APA Presentation

Substance Abuse Pharmacotherapy: From Antabuse to Zenova-vax

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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**

- **Normal**
  - Normal levels of dopamine
  - Normal number of dopamine receptors

- **Overactivity**
  - Increased dopamine levels
  - Increased sensitivity of dopamine receptors
  - Increased dopamine reuptake

**Sites of Dmrmcg Action at the Synapse**

- Dopamine release
- Reuptake of dopamine by the neuron
- Interaction with dopamine receptors
Parkinsonian (PD) Brain Abnormalities in Cocaine Abusers

%ID/cc
0.030
0.015
0.000

Control | Amphetamine | Cocaine | PD
Hypodopaminergic State In Drmcg Addiction

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).

- Low DβH reduces DA to NE conversion.
- Higher Dopamine (lower NE) for release.

DA and NE-responsive Neuron
Alpha 2 and DA1 receptors.
**Disulfiram Effects on Acute Cocaine (2mg/kg I.N.)**

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

**Craving for cocaine**
- Red: Disulfiram
- Yellow: Placebo
- Green: Placebo Coke/D
- Blue: Placebo/Placebo

**Nervousness from cocaine**
- Red: Disulfiram
- Yellow: Placebo
- Green: Placebo Coke/D
- Blue: Placebo/Placebo
## Cocaine Free Urines Across 5 Disulfiram Clinical Studies (n=337)

<table>
<thead>
<tr>
<th>Study (n)</th>
<th>Disulfiram vs. Placebo</th>
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<tbody>
<tr>
<td>vs Naltrexone (18)</td>
<td>90% vs 66%</td>
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<tr>
<td>w Buprenorphine (20)</td>
<td>41% vs 25%</td>
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<tr>
<td>w Methadone (67)</td>
<td>35% vs 25%</td>
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<tr>
<td>Psychotherapy (117)</td>
<td>55% vs 40%</td>
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<tr>
<td>Match Study (115)</td>
<td>57% vs 45%</td>
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<tr>
<td><strong>Meta Average</strong></td>
<td><strong>55% vs 40%</strong></td>
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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 $D\beta H$):

![Graph showing cocaine-free urines for TT + CT and CC genotypes under disulfiram and placebo conditions.](image-url)
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

Brain
Antibodies can reduce brain concentrations.
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)

Z = -3.17, p = 0.0015
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)

Titer

Weeks

High Antibody

Low Antibody
Good Drug Effect

High AB

Low AB

Smoked Cocaine Dose (mg)
Self-reported Cocaine Use

High AB

Low AB

Dollars/5 days

Week 13

Week 3

Week 13

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
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.