

# Alcohol and Substance Abuse Disorders Research Program

**Alcohol and Substance Use Disorders (ASUDs) impact U.S. Service members and Veterans:** Substance abuse was involved in 30% of the Army's suicide deaths from 2005–2009 (National Institute on Drug Abuse. 2013. *Substance Abuse in the Military*). Veterans with both PTSD and ASUD exhibit more persistent, severe, and treatment-resistant symptoms and are at much higher risk for suicide than Veterans who have either disorder alone (McCarthy E and Petrakis I. 2010. *CNS Drugs*. 24(12):997–1007). The 2013 Institute of Medicine report, *Substance Use Disorders in the U.S. Armed Forces*, characterized the overall prevalence of heavy drinking at 20% and the overall prevalence of illicit drug use at 12%.

## VISION

Decrease the clinical impact of alcohol and substance abuse

## MISSION

To explore integrated approaches to address alcohol and substance use disorders, especially related to TBI and PTSD, through multidisciplinary, team-based research efforts that translate basic knowledge into enhanced clinical pharmacological treatment protocols for Service members, Veterans, and the American public

## PROGRAM HISTORY

The Department of Defense (DoD) Alcohol and Substance Abuse Disorders Research Program (ASADRP) was established in fiscal year 2010 (FY10) with a Congressional appropriation of \$6.375 million (M). Since then, the program has established a network of multidisciplinary, translational research teams with the explicit goal of accelerating the delivery of new or improved treatments for ASUD, and federal funding for its research has led to a total appropriation of \$36.075M to the ASADRP. The goal of the program is to identify and develop new medications to improve treatment outcomes

for ASUD, especially related to traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD). The program's approach is to organize multidisciplinary, team-based translational research efforts to identify promising compounds, conduct proof-of-principle basic research to determine which compounds are most appropriate for human research trials, and conduct human proof-of-principle trials with promising compounds. The goal of this approach is to translate contemporary basic science knowledge into enhanced clinical pharmacological treatment protocols for ASUD.

## RESEARCH STRATEGY

The Pharmacotherapies for Alcohol and Substance Abuse (PASA) Consortium has three aims under the primary objective to develop medications to treat ASUD in the context of the reciprocal relationship among ASUD, the physiological state of stress, and the subjective state of anxiety as manifested in PTSD or TBI. The three broad aims are:

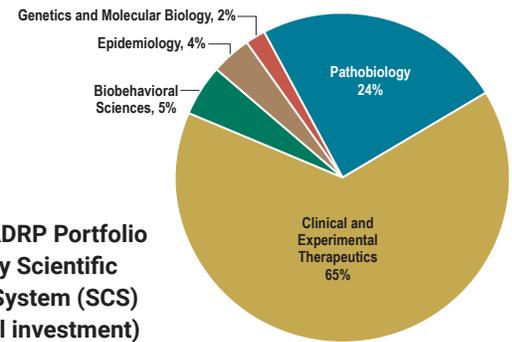
1. Discover novel medications and combination medications for ASUD.
2. Develop these medications through a rational Phase I proof-of-concept pipeline.
3. Conduct Phase II preliminary safety and efficacy trials of potential medication combinations in optimal target populations and explore functional genetic polymorphisms for matching patients to these medications.



## PROGRAM PORTFOLIO: FUNDING RESEARCH FROM BENCH TO BEDSIDE

The ASADRP designed an investment strategy that emphasizes high-impact translational research, innovation, and development for talented young investigators who are committed to studying this disease. The ASADRP investment strategy portfolio in the figure at right shows the percentage of awards funded in each research area. There is widespread funding across scientific areas.

**FY10-FY17 ASADRP Portfolio Investment by Scientific Classification System (SCS) Code (% of total investment)**



## THE INSTITUTE FOR TRANSLATIONAL NEUROSCIENCE (ITN) CONSORTIUM



**Lori A. Knackstedt, Ph.D., Development of an Animal Model and Novel Treatments for Comorbid Post-Traumatic Stress Disorder (PTSD) and Cocaine Addiction, University of Florida**

Dr. Knackstedt's team developed a novel animal model of comorbid PTSD and cocaine addiction in order to screen medications for their ability to reduce cocaine relapse. Following a brief exposure to a stressor, rats characterized as displaying long-lasting PTSD-like anxiety display greater levels of persistent cocaine-seeking than do stressed rats that are "resilient" to the stressor. Ceftriaxone, an antibiotic, prevented cocaine relapse in non-stressed controls and resilient rats and had only a modest effect in PTSD-like rats. Combination therapy with ceftriaxone and a positive allosteric modulator of the mGlu5 receptor was able to fully prevent cocaine relapse in PTSD-like rats while also reducing signs of anxiety.



**Steven L. Batki, M.D., N-Acetylcysteine Treatment of Hazardous or Harmful Alcohol use in Veterans with TBI. Northern California Institute for Research & Education; the University of California, San Francisco, School of Medicine; and the San Francisco Veterans Health Care System**

Dr. Batki's clinical research aims to improve the treatment of Alcohol Use Disorder (AUD) in Veterans with the complex co-occurring disorders of TBI and PTSD. Veterans with this form of polytrauma have high rates of alcohol misuse and are especially vulnerable to the harmful effects of alcohol, yet there have been few efforts to design treatments that address their multiple problems. Dr. Batki is conducting clinical trials of medications such as N-acetylcysteine (NAC), an over-the-counter nutritional supplement with very few side effects, to treat Veterans with TBI and AUD. Findings from his current work—a pilot controlled clinical trial of NAC— suggest that NAC may help reduce alcohol use, PTSD symptoms, and impulsivity in Veterans with TBI and may therefore improve the care of these patients.

## THE PHARMACOTHERAPIES FOR ALCOHOL AND SUBSTANCE ABUSE (PASA) CONSORTIUM



**Colin N. Haile, M.D., Ph.D., Assessing Pharmacotherapies in Animal Models of Post-Traumatic Stress Disorder (PTSD) and Alcohol Use Disorder (AUD), University of Houston**

Dr. Haile's work focuses on assessing promising medications in animal models of PTSD and AUD to determine whether they have potential therapeutic use for humans who suffer from these disorders. Dr. Haile's preclinical trial is testing the ability of medications (a kappa opioid antagonist; doxazosin; a GABA-B Positive Allosteric Modulator; and baclofen) to reduce behavioral signs of PTSD and AUD in the animal models to assess the mechanism of action and as proof-of-concept enabling studies for Food and Drug Administration approval of human Phase II clinical trials.



**Christopher Verrico, Ph.D., Zonisamide as a New Treatment for PTSD and Co-Occurring AUD, Baylor College of Medicine**

Dr. Verrico's two current studies focus on treating PTSD and AUD concurrently to facilitate improvements in PTSD symptoms and reductions in alcohol use. The Alcohol Interaction Study (with co-Principal Investigator, Dr. Dewleen Baker) is a human laboratory study on 10 subjects that is intended to provide the safety data needed for additional study of a novel, selective, glucocorticoid antagonist. The objective of the zonisamide study is to determine whether, compared to placebo, zonisamide is a safe and efficacious treatment for PTSD and AUD in Veterans with PTSD and co-occurring AUD. This trial is a randomized, double-blind study of 5 weeks of treatment with zonisamide in 60 Veterans.