Update on Pharmacological Treatment for Drug and Alcohol Dependence

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Chair, Addictions IRB (NIDA & NIAAA)
Faculty/Presenter Disclosure

• Relationship with commercial Interest
  – Grants/Research Support: None
  – Speakers Bureau/Honoraria: None
  – Consulting Fees: None
  – Other: Employee of NIDA

Disclosure of Commercial Support: None

No potential bias to mitigate
Illicit Drug Use Tx Success

- 24.6M illicit drug users
- 4.2 M seek treatment
- 1M tx success 1 month
- 0.1M Tx success 1 year
Medicines in Development for Mental Illnesses*

- Addictive Disorders: 26
- Anxiety Disorders: 26
- Attention-Deficit/Hyperactivity Disorder: 20
- Cognition Disorders: 10
- Depression: 52
- Developmental Disorders: 10
- Eating Disorders: 3
- Schizophrenia: 36
- Sleep Disorders: 22
- Other: 9

Source: [http://www.phrma.org/](http://www.phrma.org/)
Pharmacotherapy Approaches

• Prevention
  – Use
    Progression of use to addiction

• Treatment
  – Abstinence
  – Symptomatic
    • Intoxication
    • Withdrawal
    • Craving
  – Risk factors (cognitive deficit, impulsivity)
  – Psychiatric Co-morbidity
  – Medical Complications

• Rehabilitation
  – Relapse Prevention
  – Management of complications
  – Reduction or use
Drugs of Abuse

- Opioids
- Cocaine
- Cannabis
- Alcohol
Opioid Addiction: Pharmacotherapies

Opiate Agonists
- Methadone
- Buprenorphine
- LAAM

Opiate Antagonists
- Naltrexone
- Naloxone

Other
- Lofexidine
- Clonidine
Opioid Addiction Tx – New Research

- Generic buprenorphine/naloxone
- New Buprenorphine products
- New opioid antagonist
- Other
Generic Buprenorphine/naloxone: FDA approved in Feb 2013

### Buprenorphine HCl & Naloxone HCl Dihydrate

<table>
<thead>
<tr>
<th>Description</th>
<th>Active</th>
<th>NDC</th>
<th>AB</th>
<th>Suboxone®</th>
<th>Detail</th>
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<tbody>
<tr>
<td>2mg/0.5mg Sublingual Tablet</td>
<td>65162-0416-03</td>
<td>30</td>
<td>AB</td>
<td>Suboxone®</td>
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<tr>
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<td>Suboxone®</td>
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### Actavis

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Description</th>
<th>Additional Information</th>
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<tbody>
<tr>
<td>BUPRENOPHINE NALOXONE</td>
<td>BUPRENOPHINE HCl and NALOXONE HCl DIHYDRATE SUBLINGUAL TABLETS 2 mg / 0.5 mg 30s NDC: 00228-3154-03 *Compare to: Suboxone®</td>
<td>U.S. Prescribing Info Medication Guide Product Label</td>
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<tr>
<td></td>
<td>BUPRENOPHINE HCl and NALOXONE HCl DIHYDRATE SUBLINGUAL TABLETS 8 mg / 2 mg 30s NDC: 00228-3155-03 *Compare to: Suboxone®</td>
<td>U.S. Prescribing Info Medication Guide Product Label</td>
</tr>
</tbody>
</table>

*Brand names are the trademarks of the products’ manufacturers and/or owners.
**Products illustrated may not appear at actual size and/or exact color.
Zubsolv®

- Orexo U.S., Inc.
- Buprenorphine + Naloxone (1.4+.36 & 5.7+1.4 mg)
- Approved by the FDA in July 2013
- Now in the US market

<table>
<thead>
<tr>
<th>Zubsolv</th>
<th>Suboxone</th>
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<tbody>
<tr>
<td>Mint-like taste</td>
<td>Orange/citrus</td>
</tr>
<tr>
<td>Small tablet</td>
<td>Film</td>
</tr>
<tr>
<td>Better bioavailability</td>
<td></td>
</tr>
<tr>
<td>Less buprenorphine</td>
<td></td>
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<tr>
<td>Less risk of abuse?</td>
<td></td>
</tr>
</tbody>
</table>
Bunavail ™

• Biodelivery Sciences International
• BioErodible MucoAdhesive (BEMA®) delivery technology
• Buccal film:
  – 2.1 mg buprenorphine/0.3 mg naloxone
  – 4.2 mg buprenorphine/0.7 mg naloxone
  – 6.3 mg buprenorphine/1 mg naloxone
• Small patch that adheres to the inside of the mouth with the drug being absorbed through the cheek
• The drug dissolves across the mucosal membrane in about 15 minutes
• Easy to use and leaves little to no aftertaste
• Maintenance treatment of opioid dependence
• NDA approved on June 6, 2014
Bunavail™
Depot Buprenorphine

• Sponsor: Reckitt Benckiser Pharmaceuticals Inc.
• NCT01738503
• Open-Label, Multicenter, Multiple Dose Study of Safety, Tolerability, Pharmacokinetics, Efficacy Markers, and Opioid Receptor Availability of Subcutaneous Injections of Depot Buprenorphine in Treatment Seeking Opioid-Dependent Subjects
• RBP-6000: 50mg, 100mg, 200mg SC c/28 days
• Recruiting
Depot Buprenorphine

- Sponsor: Camurus
- CAM2038: once-weekly or once-monthly subcutaneous administration that can be given by health-care professional in a clinical setting.
- Ready-to-use pre-filled syringe containing a lipid solution of buprenorphine.
- Once injected, the lipids instantly start to self-assemble into the "active" FluidCrystal® controlled release matrix.
- Phase II trial: Completed on October 2011 (n=41). Well tolerated.
  - PK: buprenorphine over at least 7 days, with a rapid onset followed by slowly declining therapeutic serum levels.
  - PD: opiate withdrawal symptoms (SOWS and COWS) were well controlled for up to 10 days after single-dose injection.
Buprenorphine Implant
Implantable Formulation of Buprenorphine (Probuphine®)

Titan Pharmaceuticals
Subcutaneous, solid matrix implant that delivers around-the-clock, non-fluctuating, steady-state levels of buprenorphine for 6 months

– Eliminates daily peaks and troughs
– Lowers total opioid exposure
– Improves treatment adherence/compliance
– Reduces diversion and non-medical use
Implantable Formulation of Buprenorphine
Buprenorphine Implant

Example to understand this cumulative graph:
About 50% of patients in the buprenorphine implant group and also in the sublingual buprenorphine group had 20% or fewer of their 72 urines negative for illicit opioids over 24 weeks (50% were more successful), and about 80% of those in the placebo group had 20% or fewer negative urines (20% were more successful).

Rosenthal et al, 2013
Buprenorphine Implant

- NCT01114308
- A Six-Month Randomized Controlled Trial (RCT) of Probuphine Safety and Efficacy in Opioid Addiction
- N=287
- Experimental: Probuphine. Patients are first inducted on SL BPN then switched to 4 buprenorphine implants
- Placebo Comparator: placebo implant. Patients are first inducted on SL BPN then switched to 4 placebo implants
- Active Comparator: sublingual buprenorphine. Patients are inducted on SL BPN, then continue on SL BPN
- Recruitment completed
Samidorphan® (ALKS33)

- Alkermes
- Selective opioid antagonist \( \mu \)-opioid receptor
- Without affecting the \( \delta \)-opioid or \( \kappa \)-opioid R
- Similar to naltrexone but reduced S-E
- Rx/ opioid, alcohol dep, MDD, binge eating
Lofexidine

- α-2 agonist
- ~ clonidine
- Clinical trials - Reduce opiate withdrawal signs and symptoms
- Less hypotension than clonidine
- Pending second pivotal trial for an NDA application to FDA
Lofexidine for Opioid Withdrawal

Study Day

N of evaluable patients still participating:
Lofexidine  
Placebo  

Yu, 2008
Lofexidine for Opioid Withdrawal
NCT01863186

- 7-day inpatient double-blind, randomly assigned to one of three doses of study medication (3.2, 2.4 mg total daily dose of lofexidine or placebo)
- Up to 7-day optional open-label treatment inpatient or outpatient lofexidine at variable dosing
- N=600
- 11 sites
- Recruiting
A major unmet medical need is the physical difficulty of withdrawal from the agonist.

FDA-approved diabetes medication pioglitazone (Actos),

Activates the gamma (g) subtype of peroxisome-proliferator-activated receptors (PPARs).

PPAR receptors are expressed in brain, both neurons and glial cells.

In the VTA, PPARg receptors are expressed in cells that produce dopamine (Sarruf et al., 2009).

Pioglitazone prevents signs of opioid withdrawal.
Pioglitazone

- NCT01517165
- N=80
- Pioglitazone (45 mg oral daily) and placebo.
- Treatment for 17 weeks.
- After buprenorphine taper, participants take pioglitazone or a placebo every day for 13 weeks
Cocaine Addiction – Candidate Medications 2013

- Vigabatrin
- Buspirone
- Modafinil
- Topiramate
- Nepicastat
- Buprenorphine
- Cocaine vaccine
- Butyrylcholinesterase
A Multisite, Double-blind, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of Vigabatrin for Treating Cocaine Dependence

Eugene C. Somova, MD, PhD; Douglas Winship, BS; Charles W. Gorodetzky, MD, PhD; Daniel Lewis, BS; Domenic A. Ciraulo, MD; Ganit P. Galloway, PharmD; Scott D. Segal, MD; Michael Sheehan, MD; John D. Roache, PhD; Warren K. Bickel, PhD; Donald Jasinski, MD; Donnie W. Watson, PhD; Steven R. Miller, PhD; Peggy Somova, MS; Theresa Winhusen, PhD

**Importance:** Cocaine dependence is a significant public health problem, yet no validated pharmacological treatment exists. The potent γ-aminobutyric acid (GABA)ergic medication vigabatrin has previously been shown to be effective in a double-blind single-site study conducted in Mexico.

**Objective:** To evaluate the safety and efficacy of vigabatrin for the treatment of cocaine dependence in a US sample.

**Design and Setting:** Multisite, randomized, double-blind, placebo-controlled, 12-week clinical trial with follow-up visits at weeks 13, 16, 20, and 24 in 11 US sites.

**Participants:** In total, 186 treatment-seeking participants with cocaine dependence (mean age, 45 years). Approximately 67% were male, and about 60% were of African American race/ethnicity.

**Interventions:** Participants received twice-daily doses of vigabatrin (total dosage, 3.0 g/d) or matched placebo, plus weekly computerized cognitive behavioral therapy and biweekly individual counseling for 13 weeks. Contingency management encouraged the provision of urine samples.

**Results:** No significant differences were observed between the vigabatrin group and the placebo group on the primary outcome measure (P = .67), key secondary measures (P > .99), or other outcome measures. However, while pill counts and self-reports indicated that more than 66% of all participants (and >63% of the vigabatrin group) took more than 70% of their medication, post hoc vigabatrin urine concentration levels suggested that approximately 40% to 60% of patients taking vigabatrin may not have been adherent. This lack of adherence may have obscured any evidence of vigabatrin efficacy. No visual acuity or visual field deterioration occurred in any of the participants.

**Conclusions and Relevance:** No protocol-defined differences in efficacy between vigabatrin treatment and placebo were detected for any outcome variable. This may have been due to medication nonadherence or, alternatively, due to the weak efficacy of vigabatrin.

**Trial Registration:** clinicaltrials.gov Identifier: NCT00611130
Multisite, Randomized, Double-Blind, Placebo-Controlled Pilot Clinical Trial to Evaluate the Efficacy of Buspirone as a Relapse-Prevention Treatment for Cocaine Dependence

Theresa M. Winhusen, PhD; Frankie Kropp, MS; Robert Lindblad, MD; Antoine Douaihy, MD; Louise Haynes, MSW; Candace Hodgkins, PhD; Karen Chartier, PhD; Kyle M. Kampman, MD; Gaurav Sharma, PhD; Daniel F. Lewis, BA; Paul VanVeldhuisen, PhD; Jeff Theobald, BS; Jeanine May, PhD; and Gregory S. Brigham, PhD

ABSTRACT

Objective: To evaluate the potential efficacy of buspirone as a relapse-prevention treatment for cocaine dependence.

Method: A randomized, double-blind, placebo-controlled, 16-week pilot trial was conducted at 6 clinical sites between August 2012 and June 2013. Adult cocaine users meeting DSM-IV-TR criteria for current cocaine dependence who were scheduled to be in outpatient treatments with substance use disorder (SUD) treatment for 12–10 days when randomized and planning to enroll in local outpatient treatment at any time during the trial's active treatment phase were randomized to buspirone, titrated to 60 mg/d (n = 35) or placebo (n = 27). All participants received psychosocial treatment as provided by the SUD treatment program, but only those in the buspirone group received buspirone. Four weeks after the initial randomization, participants were enrolled. Treatment measures included maximum days of continuous cocaine abstinence (primary), proportion of cocaine use days, and days to first cocaine use during the outcome treatment phase (study weeks 4–15) as assessed by self-report and urine drug screens.

Results: There were no significant treatment effects on maximum continuous days of cocaine abstinence or days to first cocaine use in the female participants (n = 20), with a significant treatment effect by time interaction (F1, 167 = 5.26, P < .001), reflecting an increase in cocaine use by those receiving buspirone, relative to placebo, early in the outpatient treatment phase. A similar effect was not detected in the male participants (n = 23; F1, 169 = 0.14, P = .70).

Conclusions: The results suggest that buspirone is unlikely to have a beneficial effect on preventing relapse to cocaine use and that buspirone for cocaine-dependent women may worsen their cocaine use outcomes.

Trial Registration: ClinicalTrials.gov Identifier: NCT01541159

In 2010, over 1 million people in the United States were abusing or dependent on cocaine,¹ and in Europe, cocaine use has increased significantly in recent years.² Although psychosocial interventions can help, treatment dropout followed by relapse to cocaine use is high. Despite extensive work, there is no US Food and Drug Administration (FDA)–approved treatment for cocaine dependence. Preclinical research has found that dopamine D₂ receptor antagonists can reduce the rewarding effects of cocaine and reinstatement of cocaine seeking.³ In addition, imaging research suggests that dopamine D₂ receptors may be up-regulated in stimulant abusers.⁴ Buspirone is an FDA-approved treatment for generalized anxiety disorder with little abuse potential⁵ and a well-established safety profile.⁶ Buspirone has long been established to be a 5-HT1A agonist,⁷ but in more recent years has been determined to be a dopamine D₂ receptor antagonist⁸ and D₄ agonist⁹ as well. Buspirone has been found to decrease cocaine-cue reinstatement in rats,¹⁰ and both acute⁵ and chronic⁶ buspirone have been found to decrease cocaine self-administration in rhesus monkeys.¹¹ On the basis of the preclinical data showing the ability of buspirone to decrease cocaine reinstatement and self-administration, combined with buspirone’s favorable safety profile, a clinical trial, A Randomized Controlled Evaluation of Buspirone for Relapse-Prevention in Adults with Cocaine Dependence (BRAC), was conducted by the National Institute on Drug Abuse National Drug Abuse Treatment Clinical Trials Network to test the efficacy of buspirone as a cocaine dependence treatment. Prior research suggests that stimulant-dependent patients vary substantially in their response to dopaminergic agents,¹² and thus testing for subgroups for whom buspirone might be differentially effective was planned for in the trial.¹³ One subgroup of interest is gender, given evidence that gender plays a significant role in dopaminergic function and response to dopaminergic agents.¹⁴ Specfic to cocaine, research has found that male monkeys who become dominant have an increase in dopamine D₃/D₄ receptors and evidence less vulnerability to the reinforcing effects of cocaine, whereas female monkeys who become dominant also have an increase in dopamine D₃/D₄ receptors but evidence more vulnerability to cocaine’s reinforcing effects.¹⁵ As described elsewhere,¹⁶ BRAC was designed to be a 2-stage process in which a pilot trial would first be completed to obtain information needed to address important operational aspects critical to the design of the full-scale clinical trial (medication tolerability, adherence, missing data rates, efficacy criteria, etc). The results from the pilot, including an evaluation of gender effects, are reported in the present article.


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Corresponding Author: Theresa M. Winhusen, PhD, University of Cincinnati, Department of Psychiatry, 3131 Harvey Ave, Cincinnati, OH 45229 (Winhusent@uc.edu).
Abstract

This is a randomized, double-blind, placebo-controlled study of modafinil treatment for cocaine dependence. Patients (N = 210) who were actively using cocaine at baseline were randomized to 8 weeks of modafinil (0 mg/day, 200 mg/day, or 400 mg/day) combined with once-weekly cognitive-behavioral therapy. Our primary efficacy measure was cocaine abstinence, based on urine benzoylcegonine (BE) levels, with secondary measures of craving, cocaine withdrawal, retention, and tolerability. We found no significant differences between modafinil and placebo patients on any of these measures. However, there was a significant gender difference in that male patients treated with 400 mg/day tended to be more abstinent than their placebo-treated counterparts (p = .06). Our negative findings might be explained by gender differences and/or inadequate psychosocial treatment intensity in patients with severe cocaine dependence. © 2012 Elsevier Inc. All rights reserved.

Keywords: Modafinil; Cocaine; Pharmacotherapy; Abstinence, Addiction
Modafinil

Fig. 2. Cocaine abstinence rates in the overall sample.
Original Investigation

Topiramate for the Treatment of Cocaine Addiction

Bankole A. Johnson, DSc, MD; Nassima Ait-Daoud, MD; Xin-Qun Wang, MS; J. Kim Penberthy, PhD; Martin A. Javors, PhD; Chamindi Seneviratne, MD; Lei Liu, PhD

Importance: No medication has been established as an efficacious treatment for cocaine dependence. We hypothesized that dual modulation of the mesocorticolimbic dopamine system by topiramate—a glutamate receptor antagonist and γ-aminobutyric acid receptor agonist—would result in efficacious treatment for cocaine dependence compared with placebo.

Objective: To determine the efficacy of topiramate vs placebo as a treatment for cocaine dependence.

Design, Setting, and Participants: Double-blind, randomized, placebo-controlled, 12-week trial of 142 cocaine-dependent adults in clinical research facilities at the University of Virginia between November 22, 2005, and July 25, 2011.

Interventions: Topiramate (n = 71) or placebo (n = 71) in escalating doses from 50 mg/d to the target maintenance dose of 200 mg/d in weeks 6 to 12, combined with weekly cognitive-behavioral treatment.

Main Outcomes and Measures: For the efficacy period, weeks 6 to 12, the primary outcome was the weekly difference from baseline in the proportion of cocaine nonuse days, the secondary outcome was urinary cocaine-free weeks, and exploratory outcomes included craving and self- and observer-rated global functioning on the Clinical Global Impression Scales.

Results: Using an intent-to-treat analysis, topiramate was more efficacious than placebo at increasing the weekly proportion of cocaine nonuse days, irrespective of whether missing data were not or were imputed conservatively to the baseline value (13.3% vs 5.3%, 95% CI for the estimated mean difference, 1.4%–14.6%, \(P = .02\) or 8.9% vs 2.7%, 95% CI for the estimated mean difference, 0.2%–10.1%, \(P = .04\), respectively). Topiramate also was associated, significantly more than placebo, with increasing the likelihood of urinary cocaine-free weeks (16.6% vs 5.8%; odds ratio, 3.21; 95% CI, 1.24–8.32; \(P = .02\)), as well as decreasing craving and improving observer-rated global functioning (all \(P < .05\)).

Conclusions and Relevance: Topiramate is more efficacious than placebo at increasing the mean weekly proportion of cocaine nonuse days and associated measures of clinical improvement among cocaine-dependent individuals.

Trial Registration: clinicaltrials.gov Identifier: NCT00249691
Topiramate

Figure 2. Weekly Mean Proportion of Cocaine Nonuse Days From Baseline Through Study Week 12

Each symbol represents the mean proportion of cocaine nonuse days for each study week, and the error bars indicate standard error (SEM). Weekly mean proportion of cocaine nonuse days was analyzed (A) without imputing missing data and (B) imputing missing data using baseline values. Mean (SEM) values for the weekly proportion of cocaine nonuse days at baseline (i.e., mean cocaine use during the 2-week baseline period) for the 2 groups receiving topiramate and placebo were 0.5775 (0.0294) and 0.5665 (0.0302), respectively. Participants were allocated to treatment groups at the end of the 2-week baseline period. Study medication was provided at week 0 and, therefore, week 1 contains those individuals who had received 1 or more weeks of double-blind treatment.

Johnson et al: JAMA Psychiatry December 2013
The rationale for evaluation of nepicastat (a selective DBH inhibitor) vs. cocaine dependence primarily stems from reports of decreased cocaine use following disulfiram treatment.

Preclinical data are also supportive.

Nepicastat blunts cocaine-primed reinstatement of cocaine-seeking behavior (Schroeder et al., 2010).
A Double Blind, Placebo Controlled Trial Of NEPICASTAT (Dβh Inhibitor) In Cocaine Dependence [Biotie/NIDA]

Nepicastat attenuates cue-induced reinstatement of cocaine seeking

Nepicastat increases DA in PFC (but not in Nac)

Schroeder et al., Neuropsychopharmacology. 2013

Devoto et al., Addict Biol. 2013
Nepicastat

- NCT01704196
- Phase 2, Double-Blind, Placebo-Controlled, Parallel Group, Multi-Center
- N=180
- Recruitment completed
Buprenorphine for Cocaine Dependence

(Montoya, 2004)
Buprenorphine + Naltrexone

- NCT01402492
- Following a successful naloxone challenge, induction onto extended-release naltrexone by injection (Vivitrol®), and a final assessment of eligibility
- Participants randomly assigned to:
  - 4mg buprenorphine plus naltrexone
  - 16 mg buprenorphine plus naltrexone
  - or placebo plus naltrexone
- 8 weeks of treatment.
- N=302
ALKS5461: Buprenorphine + ALKS33

- Blocks mu agonist effects
- Acts more like a selective kappa antagonist
- Cocaine addiction
- Antidepressant
- FDA fast-track designation for MDD
  - The pivotal clinical program will include three core phase 3 efficacy studies and is expected to enroll a total of approximately 1,500 patients with MDD who have had an inadequate response to standard therapies
March 6, 2024, Alkermes announced the initiation of the pivotal clinical development program for ALKS 5461, a once-daily adjunctive treatment for major depressive disorder (MDD). The program includes a total of 12 studies, comprising three core phase 3 efficacy studies and nine supportive studies.
Cocaine Vaccine

• Cocaine is a small molecule. Not expected to elicit an antibody response.

• TA-CD: conjugation of cocaine to the B subunit of cholera toxin (CTB) can enable production of antibodies.

• Antibodies bind to cocaine entering the bloodstream, forming antigen-antibody complexes too large to cross the blood-brain barrier, therefore preventing high concentrations of cocaine reaching the mid-brain.

• Absence of reward stimulus in the brain should reduce the reinforcing psychoactive effects of cocaine.

• By blocking the pleasurable response to cocaine, it is expected that cocaine usage could be reduced in subjects undergoing treatment for cocaine dependence.
Cocaine Vaccine

(Martell et al, 2005)
Cocaine Vaccine (TA-CD)

- Compare TA-CD to placebo on cocaine use in cocaine-dependent individuals who are motivated to quit or reduce use of cocaine
- Phase IIb, RCT, 6 treatment centers
- Primary objective: to evaluate the effect of 5 doses of TA-CD 400 µg versus placebo
- Vaccinations: weeks 1, 3, 5, 9 and 13 with at least 10 days between vaccinations
- 300 subjects were randomized, 152 to the active vaccine and 148 to placebo
Full length article

Vaccine for cocaine dependence:
A randomized double-blind placebo-controlled efficacy trial

Thomas R. Kosten\textsuperscript{a,}*, Coreen B. Domingo\textsuperscript{a}, Daryl Shorter\textsuperscript{a}, Frank Orson\textsuperscript{a}, Charles Green\textsuperscript{b}, Eugene Somoza\textsuperscript{c}, Rachelle Sekerka\textsuperscript{c}, Frances R. Levin\textsuperscript{d}, John J. Mariani\textsuperscript{d}, Maxine Stitzer\textsuperscript{e}, D. Andrew Tompkins\textsuperscript{e}, John Rotrosen\textsuperscript{f}, Vatsal Thakkar\textsuperscript{f}, Benjamin Smoak\textsuperscript{f}, Kyle Kampman\textsuperscript{g}

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\textbf{ABSTRACT}

\textbf{Aims:} We evaluated the immunogenicity, efficacy, and safety of succinylnorcocaine conjugated to cholera toxin B protein as a vaccine for cocaine dependence.

\textbf{Methods:} This 6-site, 24 week Phase III randomized double-blind placebo-controlled trial assessed efficacy during weeks 8 to 16. We measured urine cocaine metabolites thrice weekly as the main outcome.

\textbf{Results:} The 300 subjects (76\% male, 72\% African–American, mean age 46 years) had smoked cocaine on average for 13 days monthly at baseline. We hypothesized that retention might be better and positive urines lower for subjects with anti-cocaine IgG levels of $\geq 42 \mu g/mL$ (high IgG), which was attained by 67\% of the 130 vaccine subjects receiving five vaccinations. Almost 3-times fewer high than low IgG subjects dropped out (7\% vs 20\%). Although for the full 16 weeks cocaine positive urine rates showed no significant difference between the three groups (placebo, high, low IgG), after week 8, more vaccinated than placebo subjects attained abstinence for at least two weeks of the trial (24\% vs 18\%), and the high IgG group had the most cocaine-free urines for the last 2 weeks of treatment (OR 3.02), but neither were significant. Injection site reactions of induration and tenderness differed between placebo and active vaccine, and the 29 serious adverse events did not lead to treatment related withdrawals, or deaths.

\textbf{Conclusions:} The vaccine was safe, but it only partially replicated the efficacy found in the previous study based on retention and attaining abstinence.
Cocaine Vaccine

![Graph showing proportion of cocaine positive urines between active vs placebo groups by biweekly treatment intervals (16 weeks of treatment, n=300).]

Fig. 3. Proportion of cocaine positive urines between active vs placebo groups by biweekly treatment intervals (16 weeks of treatment, n=300).
Cocaine Metabolism

(-)-Cocaine

(-)-Norcocaine

(-)-Norecgonine methyl ester ~5%

(+)-Norecholamine methyl ester ~5%

Methanol

Benzoic acid

Butyrylcholinesterase

Liver carboxylesterase

(+)-Norecholamine methyl ester ~5%
A Double Blind, Placebo Controlled Trial Of TV-1380 (A Bioengineered Esterase) In Cocaine Dependence [Teva/NIDA]

Accelerated cocaine clearance (3.5 mg/kg, i.v.) in male rats with tx with Cocaine Hydrolase

Cocaine Hydrolase Engineered from Human Butyrylcholinesterase (E) Blocks Reinstatement of Drug Seeking in Rats C=cocaine; A= Amphetamine S=Saline

Brimijoin et al., Neuropsychopharmacology. 200
TV-1380

- NCT01887366
- 12-week
- Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study
- Efficacy and Safety of Once-Weekly Intra-Muscular Injections of TV-1380 (150 mg/Week or 300 mg/Week)
- Facilitation of Abstinence in Cocaine-Dependent
- Recruitment completed
Meet The Scientists Who May Have Found The Cure For Drug Addiction

Researchers are closer than ever before to finding a cure for dependence on stimulants like methamphetamine and cocaine. But will big pharma and the FDA stand in the way?

posted on Oct. 9, 2014, at 10:10 p.m.

Keegan Hamilton
BuzzFeed Contributor
18-MC

- 18-methoxycoronaridine hydrochloride (18-MC)
- Shares all the putative anti-addictive effects of ibogaine
- Lacks the neurological and cardiovascular toxicity
- Orally active
- Modulate indirectly the dopaminergic mesolimbic pathway via the blockade of α3β4 nicotinic receptors in the habenulo-interpeduncular pathway and the basolateral amygdala associated with the dorsal diencephalic conduction system (Glick et al., 2008).
FIGURE 2. Comparison of the dose-response effects of intraperitoneally administered ibogaine and 18-MC (40 mg/kg, ip, 30 min earlier) on the self-administration of cocaine (top, left), morphine (top, right), nicotine (bottom, left), and water (bottom, right). Each bar represents the mean (±SEM) of at least 6 rats. Asterisks indicate significant differences (p < 0.05) from vehicle (0 mg/kg).
18-MC

- Reduce the reinforcing efficacy of morphine.
- Enhance the sensitivity of animals to the locomotor and stereotypic effects of cocaine and amphetamines.
- Decrease drug self-administration of stimulants in animals by potentiating the aversive effects of these drugs.
- Signs of withdrawal are typically absent following treatment with adequate single doses.
- Individuals typically do not go back into withdrawal following opioid detoxification with single doses of ibogaine despite opioid abstinence, suggesting a persistent modification of neuroadaptations associated with opioid tolerance or dependence.
- In late 2012, after preliminary toxicology studies were negative, NIDA awarded Savant a grant to support IND-enabling studies and develop a 1 Kg scale cGMP manufacturing process (U01-DA034986).
- Pre-clinical activity against *Leishmania amazonensis* (Delorenzi et al., 2002). Initial clinical study appears well tolerated.
- IND for cocaine addiction.
Cocaine is a small molecule that, although foreign, is too small to activate the immune system.

Leveraging the adenovirus (Ad) gene transfer vector, which is a potent Immunogen, two approaches:

- Conjugate of cocaine analogs to a replication defective adenovirus including alternative serotypes to evade preexisting immunity of the common human Isolates.
- Hybrid synthetic/viral protein strategy to elicit high titer anticocaine antibodies consisting of a cocaine analog coupled to the proteins of a heat and detergent disrupted serotype 5 adenovirus (dAd5) which we hypothesized retains many of the immunogenic adjuvant-like properties of the live Ad vector.

A cocaine hapten synthesized by the Janda lab, GNC (6-(2R,3S)-3-(benzoyloxy)-8-methyl-8-azabicyclo[3.2.1]octane-2-carbonyloxy hexanoic acid) was conjugated to each carrier.

The vaccine dAd5GNC evoked higher titer antibodies.

Vaccinated mice had 4 1% lower brain cocaine levels compared to similarly challenged control naïve mice and the ratio of blood to brain cocaine was 2.5 fold higher the vaccinated group.

Vaccination mediated a suppression of cocaine-induced hyperlocomotor activity after Intravenous challenge with the drug.
Adenovirus-based Cocaine Vaccine

Hicks et al, 2011
Adenovirus-based Cocaine Vaccine

Hicks et al, 2011
Emerging Targets

- Neurokinin Receptor type 1 (NK1) antagonist (aprepitant)
- Toll-Like Receptors (TLR) antagonists
- D4 antagonists
- Acetaldehyde dehydrogenase (ALDH) -2 inhibitors
- Peroxisome proliferator-activated receptor (PPAR) -1 inhibitors
- Actin filament (F-actin) polymerization
- Metabotropic Glutamate Receptor (mGluR) 7 agonists
- phosphodiesterase 7 (PDE7) inhibitors
- Glutamate transporter activators
- Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) inhibition
- Histone deacetylases (HDAC) inhibition
Cannabis

- PF-0445784
- N-acetylcysteine
- Buspirone
- Dronabinol
- Gabapentin
- Quetiapine
- Zolpidem
- Varenicline
- Nabilone
- Nabilone
- Sativex
- Clozapine
- Vilozodone
PF-04457845

- Orally active, long-acting, time-dependent, selective covalent inhibitor of FAAH, which increases anandamide levels
- Shares some similarities with CB1R agonists
- Does not have psychoactive or cognitive effects
- No effects suggestive of abuse liability
- No discontinuation-related withdrawal symptoms
- Phase II clinical trial (n=120) is ongoing
Dronabinol for Marijuana Dependence

Synthetic form of delta-9-THC
RCT double blind
20 mg/day
N= 156
Outpatient

Levin et al, 2011
Dronabinol for Marijuana Dependence

Levin et al, 2011
Gabapentin (Neurontin®)

- Alkylated analog of gamma butyric acid (GABA) and indirectly modulate GABAergic mechanism
- Approved by FDA for epileptic seizures and neuropathic pain.
- Cannabis withdrawal, like alcohol withdrawal, produces both an anxiogenic-like state and increased extrahypothalamic CRF release in the central nucleus of the amygdala in rodents
- These GABA–CRF interactions and their role in the motivational aspects of cannabis relapse supported exploring the efficacy of gabapentin in cannabis dependence
Gabapentin

Cannabis Use Measures

Grams of marijuana smoked per week and corresponding CN-THCCOOH ratios.

- Gabapentin (grams MJ per week)
- Gabapentin (CN-THCCOOH ratio)
- Placebo (grams MJ per week)
- Placebo (CN-THCCOOH ratio)

Mason, 2012
Figure 2  Effects of gabapentin vs placebo on cannabis use measures over the 12-week course of treatment (bars = SEM). (a) Grams of marijuana smoked per week and corresponding CN-THCCOOH ratios. Inset: Details for weeks 9 through 12. (b) Days per week of marijuana use.

Mason, 2012
Gabapentin

- NCT00974376
- N=250
- 12-week, double blind, placebo controlled study
- Evaluate the efficacy of gabapentin in treating outpatients with cannabis dependence
- Dose 1,200 mg/day for 12 weeks
- Recruiting
N-acetylcysteine (NAC)

- Antioxidant
- Naturally occurring amino acid cysteine,
- Role of the neurotransmitter glutamate in addiction
- Animal studies: chronic drug self-administration down-regulates the cystine-glutamate exchanger in the nucleus accumbens
- NAC regulates this exchanger, normalizing a drug-induced pathology and reducing reinstatement of drug seeking
N-acetylcysteine

Grey et al, 2012
NAC

• NCT01675661
• N=300 treatment-seeking cannabis-dependent adults
• Double-blind
• NAC 1200 mg versus matched placebo twice daily
• Contingency management (CM)
• Recruiting
Alcohol

- Disulfiram
- Naltrexone
- Acamprosate
- Nalmefene
- Topiramate
- Ondansetron
- Baclofen
- Varenicline
- Gabapentin
Varenicline for Alcohol

N=200 alcohol dep
Varenicline 2 mg/day or placebo
13 weeks
Alcohol

- Corticotropin-releasing hormone (CRH) type 1 antagonists (e.g., antalarmin)
- Glutamate transporter 1 (GLT-1) activators (e.g. ceftriaxone)
- Metabotropic Glutamate Receptor (mGluR) 1 and 5
- Co-agonists of NMDA receptor (Serine, Glycine)
- Glycine receptor (GlyR) and transporter (GlyT) modulators
- D3 receptor antagonists
- Monoamine stabilizer (e.g., OSU6162)
- Kappa Opiate Receptor Antagonists
- CB1 receptor antagonists, FAAH inhibitors
- Ghreling receptor antagonism
- Alpha 1 adrenergic receptor antagonist (e.g. prazosin)
- Peroxisome proliferator-activated receptor (PPAR) gamma modulator (e.g. Pioglitazone)
- Neurokinin Receptor type 1 (NK1) antagonist (aprepitant)
- GABA-B antagonist (baclofen)
Conclusions

• FDA approved meds for opioid, alcohol, and nicotine dependence
• Long-term success of meds is low
• No meds approved for marijuana and cocaine
• Multiple medications being investigated
• Clinical trials failure is frequent
• Some promising medication candidates
• Keep investigating... Don’t give up!