

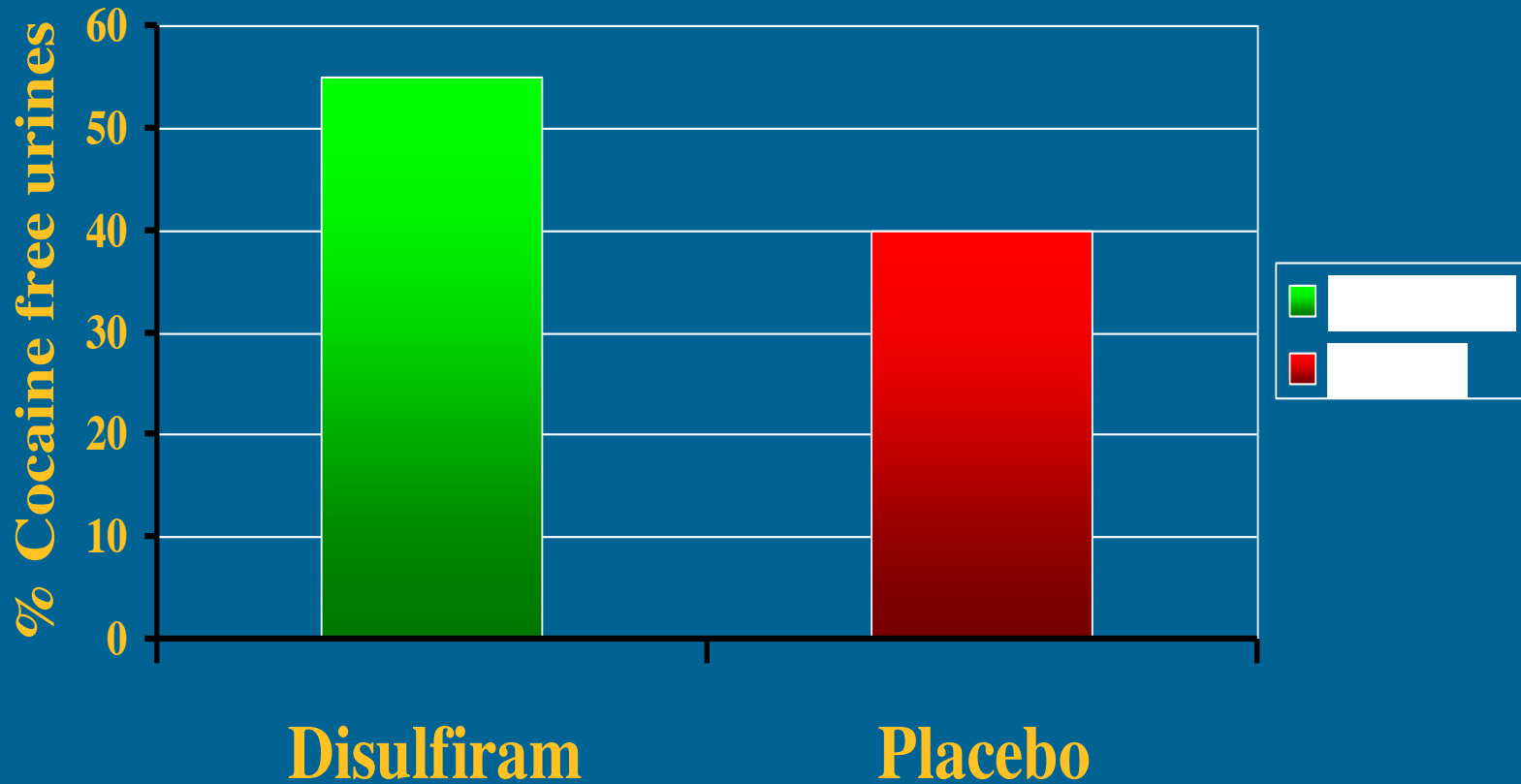
Advances in the Pharmacotherapy of Stimulant Dependence: From A (Antabuse) to Z (ZenovaVac)

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Outline of Presentation

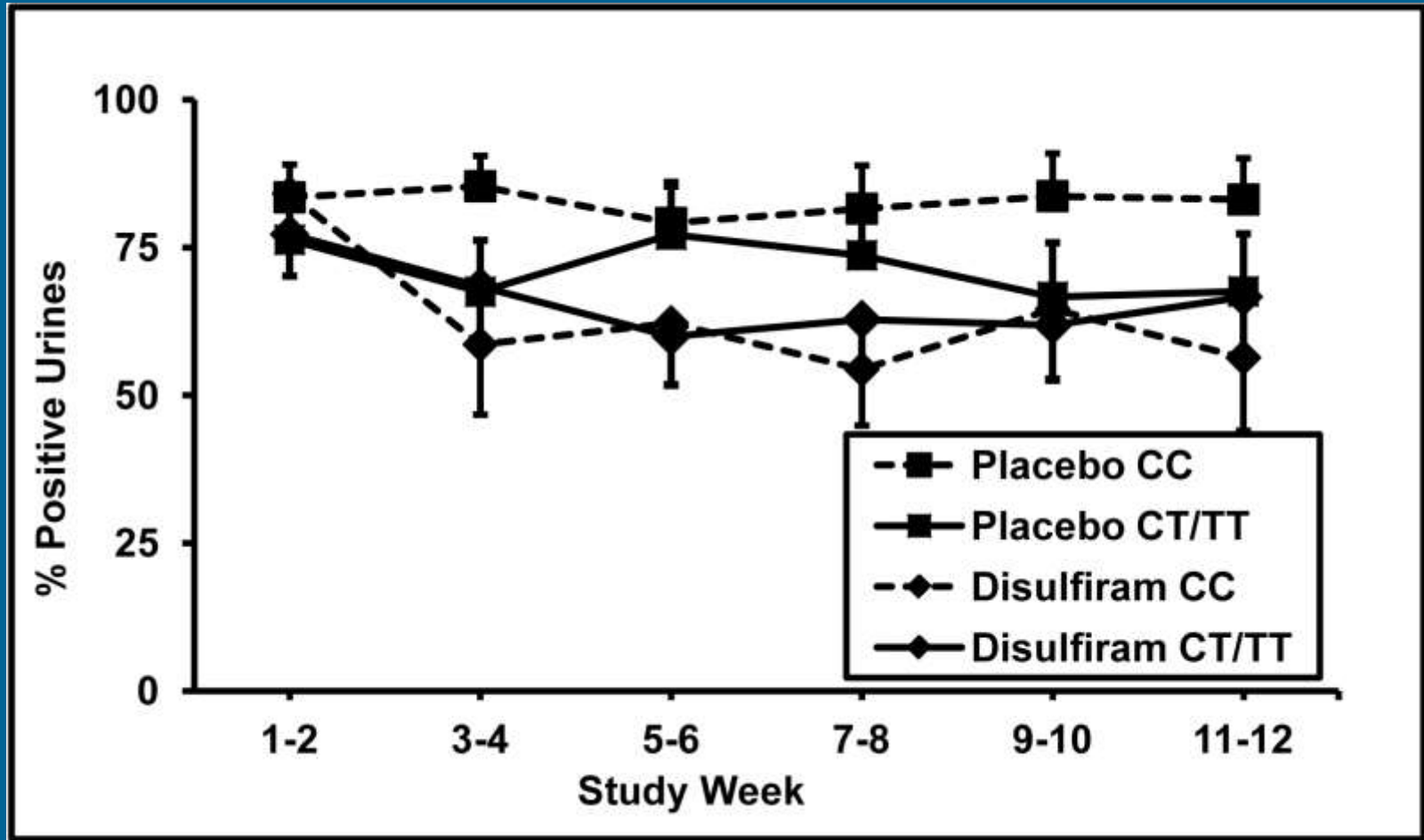
- ▶ **Disulfiram – alcohol “antagonist”**
 - Dopamine & pharmacogenetics
- ▶ **Adrenergic blockers & withdrawal**
- ▶ **Glutamate enhancers & learning**
- ▶ **Cocaine vaccine by Xenova**
 - Preventing cocaine from getting to the brain

Disulfiram increases Cocaine-Free Urines in over 600 Outpatients (7 Studies - $P < 0.001$)

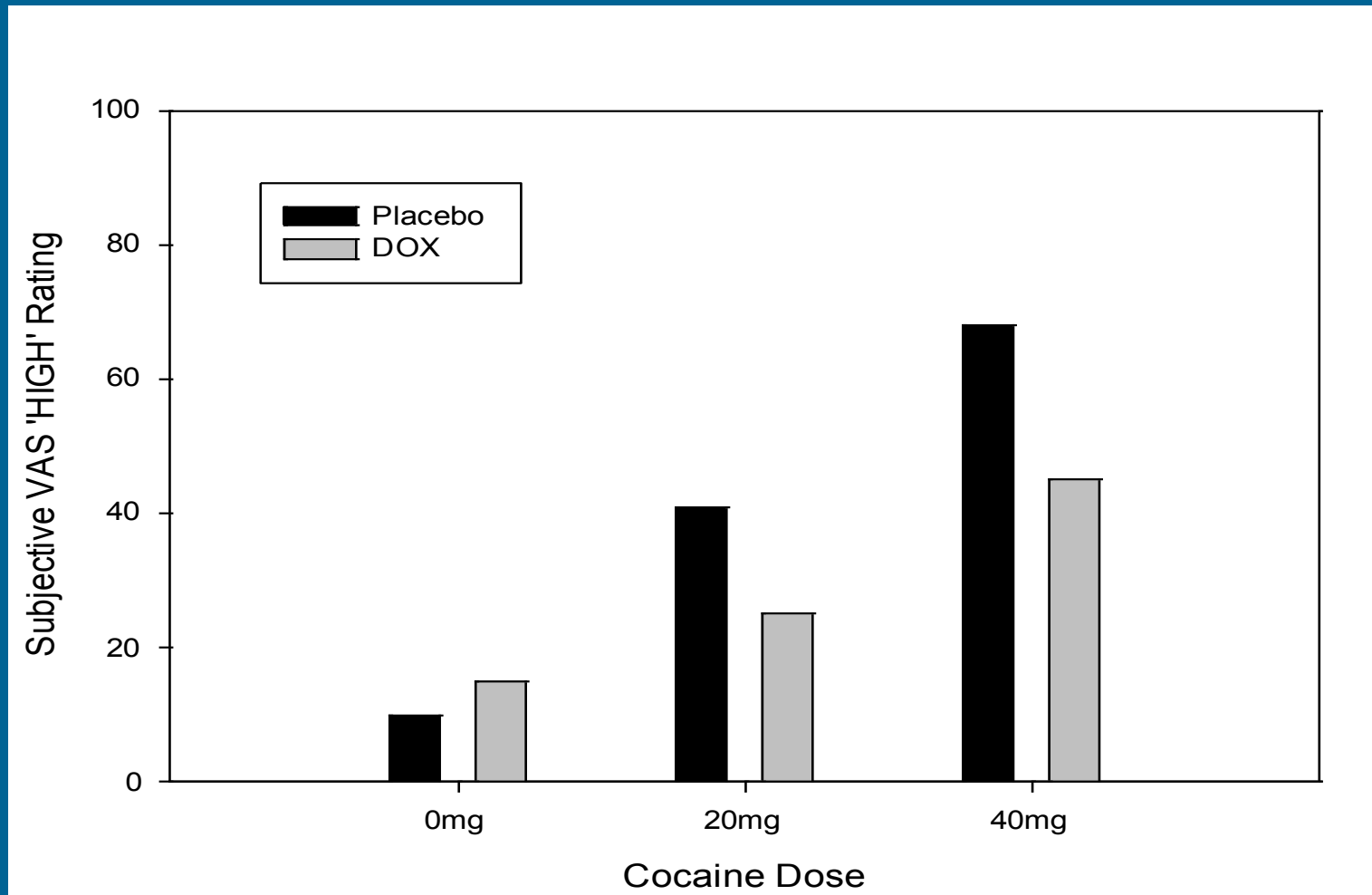


Meta average = 55% vs 40%

Pharmacogenetics of DBH and Disulfiram for cocaine abuse treatment (Kosten 2012)

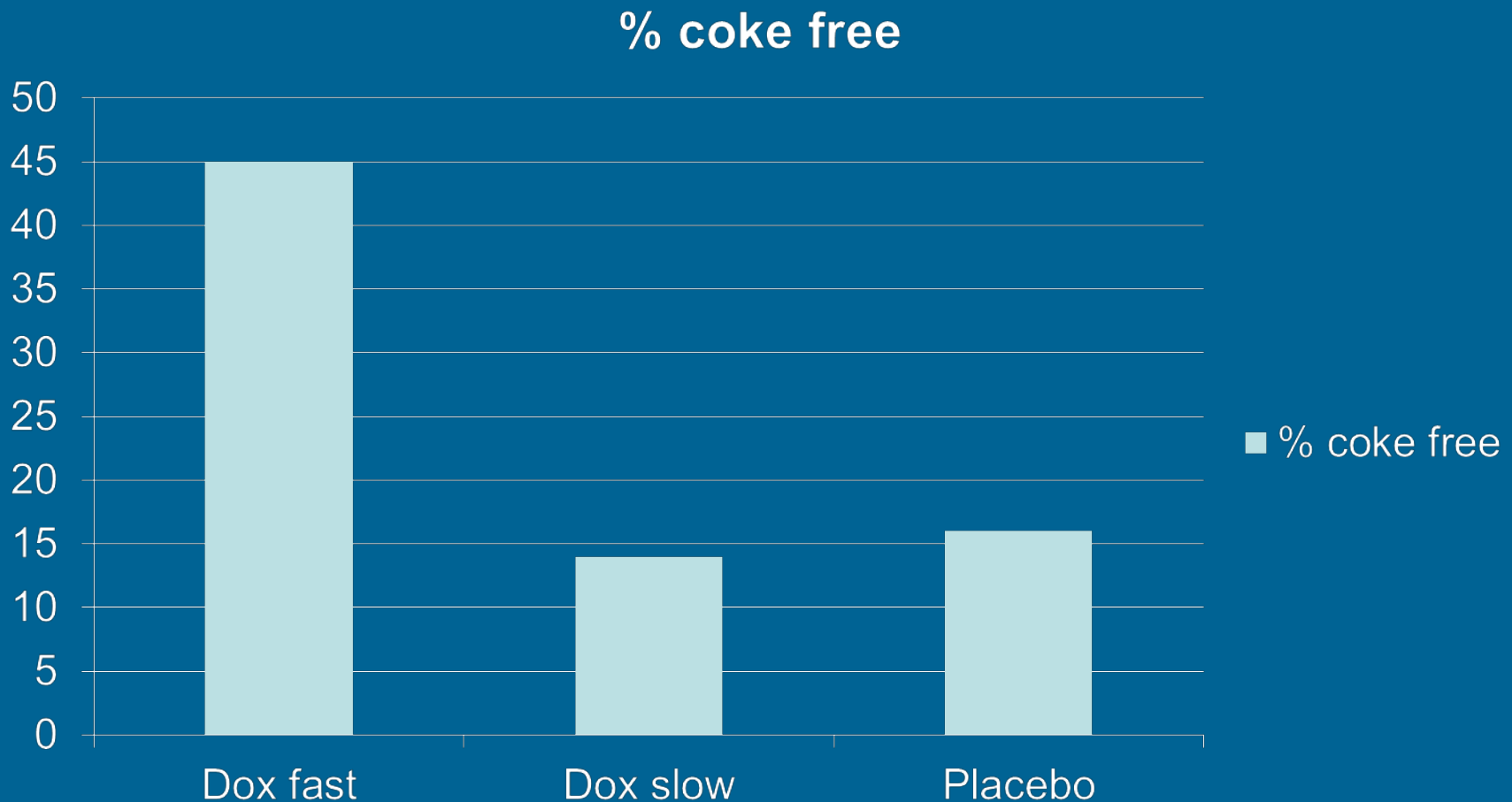


Effect of Doxazosin on VAS 'HIGH' rating 5 minutes post-infusion (IV) of cocaine (N=7)



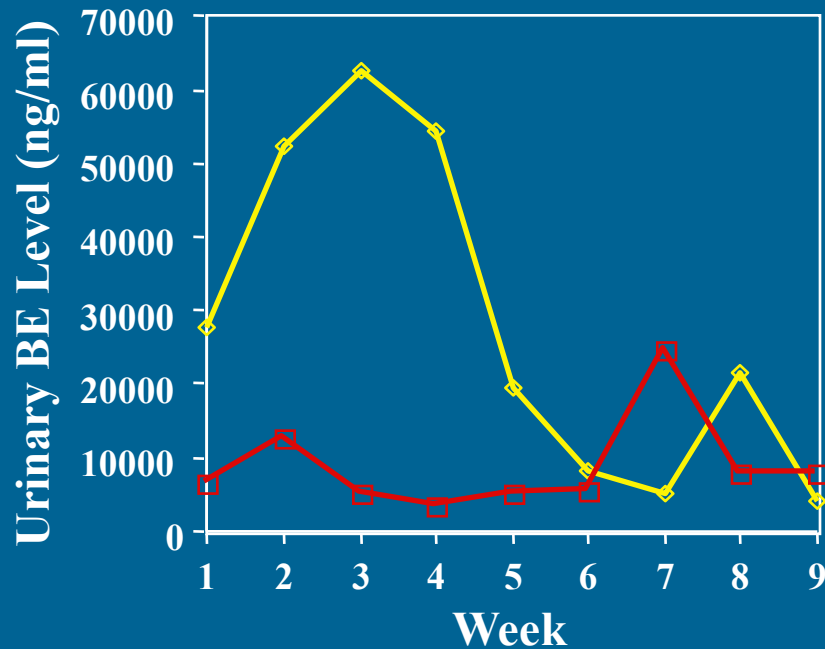
Doxazosin and cocaine free urines

12 week outpatient RCT (n=35) (Shorter 2012)



Propranolol Reduced Cocaine Use in high withdrawal severity only (n=108)

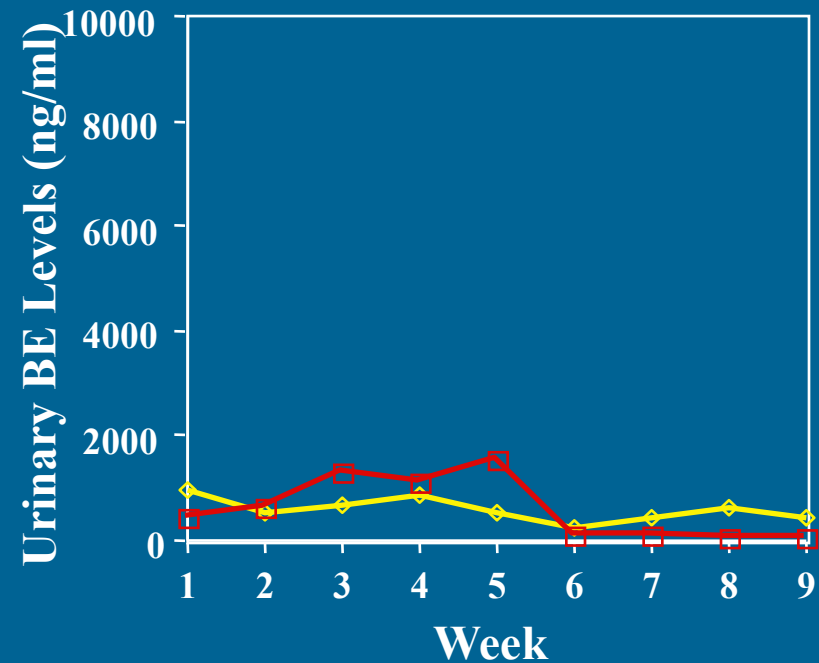
High CSSA



—■— Propranolol, High CSSA

—◇— Placebo, High CSSA

Low CSSA



—■— Propranolol, Low CSSA

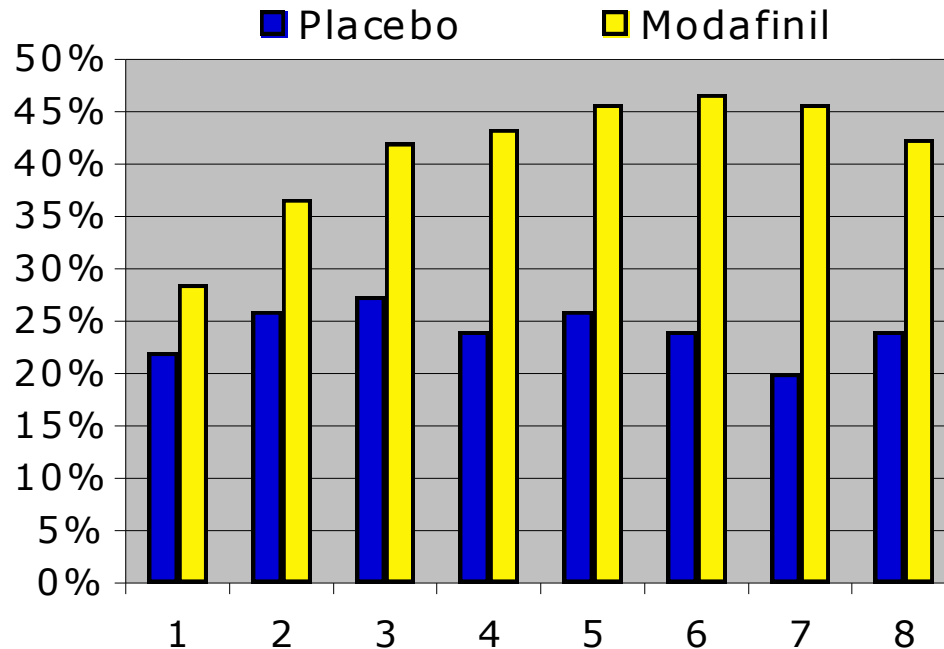
—◇— Placebo, Low CSSA

Glutamate & GABA agonists

Modafinil is glutamate-enhancing and has other unknown actions. It reduces cocaine use perhaps by enhancing ability to learn new “stopping” behaviors.

N-Acetylcysteine may also reduce cocaine craving/withdrawal symptoms.

Modafinil % BE-Free Urines (Dackis et al 2004) (n=62)

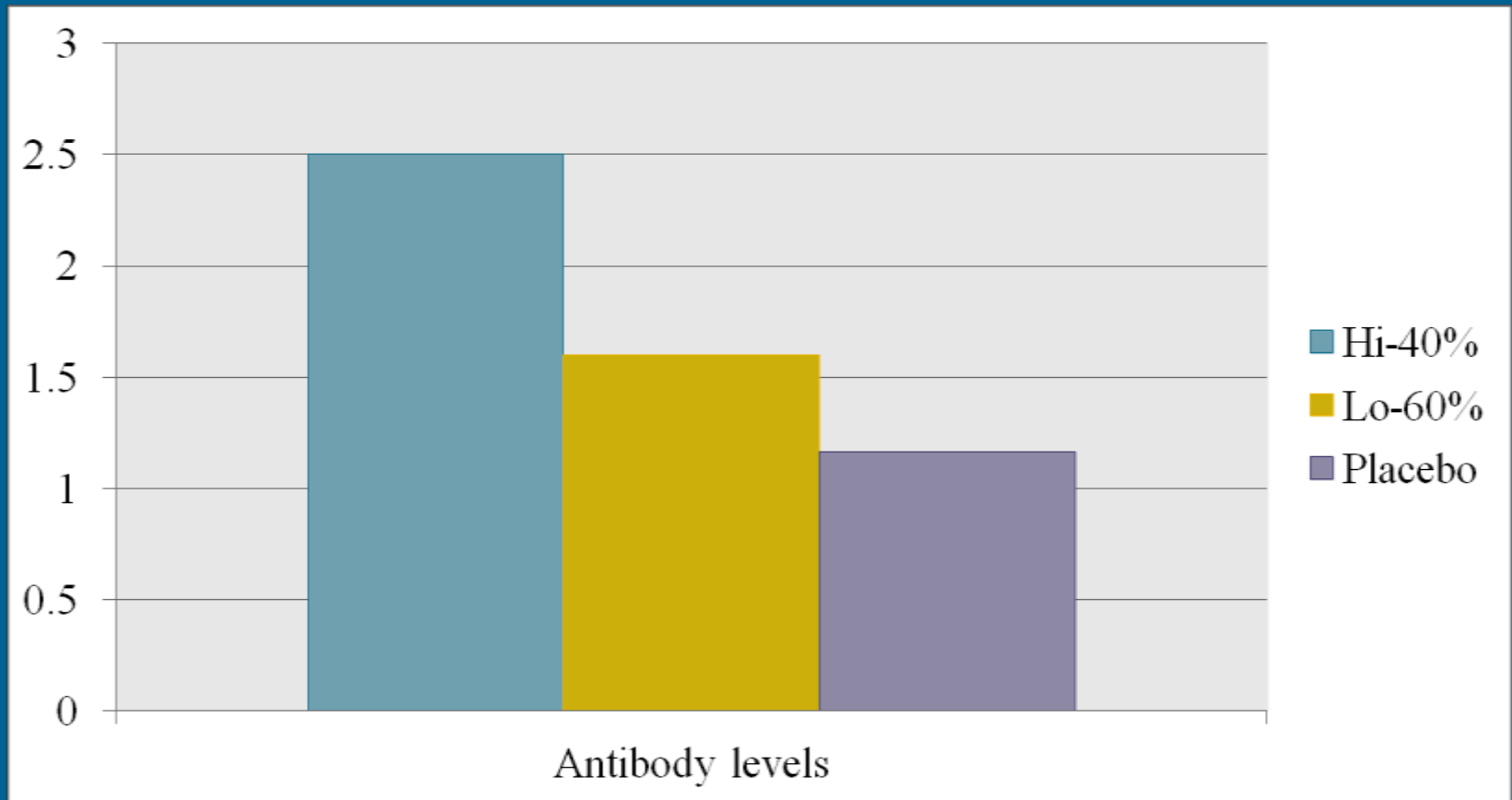


Longitudinal GEE models showed a significant main effect for cocaine abstinence in the modafinil group (odds ratio = 2.41, 95% CI 1.09-5.31, $p = 0.03$)

Anti-Cocaine Vaccine

- ▶ **Vaccine shows antibody production in animals**
- ▶ **Vaccine generated antibodies bind injected cocaine**
- ▶ **Vaccine decreased cocaine self-administration in rodents**
- ▶ **Produces substantial amount of antibodies in patients after 3-5 vaccinations**

Cocaine Vaccine Proportion of Cocaine-free Urines: Weeks 9-17 vs Baseline: Hi vs. Lo antibody vs. Placebo



Promise of Stimulant Pharmacotherapies

- ▶ **Disulfiram reduces stimulant abuse perhaps by increasing dopamine available in brain and reducing norepinephrine (like doxazosin & propranolol)**
- ▶ **Pharmacogenetic matching of patients to disulfiram treatment shows promise**
- ▶ **Sustained treatments such as the cocaine vaccine offer great promise**
- ▶ **Newer treatments include GABA agonists like topiramate, baclofen, vigabatrin and the narcolepsy treatment – modafinil, and the indirect glutamate agonist N-Acetylcysteine**