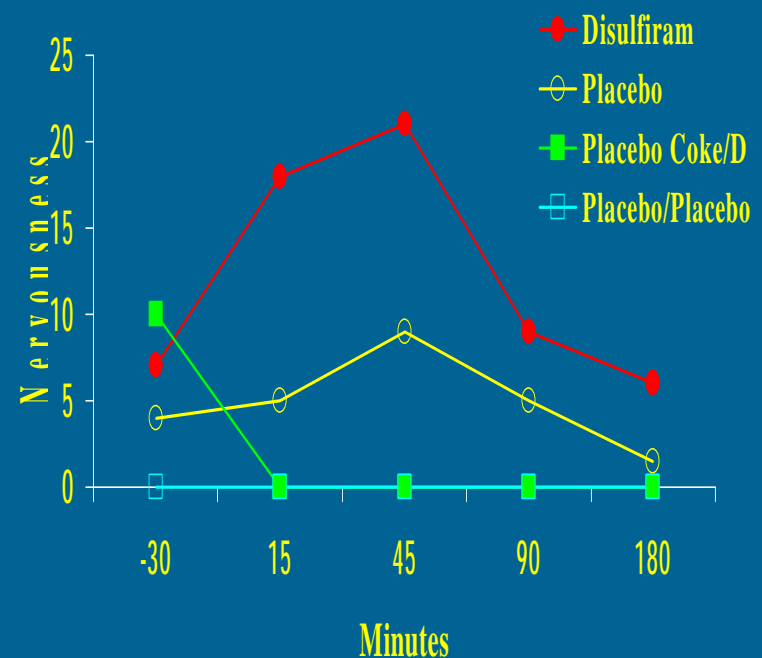
Disulfiram Effects on Acute Cocaine (2mg/kg I.N.)

Yellow (cocaine alone), Red (disulfiram + cocaine)

Craving for cocaine



Nervousness from cocaine



Cocaine Free Urines Across 5 Disulfiram Clinical Studies (n=337)

<u>Study (n)</u>	<u>Disulfiram vs. Placebo</u> <u>% Cocaine Free Urines</u>
vs Naltrexone (18)	90% vs 66%
w Buprenorphine (20)	41% vs 25%
w Methadone (67)	35% vs 25%
- Psychotherapy (117)	55% vs 40%
- Match Study (115)	57% vs 45%
Meta Average	55% vs 40%

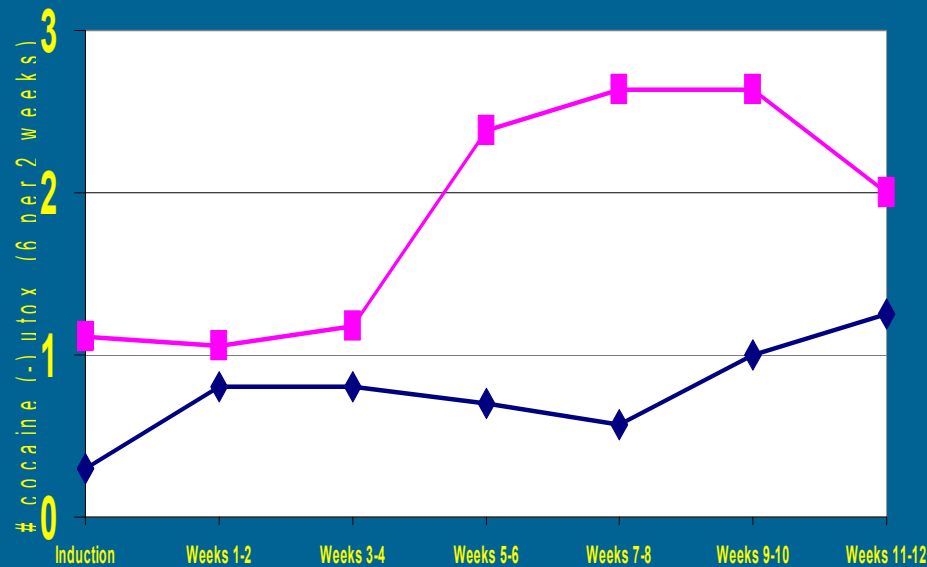
Disulfiram vs. Placebo: Cocaine-free urines

High cocaine use group, stratified by *DBH* genotype

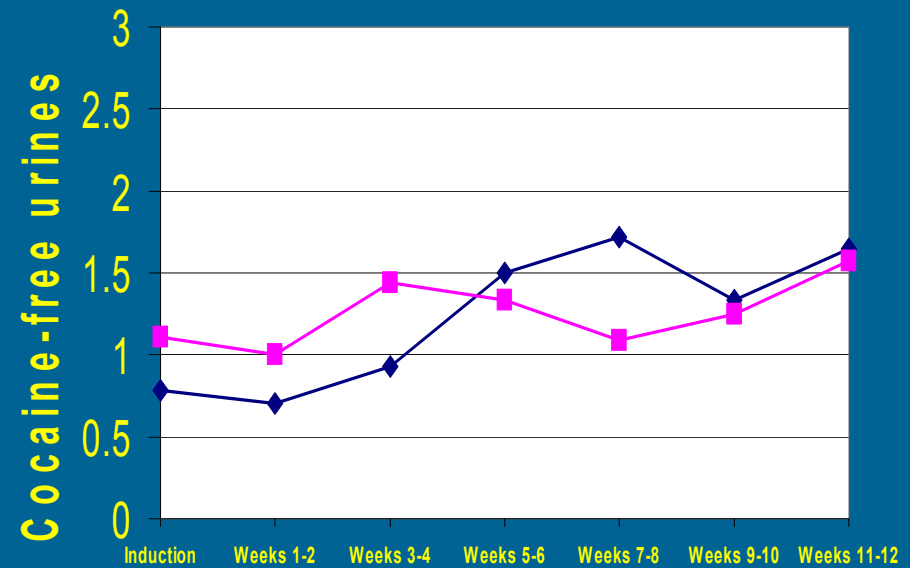
Pink line is disulfiram (n=75) (Schottenfeld 2004)

TT + CT (lower $D\beta H$):

CC (higher $D\beta H$):



◆ Placebo T-allele ■ Disulfiram T-allele



◆ Placebo CC-homozygous ■ Disulfiram CC-homozygous

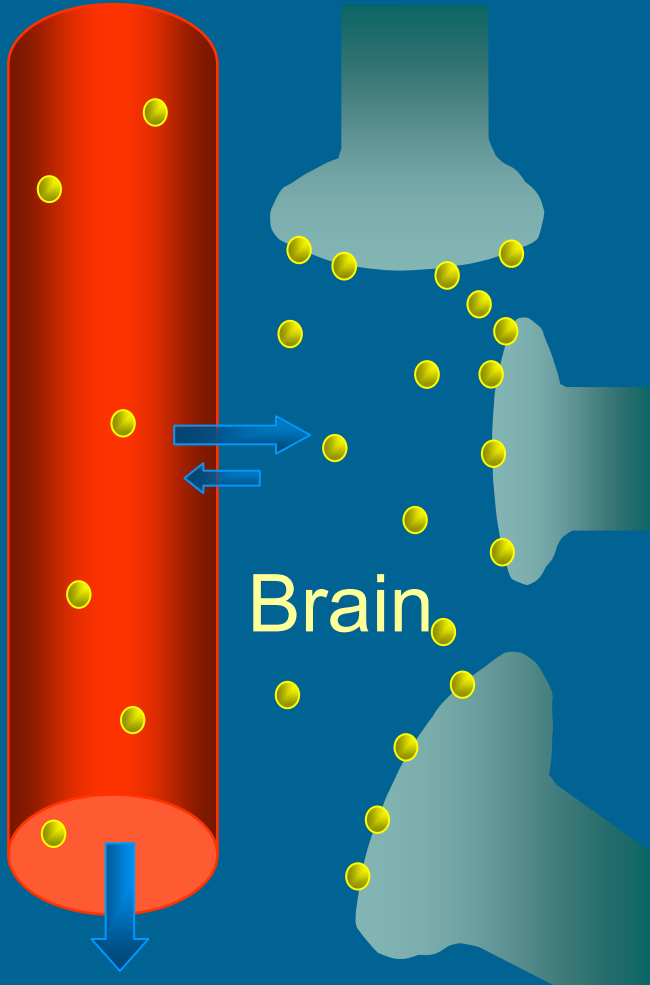
Conclusions for Disulfiram

- ▶ **Disulfiram increases cocaine-free urines more than placebo (55% vs 40%)**
- ▶ **Individuals with genetically lower plasma DBH levels (CT and TT genotypes at -1021C>T) showed the best response to disulfiram.**
- ▶ **Mechanism may be reduced craving, reduced withdrawal and increased cocaine-induced dysphoria**

Immunotherapy and Vaccines for Cocaine Dependence

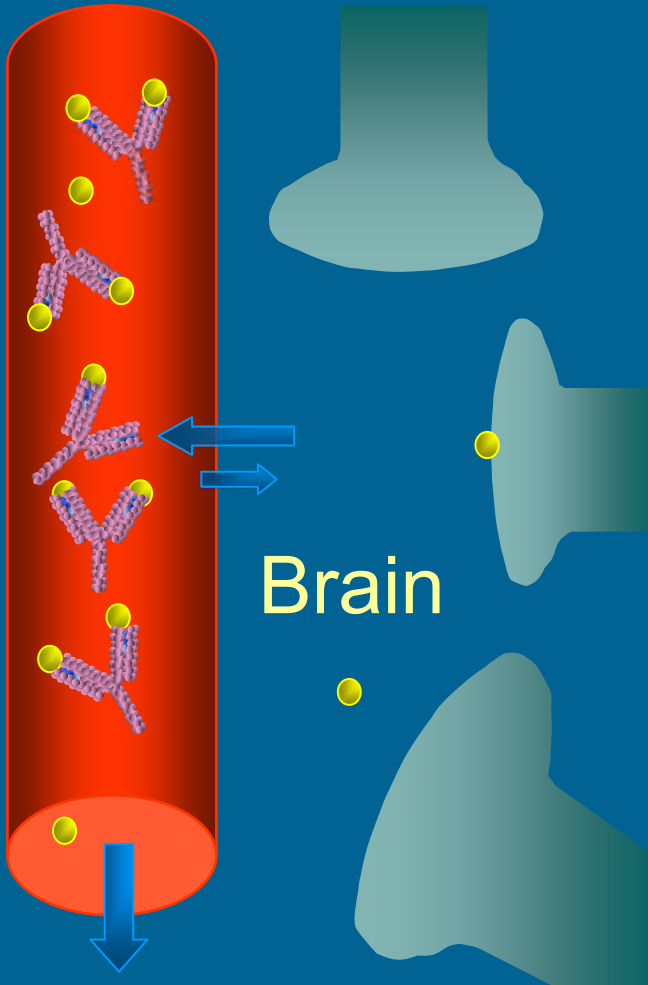
Drugs of abuse easily enter the brain

Capillary
Blood Flow

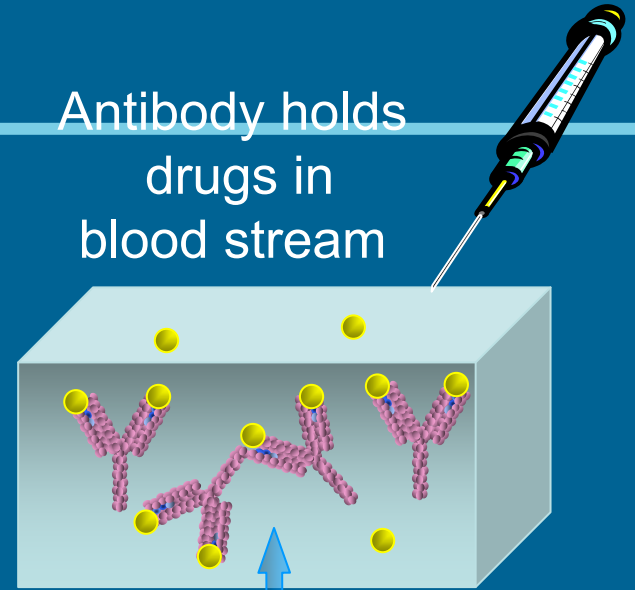


Antibodies can reduce brain concentrations

Capillary
Blood Flow



Antibody holds
drugs in
blood stream

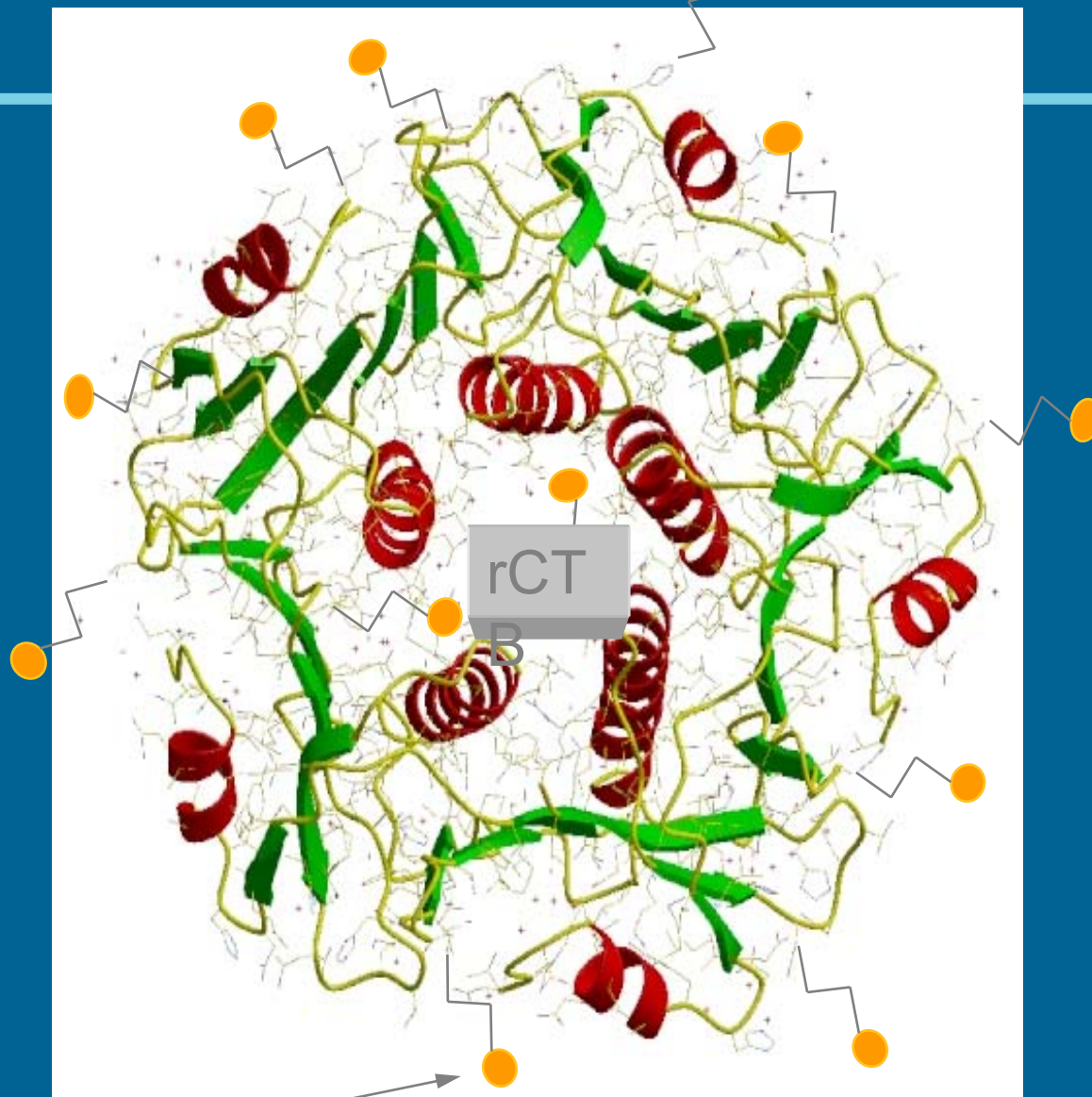




Cocaine Vaccine: What is it?

- ▶ **Active immunisation**
- ▶ **Hapten: Cocaine derivative**
- ▶ **Carrier protein: Cholera toxin B (rCTB)**
- ▶ **Aluminium hydroxide adjuvant**

Cocaine bound to Cholera toxin



cocaine derivative

Effects of cocaine vaccine in animals

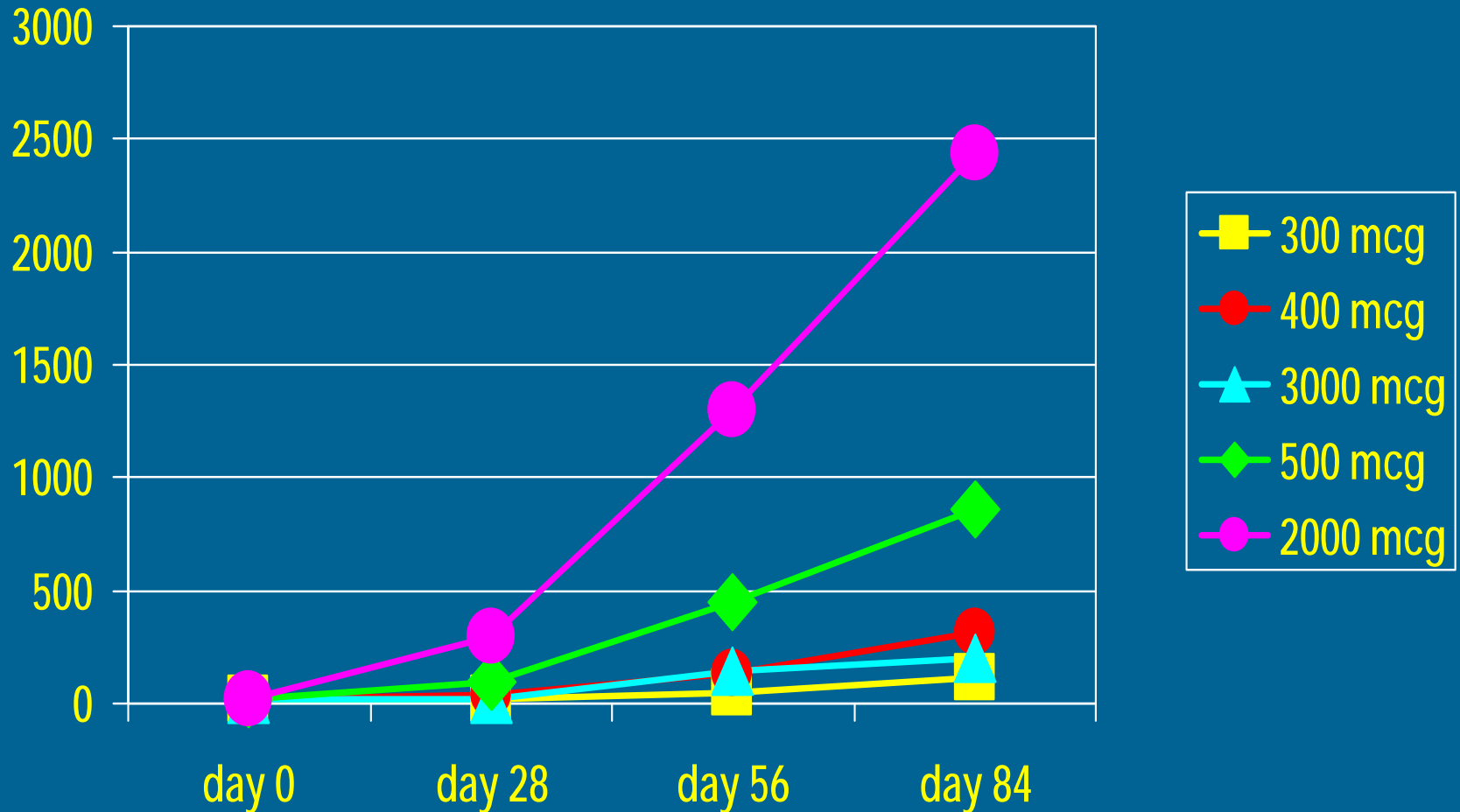
- ▶ **Vaccine generated antibodies can bind modest amounts of injected cocaine**
- ▶ **NO animal toxicity. Even at several times a clinically relevant dose**
- ▶ **Vaccine decreased cocaine self administration (SA) in rodents**

Safety of Vaccine & Cocaine Antibodies in Humans

- ▶ **Safety: no major adverse events: year FU**
- ▶ **Injection events: temperature elevations (minimal), headache (10%), sore throat (6%)**
- ▶ **Rise in antibody significant after third dose at week 4 and peaks after fifth (12 wk) dose.**
- ▶ **Decline in antibody levels from peak evident by four months after initial vaccination and drops to undetectable after 9-12 months**

Cocaine Antibody (AB) rise with 3 months of dosing

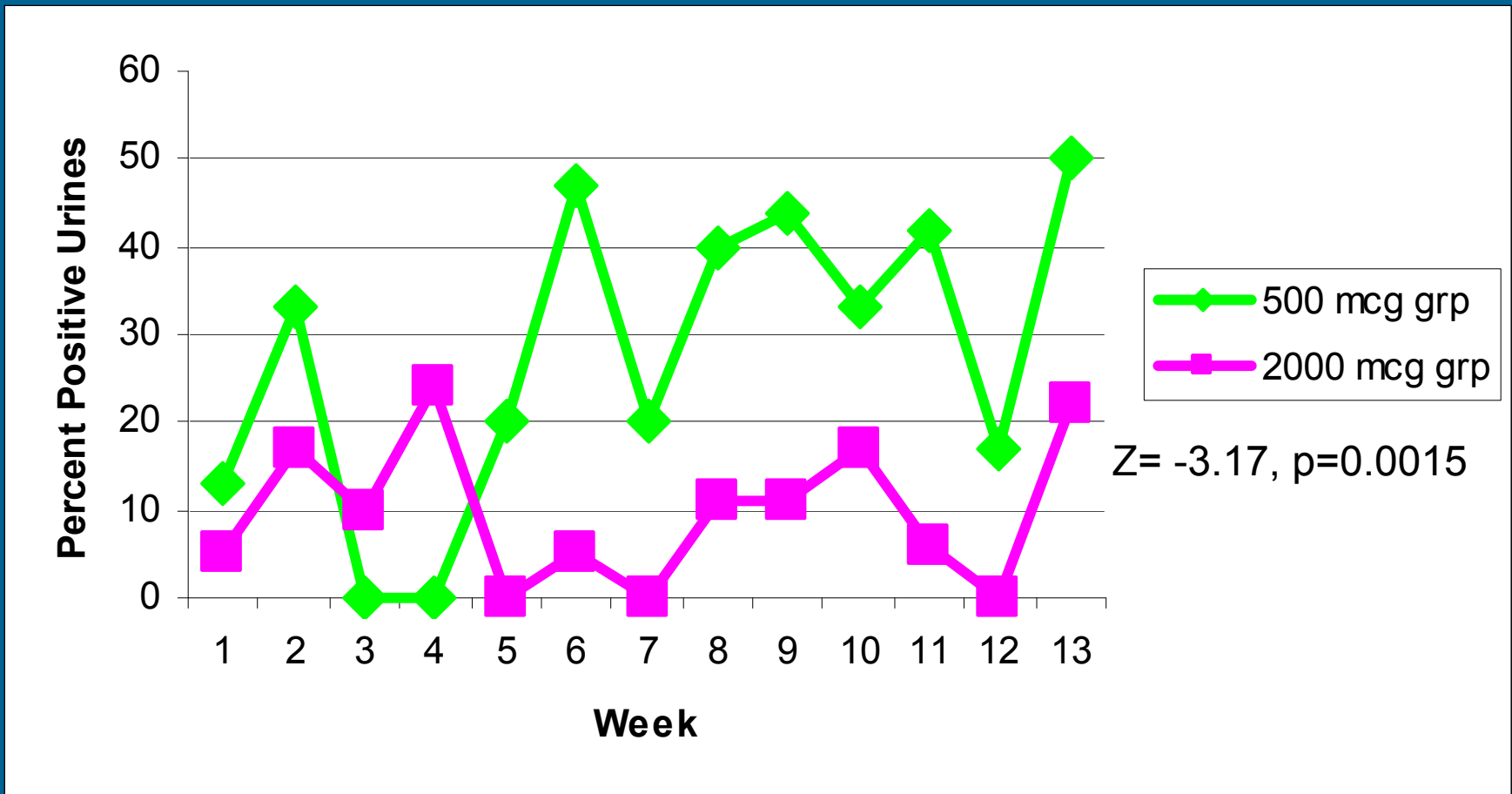
Five dosing schedules: 3 to 5 doses, 100, 400, 1000 mcg





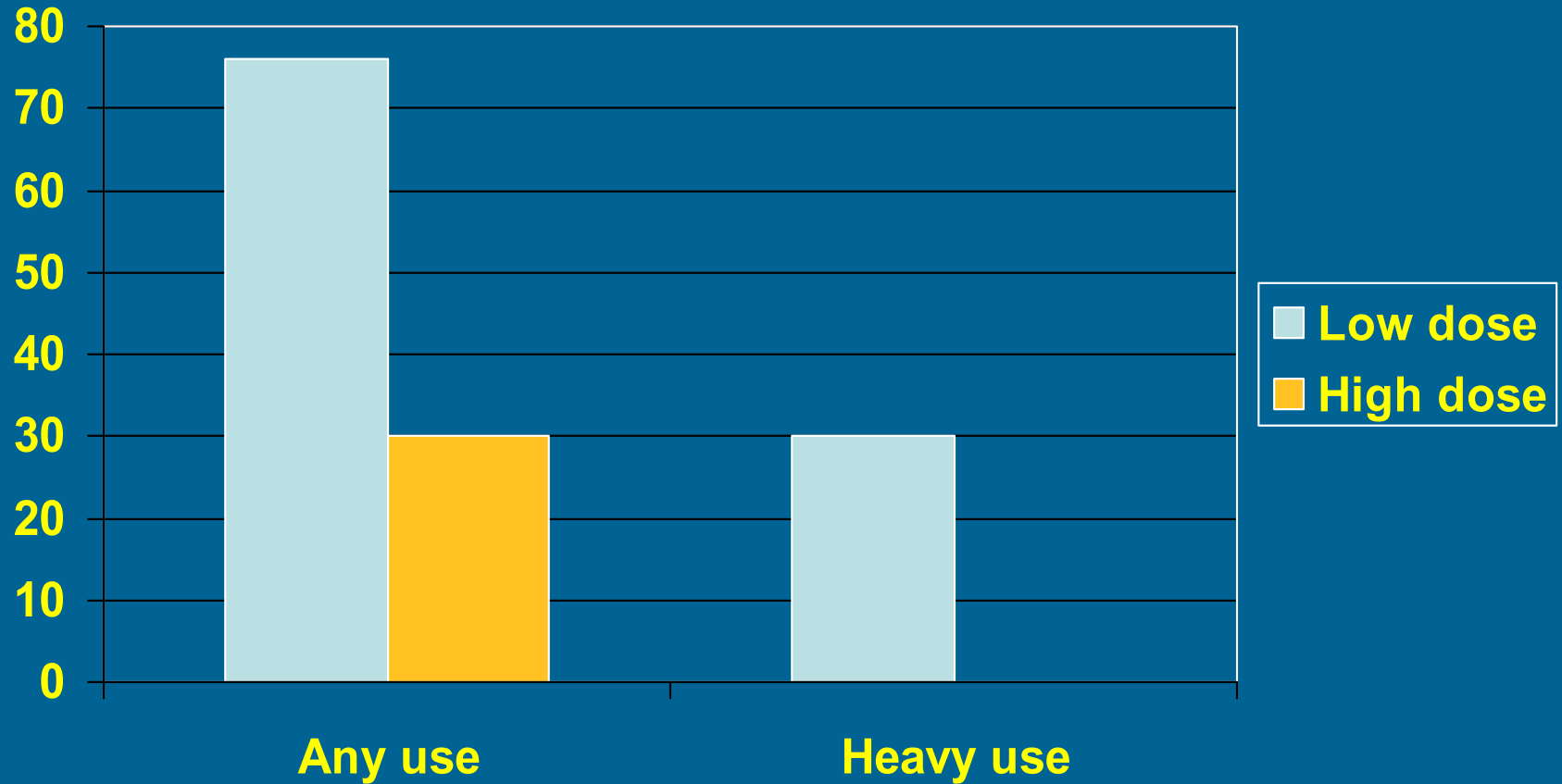
Fewer cocaine urines at higher Vaccine Dose

Vaccination makes antibodies by Week 4 (n=11)



Less relapse to cocaine use with high vs low dose vaccination

(Percent of patients relapsing in each dosage group)



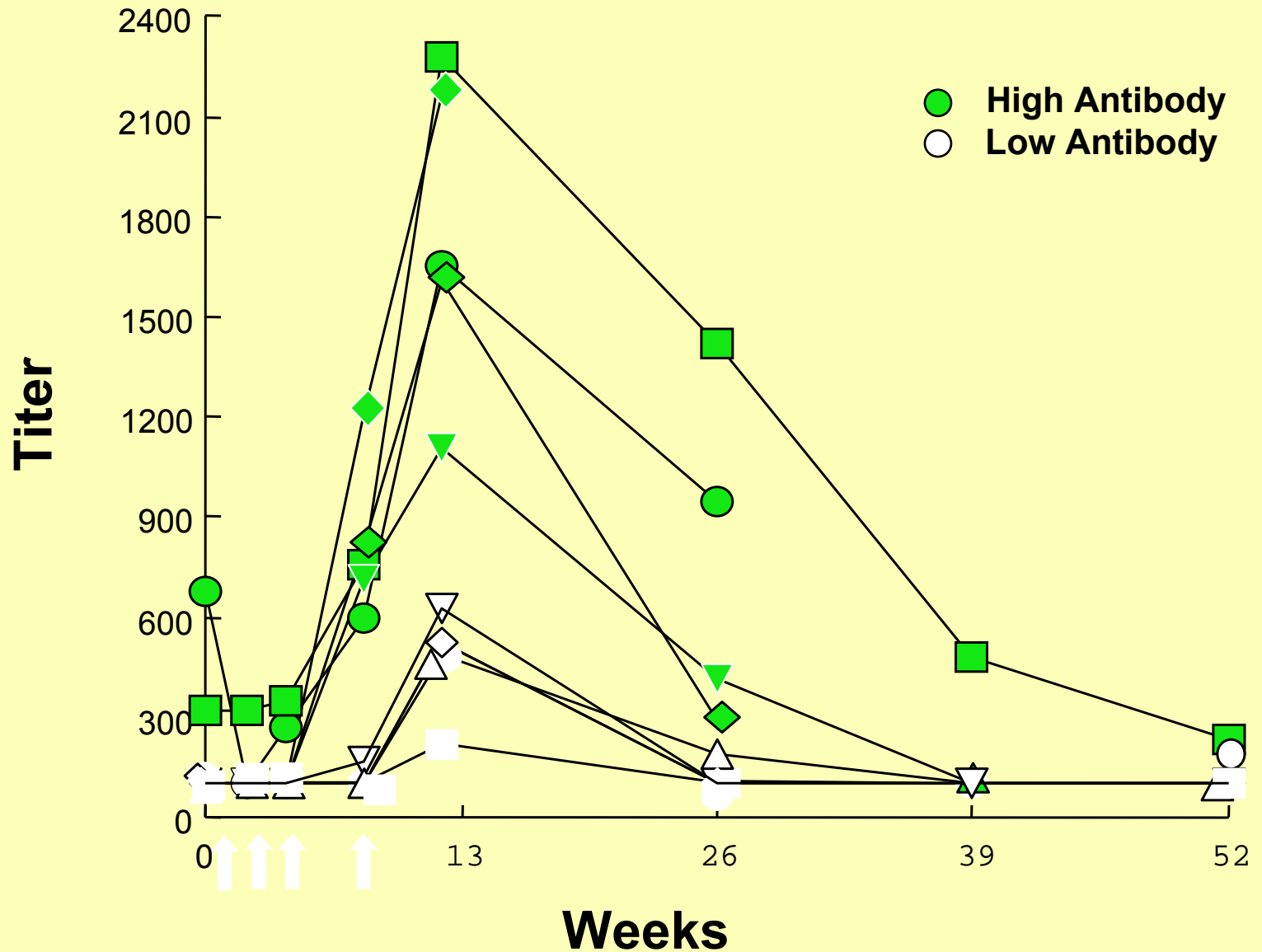


Human Laboratory Study

Meg Haney – Columbia University

- Determine direct relationship between plasma antibody levels and cocaine's subjective and cardiovascular effects
- Administer smoked cocaine (0, 25, 50 mg) to non-treatment seeking, cocaine-dependent research volunteers pre-vaccine and for 12 weeks post-vaccine

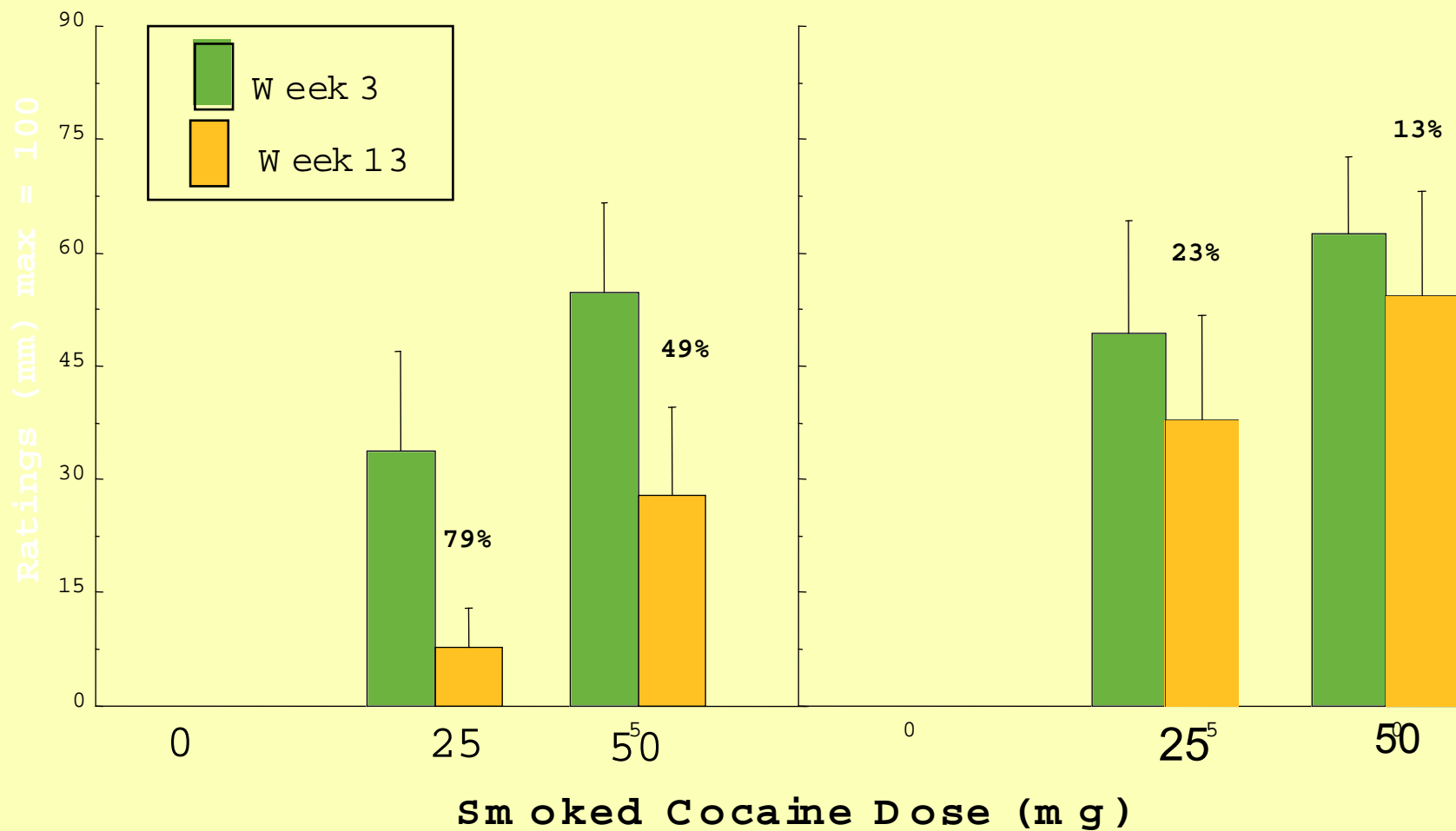
Plasma Antibody (n=10)



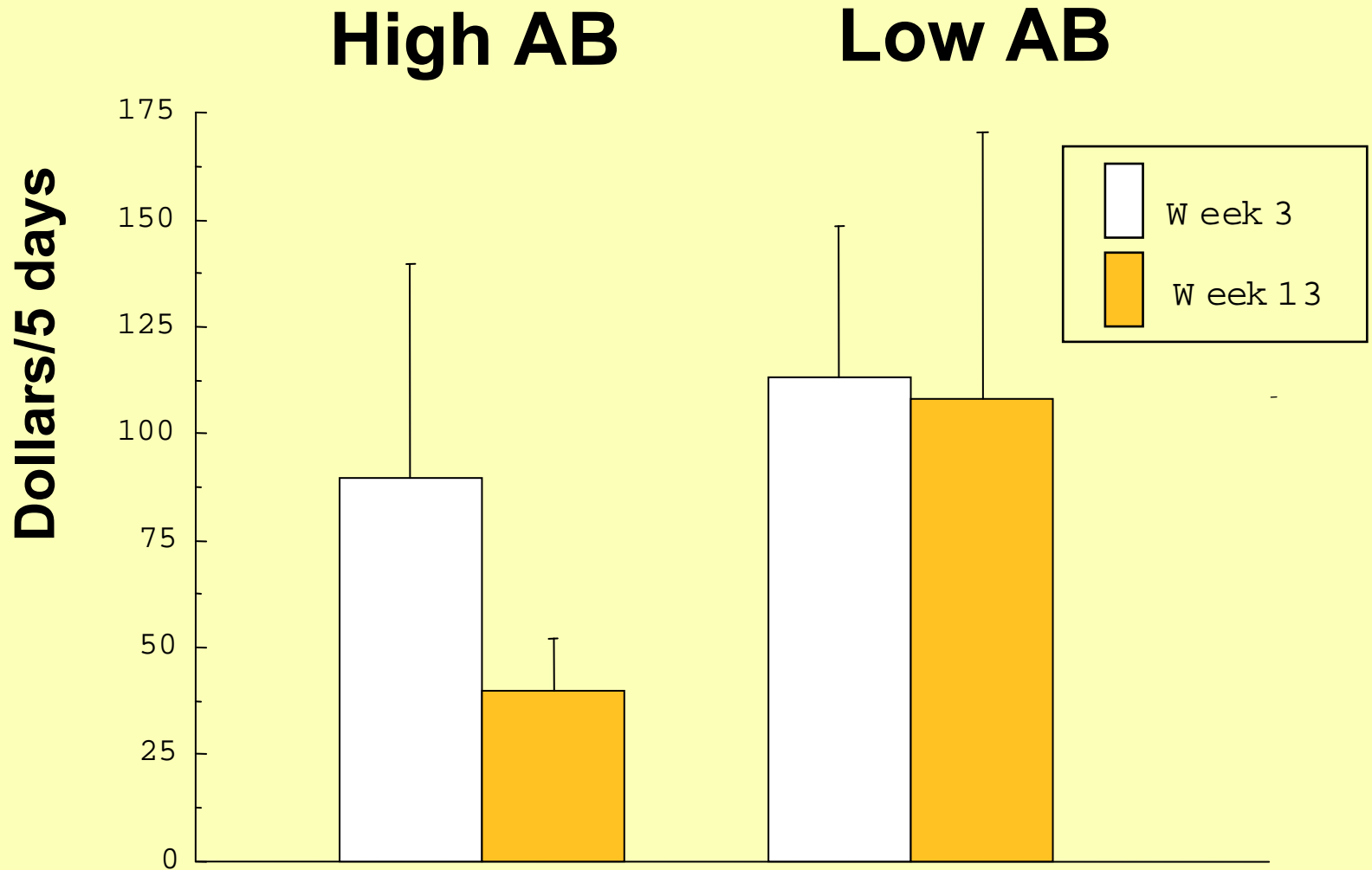
Good Drug Effect

High AB

Low AB



Self-reported Cocaine Use



Conclusions:

Human cocaine administration

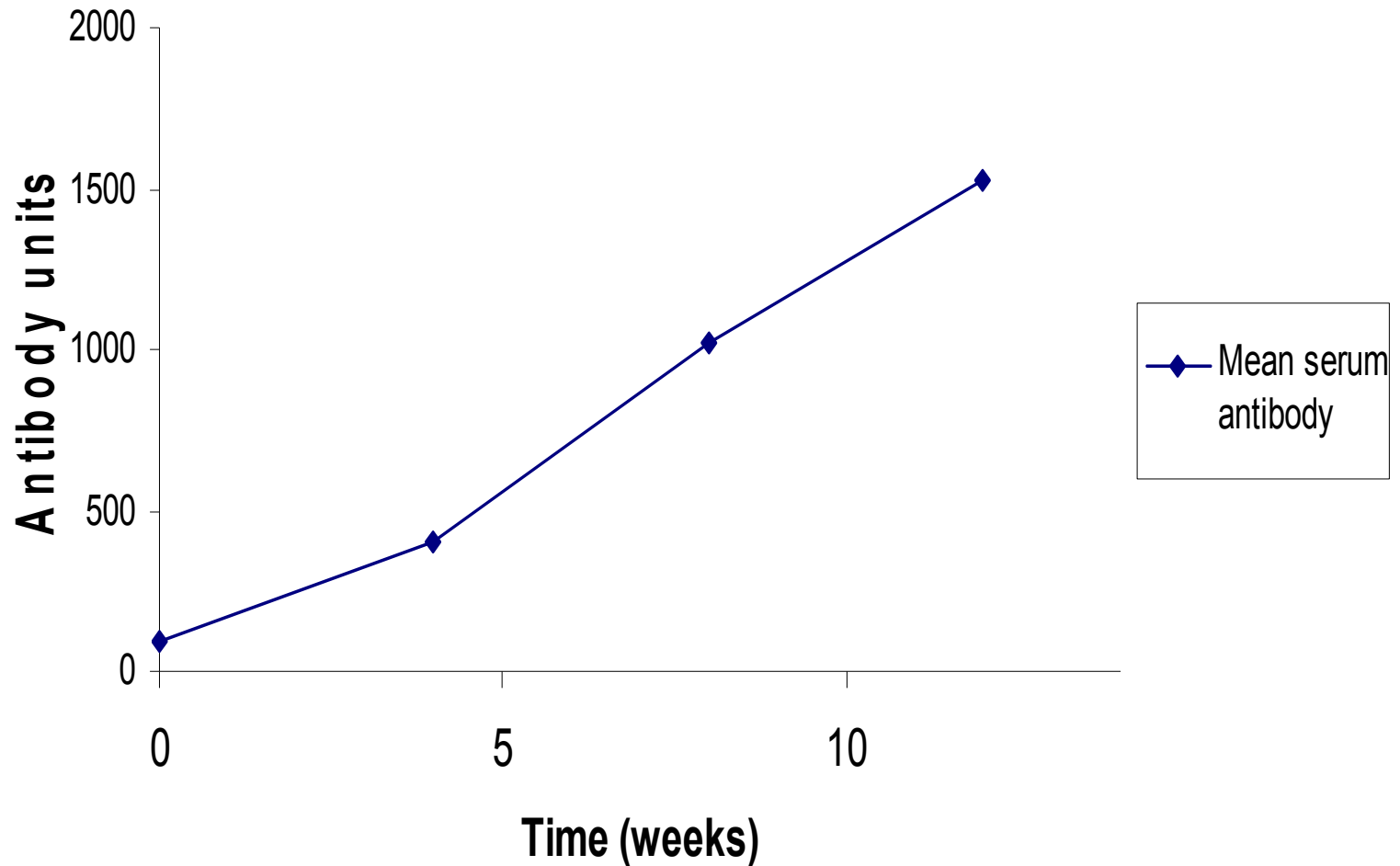
- **Current results encouraging:**
 - **Vaccine well tolerated; safe in combination with cocaine**
 - **Reliable antibody production: 50% volunteers**
 - **Those who produced antibody showed a substantial decrease in cocaine intoxication**
- **Outpatient cocaine use reduced in those producing high antibody levels**

Outpatient cocaine vaccine RCT in methadone patients

Cocaine Vaccine Study Design (methadone patients)

- ▶ **Double blind placebo-controlled randomised clinical trial**
- ▶ **114 methadone-maintained cocaine dependent patients**
- ▶ **Vaccinated with 5 x 360 µg TA-CD over 12 weeks**
- ▶ **Urine toxicology 3x/week**
- ▶ **Serum antibody levels assessed at 0, 4, 8, 12 weeks**

Mean serum antibody levels (0-12 weeks)



Promise of Stimulant Pharmacotherapies

- ▶ **Disulfiram reduces stimulant abuse perhaps by increasing dopamine available in brain and reducing norepinephrine**
- ▶ **Pharmacogenetic matching of patients to disulfiram treatment shows promise**
- ▶ **Newer treatments include cocaine vaccine with efficacy support from human cocaine administration and recent placebo RCT**