Research Projects - current

Current Extend and Confirm Projects funded by the ITN

Glial Regulators for Treating Comorbid Posttraumatic Stress Disorder and Substance Use Disorders
Principal Investigator(s): Sudie Back, Ph.D. [1]
Medical University of South Carolina [2]

<table>
<thead>
<tr>
<th>Lay Abstract</th>
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<td>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.</td>
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<table>
<thead>
<tr>
<th>Keywords</th>
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<td>PTSD, addiction, stress, glutamate, alcohol, substance abuse, Glia, N-acetylcysteine (NAC)</td>
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<tr>
<th>Recruiting</th>
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<th>Treatment Type</th>
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<td>Pharmacological: N-acetylcysteine</td>
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<th>Target Population</th>
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<td>Veterans</td>
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<td>this study has an active IND</td>
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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

Neuroprotection Against Alcohol Neurotoxicity and Traumatic Brain Injury in a Cerebellar Slice Model
Principal Investigator(s): Michael E. Charness, M.D. [12]
Boston VA Research Institute [13]

Lay Abstract
Task #1: To establish a model of focal mechanical injury to cultured cerebellar slices from young adult mice. Task #2: To determine whether ethanol potentiates the effects of TBI. Task #3: To determine whether NAP protects against the effects of TBI, ethanol exposure, or both.

Keywords
alcohol abuse, TBI, NAP, mouse studies
| Recruiting | n/a |
| Treatment Type | Pharmacological: NAPVSIPQ (NAP) |
| Target Population | Mouse Studies |
| IND | n/a |

**Use of kappa opioid receptor antagonists to prevent opiate abuse after use of prescription opioid painkillers**  
Principal Investigator(s): Elena Chartoff, Ph.D. [14]  
*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 |
| Recruiting | n/a |
| Treatment Type | Pharmacological: kappa opioid antagonists |
| Target Population | Rat Studies |
| IND | n/a |

**Restoration of glial glutamate transport to prevent posttraumatic stress and vulnerability to alcohol and marijuana use and relapse**  
Principal Investigator(s): Peter W. Kalivas, Ph.D. [15]  
*Medical University of South Carolina* [2]
Although we used NAC in a pilot study with success in treating Veterans with comorbid PTSD/SUDs, it is unknown if using NAC either prophylactically, or immediately after a stressful experience can prevent vulnerability to developing PTSD or comorbid PTSD/SUDs. We propose preclinical validation for the use of NAC prophylactically or immediately post-combat stress to reduce the neurological sequelae that establishes PTSD and PTSD/SUDs comorbidity. 1) We have expanded the validity of the animal model by associating an odor with the immobilization stress, and we use exposure to the odor to provoke relapse (reinstated lever pressing) in animals trained to self-administer drug. 2) We will treat rats with N-acetylcysteine either during or immediately after exposure to immobilization stress, and determine if this prevents stress-induced augmented acquisition of drug self-administration and the capacity of the stress-associated odor to reinstate drug seeking. Simultaneously, we will validate that NAC has normalized EAAT2 levels, a key neurological action of NAC’s protective effects. 3) We recently developed an animal model of rat i.v. self-administration and reinstatement of the key constituents of marijuana, ?9-tetrahydrocannabinol and cannabidiol. Marijuana abuse is a substantially larger problem in Veterans with comorbid PTSD and SUDs than cocaine abuse, making use of this model for the determining the biological basis of PTSD/SUDs comorbidity more clinically relevant.

**Lay Abstract**

**Keywords** PTSD, SUDs, Marijuana Abuse, Stress, Prevention, Glutamate transport, N-acetylcysteine

**Recruiting** n/a

**Treatment Type** NAC

**Target Population** Rat Studies

**IND** n/a

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**Oxytocin Supresses SUD Associated with Chronic Stress**

Principal Investigator(s): Jennifer Mitchell, Ph.D. [16]

*University of California, San Francisco* [17]

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 In-patient AD
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. [16]
University of California, San Francisco [17]

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
Yes, check here [3]

Treatment Type
Pharmacological: Tolcapone

Target Population
Human

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. [18]
Northern California Institute for Research and Education [11]
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 [19]

Sept.15.16 ASUD_MOMR_Project list_ITN.xlsx [20]

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