

Alcohol and Substance Abuse Disorders Research Program

Strategic Plan

INTRODUCTION

Since the program's inception, the Alcohol and Substance Abuse Disorders Research Program (ASADRP) has followed the 1993 Institute of Medicine (IOM) recommendations to the Department of Defense (DoD) Congressionally Directed Medical Research Programs (CDMRP) on the peer review procedures to be used in evaluating an application's scientific merit and the preferred programmatic investment strategy for funding.¹ A two-tiered peer review system is used where the primary criterion for awarding grants is scientific excellence (first tier – peer review). Programmatic relevance is a secondary criterion (second tier – programmatic review), to ensure that awards are made to those applications that best meet the ASADRP's programmatic goals.

In 2015, an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine (NASEM) was assembled to evaluate the review process utilized by the CDMRP in managing the Congressional Special Interest programs. This evaluation, which was the fourth time the CDMRP was evaluated by the NASEM, included (1) a review of the CDMRP's two-tiered peer review process¹ and (2) its coordination of research priorities with the National Institutes of Health (NIH) and Department of Veterans Affairs (VA). The committee's report provided recommendations on how the process for reviewing and selecting studies might be improved. The committee found that, overall, "the CDMRP review process is effective in dispensing research funding across its programs and is not in need of extensive revisions." However, the committee also recommended ways to potentially improve the CDMRP review process, including the development of a strategic plan for each research program. Although the CDMRP has no guarantee that Congress will appropriate funds for any program in any given year, the committee recommended:

"Each CDMRP research program should develop a strategic plan that identifies and evaluates research foci, benchmarks for success, and investment opportunities for 3–5 years into the future. The plan should be re-evaluated and updated as necessary at the end of that interval. Each strategic plan should specify the mission of the program, coordination activities with other organizations, research priorities, how those priorities will be addressed by future award mechanisms, how research outcomes will be tracked, and how outcomes will inform future research initiatives."²

A distinct feature of the CDMRP is the consumer-informed approach to understanding the gaps in research and recommending investments based on them. The consumer advocates on the CDMRP Programmatic Panels provide perspective on the needs of individuals and family members. Consumer inputs offer a different perspective by providing real-life experiences and raising issues not previously considered. Consumer voices can also help focus the clinical research program and influence the choice of endpoints to better reflect their expectations for the drug under development. Consumer engagement renders better outcomes, contributes toward a transparent and holistic decision-making process, increases acceptability, and builds trust.

ASADRP BACKGROUND AND OVERVIEW

The 2013 IOM report, *Substance Use Disorders in the U.S. Armed Forces*,³ characterized the overall prevalence of heavy drinking at 20% and the overall prevalence of illicit drug use at 12% in 2008. Rates of acute and chronic incident alcohol diagnoses increased from 2001 through 2010, especially for the active duty component, indicating the increasing medical burden imposed on the Military Health System by excessive alcohol use. The report recommended that the DoD assume leadership to ensure the consistency and quality of treatment services available to those with alcohol and substance use disorders (ASUDs), given the burden of

such disorders in the military. Substance abuse was involved in 30% of the Army’s suicide deaths since 2003.⁴ Veterans with both post-traumatic stress disorder (PTSD) and ASUDs exhibit more persistent, severe, and treatment-resistant symptoms and are at much higher risk for suicide than Veterans who have either disorder alone.⁵ Veterans can have their PTSD complicated by chronic traumatic brain injury (TBI) effects, which are worsened by ASUDs. Compared to individuals with PTSD or an ASUD alone, those with PTSD and a coexisting ASUD exhibit a greater severity of both PTSD and ASUD symptoms.^{6,7}

In fiscal year 2010 (FY10), the DoD and the Congress expressed strong concern about increasing problems associated with alcohol and drug abuse among military personnel. As a result, the ASADRP was established in 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 ASUDs, and federal funding for related 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 ASUDs, especially disorders related to TBI and 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. If successful, this approach could result in translation of contemporary basic science knowledge into enhanced clinical pharmacological treatment protocols for ASUDs.

FUNDING HISTORY AND NUMBER OF AWARDS

From FY10–FY19, a total of \$44.075M has been appropriated to the ASADRP. The program supports multidisciplinary, team-based research efforts that translate basic knowledge into enhanced clinical protocols and selects awards through a competitive, peer-reviewed process according to the two-tier review model recommended by the IOM.¹ Consumers participate as full members on the Programmatic Panel and all peer review panels. The overall goal is to fund scientifically meritorious research in accordance with directives received from Congress using a competitive peer review process. Appropriations supported four awards to the University of California, San Francisco, for the Institute for Translational Neuroscience (ITN) Consortium (formerly at the Ernest Gallo Clinic and Research Center), as well as two awards to the Research Triangle Institute for the Pharmacotherapies for Alcohol and Substance Abuse (PASA) Consortium. The ASADRP funds research at military (Naval Medical Center San Diego and Fort Gordon) and non-military (VA and academic) institutions. The ITN period of performance has expired and all awards have closed.

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

Consortium	Principle Investigator	Institution
PASA	Dr. Tracy Nolen	Research Triangle Institute

PASA CONSORTIUM MEMBER INSTITUTIONS

- Baylor College of Medicine
- Department of Veterans Affairs
- Medical University of South Carolina
- RTI International
- Uniformed Services University
- University of California, San Diego
- University of Houston
- University of Washington School of Medicine
- Virginia Commonwealth University
- Williams College
- University of Kentucky
- Scripps Research Institute
- VA Connecticut Healthcare System
- University of Texas Houston Czik Scholl of Nursing

ASADRP RESEARCH PORTFOLIO

Projects FY10-FY19



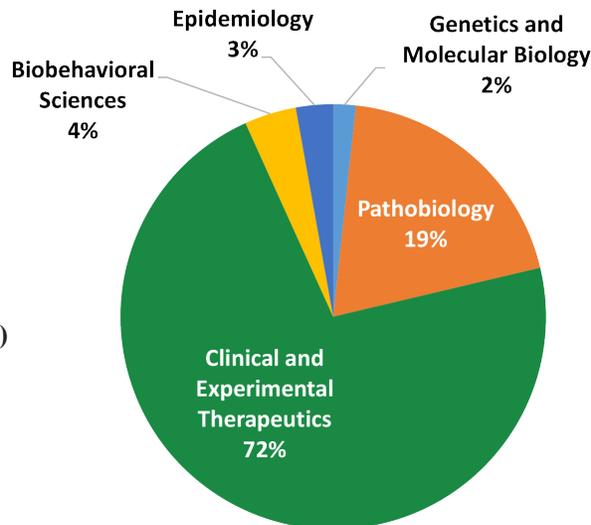
Consortium	Open	Closed
ITN	0	29
PASA	10	4

The following medications/compounds are being studied by PASA for their effects on alcohol use disorder (AUD) and opioid use disorders (OUDs) on patients with comorbid PTSD:

- A kappa opiate receptor antagonist (CERC-501)
- Alpha adrenergic blockers (doxazosin and lofexidine)
- A cortisol blocker (PT-150)
- A gamma amino butyric acid type B(GABAB) receptor allosteric modulator (ASP8062)
- A GABA receptor agonist (baclofen)
- A complex anti-seizure medication (zonisamide)
- A partial opioid agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor (buprenorphine)
- An opioid antagonist (naltrexone)
- A highly selective α 2a adrenergic receptor agonist (BXCL 501 – a sublingual film containing dexmedetomidine)
- An aldehyde dehydrogenase 2 (ALDH2) inhibitor (ANS-6637)
- An FKBP5 inhibitor (benztropine mesylate)
- A vaccine formulation of CRM-GFEN+Alum+dmLT (CRM197-glutaryl fentanyl plus the adjuvants aluminum hydroxide and dmLT)

Nine medications are undergoing or have completed preclinical investigation (baclofen, doxazosin, zonisamide, ASP8062, CERC-501, PT150, FKBP5 inhibitor, buprenorphine, and a TT-GFEN vaccine), and six are undergoing or being considered for clinical evaluations (PT150, buprenorphine, naltrexone, lofexidine, BXCL 501, and ANS-6637). To broadly explore the treatment of AUD and PTSD, we have selected compounds with a range of non-overlapping mechanisms of action that have been shown to be relevant in these diseases.

FY10–FY19 ASADRP Portfolio Investment by Research Category (% of Total Investment)





RESEARCH AND FUNDING LANDSCAPE

STATE OF THE SCIENCE

AUD and PTSD Comorbidity in the Military — Understanding the Problem

Despite estimates that comorbidities between PTSD and AUD are higher in Veterans than civilians,⁸ there have been few randomized controlled trials of medications in Veterans, and clinical studies devoted to investigating the treatment of PTSD with comorbid substance abuse disorders (SUDs) have yielded little progress in developing new therapeutics.^{9,10} Current services offered to Veterans do not adequately address co-occurring SUDs and PTSD, and there is an immediate need for the development of novel, evidence-based treatments. The hazards for AUD were significantly elevated in those with mild TBI compared to controls.¹¹ Veterans with both PTSD and AUD exhibit more persistent, severe, and treatment-resistant symptoms and are at much higher risk for suicide than Veterans who have either disorder alone.⁵

Addiction is characterized by cycles of binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation, with high rates of relapse. Repeated cycles of withdrawal and relapse promote adverse neuroadaptation.

Stress and prior trauma are important risk factors for substance abuse, which is influenced by a complex combination of biological (e.g., genetic), psychological, and social factors, as well as age or stage of development.

Pharmacotherapies for PTSD in Combat Veterans

The Food and Drug Administration (FDA) has approved two selective serotonin reuptake inhibitor (SSRI) oral medications, Zoloft (sertraline) and Paxil (paroxetine), for treating PTSD.

The 2010 VA/DoD Clinical Practice Guideline for Management of Post-Traumatic Stress¹² recommends selective SSRIs (fluoxetine, paroxetine, or sertraline) or the serotonin norepinephrine reuptake inhibitor, venlafaxine. Studies in combat Veterans with PTSD, however, have reported variable responses to SSRI therapy. These findings suggest that SSRIs might not be as useful for Veterans with combat-related PTSD as they are for civilian patients with PTSD.¹³ SSRIs are more effective in women than in men and more effective in treating acute PTSD than chronic disease.¹⁴ An early study with sertraline demonstrated clinical efficacy in patients with PTSD and comorbid alcohol dependence.¹⁵

An impediment to development of PTSD treatments has been the high placebo-response rates across PTSD clinical trials (> 25%) using subjective PTSD symptom ratings.¹⁶

Pharmacologic Treatment for AUD

Pharmacologic treatment of drug withdrawal often involves substituting a long-acting agent for the abused drug, then gradually tapering its dosage. Desirable qualities for outpatient medications include administration by mouth, low potential for abuse and overdose, and low incidence of side effects. Outpatient management is appropriate for patients with mild-to-moderate withdrawal symptoms who have no important coexisting conditions and have supportive personnel who are willing to monitor their progress. Patients often achieve abstinence without pharmacologic interventions.

FDA-Approved Medications for AUD

Naltrexone

- Mechanism of Action: Oral opioid antagonist
- Oral formulation (approved 1994)
- Inexpensive, modest efficacy
- Long-acting, intramuscular naltrexone (approved 2006)
- Improved compliance, well-tolerated, effective

Antabuse (in use for over 50 years)

- Mechanism of Action: Inhibits aldehyde dehydrogenase
- Efficacy linked to compliance

Campral (approved 2004)

- Synthetic derivative of homotaurine (analogue of GABA); may effect GABA or glutamate system
- Most studies conducted in Europe; more recently tested in United States; dose-response effect

These medications, however, are not widely used due to limited effectiveness.¹⁷ There is a need to find novel, safe, well-tolerated, and low-cost medications for the treatment of AUD, especially related to PTSD and TBI.



RESEARCH FUNDING LANDSCAPE

Funding for ASUD research comes from many sources through a variety of programs. Many are funded by the Federal Government through the NIH, CDMRP, and VA. To help coordinate the ASADRP investment strategy, the ASADRP Programmatic Panel has representation from federal ASUD funding agencies such as the VA, National Institute on Alcohol Abuse and Alcoholism, and National Institute on Drug Abuse. As the ASADRP develops its own research program focus and portfolio, it remains mindful of the research efforts of other funding organizations.

Today's medical research environment is dynamic. New compounds are being created and made available to researchers at an ever-faster rate; new technologies are emerging that will enable research in the future that is impossible today. The ASADRP continually monitors new technological advances that may provide a better understanding of pharmacological interventions for ASUDs, especially with comorbid PTSD and/or TBI.

In developing the ASADRP Strategic Plan, the Programmatic Panel members reviewed the current research and funding environment for ASUDs and considered the existing research portfolios and emerging technologies that offer the potential to transform the pharmacological treatment of these disorders. A core component of the ASADRP's ongoing strategic planning efforts is an evaluation of pharmacological interventions for ASUDs, especially with comorbid PTSD and/or TBI. The ASADRP must fit within this environment and effectively respond to changes to maximize the value and impact of funded ASUD research.

STRATEGIC DIRECTION

Based on the current state of ASUD research, as well as the funding landscape provided by other federal and private organizations and the needs of the ASUD community, the ASADRP developed its research consortium roadmap to fund applications for developing new medications that can be brought to therapeutic use to improve treatment outcomes for ASUDs, especially ASUDs with TBI and/or PTSD comorbidities. Studies of military and Veteran populations are encouraged. These medications will ideally address the comorbidity between ASUDs and PTSD because this comorbidity is common in a military population along with mild to moderate TBI. AUD is the most common ASUD in the military, but OUD also has developed significant clinical importance due to prolonged pain treatments with opiates. Since both ASUDs and PTSD have FDA-approved pharmacotherapies, one logical starting point for treating this comorbidity might be to augment or combine these agents. The approved agents for AUD are disulfiram, acamprosate, and naltrexone in either an oral and long-acting injection formulation. For OUD, approved agents include methadone, buprenorphine, and naltrexone. For PTSD, two serotonin reuptake inhibitors are FDA-approved pharmacotherapies. While TBI is of interest, it has no FDA-approved specific pharmacotherapies, and no combination of these disorders has an FDA-approved pharmacotherapy. Commercialization linked to FDA approval for these new medications or combinations of medications is critical so that early linkages to pharmaceutical companies are considered among the strengths of any application for ASADRP funding.

The ASADRP developed its research consortium roadmap to address the following Specific Aims:

Aim 1. Discover novel medications and medication combinations in animal models for ASUD.

Aim 2. Develop medications through a rational proof-of-concept pipeline in small human studies.

Aim 3. Conduct medication safety and efficacy clinical trials of potential medication combinations in optimal target populations and explore functional genetic polymorphisms for matching patients to these medications.

TYPES OF STUDIES

Aim 1 discovery studies will screen potential compounds for therapeutic potential in relevant animal models for ASUDs and PTSD.

Aim 2 human proof-of-concept studies will take the best candidate compounds from preclinical discovery for further development. The candidate compounds could be selected from those examined as part of Aim 1 or from compounds that have previously completed similar preclinical testing. The screened compounds may include medications approved by the FDA for other indications that will be considered for repurposing to use in treating for ASUDs. This efficient repurposing avoids the long and costly preclinical need for developing Good Manufacturing Practice (GMP) manufacturing procedures to produce the compound, Good Laboratory Practice (GLP) toxicology testing in animals, and human safety and dose-ranging studies in normal subjects. After successful discovery testing for potential therapeutic effect in animal models, we can directly move repurposed medications into our human target population of alcohol- or substance-abusing patients who also have PTSD and possibly TBI.

For novel compounds that do not yet have FDA approval for use in humans, two options are possible. First, we may recruit an industry partner to conduct GLP animal toxicology and GMP manufacturing and then submit an Investigational New Drug (IND) application with this partner for human studies. Second, we may approach the NIH for resources and funds to conduct the essential toxicology studies and manufacturing. On the other hand, if the candidate is a repurposed medication with FDA approval for some



other indication or a pharmaceutical industry compound that has an active IND approval and already has been given to humans, then we can start testing them for medical safety and proof of concept in humans at various dosages in combination with alcohol (or the relevant drug of abuse) and for surrogate markers of potential efficacy. The preference for the purposes of the ASADRP is clearly to have compounds that are repurposed or already have a pharmaceutical company sponsor who has an IND approval for use in humans.

Aim 3 efficacy clinical trials will be the most costly and time-consuming of the three components of our rational pipeline, but they will provide the information necessary to plan the future, definitive Phase 3 clinical trials that are required for New Drug Applications (NDAs) and FDA approval of our successful ASUD medications or medication combinations. The Aim 3 trials could also provide an opportunity to explore pharmacogenetics for selecting optimal patients in whom to use these medications. Medications for these clinical trials will be selected through our pipeline process for evaluating promising medications using available data from Specific Aims 1 and 2, as well as solicited study proposals.

PHARMACEUTICAL COMPANY PARTICIPATION

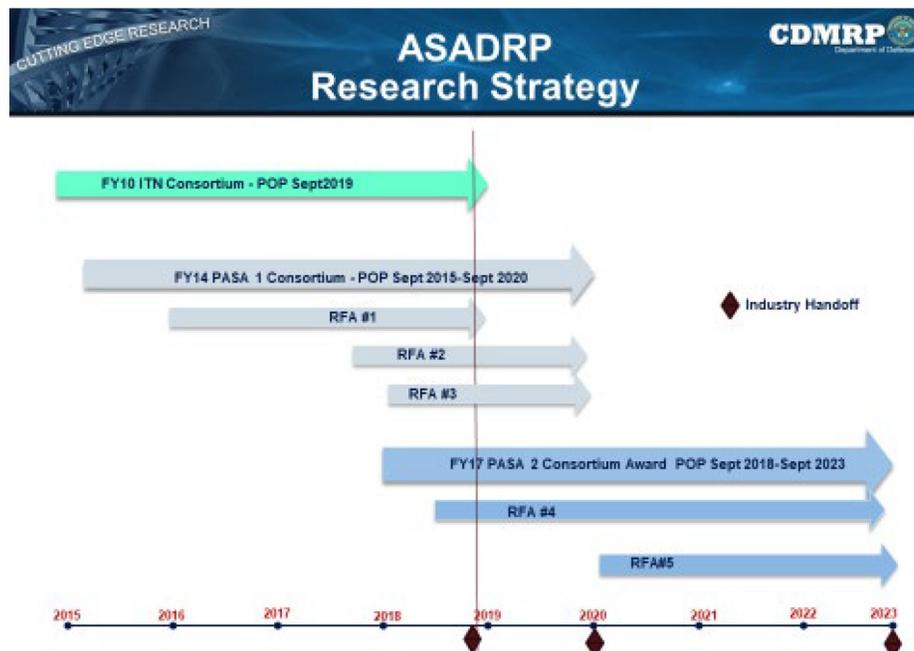
Obtaining FDA approval for a pharmacotherapy usually is facilitated by partnership with a pharmaceutical company for the NDA filing and eventual Phase 3 testing. It is recommended that such a commercial partner be obtained as early in the medication development process as possible. The consortia have recruited several interested commercial partners with potential compounds to test. These partners include Astellas, POP Test, Alkermes, TONIX Pharmaceuticals, US World Meds, Amygdala, and BioXcel Therapeutics. Based on Dr. Haile’s findings from his PASA-supported study titled, “Assessing Pharmacotherapies in Animal Models of Post-Traumatic Stress Disorder and Alcohol Use Disorder,” manuscript pending, Astellas moved the compound onto their fast track for development in substance used disorder. For most of their compounds, these commercial partners are considering dual indications of ASUD and PTSD.

STUDY SITES

Studies of military and Veteran populations are encouraged. To this end, the Management Core is available to facilitate collaboration between applicants and military and Veteran medical centers.

INVESTMENT STRATEGY

Below is the overall research strategy of the ASADRP that integrates both the ITN and PASA consortia and future efforts of subsequent awards. The consortia will serve as translating centers to move projects from discovery to proof-of-concept Phase 2 trials that seek to inform the planning of future multisite Phase 2 efficacy/dosing studies with the goal of industry handoffs in 2020 and 2023.





NEAR-TERM STRATEGY (1-2 YEARS)

- Discovery studies
- Proof-of-concept studies

MID-TERM STUDIES (3-5 YEARS)

- Discovery studies
- Proof-of-concept studies
- Multisite activity/dosing studies
- Industry handoff/efficacy studies

LONG-TERM STRATEGY (5+ YEARS)

- Discovery studies
- Proof-of-concept studies
- Multisite activity/dosing studies
- Industry handoff/efficacy studies
- Industry handoff/pivotal studies leading to licensing and product development

MEASURING PROGRESS

The achievements and progress of the projects funded by the ASADRP consortia correspond to the following Aims:

Aim 1. Studies that discover novel medications and medication combinations in animal models for ASUD that advance the science of addiction research and translate into larger animal studies or whose promising findings translate into human safety studies.

Aim 2. Studies that develop medications through a rational proof-of-concept pipeline in small human studies.

Aim 3. Studies that conduct medication safety and efficacy clinical trials of potential medication combinations in optimal target populations and explore functional genetic polymorphisms for matching patients to these medications. Since these types of studies should be conducted with industry partners under a regulatory strategy for FDA compliance, the expectation is that our partner will translate promising results into larger multisite confirmatory/pivotal studies that could potentially lead to licensing and product development.

The ASADRP will measure its success in the near term based on successful investments in the research areas important to fulfilling the strategy. Longer-term success will be evaluated based on contributions to the scientific community, follow-on research that is attributed to ASADRP-funded projects, the impact of ASADRP-funded research on clinical treatments and interventions, and handoffs to industry partners.

CURRENT OUTCOMES

The following is a breakdown of the outcomes accomplished so far:

ITN Consortium

- 18 member institutions
- 48 published papers with an additional 2 manuscripts currently under review
- Six FDA-approved, currently active IND applications
- Three promising potential therapeutics currently in human testing

PASA Consortium

- 14 member institutions
- Three promising potential therapeutics planned for human testing
- One FDA IND application approved

ANTICIPATED SHORT-TERM OUTCOMES

- Application and funding activity
 - Quality and quantity of applications received in response to the Areas of Interest
- Contributions to the scientific community
 - Publications
 - Presentations
 - Patent applications and patents

ANTICIPATED MID-TERM OUTCOMES

- Contributions to the scientific community
 - Publications
 - Presentations
 - Patent applications and patents
- Career advancement of scientists/researchers
- Receipt of subsequent funding by ASADRP-funded investigators
- Impact on Clinical Practice Guidelines
- Industry handoff

ANTICIPATED LONG-TERM OUTCOMES

- Contributions to the scientific community
 - Publications
 - Presentations
 - Patent applications and patents
- Career advancement of scientists/researchers
- Receipt of subsequent funding by ASADRP-funded investigators
- Impact on Clinical Practice Guidelines
- Industry handoff



CONCLUSION

The ASADRP will not receive an additional Congressional appropriation in FY20. The current consortium award's period of performance ends on 14 September 2023. The funds expire for use on 30 September 2025. There is a budget and Statement of Work in place to fund the subawards and manage the PASA consortium.

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