The Latest in Medications Development

Frank Vocci, Ph.D.
Division of Pharmacotherapies and Medical Consequences of Drug Abuse

Disclosure

• I do not own any pharmaceutical stocks. Neither does any immediate members of my family.

• Neither I nor any immediate family members have any ownership in mutual funds that target the health sector.

• I do, on occasion, consult for pharmaceutical companies as an official US Government duty. NIDA pays my travel expenses to the companies. I receive no monetary compensation but have been known to eat a ham sandwich at working lunches at these consultations.

Outline of Presentation

• Update on clinical studies with buprenorphine for treatment of opiate dependence

• Update on clinical studies of medications for treatment of stimulant dependence

• Introduction to altering cognitive systems with medications as a means for treating stimulant dependence disorders
April 1978 – Jasinski publishes study on the human pharmacology and abuse potential of buprenorphine. He concludes that buprenorphine's unique pharmacology would give it therapeutic application as a maintenance drug in narcotic addiction. (Arch Gen Psychiatry, Vol 35, April 1978, pp 501-516)

October 2002 – Approved for treatment of opiate dependence - can be prescribed in patients 16 and older

August 2006 – Over 200,000 patients treated

Buprenorphine

Drug Misuse/Abuse-Related Emergency Department (ED) Visits in the United States
(Source: U.S. SAMHSA, DAWN Live! March 23, 2006)

http://dawninfo.samhsa.gov

How do I find a physician?
Over 7,000 Registered Physicians

New Research on Buprenorphine

- Buprenorphine/naloxone in Primary Care
  - Buprenorphine in Adolescents
  - Buprenorphine for Detoxification
  - Mother trial
  - BUP-START
  - POATS
  - Buprenorphine/nx and computerized counseling

Primary Care Research

- Buprenorphine/naloxone treatment to opiate dependent patients in a primary care clinic
- Patients were randomized to once or three times weekly standard counseling or enhanced counseling
- No differences seen in the major study objectives across groups: retention and drug use
Buprenorphine in Adolescents

- Adolescent (age 13-18) opiate users were randomized to either buprenorphine or clonidine and followed through a detoxification regimen for 4 weeks.
- Opiate abstinence was reinforced with vouchers.
- Retention, opiate use and post-detox treatment were assessed.
Bupremorphine in Adolescents

• Multi-Center trial in the NIDA CTN
• Used both inpatient (n = 113) and outpatient (n=231) treatment programs sites
• Buprenorphine/naloxone versus clonidine in a 2:1 randomized scheme
• 13 day regimen
• Retention and opiate-free urine on last day of study
• Ling et al Addiction 100(8):1090, 2005
Bup in Detox

- 1000 opiate dependent patients will be randomized to either Bup/Nx or methadone in opiate treatment programs associated with the CTN
- Patients will have viral hepatitis exposure and HIV status assessed at beginning of trial
- Liver transaminases will be assessed
- POATS – evaluation of Bup/Nx in prescription opiate dependent patients- CTN study
- Prescription opiate dependent patients can be treated now with Bup/Nx !!!

Bup in Pregnant Women

- Mother study: multicenter trial evaluating the effects of buprenorphine or methadone in the treatment of opiate dependent pregnant women
- 340 subjects will be randomized to either bup or methadone
- Outcome variables: Maternal opiate use, incidence of neonatal abstinence
- Results will be used to support the change in product labeling of these medications

BUP-START & POATS

- 1000 opiate dependent patients will be randomized to either Bup/Nx or methadone in opiate treatment programs associated with the CTN
- Patients will have viral hepatitis exposure and HIV status assessed at beginning of trial
- Liver transaminases will be assessed
- POATS – evaluation of Bup/Nx in prescription opiate dependent patients- CTN study
- Prescription opiate dependent patients can be treated now with Bup/Nx !!!
Computerized CBT for Addiction

Warren K. Bickel, Ph.D. and Lisa A. Marsch, Ph.D.
University of Arkansas for Medical Sciences, National Development and Research Institutes, and HealthSim Inc.

Supported by Grants from NIDA

Randomized Controlled Trial

- Participants: Opioid-dependent individuals randomly assigned to:
  - **Therapist Delivered CRA**: 30 mins. 3x/wk. w/therapist & CM (Budney & Higgins, 1998)
  - **Computer Assisted CRA**: 30 mins. 3x/wk. w/computer & CM; 1 biweekly w/therapist
  - **Standard Counseling**: 37 mins. 1/wk. w/therapist - focus on rehabilitation & compliance with treatment program (Ball & Ross, 1991)
  - All received buprenorphine maintenance treatment

List of Module Topics in Therapeutic Education System (TES)

1. Training Module
2. What is a Functional Analyze?
3. Conducting a Functional Analyze
4. Self-Management Planning
5. Drug Refusal Skills Training
6. Awareness of Negative Thinking
7. Managing Negative Thoughts and Depression
8. Conducting a Functional Analyze
9. Training to Manage Negative Thoughts
10. Introduction to Problem-Solving
11. Effective Problem-Solving
12. Introduction to Relaxation Training
13. Relaxing Critiques
14. Making Involvement Decisions
15. Other Drug Use
16. Coping with Thoughts About Using
17. Introduction to Assertiveness
18. How to Express Opinions in an Assertive Manner
19. Maintaining Assertiveness
20. How to Become More Aware of the Feeling of Anger
21. Coping with Anger
22. Introduction to Relaxation Training
23. Progressive Muscle Relaxation Generalization
24. Steps for Giving Condicitive Criticism
25. Receiving Critiques
26. Giving and Receiving Compliments
27. Sharing Feelings
28. Vocational Counseling
29. Unfamiliar Use
30. Financial Management
31. Insurance
32. Time Management
33. Behavioral Counseling Part 1
34. Relational Counseling Part 1
35. Alcohol and Opiates
36. Communication Skills
37. Nonverbal Communication
38. Social/Recreational Counseling
39. HIV and AIDS
40. Sexually Transmitted Infections (STIs)
41. Social Transcription of HIV and STIs
42. The Female Condom
43. Birth Control Use and HIV and STIs
44. Drug Use, HIV and Hepatitis
45. Combating HIV, STIs and Hepatitis
46. Finding Safe HIV, STIs and Hepatitis Information
47. Negotiating Safer Sex
48. Decision-Making Skills
49. Identifying and Managing Triggers for risky use
50. Overcoming the Impact of Decision-Making
51. Taking Responsibility for Choices
52. Living with HIV: Managing Treatment, Promoting Health
53. Living with HIV: Managing Treatment, Promoting Health
54. Living with HIV: Coping Skills and Managing Stigma
55. Living with HIV: Coping Skills and Managing Stigma
56. Living with HIV: Coping Skills and Managing Stigma
57. Living with HIV: Coping Skills and Managing Stigma
58. Living with HIV: Coping Skills and Managing Stigma
59. Living with HIV: Coping Skills and Managing Stigma
60. Living with HIV: Coping Skills and Managing Stigma
61. Living with HIV: Coping Skills and Managing Stigma
Summary

- Computer-Assisted Therapy is generally as effective as comparable counselor-delivered therapy.
- The computer-based intervention greatly decreases cost of treatment via reduced patient-therapist contact time.
- The system enables counselors to focus on aspects of treatment they are uniquely skilled to address and enables more patients to receive treatment.

Vocci personal opinion-Computerized therapy would seem to be suited to rural situations where counseling is difficult to obtain, where large groups of patients are being treated in a group practice or HMO setting, could be provided over the internet or an intranet system.
**Medications to Treat Cocaine Addiction**

**“TOP DOWN” APPROACH**
- Marketed medications with good rationale to test in addicted subjects
  - Cocaine pharmacotherapies
  - Grantee approaches

**“BOTTOM UP” APPROACH**
- A basic science, discovery, driven process
  - Biochemical studies
  - Behavioral studies

**Top Down Approach – Cocaine Medications**
- Over 60 medications have been tested either alone or in combination
- Phase II studies for Cocaine Vaccine, & Ondansetron - completed
- Follow up studies have been conducted for:
  - Modafinil (MCT completed) and two grantees have ongoing studies
  - Baclofen (MCT recently completed)
  - Amantadine and propranolol (completed)
  - Cabergoline, Reserpine, Tiagabine (completed)
  - Naltrexone and Disulfiram - completed
- Phase I studies for Aripiprazole & GVG (planned)
- Phase I studies with CB1 antagonist, D3 antagonist, CRF antagonist (antaralmin), V1B antagonist planned

**Ondansetron for Treatment of Cocaine Dependence**
- Pilot Study
- 60 subjects randomized to placebo and 3 doses of Ondansetron
- Baseline and eight weeks of treatment
- GEE analysis of Cocaine use by week of study
Disulfiram - Cocaine Free Urines
Across 5 Clinical Studies

Study (n) | Disulfiram vs. Placebo % Cocaine Free Urines
---|---
v. Naltrexone (18) | 90% vs 66%
w. Buprenorphine (20) | 41% vs 25%
w. Methadone (67) | 35% vs 25%
Psychotherapy (121) | 55% vs 40%
Match Study (115) | 57% vs 45%

Meta Average | 55% vs 40%

Disulfiram - Latest Findings -
Carroll et al 2004
Disulfiram- Current Status

- Is effective in males
- Analysis of females in the trials does not show efficacy of disulfiram
- Only works in non-alcohol using subjects
- Treatment effect has been associated with an allelic variant (1021T→C) of the DβH gene
- Patients with at least one copy of the T allele have lower DβH activity
- Current hypothesis is that this is the group that responds to disulfiram

Naltrexone as an Anti-Cocaine Pharmacotherapy

- Effective with relapse prevention in cocaine using subjects Grabowski et al 2002
- A second trial of naltrexone in cocaine-alcohol using subjects failed to confirm the effect of naltrexone (Schmitz, Grabowski et al, 2004)
- Tested with disulfiram combo in alcoholic cocaine addicts: U.Penn (Completed)

Disulfiram plus Naltrexone for Cocaine & Alcohol Dependence

<table>
<thead>
<tr>
<th>Medication groups N=208:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Naltrexone (100 mg) + Disulfiram (250mg) (n=49)</td>
</tr>
<tr>
<td>2. Naltrexone (100 mg) + Placebo (n=52)</td>
</tr>
<tr>
<td>3. Disulfiram (250 mg) + Placebo (n=53)</td>
</tr>
<tr>
<td>4. Double Placebo (n=54)</td>
</tr>
</tbody>
</table>

2 week baseline 12 weeks medication + CBT

Disulfiram plus Naltrexone for Cocaine & Alcohol Dependence
Disulfiram-Naltrexone Study Recruitment
January 2000 – March 2004

Eligible Drop: 78
Ineligible Drop: 9
Screen Drop: 87
Eligible Drop: 99
Ineligible Drop: 39
Pre-Randomization Drop: 138
Tx Completer: 154
MIA: 48
Death: 0
Patient Choice: 6
Tx Non-Completer: 54
Randomized: 208
Screened: 416
TRC Cocaine Intakes during recruitment: 856

LEGEND
Pre-randomization - Consented to Disulfiram-Naltrexone Study but did not make it to randomization.
Eligible Drop - Patient decided to stop coming or became MIA.
Ineligible Drop - Met exclusion criteria (i.e. medical) or did not meet inclusion criteria (i.e. use).

% Clean Urines by Week for n=106 Med-Adherent Ss: Combined Disulf-Ntx vs Placebo Groups

% Medication Adherent Cocaine-Alcohol Patients (n=106) with 3 Consecutive Weeks of Clean Urines

** p < 0.05
Biological Factors Affecting Response to Medications

- Cocaine withdrawal syndrome has been reported
- Consists of affective, appetite, sleep disturbances, cocaine and carbohydrate cravings, and cardiovascular features
- Not reported in all individuals
- Scale developed by Dr. Kyle Kampman (U Penn group)

Cocaine Withdrawal Syndrome

Propranolol Reduced Cocaine Use

Kampman et al., 2001
Amantadine and Propranolol Follow Up Study

Abstinence in Adherent Subjects (n=94)

% Abstinent

% Patients Abstinent Weeks 8-9-10

Fig. 2. Percent patients abstinence each week in the intent-to-treat sample, and in the highly adherent sample.
Baclofen- a GABA B Agonist

Baclofen Follow up Trial

- Completed double blind, placebo controlled multi-center trial in cocaine using subjects who have regular cocaine use
- Regular cocaine use was defined as having at least 3 or more BE positive urines during a 2 week screening phase
- 160 subjects were randomized to baclofen (60 mg/day final dosage) or placebo

Baclofen Multi-Center Study

Vigabatrin (Sabril®)
A GABA Transaminase inhibitor

H₂N
CO₂H

GABA

H₂N
CO₂H

γ-Vinyl GABA (Vigabatrin)
Open Label Efficacy Study of γ-vinyl GABA (GVG) for the Treatment of Cocaine Addiction

Emilia Figueroa, MD
Stephen L Dewey, PhD
Jonathan D Brodie, PhD, MD

Days Clean While in Study (p=0.004)

<table>
<thead>
<tr>
<th>Column</th>
<th>0</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long term responder (n=8) v long term failures (n=4)</td>
<td>90</td>
<td>15</td>
</tr>
</tbody>
</table>

Mean and Standard Deviation

Vigabatrin

- Two open label studies: 11/20 responders in study # 1 and 16/30 responders in study # 2
- Will soon enter Phase I testing to assess its interactions with cocaine and methamphetamine
- NIDA is planning to perform Phase II studies in cocaine and methamphetamine dependent outpatients
Medication groups:
1. Topiramate 200 mg daily (n=20)
2. Placebo (n=20)

Study design
- 1 week baseline
- 3 days abstinence
- CSSA < 22
- 8 week titration
- 4 weeks at max dose

Results: Continuous abstinence

% Patients with 3 Consecutive Abstinent Weeks

- Topiramate: 99%
- Placebo: 36%

p < .05

Background

Topiramate for Alcoholism
- drinks / day
- heavy drinking days

Johnson et al., Lancet 2003; 361: 1677-85
Topiramate Follow up Studies

- Will be performed at U Penn and UVa in cocaine and alcohol using populations under grants
- May also have utility as an anti-smoking therapy
- Topiramate for the treatment of methamphetamine dependence is being evaluated in a contract trial...MCT started in May 2006

Modafinil (PROVIGIL)

Introduction

- Search for cocaine dependence pharmacotherapies continues
- Modafinil (Provigil®)
  - Approved to promote wakefulness in patients with excessive daytime sleepiness
- Mechanism of action remains unclear, but
  - Hypothesized to exert therapeutic effects by increasing catecholaminergic activity
  - Also shown to increase glutamatergic and histaminergic transmission and decrease GABAergic transmission
  - Recently evaluated as potential treatment medication for cocaine dependence
Figure 4

Least Square Means of VAS “High”
N=12

<table>
<thead>
<tr>
<th>Cocaine Alone (Baseline)</th>
<th>Cocaine + Modafinil 250 mg</th>
<th>Cocaine + Modafinil 500 mg</th>
<th>Cocaine Alone (Baseline)</th>
<th>Cocaine + Modafinil 250 mg</th>
<th>Cocaine + Modafinil 500 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20 mg IV Cocaine</td>
<td>40 mg IV Cocaine</td>
<td></td>
<td>20 mg IV Cocaine</td>
<td>40 mg IV Cocaine</td>
</tr>
</tbody>
</table>

*Significantly different from baseline, p<0.017

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Modafinil

- 3 Clinical trials ongoing in cocaine dependent subjects with many identical endpoints
- The first trial has completed enrollment
- The other two are expected to complete in @ 1 ½ years
- The trials will be analyzed separately as then as a meta-analysis
Smoked Cocaine Self-administration Decreased by Modafinil: Preliminary Findings

Carl L. Hart, Margaret Haney, Suzanne K. Vosburg, Eric Rubin, & Richard W. Follin
Division on Substance Abuse, New York State Psychiatric Institute, Department of Psychiatry, College of Physicians & Surgeons of Columbia University, and Department of Psychology, Columbia University

Encouraging Findings

• Controlled laboratory study (Dackis et al. 2003)
  – Decreased one rating of euphoria produced by i.v. cocaine
  – Concern: subjective response and self-administration dissociable
• Double-blind, clinical trial (Dackis et al. 2005)
  – Decreased cocaine use, as measured by urine toxicology

Heart Rate

![Heart Rate Chart](chart.png)
Summary

• These preliminary laboratory data show that modafinil:
  – decreased cocaine self-administration
  – attenuated cardiovascular and subjective responses produced by larger cocaine doses
  – in combination with cocaine was well tolerated and did not produce untoward effects
Desipramine Pharmacotherapy Studies

Mendelson J, Mello N. *New Pharmacotherapies for Cocaine Dependence*. Arch Gen Psychiatry, 1996, 49: 900-904

Gawin F, Kolber H. *Cocaine Abuse Treatment. Open Pilot Trial with Desipramine and Lithium Carbonate*. Arch Gen Psychiatry, 1984, 41: 903-909

Gawin F, Kolber H. *Desipramine Facilitation of Initial Cocaine Abstinence*. Arch Gen Psychiatry, 1989, 46: 117-121


Desipramine and Contingency Management

Bupropion and Contingency Management
Cocaine Promising Medications: So Far

- Disulfiram
- Modafinil ?
- Topiramate
- Propranolol
- Naltrexone and disulfiram combo
- Desipramine and contingency mgmt
- Bupropion and contingency mgmt
- Vigabatrin /GVG ?
- Ondansetron ? (needs confirmation)

Bupropion for the Treatment of Methamphetamine Dependence


Submitted for publication

Rationale

- Bupropion is a modest monoamines uptake inhibitor (DAT binding 22%)
- Chemically related to PEA
- Animal models:
  - Stimulants-like properties
  - Antagonizes methamphetamine-induced stereotypy (Muley et al. 1984)
  - Reduces methamphetamine-induced neurotoxicity (Marik et al. 1990)
- Nicotinic agonist properties may improve cognition
Weekly Percentage of Participants with Methamphetamine-Free Urine

Percentage of patients with Methamphetamine-free study wk

Study Week Elapsed Since Randomization

*p = 0.09 by GEE

Group means

Bupropion
Placebo

GEE fitted lines

Study Week Elapsed Since Randomization

*p = 0.03 by GEE

Group means

Bupropion
Placebo

GEE fitted lines

Study Week Elapsed Since Randomization

*p = 0.08 by GEE

Group means

Bupropion
Placebo

GEE fitted lines

Study Week Elapsed Since Randomization

*p = 0.15 by GEE

Group means

Bupropion
Placebo

GEE fitted lines

Study Week Elapsed Since Randomization

*p = 0.04 by GEE

Group means

Bupropion
Placebo

GEE fitted lines

Study Week Elapsed Since Randomization

*p = 0.86 by GEE

Group means

Bupropion
Placebo

GEE fitted lines

Study Week Elapsed Since Randomization

**Difference in Group Mean (bupropion-placebo) of Weekly Total Craving Score at 3-Week Intervals**

* p = 0.0290
* p = 0.0318
* p = 0.0359
* p = 0.0412

**Pooled**

* p = 0.2360
* p = 0.3157
* p = 0.4861
* p = 0.7682

**Low Baseline**

**High Baseline**
Serious Adverse Events

• Three SAEs (2 placebo, one active).
• All psychiatric.
• None on medication at the time.

Ongoing Pharmacotherapy Research for Treatments for Methamphetamine Dependence

• Modafinil – Phase II
• Topiramate- Phase II
• Bupropion- Phase II confirmatory trial (planned)
• Bupropion and Contingency Management- Phase II
• Lobeline- Phase I interaction study
• Vigabatrin - Phase I interaction study
• Concerta- Phase I interaction study

Cognitive Systems, Behavior, and Medication Opportunities

• Bottom Up and Top Down Cognitive Systems
• Bottom Up is a fast reacting system that propels appetitive behaviors
• Is reinforced through association learning, consumption and stress
• Top Down system is a more reflective cognitive system that weighs reward, harm avoidance, punishment, and long-term consequences
### Cognitive Systems and Behavior

- Hypothesis: Appetitive systems are out of balance relative to cognitive systems in addiction
- Two main concepts to restore balance
  - Modulation of appetitive/bottom up systems
  - Strengthening of cognitive systems/top down
- The remainder of the presentation is on top down cognitive systems, their dysregulation by stimulants, primarily methamphetamine, and how to correct this situation

### Current Treatments

- Behavioral treatments for methamphetamine users
  - Cognitive behavioral therapy
  - Contingency management
  - Treatments have reported efficacy but are not universally efficacious; e.g., 60% dropout
- Hypothesis: Treatment retention and efficacy can be improved by cognitive enhancers and other medications that affect decision-making
- Substance abuse produces functional changes in the brain that can be identified and modulated by medications

### “Matrix Therapy”-Rawson et al 2004

- Outpatient manualized therapy for cocaine and methamphetamine users
- Has been used in over 10,000 patients
- Uses elements of cognitive behavioral therapy
- Enables patients to recognize internal and external stimuli that increase probability of relapse
- Is a learning experience
- Has a dropout rate of @ 50 - 60%
Treatment Comparisons- Rawson et al 2006
• Compared CBT, CM, CBT +CM treatment retention and abstinence
• % Retention
  CBT (40), CM (63), CBT +CM (59)
• % Achieving 3 weeks abstinence
  – CBT (35), CM (60), CBT +CM (69)

Why Do Patients Dropout of Treatment?
• Cognitive deficits
• Impulsivity
• Excessive reward dependency
• Insensitivity to consequences
• New drug use provokes relapse or psychiatric complications

Cognitive Deficits in Cocaine Users – Aharonovich et al ’05

Fig: Odds of attrition from cognitive behavioral therapy relative to global cognitive functioning in cocaine abusers at baseline (x=50).
Impulsivity and Treatment Retention in Cocaine Users - Moeller et al 2001

Meth Users and Cognitive Dysregulation

- Problems in attentional set shifting, similar to schizophrenic patients
- Deficits in response inhibition (Monterosso et al, 2005)
- Deficient response inhibition on the Stroop test (Salo et al, 2002)
- Deficits in verbal memory recall, attention/concentration, and delayed recall (McKetin and Mattick, 1998)

Meth Users and Cognitive Dysregulation

- Reduced verbal encoding, learning (cue-association) and utilization of semantic clustering (strategic) on the Hopkins Verbal Learning Test (Woods et al, 2005)
- Increased impulsivity (Simons et al, 2005; Semple et al, 2005)
- Lower quality of decision making (Rogers et al, 1999)
- Deficient decision making on the Iowa Gambling Task (Bechara et al, 2001)
- Deficient decision making based on stimulus predictability versus success (Paulus et al, 2003)
Amphetamine Users and Cognitive Dysregulation

- Deficient in verbal fluency
- Deficient in strategic thinking task (TOL)
- Deficient in visual-spatial strategy sequence generation task (novel sequences generation) Ornstein et al 2000

Cognitive tasks

- Attentional Set shifting - generation of rules
  - Internal Dimension shifts are within a concept
    - Discriminations within a relevant dimension
    - Shape or color or number of objects on a card
  - External Dimension shifts are across concepts
    - Discriminations shift to previously irrelevant dimension
    - Shape to color or number

Amphetamine Users and Cognitive Dysregulation
Amphetamine Users and Cognitive Dysregulation

Amphetamine Produces the EDS Deficit in Rats - Fletcher et al 2005

D-1 Dopamine Agonist Effects
A 5-HT-6 Antagonist Improves Attentional Set Shifting—Hatcher et al 2005

D-4 Dopamine Antagonists and Set Shifting in Rats—Floresco et al 2006

Set Shifting In Schizophrenic Patients—Effect of Modafinil
Possible Medications for Alteration of Set Shifting in MA Users

- Modafinil
- A D-1 agonist or DA releaser (MPH)
- A D-4 antagonist?
- A 5-HT 6 antagonist

Modeling Inhibitory Deficits

- Inhibitory deficits in substance abusers are being reported more frequently in the literature
- The deficits are not unitary; i.e., more than one type exists
- May correlate to impulsive nature of may drug users
- Adverse life events can increase impulsivity
- Impulsivity can be modeled in the laboratory

Methamphetamine Users and Impulsivity

- Methamphetamine patients have increased impulsivity
- Correlated to high Beck Depression Inventory scores (Semple et al., 2005)
- Methamphetamine use in a rural US population was associated with female gender, use frequency, injection use, and impulsivity (Simons et al., 2005)
- Can be measured by the Barratt Impulsivity Scale
- Motor impulsivity can be measured with reaction time tests
Cognitive Deficits in Stimulant Abusers

- Decision-Making
- Inhibitory Control

Reversal Learning  Go/No Go Stop Signal

Stop-Signal Reaction Time

- Measures the speed of a cognitive process invoked to cancel an intended movement
- Tests of Go-No Go and stop-signals are thought to engage the Right Inferior Frontal Gyrus
- These tests are sensitive to damage to this brain region in patients with damage from strokes, tumors, and trauma
Methamphetamine Abusers are Impaired on the Stop-Signal Task

Deficit in Inhibition is Related to Methamphetamine Use

Gray Matter Deficit in Inferior Frontal Gyrus
Relation of Inhibitory Control to IFG Gray Matter Concentration

A. Aron et al., unpublished

Modafinil STOP SSRT

Turner et al. 2003

Modafinil STOP ‘mean go errors’

Turner et al. 2003
Tests of Strategic Thinking

- Strategic thinking is altered in methamphetamine users
- Tower of London test
- Can discriminate drug effects

Modafinil NTOL latency

Modafinil NTOL mean attempts
Decision-Making

**GAMBLING TASK**

<table>
<thead>
<tr>
<th>Payoff/Card</th>
<th>Loss/10 Cards</th>
<th>Profit/10 Cards</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>$100</td>
<td>$250</td>
</tr>
<tr>
<td>B</td>
<td>$1250</td>
<td>$250</td>
</tr>
<tr>
<td>C</td>
<td>$100</td>
<td>$250</td>
</tr>
<tr>
<td>D</td>
<td>$50</td>
<td>$250</td>
</tr>
</tbody>
</table>

NET SCORE = (C+D) - (A+B)

Decision-Making in Drug Users

- Employs both Bottom Up and Top Down systems
- Mesocortical dopamine inputs influence prefrontal functions; e.g., judgment and decision-making
- Drug use is a decision with short-term and long-term consequences
- Gambling task allows evaluation of this cognitive process in drug users

Cortical Activations During Gambling Task: Controls vs. Drug Abusers

Overlap p<0.005, uncorrected Extent = 10 pixels
Nucleus Accumbens Activation Predicts Poor Performance in Drug Abusers

$r < -0.73$

$p<0.005$, Extent = 20 pixels, uncorrected (11 Controls)

SUMMARY

Where do drug abusers and controls exhibit different performance correlations?

Controls (+)
- R. Insula
- R. Superior Frontal Cortex
- R. Hippocampus/Parahippocampus
- R. Superior Parietal Cortex
- R. Inferior Temporal Cortex
- Dorsomedial Thalamus (-)
- Posterior Cingulate

Abusers (-)
- L. Basal Forebrain/Nucleus Accumbens
- L. Parahippocampus
- L. Cuneus

Gambling Task Performance

300 Cards

Controls > Drug Abusers $p < 0.001$
Amphetamine Users in the Iowa Gambling Task

- Did not choose the advantageous cards
- Suggestive of Ventromedial Frontal Cortex lesions
- Challenge for new learning in therapy
- Likely will require sensitivity to decision contingencies

Amphetamine Users

Decision choices in ADHD Patients
Decision Making on the Cambridge Risk Task

- Evaluated Controls, Amphetamine, Opiate and ex-drug users in a task that measures the choice between an unlikely high reward and a likely low reward
- Does not rely on past choices or memory of past choices
- Amphetamine, Opiate and ex-drug users are more likely to choose an unlikely high reward (risk-taking)
- Hypothesis: Modafinil could be evaluated for changes in risk taking

Decision Making and Relapse-Paulus et al Arch Gen Psychiatry 2005

- Decision-making:
  - Person has to select among several options.
  - Each option can be associated with positive or negative outcomes, which may be uncertain.
  
- Key elements of decision situations:
  - Probability of an outcome associated with an option.
  - The positive or negative consequence.
  - The magnitude of the consequence

Functional Magnetic Resonance Imaging

- Magnetic resonance imaging
- Behavioral task
- Changes in blood oxygenation
- Identify brain areas involved in task-related processing
Study Goals

- Neurobiology of decision-making dysfunctions in stimulant dependent subjects.
- Can functional magnetic resonance imaging be used as a tool to predict relapse?

Subjects

46 methamphetamine dependent subjects sober for a median of 23 days

6 lost to follow up

40 subjects followed up a median of 370 days

279 days median sober time

NO RELAPSE: 22
RELAPSE: 18

Assessment Protocol

Baseline Assessment:
- Diagnostic: DSM
- Symptoms: BPRS / HDRS / YMRS

Neuropsychology: DKEFS

Decision-making: Two-choice Prediction task, Iowa Gambling Task

Two-Choice Prediction Task

Two-Choice Response Task
Brain Activation and Relapse

Prediction Accuracy

<table>
<thead>
<tr>
<th></th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>YES</td>
</tr>
<tr>
<td>N (40 after a median of 370 days)</td>
<td>18</td>
</tr>
<tr>
<td>Correctly Predicted by Imaging</td>
<td>17</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>94.4%</td>
</tr>
</tbody>
</table>

Receiver Operator Curves

- With a specificity of at least 83.3%
- Sensitivity ranged from 54.5% to 90.9%.
Medications for Enhancement of Cognitive Processes

- Multiple cognitive processes are altered in methamphetamine users:
  - Set shifting
  - Inhibition of appetitive mechanisms
  - Impulsivity/ lack of planning
  - Learning new material
  - Deficient strategic thinking
  - Altered decision making
  - Insensitivity to consequences ?
  - Excessive reward dependence ?

Decision-making and Medications

- New data suggest that different cognitive strategies are used in decision-making in cocaine and methamphetamine users versus controls
- Multiple points of intervention are suggested by the data
- What remains to be determined is whether the cognitive testing done in laboratory settings has external validity and, if so, whether altered cognition will alter drug taking behavior

Medications for Cognitive Processes

- A rationale has been provided for medications that may have salutary effects on cognition
- Top four choices:
  - Modafinil for enhanced strategic/reflective thinking
  - Modafinil for attentional set shifting (EDS)
  - Modafinil to reduce impulsivity
  - Modafinil to block “priming”
- Modafinil could be evaluated in patients exhibiting specific cognitive deficits
- Methylphenidate (Concerta) or Atomoxetine to improve DA function in frontal cortex
- These meds could be assessed for cognitive remediation also
- NMDA/ glutamatergic agonists to facilitate extinction of conditioned cues
- Cognitive enhancers (bryostatin) for new learning
Medications for Cognitive Processes

- Specific hypotheses for testing of these medications have been provided.
- Although two are considered stimulants... the proposed mechanism is correction of deficits, not substituting “One addiction for another”
- Medications can be tested in meth patients who could be assessed at treatment initiation for their impulsivity, strategic thinking, inhibitory deficits, etc.
- Clinical trials would measure changes in the cognitive target of interest and its relationship to reduction or elimination of cocaine/methamphetamine abuse.

Possibilities of Cognitive Therapy… If Correct

- Characterize the patients’ deficits and match with appropriate medications
- Would enable an evidence-based approach to medication prescribing for the methamphetamine patient
- Improved retention in treatment
- Less impulsivity
- Better cognition in a number of domains
- Better decision making
- Reduction or elimination of methamphetamine use
- A more functional individual

Thanks for your attention