Cocaine and Methamphetamine: Pharmacology to Pipeline Treatments

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Disclosure
Thomas Kosten, MD

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Objectives #1

The learner should be more competent in the diagnosis and treatment of stimulant addiction:

1. Recognize the signs and symptoms of dependence and withdrawal from the overuse of methamphetamine, amphetamines, cocaine, and crack cocaine, and dextroamphetamine + amphetamine (such as Adderall).

Objectives #2

2. Understand the genetics behind abuse and addiction of these substances, as well as the psychosocial pre- dispositions to this behavior.
3. Understand any treatment issues specific to this form of addiction.
4. Understand the epidemiology, both analytic and descriptive of stimulant addiction.
5. Be aware of and sensitive to specific cultural and linguistic differences in patients who abuse and become addicted to stimulants.

References

- Kosten TR, et al. *Cocaine and Methamphetamine Dependence*. American Psychiatric Publishing. Washington, DC, 2012.
- Kosten TR(Pharmacology editor), Ries, Fiellin, Miller, Saitz (General Editors). *Principles of Addiction Medicine, 5th edition.* Lippincott Williams & Wilkins, April 2014. Washington, DC: American Society of Addiction Medicine.

Question #1

To detect cocaine abuse a urine toxicology can be useful and typically is positive if the urine contains:

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B. benzoylecognine > 300 ng/ml
C. norcocaine < 60 ng/ml
D. cocaine < 60 ng/ml
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Question #2

Stimulant dependence can produce brain changes most typically resembling which disease:

A. Alzheimers
B. Hemmorhagic Stroke
C. Parkinsons
D. Picks
E. Cerebellar ataxia

Question #3

In the NESARC study the highest rate of dysthymia is comorbid with which of the following drugs:

A. stimulants
B. hallucinogens
C. marijuana
D. opiates
E. sedatives

Question #4

The pharmacogenetics of cocaine is most likely to involve disulfiram and which of the following genes:

A. dopamine beta hydroxylase
B. aldehyde dehydroxylase
C. CYP450 2A6
D. Monoamine oxidase
E. glutathione hydrolase

Epidemiology

- Cocaine and methamphetamine abuse and dependence relatively stable last 5 years
- "Bath salts" = mephedrone & methylone are the current epidemic & remain "legal"
- Prescription stimulants – amphetamines- are widely used in adolescents typically at levels below dependence

Cocaine: Epidemiology
Prevalence of Cocaine Use (in >12 y.o.)

- 5 million (0.7%) Americans report cocaine use within the past month which is trending downwards from 1% in 2005-2006 (NSDUH 2010)
- 1.1 million (0.6%) Americans met criteria for cocaine abuse or dependence in 2009 (NSDUH 2009)
- Most common in 18-25 age group
- 699,000 received treatment for cocaine in the past year (NSDUH 2010)

Prevalence of Methamphetamine Use
2010 National Household Survey on Drug Abuse

- 1 million (0.4%) reported non-medical use of stimulants (not including cocaine) in the last month
- 0.1% report using methamphetamine within the last month- a number that reflects a downward trend from 2002-6 when it was 0.3%
- Most common in 18-25 yo age group
- 343,000 received treatment for stimulants (not including cocaine) in the past year (NSDUH 2010)

Female Methamphetamine Users

- Female youth are more likely to use methamphetamine than their male counterparts
- Report initial use stems from desire to lose weight or cope with depression
- More likely to report previous physical and sexual abuse
- More likely to suffer from mood disorders and suicidality
- Nearly as many women enter treatment for methamphetamine dependency as men

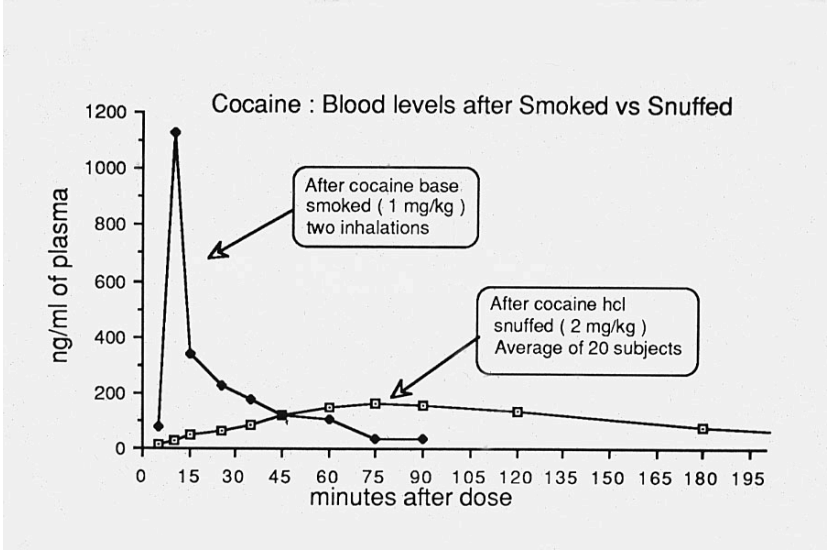
Cultural and psychosocial pre-dispositions

- Cultural factors most evident for cocaine in Columbia and Peru with natives in Andes not abusing cocaine until smoking started
- Amphetamine tends to have fewer African American users and high use in Far East and West coast
- Psychosocial factors: current endemic use mostly among economically disadvantaged

Forms of stimulants abused, how ingestion route influences abuse potential

- Abuse potential follows order of:
- Oral < nasal (snort) < smoked < intravenous
- "Crack" is simply smoked cocaine already converted to the free base
- Oral stimulants generally not reinforcing for getting a "high," need faster onset

Kinetics of Smoked Cocaine



R.T. Jones, 1983

Cocaine & MA: Subjective and Behavioral Effects

- Onset
  - Intranasal effects within minutes (5-15)
  - Smoked effects within seconds
- Acute Effects
  - Euphoria, hyperactivity (motoric & verbal), hypersexuality initially
  - Insomnia, anorexia.
  - Persecutory delusions (paranoia) and hallucinosis (aud, vis, & tactile), agitation
  - Confusion rare except in very high doses when delirium can occur
  - Stereotyped movements may occur (teeth grinding, skin picking)
- Chronic use produces tolerance to euphoria, positive effects decrease, agitation & anxiety increase

Cocaine & MA Effects: Physiological

- Sympathomimetic effects
  - Elevated
    - BP
    - HR
    - Temp
- At high doses:
  - Hyperthermia
  - Rigidity
  - Seizures

Screening tools and how they inform treatment

- ASI – Addiction Severity Index (many items)
- DAST – Drug abuse screening test (few items)
- Urine toxicology – 3 day window
- Sweat patch – several days to a week
- Hair analysis – up to several months, not quantitative, indicates any use
- Saliva test developing – several hours after use

DSM 5 (2013)

- Abuse no longer exists, only dependence
- Same basic criteria as DSM IV
- Adding Craving to dependence syndrome
- Require only 2 criteria (not 3) for mild dependence
- Continuum of dependence from mild to severe
- Look over DSM IV list – all drugs the same

Stimulant Intoxication

- Paranoia and suicidality – time limited, serious
- Amphetamine psychosis
- Agitation, violence due to paranoia
- "Crash" – a few hours, then simply sleep
- Urine toxicology critical – >300 ng/ml benzoylecognine
- Benzodiazepine treatment, antipsychotics can induce neuroleptic malignant syndrome (hyperthermia and death)

Stimulant Withdrawal Symptoms 2-7 days of "Crash"

- strong cravings,
- fatigue, exhaustion
- anxiety,
- irritability,
- paranoid and suicidal
- unable to feel normal pleasures.

Medical Complications of Cocaine & MA

- Complications reflect primarily:
  - excessive CNS stimulation
  - vasoconstriction
- Cardiac
  - Myocardial ischemia/infarct
  - Arrhythmias
  - Myocarditis
- Central Nervous System
  - Hyperpyrexia
  - Seizures
  - Cerebral infarct
  - Cerebral hemorrhage

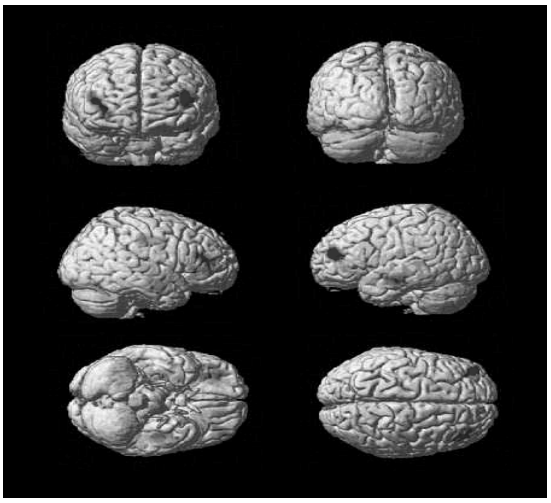
Benowitz 1993; Boghdadi & Henning 1997

Cardiovascular Effects of Cocaine

- Vasoconstriction leads to 30% blood flow reduction during human cocaine administration and cortex flow most reduced
- Chronic cerebral perfusion defects are evident even after sustained abstinence
- Platelet adherence and vasoconstriction together may contribute to the sustained perfusion defects
- Reduced cognitive functioning correlates with defects in perfusion

Hypoperfusion in High vs Low platelet aggregation groups:

dorso-lateral frontal, r insula, r cingulate and l temporal



Affective Disorders and Drug Abuse

High rates of depression

YET

Poor recognition of depression in others

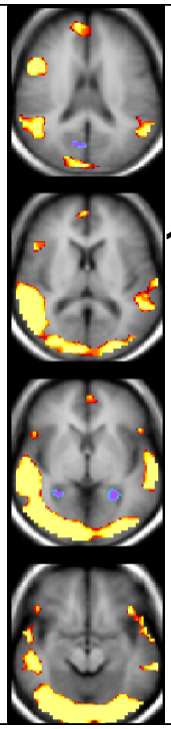
Odds ratios between affective disorders and specific drug use disorders in the NESARC

Comorbid mental disorder	Marijuana	Stimulants	Opioid
Any mood	**3.1**	**4.0**	**5.0**
Major dep	**2.6**	**3.4**	**4.4**
Dysthymia	**3.2**	**4.7**	**4.2**
Bipolar	**5.2**	**5.0**	**6.6**
Mania	**2.9**	**3.0**	**4.3**

NESARC, National Epidemiologic Survey on Alcohol and Related Conditions

Healthy normal people show
substantial brain activation
when watching a video of sad people.

Cocaine abusers do not perceive emotions such as sadness in other people



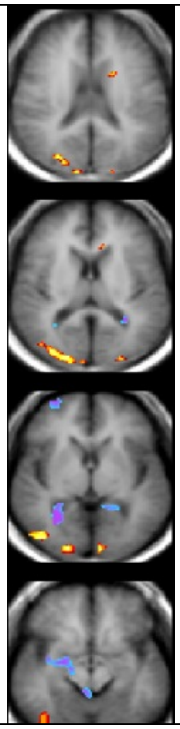
Brain activity during Sad Video

1 **1. Healthy normals**

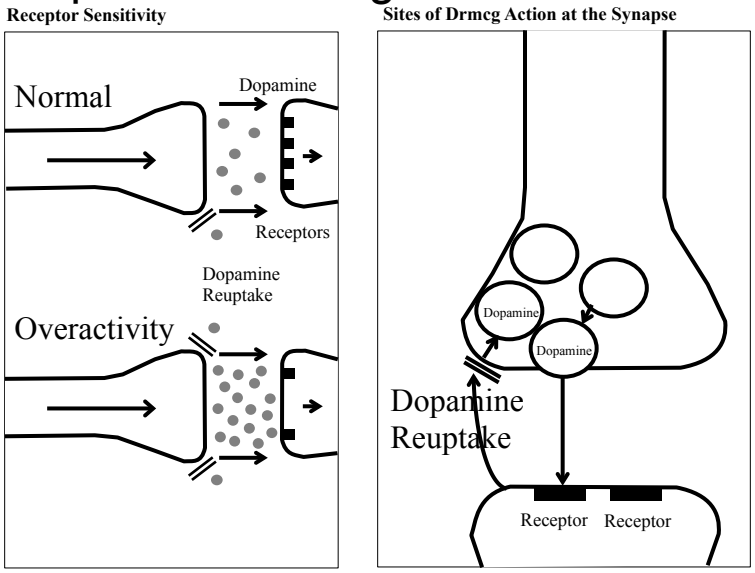
vs

2. Cocaine addicts 2

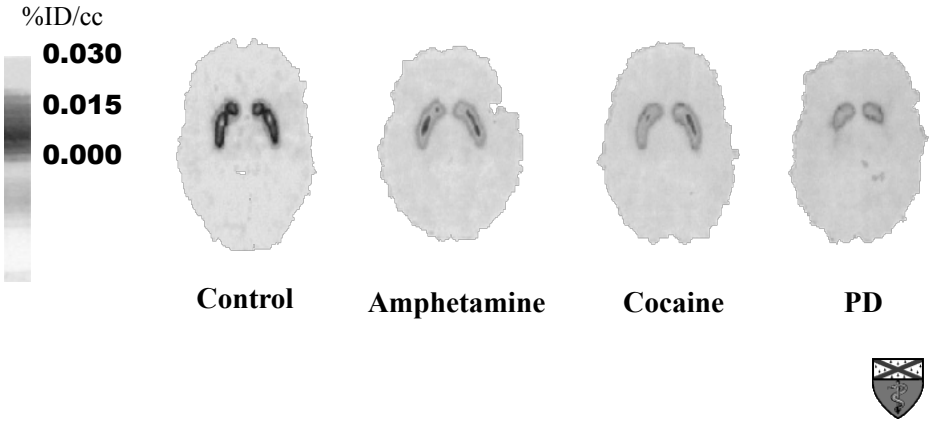
yellow – good blood flow,
blue – poor blood flow



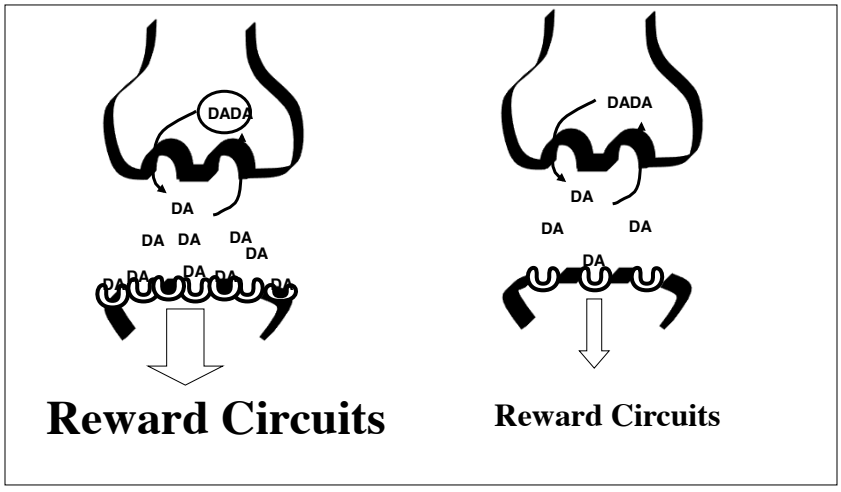
How Cocaine Alters the Brain: Dopamine Damage & Parkinsonism



Parkinson Disease (PD) Brain Abnormalities in Cocaine Abusers



Hypodopaminergic State In Drug Addiction



Non Drug Abuser *Addicted Subject*

Methamphetamine Neurotoxicity

- **History**
  - PCA-related 5HT depletion 1st shown in early 60s
  - more recently shown with MDMA, etc
- **5-HT depletion**
  - rapid decrease in 5HT synthesis
  - persistent in animals $\geq$ 110 days
- **DA depletion**
  - decreased brain DA concentration & DA receptors
  - Persist for over 6 months (human neuroimaging)

Conclusions

Brain abnormalities in stimulant abusers

- Cognitive impairment
  - Frontal/striatal brain perfusion defects
  - Correlate with degree of neuropsych deficits
- Affective/sensory dysregulation
  - Occipital brain perfusion defects
  - Functional MRI abnormalities: occipital & temporal
- Pathophysiology
  - Abnormally adherent platelets
  - Vasoconstriction
  - Dopamine deficiency

Cocaine and Pregnancy

- Irregular placental blood flow
- Placental detachment and abruption
- Premature rupture of membrane (PROM)
- Premature labor and delivery

- In a recent meta-analysis, the only adverse event significantly associated with cocaine was PROM (Addis et al. 2001 Reprod Toxicol)

Genetics of MA Use Disorders

- 60-70% heritability – twin studies
- Genetic Association with MA Use [Bousman et al, 2009]
  - 39 genes examined: 18 were found to have a significant genotypic, allelic, and/or haplotypic association with MA use disorder
  - "the genetic epidemiology of MA use disorders is complex and likely polygenic".

Genetics of Cocaine Dependence

- Genetic epidemiology: high degree of heritable vulnerability.
- Associated Polymorphisms: DA receptors & transporter, opioid receptors, endogenous opioid peptides, cannabinoid receptors, and 5-HT receptors & transporter.
- CONCLUSION: Specific genes of risk remain to be elucidated.
  - Haile CN, **Kosten TR**, Kosten TA. Pharmacogenetic treatments for drug addiction: cocaine, amphetamine and methamphetamine. *Am J Drug Alcohol Abuse.* 2009; 35(3): 161-177. PMID: 19462300.
  - Yeforov et al. 2010 Ann NY Acad Sci 1187:184-207
  - Phillips et al. 2008 Neurosci Biobehav Rev 32: 7-7-59
  - Khokhar et al 2010 Annu Rev 50:39-61

TREATMENT

Prevent Relapse to Dependence

"Let's just go in and see what happens."

Central Role of Psychotherapy in Treatment

- No FDA approved pharmacotherapy
- Drug counseling most commonly used
- Counseling has improved outcome when it follows a manualized approach
- Manualized Options: 12-step facilitation, Motivational Enhancement, Cognitive behavioral, Contingency management

Manualized Drug Counseling (IDC, TSF)

- *Manualized*, *individual* versions of drug counseling, grounded in Twelve-Step or disease models
- Good efficacy data (NIDA Cocaine Collaborative Study, Project MATCH)
- Not equivalent to AA, NA referral
- Probably not be equivalent to 'treatment as usual'

Motivational Enhancement Therapy (MET or MI)

Brief approach (1-3 sessions)

Based on principles of motivational psychology, processes of change model

FRAMES

- Feedback on consequences of use
- Emphasis on patient Responsibility for change
- Advice to change
- Menu of options
- Therapist Empathy
- Self-efficacy

Cognitive-behavioral Therapy (CBT)

- Emphasis on development of coping skills (coping with craving, dealing with thoughts about drugs, problem solving skills, refusing drug offers, etc).
- Based on functional analysis of substance use (what happens before and after each episode)

Contingency Management (CM): Basic Principles

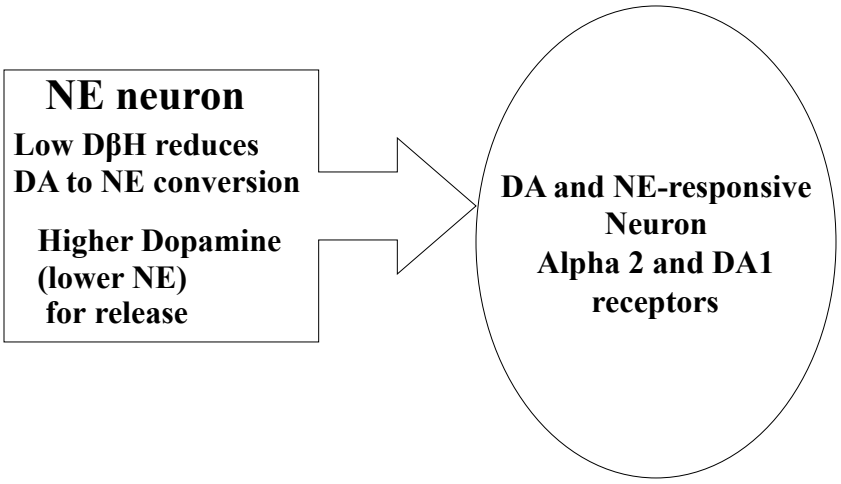
- Drug use must be swiftly detected
- Abstinence is reinforced
- Drug use results in loss of reinforcement
- Emphasis on development of competing reinforcers

Pharmacogenetics and medication usage

Cocaine and Disulfiram (dopamine beta hydroxylase)

NO FDA Approved medication

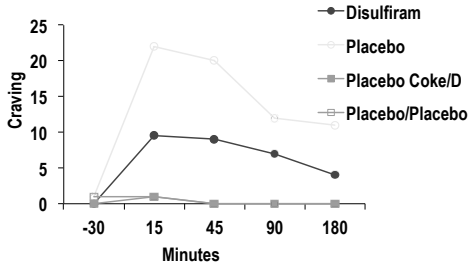
Disulfiram increases dopamine (DA) by inhibiting its conversion by dopamine beta hydroxylase to norepinephrine (NE)



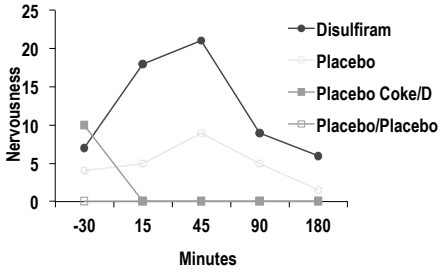
Disulfiram Effects on Acute Cocaine (2mg/kg I.N.)

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

Craving for cocaine

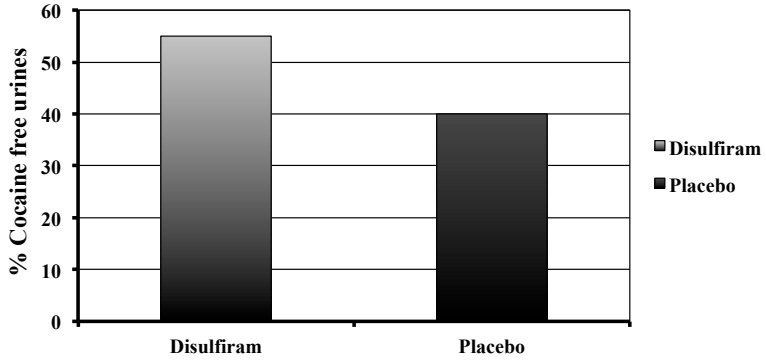


Nervousness from cocaine



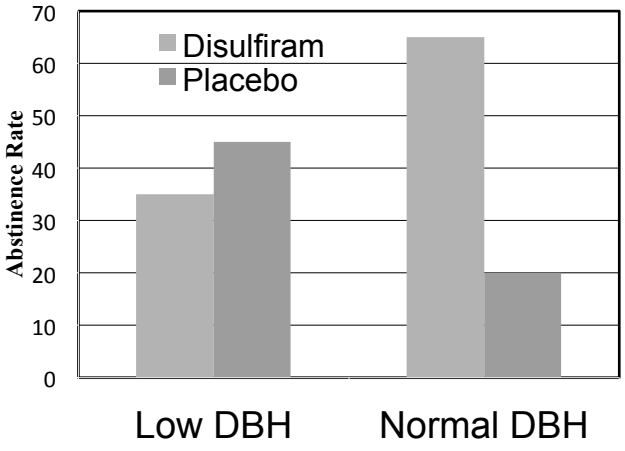
Disulfiram increases Cocaine-Free Urines in over 600 Outpatients

(7 Studies - P<0.001)



Average Weekly Abstinence Rate by Medication & DBH Genotype

(Interaction of Medication X Genotype: F=5.3; df=1, 64; P<0.03)



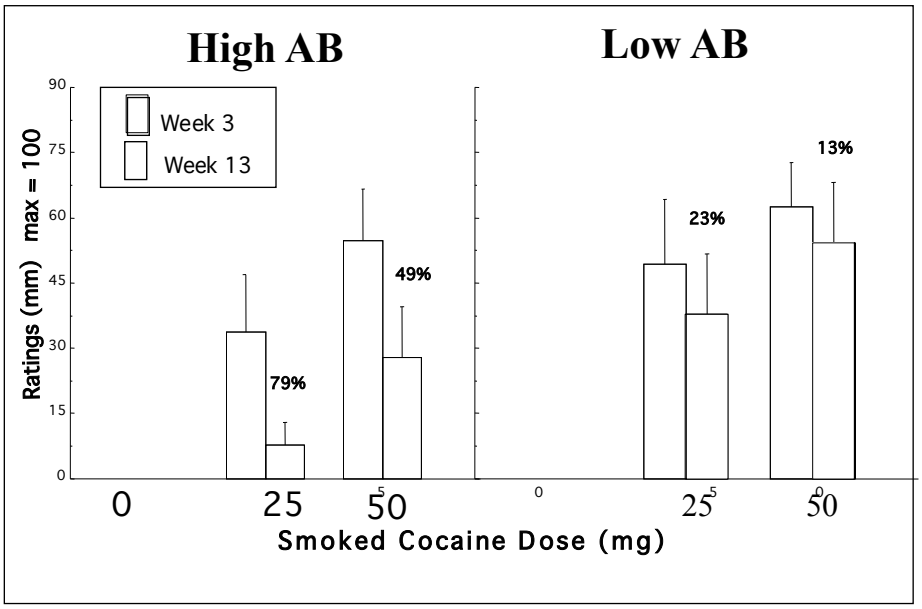
Disulfiram Effects on Cocaine: The DβH Genetic Hypothesis

- Disulfiram promotes cocaine abstinence by inhibiting DβH and altering the DA/NE ratio.
- Pharmacogenetic hypotheses for Disufiram:
  - Low DβH **non-responders**: If DβH chronically low, then alternative pathways for NE formation take over for DβH synthesis
  - (mouse DβH gene knock-out support)

"Perhaps it would help if I go over it one more time."

Vaccines for Cocaine Dependence

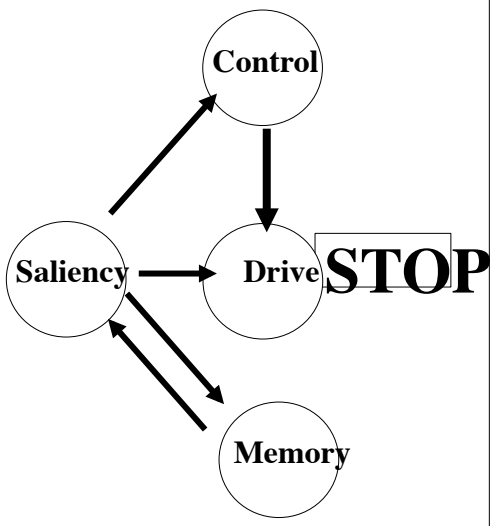
Good Drug Effect



Conclusions from Vaccine Outpatient Trial

- Cocaine vaccine better than placebo
- Cocaine-free urines increase as AB levels increase
- 75% of patients had effective antibody response
- Vaccine is medically safe, even with 10 times more cocaine use than during baseline

Medications for Relapse Prevention



- Strengthen non-drug reinforcers
- Strengthen inhibitory control
- Strengthen prefrontal-striatal communication
- Interfere with conditioned memories (craving)
- Counteract stress responses & relapse

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Good luck with your STUDY

I could not cover everything,
But I have BOOK!

Kosten TR, et al. *Cocaine and Methamphetamine Dependence*.
American Psychiatric Publishing.
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