In the proposed EC study, we will (1) employ a randomized, double-blind, between-groups experimental design that will consist of 8 weeks of treatment with NAC (2400mg) or placebo medication; (2) use standardized, repeated dependent measures to rigorously assess AUD severity and PTSD symptomatology during treatment and follow-up; (3) collect biologic measures of alcohol use; (4) measure impairment in associated areas of functioning (e.g., depression, sleep, suicidality, family/social functioning); and (5) employ advanced neuroimaging techniques before and after treatment. This proposal is directly responsive to the mission of the Institute for Translational Neuroscience (ITN) and the U.S. Army/Department of Defense in that it seeks to accelerate the development of new, medication-based treatments to mitigate the impact of AUD and comorbid psychological conditions, such as PTSD, in the military/Veteran context.

Keywords
PTSD, addiction, stress, glutamate, alcohol, substance abuse, Glia, N-acetylcysteine (NAC)

Recruiting
Yes, check here [3]

Treatment Type
Pharmacological: N-acetylcysteine

Target Population
Veterans

IND
this study has an active IND

Development of an animal model and novel treatments for comorbid PTSD and cocaine addiction
Principal Investigator(s): Lori A. Knackstedt, Ph.D. [4]  
University of Florida [5]
### Lay Abstract

The present proposal is aimed at developing an animal model of comorbid PTSD and cocaine addiction/relapse for the screening of highly translational compounds to reduce PTSD symptoms and the motivation to seek cocaine. Our overarching hypothesis is that the inhibition of the renin-angiotensin system will ameliorate the symptoms of PTSD and will be successful in attenuating cocaine-seeking in animals exposed to traumatic stress. We have chosen to test the ability of the angiotensin-1 receptor antagonist, candesartan, and the angiotensin converting enzyme (ACE) inhibitor, captopril, to reduce symptoms of PTSD and potentially reduce cocaine self-administration in this rat model.

### Keywords

cocaine addiction/relapse, PTSD, Candesartan, Captopril, Ceftriaxone, Glutamate, Endocannabinoids

### Recruiting

n/a

### Treatment Type

Pharmacological: Candesartan & Captopril

### Target Population

Rat Studies

### IND

n/a

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**Epigenetic modulation of interactions between fear and substance abuse**

Principal Investigator(s): Kennon M. Lattal, Ph.D. [6]

*Oregon Health & Science University* [7]

We found that a single traumatic event caused persistent effects on methamphetamine and alcohol self-administration that often persisted over 30 days after trauma. During our support from the ITN, we also found that a novel HDAC3 inhibitor (RGFP966) promotes extinction of drug-seeking in a rodent self-administration model, as well as extinction of fear. In this extend-and-confirm application, we bring these two findings together and ask how selective inhibition of HDAC3 may promote extinction and weaken relapse after a traumatic event. This is a novel behavioral model coupled with a novel pharmacological approach. Further, we will investigate the molecular consequences of trauma and relapse, and how they may be altered by HDAC3 inhibition during extinction. These proposed experiments have tremendous clinical promise, as RGFP966 is already in Phase 1 clinical trials for treating Friedreich’s ataxia and we have strong preliminary data showing its effects on fear and drug seeking.

### Keywords

substance abuse disorder, memory, epigenetics, methamphetamine, PTSD, extinction, histone acetylation, alcohol

### Recruiting

n/a

### Treatment Type

Pharmacological: RGFP966
Reconsolidation and extinction: Using epigenetic signatures to challenge conventional wisdom [8]
Effects of D1 receptor knockout on fear and reward learning [9]

**Current Proof of Principle Projects funded by ITN**

### N-acetylcysteine Treatment of Hazardous or Harmful Alcohol Use in Veterans with TBI

**Principal Investigator(s): Steven L. Batki, M.D. [10]**

*Northern California Institute for Research and Education* [11]

**Lay Abstract**
The overall goal of the proposed project is to improve the care of veterans with mild traumatic brain injury (mTBI) and unhealthy alcohol use. We propose to conduct a pilot controlled clinical trial to assess the efficacy of N-acetylcysteine (NAC) to reduce alcohol use and improve brain injury symptoms in veterans with mTBI who consume alcohol at hazardous or harmful levels. This proposed project builds upon our current IMN-funded research on topiramate pharmacotherapy for heavy alcohol use in veterans with mTBI.

**Keywords**
alcohol abuse, TBI, N-acetylcysteine

**Recruiting**
pending

**Treatment Type**
Pharmacological: N-acetylcysteine

**Target Population**
Veterans

**IND**
this study has an active IND

### Use of kappa opioid receptor antagonists to prevent opiate abuse after use of prescription opioid painkillers

**Principal Investigator(s): Elena Chartoff, Ph.D. [12]**

*McLean Hospital* [13]

**Lay Abstract**
determine if the orally available KOR antagonist JDTic administered to rats during morphine withdrawal blocks withdrawal-induced negative affective states and likelihood to engage in oxycodone IV self-administration.

**Keywords**
n/a
### Oxytocin Supresses SUD Associated with Chronic Stress

**Principal Investigator(s):** Jennifer Mitchell, Ph.D. [14]
**University of California, San Francisco** [15]

<table>
<thead>
<tr>
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<th>n/a</th>
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<td>Rat Studies</td>
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<tr>
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<td>n/a</td>
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**Lay Abstract**
Determine whether IN OT will decrease craving to use ETOH and stress reactivity following exposure to lab-induced stress among ADSMs with a dual-diagnosis of AUD & PTSD.

**Keywords**
Alcohol Use Disorder, AUD, PTSD, oxytocin, military

**Recruiting**
Yes, check here [3]

**Treatment Type**
Pharmacological: Oxytocin (intranasal)

**Target Population**
Fort Gordon EAMC In-patient active duty

**IND**
This study has an active IND

### Effects of Tolcapone on Decision Making and ETOH intake using a laboratory bar in moderate/heavy social drinking

**Principal Investigator(s):** Jennifer Mitchell, Ph.D. [14]
**University of California, San Francisco** [15]

<table>
<thead>
<tr>
<th>Recruiting</th>
<th>Data analysis only</th>
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<tbody>
<tr>
<td><strong>Treatment Type</strong></td>
<td>Pharmacological: Tolcapone</td>
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</table>

**Lay Abstract**
An experimental bar is a behavioral technique that can be used to pre-screen new treatment strategies for alcoholism in a rapid and inexpensive manner. It is a well-established tool to mimic a social bar setting in a clinical facility in order to study the decision making skills surrounding alcohol consumption. As we have already demonstrated effects of tolcapone on decision making in both healthy controls and abstinent alcoholics, this experiment will allow us to ascertain its effects on active alcohol consumption and real-time decision making for alcohol versus monetary rewards.

**Keywords**
Dopamine, Tolcapone, Alcohol Use Disorder, AUD, decision-making

**Recruiting**
Data analysis only
The effects of oxytocin on social ability, alcohol approach bias, and startle hyperreactivity in veterans with alcohol use disorder and post traumatic stress disorder.

Principal Investigator(s): Josh Woolley, M.D., Ph.D. [16]
Northern California Institute for Research and Education [11]

Lay Abstract
We propose to investigate the effects of oxytocin on alcohol-related behaviors, social abilities, and physiological startle responses in patients with PTSD & AUD using a randomized, placebo-controlled, dose-tiered, within-subject study design. Specifically, we will determine if intranasal administration of a single dose of the pro-social neuropeptide oxytocin decreases alcohol-related approach bias and cravings, enhances social abilities, and decreases physiological hyperactivity during a fear-potentiated startle paradigm. We will also determine the optimal dose to achieve these effects and will explore psychosocial predictors of responses to oxytocin. If successful, we will extend the proposed work with a longitudinal clinical trial of chronic oxytocin administration in patients with AUD and PTSD. The proposed work has the potential to yield a novel pharmacological treatment for AUD and PTSD, both leading causes of disability in the US Military for which currently available treatments are inadequate.

Keywords
alcohol abuse, oxytocin

Recruiting
n/a

Treatment Type
Pharmacological: Oxytocin (intranasal)

Target Population
San Francisco VAMC

IND
this study has an active IND

- American Alcohol Photo Stimuli (AAPS): A standardized set of alcohol and matched non-alcohol images [17]