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14. ABSTRACT The goal of the PASA Consortium is to fund research that aims to identify and develop new medications to improve treatment outcomes for alcohol and substance use disorders (ASUD), especially those that occur concurrently with traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD). In the fourth year, the consortium completed activities in support of RFA #3. Enrollment was completed in the PT150 Alcohol Interaction study. The consortium launched the Verrico Outpatient study and completed the 2 pre-clinical studies being conducted by Drs. Haile and Becker. The Davis and Petrakis study protocol was launched, and work was completed on two planning grants: Batki and Verrico/Domingo.					
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1. Introduction

The goal of the PASA Consortium is to fund research that aims to identify and develop new medications to improve treatment outcomes for alcohol and substance use disorders (ASUD), especially those that occur concurrently with traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD). Clinical trials that include military service member and Veteran populations are highly desirable because this comorbidity, along with mild to moderate TBI, is common in these populations. Alcohol use disorder (AUD) is the most common ASUD in the military, but opiate use disorder (OUD) also has developed significant clinical importance due to prolonged pain treatments with opiates. FDA approved pharmacotherapies are available for ASUD, OUD, and PTSD. While TBI is of interest, it has no FDA approved specific pharmacotherapies, and none of these combined disorders have FDA approved pharmacotherapies. Under a Cooperative Agreement, RTI International is partnering with the CDMRP to solicit, select, and operationalize research studies that support the goals of the PASA Consortium.

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

AIM 1. Discover novel medications and combination medications for ASUD

AIM 2. Develop these medications through a rational Phase I proof of concept pipeline

AIM 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.

2. Keywords

- alcohol and substance use disorders
- post-traumatic stress disorder
- traumatic brain injury
- request for applications
- pharmacotherapy
- research consortium

3. Accomplishments

Our primary objectives for the fourth year were:

- Complete activities in support of RFA #3.
- To complete study enrollment for PT150-alcohol interaction study.
- Launch the Verrico Outpatient study
- To complete the 2 pre-clinical studies being completed by Drs Haile and Kosten, and by Dr. Becker.
- To launch the Davis and Petrakis study protocol.
- To complete work on two planning grants, Batki and Verrico/Domingo.

3.0 PASA Core

The PASA Core research program continued in year 4 with the Requests for Research Applications (RFA) and oversight of the PASA Consortium.

3.0.a Primary objectives and milestones for the fourth year were:

Over the past year we continued the submission review process for PASA RFA #3. We reviewed 17 applications for RFA #3 with activities under PASA1 year 4 covering the GSC full application review and study selection process as well as study award.

3.0.b Accomplishments under the goals include:

The GSC approved 2 pre-clinical studies and planning grants for 2 potential clinical trials.

Funded under PASA2:

1. AS170014-A1 Novel Strategies for the Treatment of Opioid Use Disorder and Post-Traumatic Stress Disorder: Anti-Fentanyl Vaccine and Buprenorphine Combination Therapy
2. AS170014-A2 Preclinical assessment of PT-150 for opioid use disorder and PTSD

Funded PASA1:

1. AS140026-A6 [Lofexidine Combined with Buprenorphine for Reducing Symptoms of Post-Traumatic Stress Disorder and Opioid Use Relapse in Veterans – Planning Grant; PI Christopher Verrico]
2. AS140026-A7 [N-acetylcysteine Treatment to Reduce Alcohol Use, Cognitive Impairment and PTSD Symptom Severity in Veterans with Traumatic Brain Injury and Alcohol Use Disorder: A Confirmatory Study; Planning Grant; PI Steven Batki]

3.0.c Training and professional development provided:

PASA Consortium staff presented at the May 2019 Society for Clinical Trials meeting:

- Oral Presentation: Innovative Application of the Jira Software Technology in the Clinical Trial Case Report Form Development Process
- Poster: Surmounting Barriers with Targeted Solutions: Launching the Pharmacotherapies for Alcohol and Substance Abuse Consortium

3.0.d Dissemination to communities of interest:

The presentations at Society for Clinical Trials provided an opportunity to increase public knowledge of PASA related research. The awarded studies from the RFA #3 have been added to the PASA public and private website. Additionally, the public website has been updated to include a results section of PASA related publications and presentations.

3.1 AS140026-A1 Preclinical Analysis of Combined GABA B PAM and Doxazosin Treatments in Stress-Alcohol Drinking Models

3.1.a Primary objectives and milestones for the fourth year were:

The primary objective for this year was to complete the Aim 1 experiment for aim 1 which completed September 30, 2018. Both the MUSC animal protocol and the corresponding ACURO were renewed in October of 2018. A site visit was completed by RTI staff, Benjamin Carper and Dr. Rick Williams to do a final review of study data for completeness and quality. RTI and the site team worked together to clean and lock the study data including investigating any data anomalies and making data handling decisions for analysis during year 4. The data analysis process is in the final stages as the team continues with the plan to publish the data obtained from this project. The data analysis has been a collaborative process with RTI independently completing the analyses and also providing the investigator insight and training on the appropriate analytic approaches for how the study design conducted.

3.1.b Accomplishments under the goals include:

The team completed the study in female rats and is now looking to publish.

3.1.c Training and professional development provided:

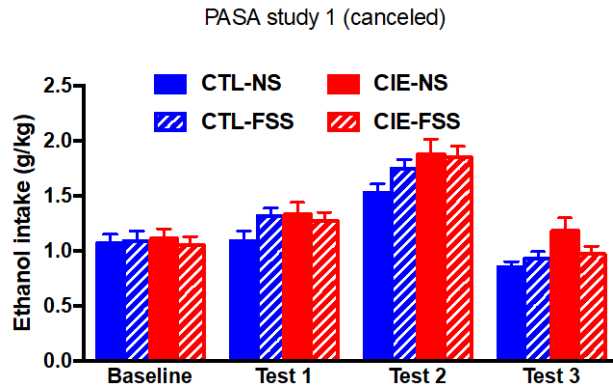
Not applicable

3.1.d Dissemination to communities of interest:

The team is in the process of publishing the data below. It will then be disseminated to communities of interest.

A total of 128 male C57BL/6J mice were purchased, singly housed and started a baseline period of ethanol intake for seven consecutive days. As indicated in the protocol, mice were never food or water deprived and had access to one bottle containing ethanol (15% v/v) for 1 hour each day starting 3 hours after the lights went off in the colony room. After this period of baseline intake, mice were randomized into four different groups defined by chronic intermittent ethanol (CIE) or air (CTL) exposure and forced swim stress (FSS) experience or no-stress (NS). After each cycle of CIE or CTL exposure mice resumed drinking in the home cage 4 hours after FSS (or NS). During baseline and all test cycles mice received saline injections (IP) 30 min before access to ethanol in the home cage to habituate mice to handling and prepare them for treatment with Doxazosin, Zonisamide, or their combination. As can be observed in the figure below, mice in the CIE-FSS group failed to show the expected increase in voluntary ethanol intake. As was discussed in several emails and in a conference call, issues related to ongoing construction in the building could have affected this outcome. Therefore, a decision was made to abort this study (**Figure 1**), use these mice to run a pilot test of the doses of Doxazosin and Zonisamide to be used, and to modify the protocol to increase the number of mice requested and start a new study for Aim I. This new group of mice is currently in the baseline intake phase of the protocol.

Figure 1



Following the same protocol as the previous canceled study a new set of 128 male mice was evaluated. After two test cycles the expected increase in ethanol intake was observed in mice that experienced CIE exposure and stress (CIE+FSS group in **Figure 2**).

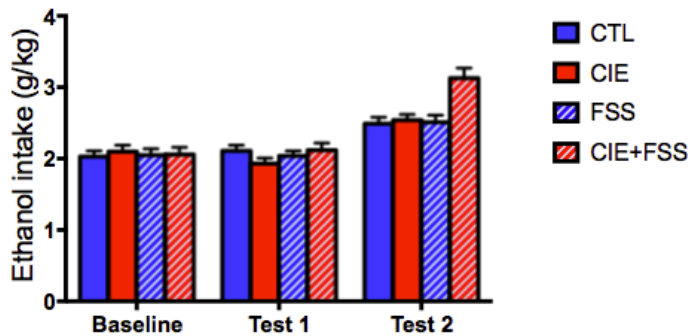
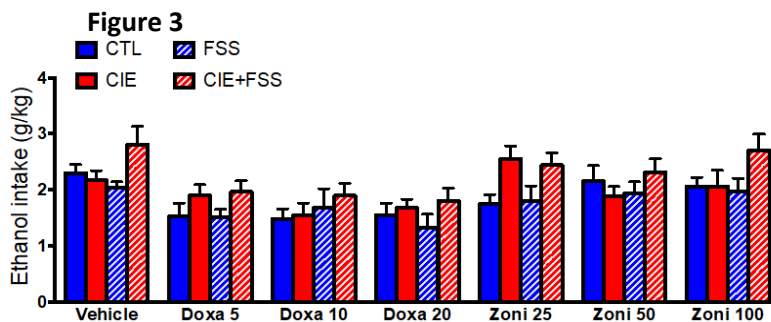


Figure 2

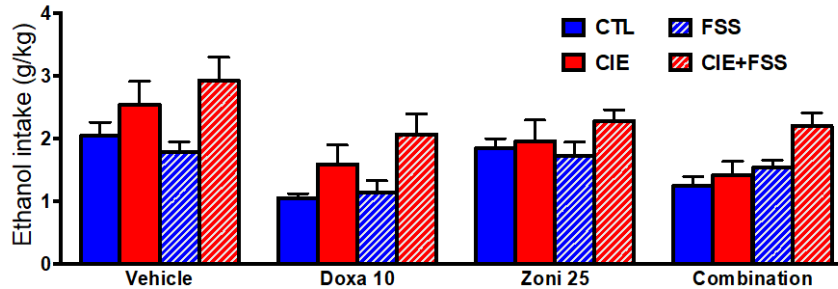
Data combined over test cycles 3 and 4 indicate that all the doses of Doxazosin were able to reduce voluntary ethanol intake particularly in mice that experienced CIE+FSS (**Figure 3**) while the three doses of Zonisamide evaluated did not reduce ethanol intake in any group (**Figure 3**).



Finally, on the last test cycle (Test 5), mice were evaluated for ethanol intake after administration of 10 mg/kg of Doxazosin, 25 mg/kg of Zonisamide, and their combination. Preliminary analyses of this final test cycle indicate that doxazosin is more efficient than zonisamide in reducing voluntary ethanol intake in all groups. The combination of both

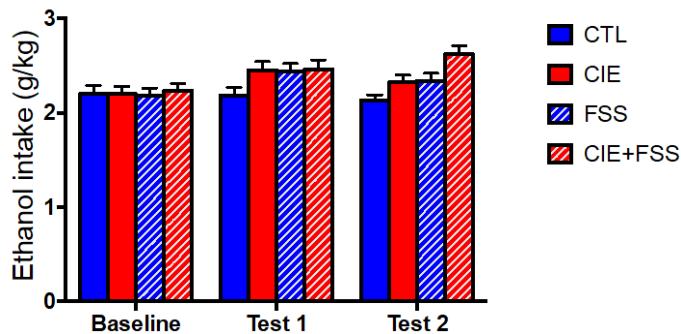
drugs showed a similar effect to that obtained with doxazosin alone (**Figure 4**). All these data have been uploaded and are currently under analysis.

Figure 4



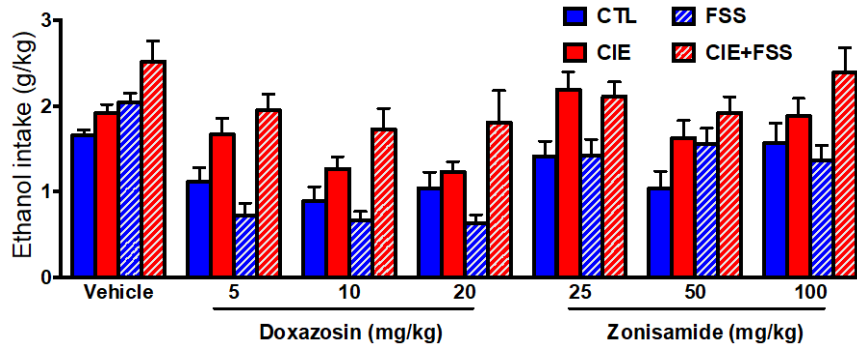
A similar study was completed with female subjects (n=128) using the same experimental protocol. **Figure 6** shows the level of voluntary ethanol intake during baseline and the first two test drinking cycles when all subjects received vehicle injections before drinking. Overall, females showed higher levels of intake compared to males in the previous study. As expected, ethanol dependent (CIE) subjects that experienced stress before drinking showed the highest level of intake.

Figure 6



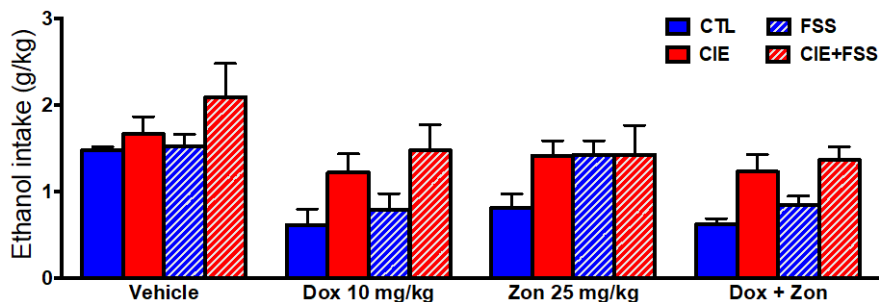
Data for cycles 3 and 4 were combined to evaluate the effect of treatment with different doses of doxazosin or zonisamide on voluntary ethanol intake. Similar to the effect found in males, doxazosin reduced voluntary ethanol intake while zonisamide had no effect on drinking in ethanol dependent or non-dependent mice that experienced stress before drinking (**Figure 7**).

Figure 7



Results of the fifth and final cycle of testing are shown in **Figure 8**. Once again, subjects that received vehicle injections showed the expected results with mice the CIE+FSS condition drinking significantly more than the rest of groups. The results of this test cycle also confirmed that doxazosin alone or in combination with zonisamide reduces voluntary ethanol intake while zonisamide alone does not have an effect on ethanol intake in female mice. All the data collected with male and female subjects is now under analysis for a publication.

Figure 8



3.1.e Plans for next reporting period to accomplish goals and objectives:

We are currently working on the publication of these data.

3.2 AS140026-A2 Assessing Pharmacotherapies in Animal Models of Post-Traumatic Stress Disorder and Alcohol Use Disorder

The subject of this research was to assess potential pharmacotherapies for PTSD (Post-Traumatic Stress Disorder) and AUD (Alcohol Use Disorder) in animal models of these disorders. The purpose of the experiments conducted during the annual period were to assess the impact of ASP8062, a GABA B allosteric modulator, and a positive control (baclofen) on male and female rats lever pressing for alcohol in an operant self-administration paradigm (AIM2) and to determine if ASP8062 and doxazosin (positive control) would block stress-induced increases in oral alcohol self-administration in male and female rats

(AIM3). Results showed ASP8062 blocked both alcohol self-administration and stress-induced increases in alcohol self-administration. Overall, all AIMs for this award have been completed with positive impact. The scope or application of this research has been immediate in that clinical trials funded by Astellas focused on assessing ASP8062 for AUD in humans began August 2019.

3.2.a Primary objectives and milestones for the fourth year were:

Complete AIM2 and AIM3 of the study.

3.2.b Accomplishments under the goals include:

SUMMARY: AIM2

The effects of ASP8062 (1, 3, and 10 mg/kg) and baclofen (0.3, 1, and 3 mg/kg) were assessed on operant self-administration in male and female rats lever pressing for EtOH (ethyl alcohol, 10%, w/v) under a FR2 schedule of reinforcement. Once maintenance responding was established rats received four consecutive days of randomly administered vehicle or ASP8062 followed by randomly administered vehicle or baclofen. Active lever presses, reinforcers earned (dipper presentations) and drug seeking (head entries) on day four of testing were analyzed. Compared to vehicle, both ASP8062 and baclofen significantly decreased all measures in both male and female rats with the highest dose producing the greatest reductions. Overall, the findings indicate ASP8062 robustly decreases EtOH reinforcement in rats to a similar degree as baclofen. Results appear to support further clinical development of ASP8062 as a potential treatment for alcohol use disorder in humans.

RESULTS

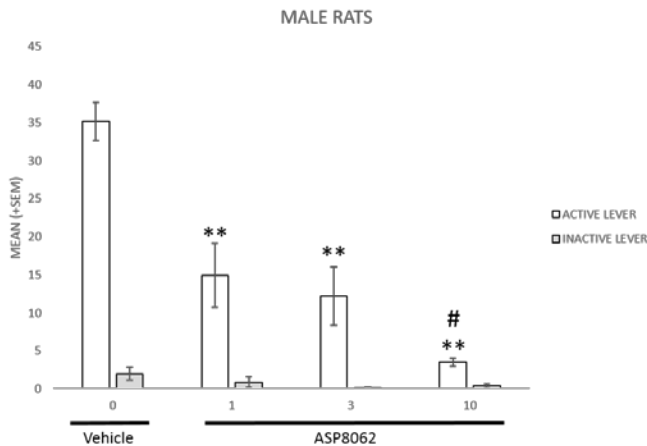


Figure 1. Effects of ASP8062 on active lever presses (MEAN±SEM) in male rats (N=10 per dose) self-administering ethyl alcohol (10%, w/v) under a FR2 schedule of reinforcement. Rats were randomly administered vehicle and various doses of ASP8062 (1, 3, and 10 mg/kg, PO) for four consecutive days. Day four tests are presented. ASP8062 significantly decreased active lever presses for EtOH.

** vs. Vehicle ($P<0.01$)

vs. ASP8062 1 mg/kg ($P<0.1$)

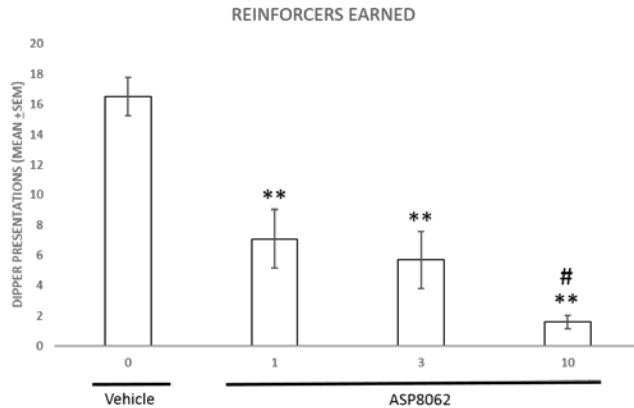


Figure 2. Effects of ASP8062 on reinforcers earned (dipper presentations, MEAN±SEM) in male rats (N=10 per dose) self-administering ethyl alcohol (10%, w/v) under a FR2 schedule of reinforcement. Rats were randomly administered vehicle and various doses of ASP8062 (1, 3, and 10 mg/kg, PO) for four consecutive days. Day four tests are presented. ASP8062 significantly decreased reinforcers earned.

** vs. Vehicle ($P<0.01$)

vs. ASP8062 1 mg/kg ($P<0.1$)

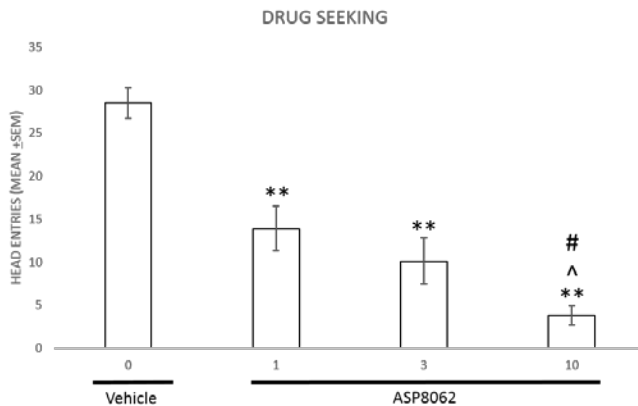


Figure 3. Effects of ASP8062 on drug seeking (head entries, MEAN±SEM) in male rats (N=10 per dose) self-administering ethyl alcohol (10%, w/v) under a FR2 schedule of reinforcement. Rats were randomly administered vehicle and various doses of ASP8062 (1, 3, and 10 mg/kg, PO) for four consecutive days. Day four tests are presented. ASP8062 significantly decreased head entries.

** vs. Vehicle ($P<0.01$)

^ vs. ASP8062 1 mg/kg ($P<0.01$)

vs. ASP8062 3 mg/kg ($P<0.1$)

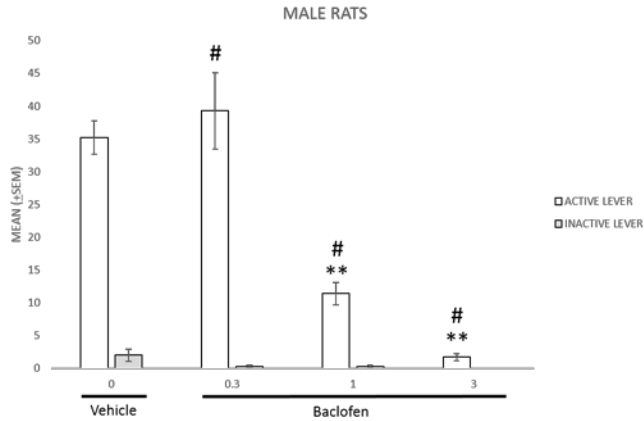


Figure 4. Effects of baclofen on active and inactive lever presses (MEAN±SEM) in male rats (N=10 per dose) self-administering ethyl alcohol (10%, w/v) under a FR2 schedule of reinforcement. Rats were randomly administered vehicle and various doses of baclofen (0.3, 1, and 3 mg/kg, IP) for four consecutive days. Day four tests are presented. Baclofen significantly decreased active lever presses for EtOH.
 ** vs. Vehicle ($P<0.001$)
 # All baclofen dose comparisons ($P<0.001$)

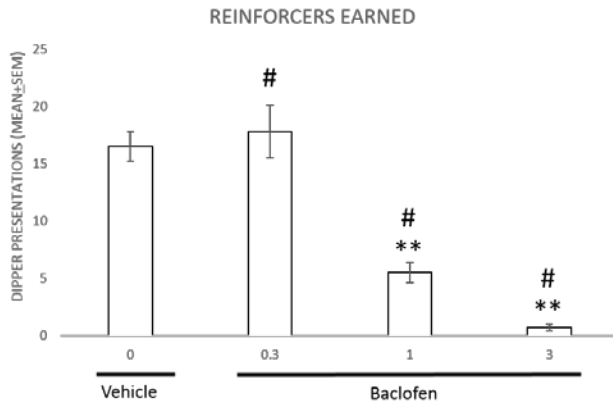


Figure 5. Effects of baclofen on reinforcers earned (dipper presentations, MEAN±SEM) in male rats (N=10 per dose) self-administering ethyl alcohol (10%, w/v) under a FR2 schedule of reinforcement. Rats were randomly administered vehicle and various doses of baclofen (0.3, 1, and 3 mg/kg, IP) for four consecutive days. Day four tests are presented. Baclofen significantly decreased reinforcers earned.
 ** vs. Vehicle ($P<0.001$)
 # All baclofen dose comparisons ($P<0.001$)

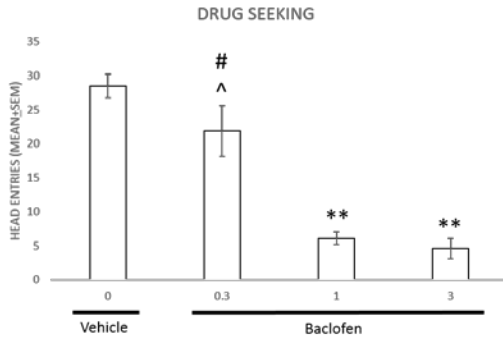


Figure 6. Effects of baclofen on drug seeking (head entries, MEAN±SEM) in male rats (N=10 per dose) self-administering ethyl alcohol (10%, w/v) under a FR2 schedule of reinforcement. Rats were randomly administered vehicle and various doses of baclofen (0.3, 1, and 3 mg/kg, IP) for four consecutive days. Day four tests are presented. Baclofen significantly decreased head entries.

** vs. Vehicle ($P<0.001$)

^ vs. Baclofen 1 mg/kg ($P<0.001$)

vs. Baclofen 3 mg/kg ($P<0.001$)

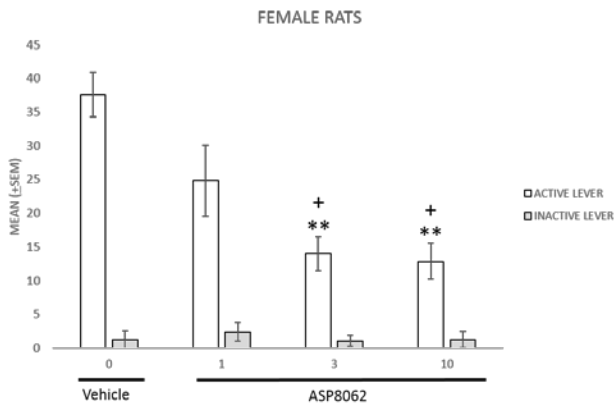


Figure 7. Effects of ASP8062 on active lever presses (MEAN±SEM) in female rats (N=10 per dose) self-administering ethyl alcohol (10%, w/v) under a FR2 schedule of reinforcement. Rats were randomly administered vehicle and various doses of ASP8062 (1, 3, and 10 mg/kg, PO) for four consecutive days. Day four tests are presented. ASP8062 significantly decreased active lever presses.

** vs. Vehicle ($P<0.01$)

+ vs. ASP8062 1.0 mg/kg ($P<0.05$)

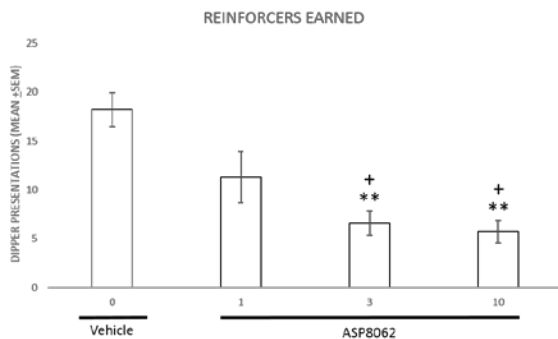


Figure 8. Effects of ASP8062 on reinforcers earned (dipper presentations, MEAN±SEM) in female rats (N=10 per dose) self-administering ethyl alcohol (10%, w/v) under a FR2 schedule of reinforcement. Rats were randomly administered vehicle and various doses of ASP8062 (1, 3, and 10 mg/kg, PO) for four consecutive days. Day four tests are presented. ASP8062 significantly decreased reinforcers earned.

** vs. Vehicle ($P<0.01$)

+ vs. ASP8062 1.0 mg/kg ($P<0.05$)

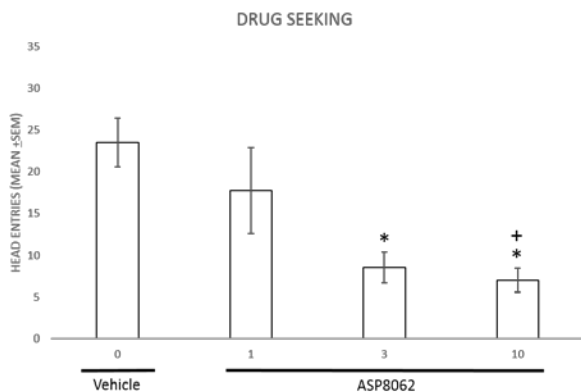


Figure 9. Effects of ASP8062 on drug seeking (head entries, MEAN±SEM) in female rats (N=10 per dose) self-administering ethyl alcohol (10%, w/v) under a FR2 schedule of reinforcement. Rats were randomly administered vehicle and various doses of ASP8062 (1, 3, and 10 mg/kg, PO) for four consecutive days. Day four tests are presented. ASP8062 significantly decreased head entries.

* vs. Vehicle ($P<0.05$)

+ vs. ASP8062 1.0 mg/kg ($P<0.05$)

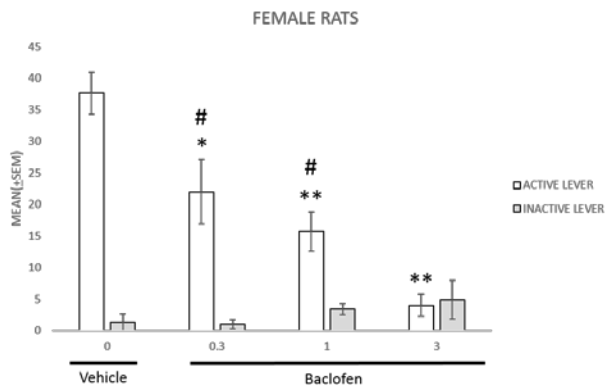


Figure 10. Effects of baclofen on active and inactive lever presses (MEAN±SEM) in female rats (N=10 per dose) self-administering ethyl alcohol (10%, w/v) under a FR2 schedule of reinforcement. Rats were randomly administered vehicle and various doses of baclofen (0.3, 1, and 3 mg/kg, IP) for four consecutive days. Day four tests are presented. Baclofen significantly decreased active lever presses.

* vs. Vehicle ($P < 0.05$)

** vs. Vehicle ($P < 0.01$)

vs. Baclofen 3 mg/kg ($P < 0.001$)

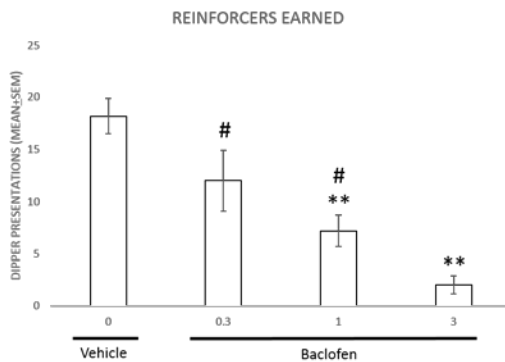


Figure 11. Effects of baclofen on reinforcers earned (dipper presentations, MEAN±SEM) in female rats (N=10 per dose) self-administering ethyl alcohol (10%, w/v) under a FR2 schedule of reinforcement. Rats were randomly administered vehicle and various doses of baclofen (0.3, 1, and 3 mg/kg, IP) for four consecutive days. Day four tests are presented. Baclofen significantly decreased reinforcers earned.

** vs. Vehicle ($P < 0.01$)

vs. Baclofen 3 mg/kg ($P < 0.01$)

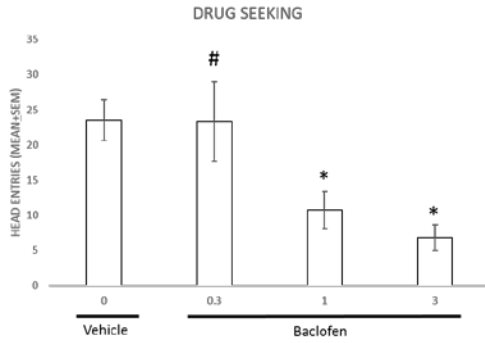


Figure 12. Effects of baclofen on drug seeking (head entries, MEAN±SEM) in female rats (N=10 per dose) self-administering ethyl alcohol (10%, w/v) under a FR2 schedule of reinforcement. Rats were randomly administered vehicle and various doses of baclofen (0.3, 1, and 3 mg/kg, IP) for four consecutive days. Day four tests are presented. Baclofen significantly decreased head entries.

* vs. Vehicle ($P<0.05$)

vs. Baclofen 3 mg/kg ($P<0.05$)

SUMMARY: AIM3

The effects of ASP8062 (10 mg/kg) and doxazosin (DOX, 1 mg/kg) were assessed on operant self-administration in male and female rats lever pressing for EtOH (ethyl alcohol, 10%, w/v) under a FR2 schedule of reinforcement. Once maintenance responding was established rats were exposed to predator odor stress (bobcat urine) then tested again on days 3, 8, 11 and 15. Three different groups of rats received vehicle, ASP8062 or DOX. Active lever presses, reinforcers earned (dipper presentations) and drug seeking (head entries) on two baseline lever pressing days and days post-odor exposure were analyzed comparing change from baseline. Compared to vehicle, ASP8062 significantly decreased all measures in both male and female rats with the greatest reductions occurring on day 15. DOX also significantly decreased certain measures however not to the extent of ASP8062. Overall, the findings indicate ASP8062 robustly attenuates predator-odor induced increases in EtOH reinforcement in rats. Results appear to support further clinical development of ASP8062 as a potential treatment for co-morbid PTSD and AUD in humans.

RESULTS

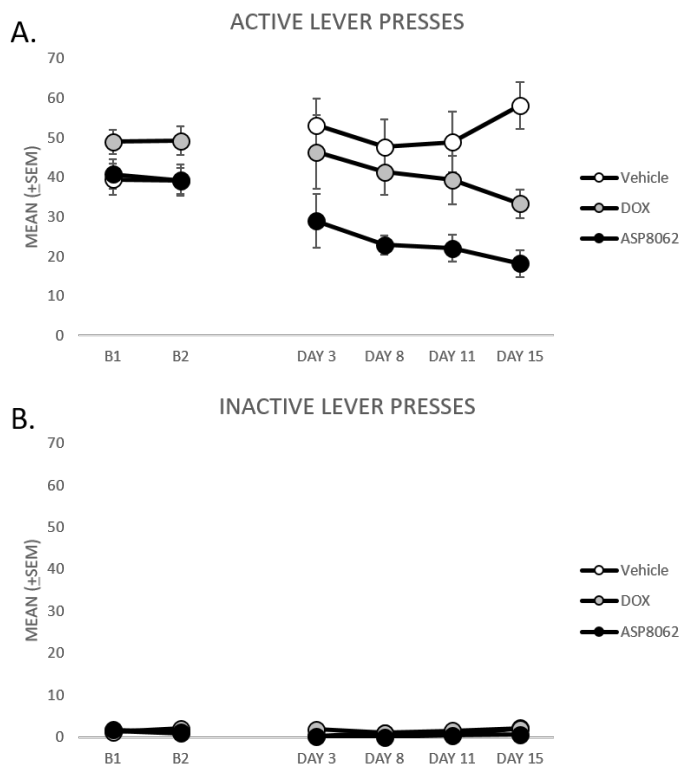


Figure13. Effects of Vehicle, ASP8062 (10 mg/kg, PO) and DOX (1 mg/kg, IP) on active (A.) and inactive (B.) lever presses (MEAN±SEM) in male rats (N=10 per group) self-administering ethyl alcohol (10%, w/v) under a FR2 schedule of reinforcement. Baseline (B1 and B2) responding and responding on days 3, 8, 11 and 15 post-odor exposure are presented. Analysis of active lever presses compared to vehicle indicated ASP8062 significantly decreased active lever presses for EtOH with no effects seen on the inactive lever.

** ASP8062 vs. Vehicle ($P<0.001$)

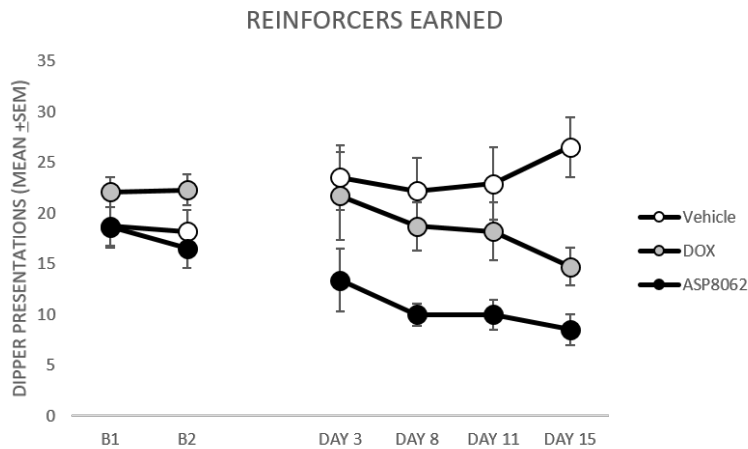


Figure 14. Effects of Vehicle, ASP8062 (10 mg/kg, PO) and DOX (1 mg/kg, IP) on reinforcers earned (dipper presentations, MEAN±SEM) in male rats (N=10 per group) self-administering ethyl alcohol (10%, w/v) under a FR2 schedule of reinforcement. Baseline (B1 and B2) responding and responding on days 3, 8, 11 and 15 post-odor exposure are presented. Compared to vehicle, ASP8062 significantly decreased reinforcers earned. ** ASP8062 vs. Vehicle ($P<0.001$)

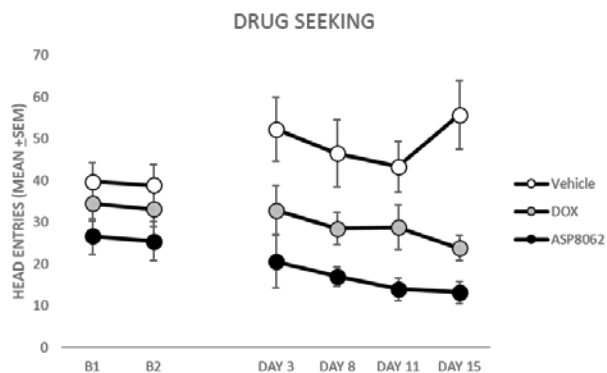


Figure 15. Effects of Vehicle, ASP8062 (10 mg/kg, PO) and DOX (1 mg/kg, IP) on drug seeking (head entries, MEAN±SEM) in male rats (N=10 per group) self-administering ethyl alcohol (10%, w/v) under a FR2 schedule of reinforcement. Baseline (B1 and B2) responding and responding on days 3, 8, 11 and 15 post-odor exposure are presented. Compared to vehicle, ASP8062 and doxazosin significantly decreased head entries. ** ASP8062 vs. Vehicle ($P<0.001$)
** DOX vs. Vehicle ($P<0.001$)

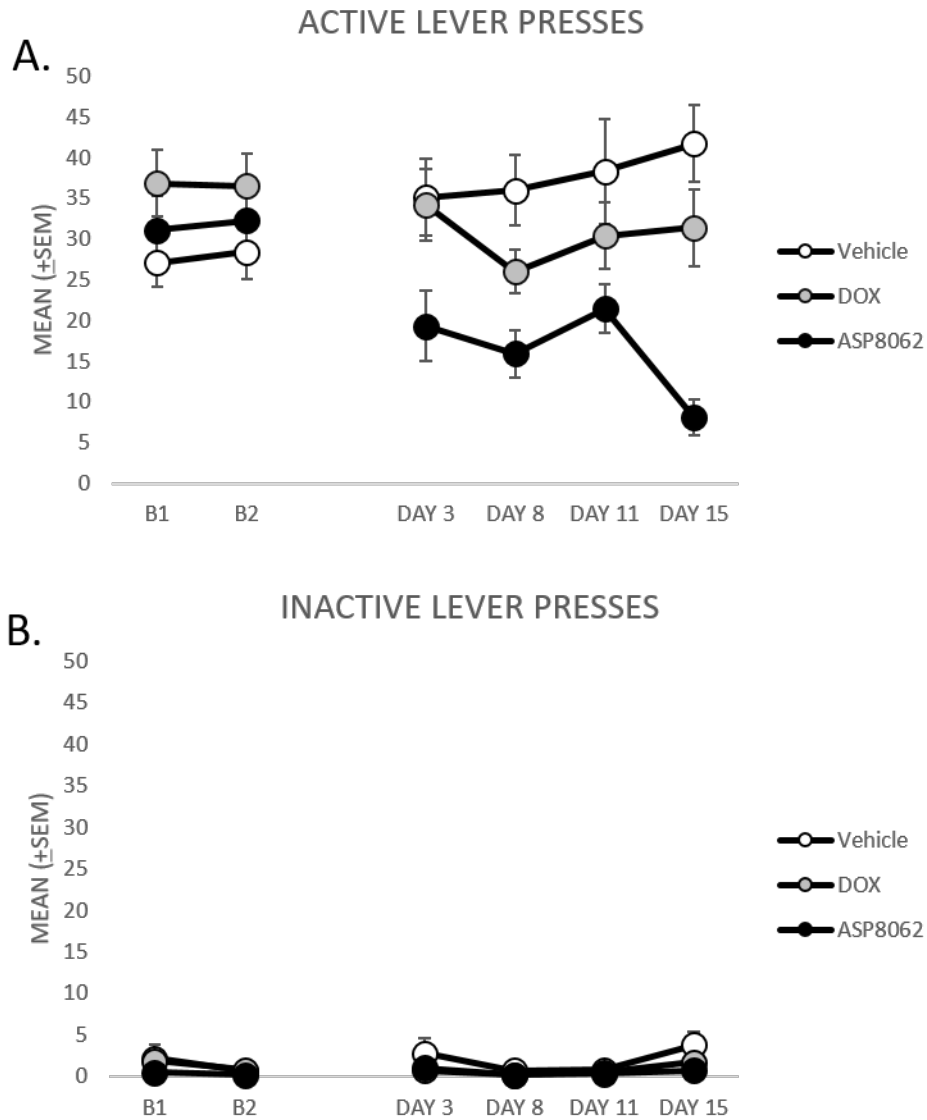


Figure 16. Effects of Vehicle, ASP8062 (10 mg/kg, PO) and DOX (1 mg/kg, IP) on active (A.) and inactive (B.) lever presses (MEAN±SEM) in female rats (N=10 per group) self-administering ethyl alcohol (10%, w/v) under a FR2 schedule of reinforcement. Baseline (B1 and B2) responding and responding on days 3, 8, 11 and 15 post-odor exposure are presented. Analysis of active lever presses compared to vehicle indicated ASP8062 significantly decreased active lever presses for EtOH with no effects seen on the inactive lever. ASP8062 decreased active lever presses to a great extent than DOX.

** ASP8062 vs. Vehicle ($P<0.001$)

* ASP8062 vs. DOX ($P<0.05$)

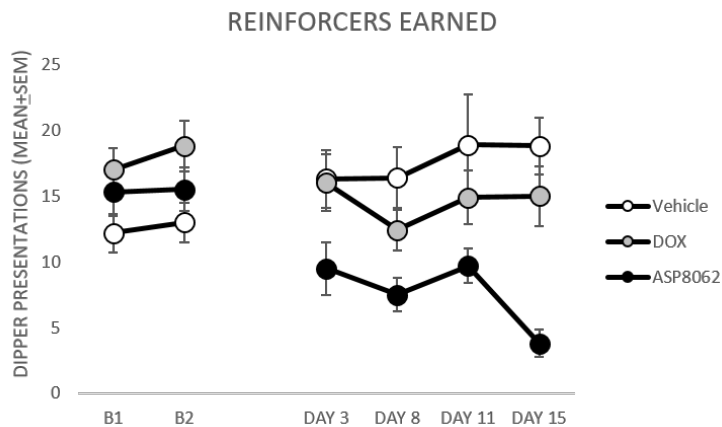


Figure 17. Effects of Vehicle, ASP8062 (10 mg/kg, PO) and DOX (1 mg/kg, IP) on reinforcers earned (dipper presentations, MEAN±SEM) in female rats (N=10 per group) self-administering ethyl alcohol (10%, w/v) under a FR2 schedule of reinforcement. Baseline (B1 and B2) responding and responding on days 3, 8, 11 and 15 post-odor exposure are presented. Compared to vehicle, ASP8062 significantly decreased reinforcers earned. ASP8062 decreased reinforcers earned to a great extent than DOX.
 ** ASP8062 vs. Vehicle ($P<0.001$)
 * ASP8062 vs. DOX ($P<0.05$)

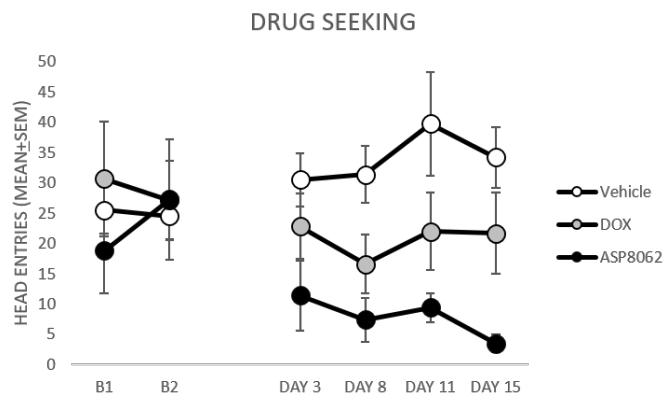


Figure 18. Effects of Vehicle, ASP8062 (10 mg/kg, PO) and DOX (1 mg/kg, IP) on drug seeking (head entries, MEAN±SEM) in male rats (N=10 per group) self-administering ethyl alcohol (10%, w/v) under a FR2 schedule of reinforcement. Baseline (B1 and B2) responding and responding on days 3, 8, 11 and 15 post-odor exposure are presented. Compared to vehicle, ASP8062 and doxazosin significantly decreased drug seeking.
 ** ASP8062 vs. Vehicle ($P<0.001$)
 * DOX vs. Vehicle ($P<0.05$)

3.2.c. Training and professional development provided:

None

3.2.d. Dissemination to communities of interest:

AIM 2 data were presented at the MOMRP meeting Ft. Detrick, MD, 09/11/2019 “Assessing Pharmacotherapies in Animal Models of Post-Traumatic Stress Disorder and Alcohol Use Disorder”

3.2.e Plans for next reporting period to accomplish goals and objectives:

All goals and objectives are complete.

3.3 AS140026-A3 PT150 (formerly ORG 34517) as a Potential Treatment for Alcohol Dependence – Alcohol Interaction Study

The primary purpose of this Phase I, single center drug study is to complete a within-subjects experimental procedure to assess the effects of PT150 on the subjective effects of alcohol in non-treatment-seeking alcohol-experienced volunteers who are veterans). The study will evaluate the safety of study drug PT150 taken concurrently with alcohol in 10 non-treatment seeking participants by evaluating pharmacodynamics and safety endpoints during alcohol challenge before and after 5 days of PT150 treatments when PT150 has reached steady state.

The objectives of this aim are to compare pharmacodynamic and safety endpoints following an alcohol challenge prior to- and concurrent with PT150 treatment. Participants will undergo two alcohol challenges on day 1 separated by 4 hours (one with alcohol, 0.8g/kg; 16% by volume, and one with placebo beverage, 1% by volume, randomly ordered) and receive active study drug (PT150) from days 1-5 (after alcohol challenge for day 1). On day 5, the study drug dosing will be followed by two more alcohol challenges (alcohol and placebo beverage randomly ordered). Physiologic, subjective effects and BAL will be obtained after the alcohol challenges. Participants will be discharged on day 6.

Aim 1 is to evaluate PT150 treatment compared to placebo taken over 14-days of active treatment, followed by 14 treatment-free days in veterans with co-occurring AUD/PTSD. The hypotheses are (a) extinction recall at 14 days after initiation of treatment will improve, (b) subjectively rated PTSD symptoms, alcohol craving and alcohol consumption at 28 days after initiation of treatment will be reduced; and (c) the treatment will be safe and well tolerated. Aim 2 is to evaluate the safety of study drug PT150 taken concurrently with alcohol consumption, in 10 non-treatment seeking AUD subjects by evaluating safety endpoints (vital signs, laboratory measures, AEs) during alcohol challenge prior to, and after 4 days of PT150 treatment, when PT150 has reached steady state. The hypothesis is that the drug will be safe and well tolerated. The study aligns with PASA aims for a proof of concept study to assess safety and surrogate markers (extinction learning) of clinical efficacy in PTSD for treatment with an existing drug compound in veterans with AUD combined with PTSD. The medication is novel and innovative, and the mechanism of action (GR antagonism) for treatment of the key symptoms/behaviors is supported by previous research, including two clinical trials currently underway (PTSD in veterans, AUD in non-veterans) using a drug with a similar mechanism of action. The efficacy is likely via modulation of the stress-axis, which is a logical target for the PTSD+AUD population.

3.3.a Primary objectives and milestones for the fourth year were:

Primary: Change in alcohol-induced effects between day 1 (before PT150 administration) and day 5 (after PT150 administration) on 1) breath-alcohol level; 2) blood pressure; 3) heart rate; 4)

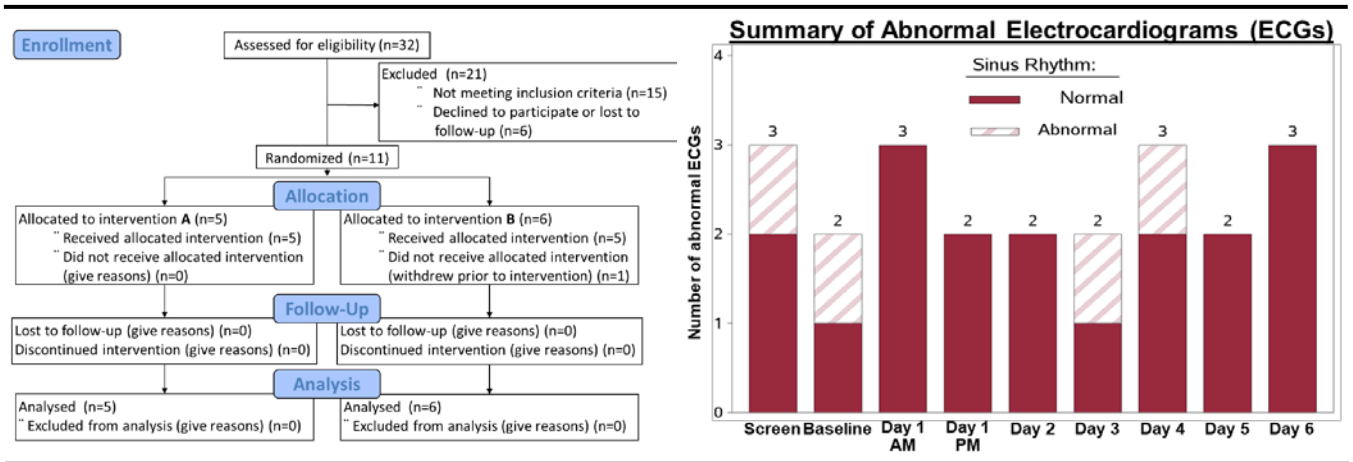
scores on the Positive and Negative Affect Schedule; 5) scores on the Alcohol Urge Questionnaire; 6) scores on the Biphasic Alcohol Effects Scale; 7) scores on the Addiction Research Center Inventory; and 8) adverse events. Change in electrocardiogram abnormalities from baseline (i.e., pre-alcohol administration on day 1) to post-treatment (day 6).

Secondary: Change in alcohol-induced effects between day 1 (before PT150 administration) and day 5 (after PT150 administration) on 1) the Hopkins Verbal Learning Task-Revised; 2) the Dual n-Back task; 3) the Continuous Performance Task-2; 4) the One-Leg Stand test; and 5) the Walk and Turn test.

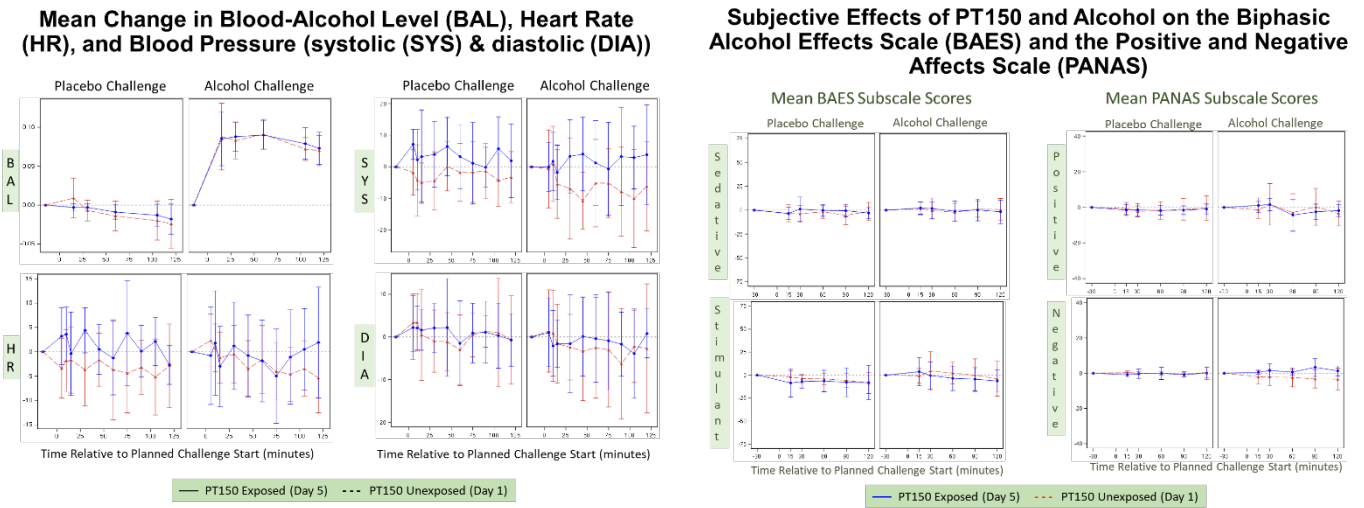
3.3.b Accomplishments under the goals include:

All goals were accomplished during the past year. The 10th and final study participant completed study procedures in JUL-2019. This study provided human safety data needed for the Food and Drug Administration to approve an Investigational New Drug (IND) application to evaluate PT150 as a potential treatment for Veterans with PTSD and co-occurring alcohol use disorder. **This study, thereby, paved the way for the recently funded pharmacokinetic study of PT150 as well as the eventual PT150 outpatient study.** The results are summarized graphically below.

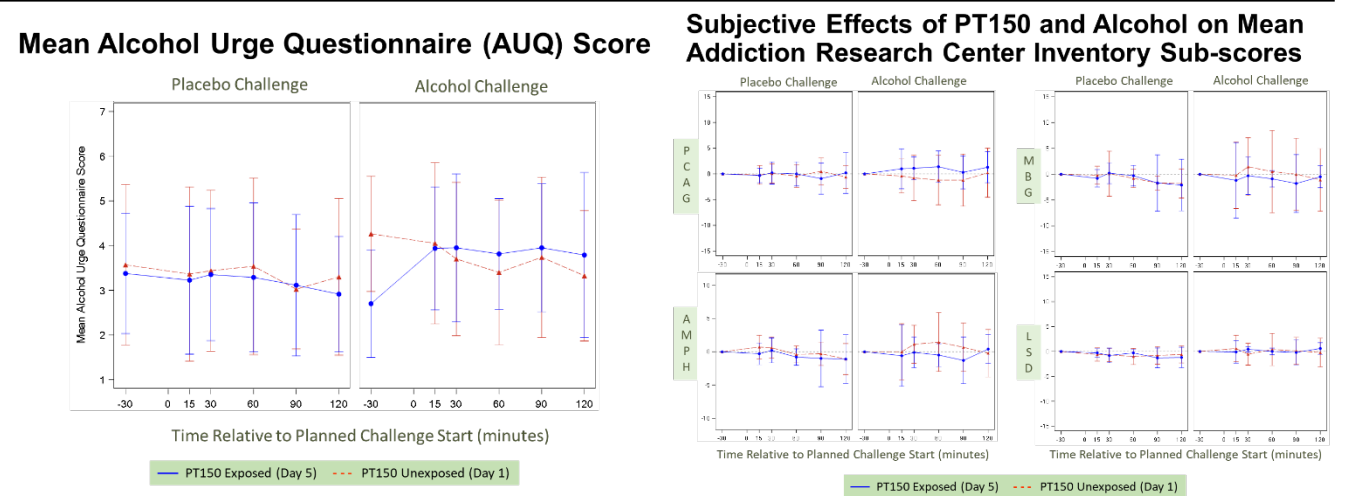
As shown on the left below, of the 32 subjects screened for the study, 11 participants were enrolled and randomized. On average (\pm SD) the participants were 46 (\pm 11.4) years old (range: 28-63); 91% (10/11) were Male; 73% (8/11) were African American; 27% (3/11) were Caucasian; 18% (2/11) identified as Hispanic or Latino. 1 participant experienced 5 AEs, all were mild severity and not related to the study drug or alcohol/placebo treatment. As shown on the right, 6 participants experienced a total of 22 abnormal ECGs, all were clinically insignificant.



The mean change relative to the pre-challenge value over the course of the placebo challenge and alcohol challenge are shown on the left below for BAL, heart rate and blood pressure. The mean change relative to the pre-challenge value over the course of the placebo challenge and alcohol challenge are shown on the right below for the subscales of the Biphasic Alcohol Effects Scales (BAES), and for the subscales of the Positive and Negative Affect Schedule (PANAS). NOTE: The 'I' bar represents +/- 1 Standard Deviation from the Mean.



The raw means over the course of the placebo challenge and alcohol challenge are shown on the left below for Alcohol Urge Questionnaire (AUQ). The mean change relative to the pre-challenge value over the course of the placebo challenge and alcohol challenge are shown on the right below for the subscales of the Addiction Research Center Inventory (ARCI), which includes the Pentobarbital-Chlorpromazine-Alcohol Group (PCAG; Range 0-15), the Amphetamine Scale (AMPH; Range 0 -11), the Morphine-Benzedrine Group (MBG; Range 0-16) and the Lysergic acid diethylamide Scale (LSD; Range 0-14). NOTE: Time 0 is the start of the beverage challenge, no collections are taken at time 0. The 'I' bar represents +/- 1 Standard Deviation from the Mean.



3.3.c Training and professional development provided:

Baylor College of Medicine regularly provides training courses for research personnel. These training seminars are conducted by Baylor College of Medicine Office of Research and are SoCRA approved training programs.

In addition, several psychiatry residents were involved in the study, providing research training opportunities.

All study personnel also utilized Medidata, an electronic data capture platform, which provided an opportunity to gain proficiency in a research database platform.

The PI and study monitor also did a podcast related to alcohol use disorder as a result of this study on 26-APR-2019, educating the broader public on an important topic. The podcast can be viewed here: [Whiskey Neat](#)

3.3.d Dissemination to communities of interest:

Study closeout occurred in July of 2019. Preliminary data analysis is underway, and dissemination of the results has not occurred except to the MOMRP at Fort Detrick on 11-SEP-2019 by the PI. An abstract describing the study results was accepted and a poster will be presented at the annual meeting of the American College of Neuropsychopharmacology on 9-DEC-2019 by the PI.

3.3.e Plans for next reporting period to accomplish goals and objectives:

All goals have been accomplished. FDA clinical reports and manuscripts will be prepared.

3.4 AS140026-A4 Zonisamide as a New Treatment for Co-occurring Post-Traumatic Stress-Disorder (PTSD) and Alcohol Use Disorder (AUD)

The primary purpose of this Phase II, randomized, double-blind, placebo-control trial is to determine if, compared to placebo, Zonisamide, an FDA-approved medication for treatment of epilepsy and seizure disorders, is a safe and efficacious treatment for PTSD and AUD in Veterans with PTSD and co-occurring AUD. Numerous clinical trials have shown that Zonisamide doesn't have the same side effects as other AUD drugs. Researchers hope Zonisamide will be a better drug for treating patients with AUD and reducing the symptoms of PTSD. The study will specifically examine the use of Zonisamide for treating PTSD and AUD symptoms in 60 Veterans with co-occurring PTSD and AUD. Veterans will be divided into two groups, one which will get the experimental drug and another which will get a placebo. Both groups will be treated with either the drug or placebo for up to 5 weeks and then tested to see if the drug had any effect on the symptoms of PTSD and AUD. Primary efficacy variables are scores on the CAPS-5, fear-potentiated startle (FPS) responses, and percent of heavy drinking days (%HDD).

While the study is not designed to formally test an efficacy hypothesis, the hypothesis motivating this study and potential future studies is that treatment with Zonisamide will decrease both PTSD symptoms and the proportion of heavy drinking days, compared to treatment with placebo.

Secondary outcomes include AEs, treatment retention, medication compliance, alcohol craving, days of abstinence, drinks per drinking day, and blood concentrations of phosphatidylethanol (PEth). Notably, the goal is to determine whether there is enough evidence of efficacy and safety of Zonisamide to support development of later phase clinical trials. Thus, in addition to traditional measures of

symptomatology (i.e., scores on the CAPS5 and self-reported %HDD) we employ surrogate measures of efficacy as well (i.e., PEth concentrations and FPS responses).

3.4.a Primary objectives and milestones for the fourth year were:

The main goal was to determine whether there is enough evidence of efficacy and safety of zonisamide versus placebo to support development of later phase clinical trials.

3.4.b Accomplishments under the goals include:

Pete Sharp from UCSD came to Houston and trained our group how to setup and use the fear-potentiated startle (FPS) equipment on **19-OCT-2018**. The study was delayed by the requirement that the UCSD group approve FPS pilot data, which was collected by **30-OCT-2018** but not reviewed until **29-JAN-2019**.

With approval of the FPS pilot data received on **29-JAN-2019**, the study was opened to enrollment; advertisements to recruit study subjects were posted on **04-FEB-2019**. However, another delay occurred on **28-MAR-2019**, when a discussion was initiated about modifying the FPS procedures to better align, and increase cross-study comparisons, with other national research studies. After several meetings with RTI, UCSD and Dr. Norrholm, an amendment was submitted to change the FPS procedures accordingly on **17-MAY-2019**, which was approved on **04-JUN-2019**.

Of the 31 potential subjects, the main causes of ineligibility are 1) concomitant medications (n=19) and 2) age (n=6). Eligibility criteria for concomitant medications allows only SSRIs and SNRIs and the age range is 18-55 years old. Nonetheless, these are two criteria that could easily be modified to increase the participant pool. Despite the major delays and eligibility issues, we implemented numerous strategies aimed at increasing recruitment as detailed in the table 1 below.

Table 1. Zonisamide Recruitment Efforts

Date	Activity/Event	Details
16-Jan-19	Direct Recruitment	VAHOU common areas: lobby, cafeteria etc.
1-Feb-19	Advertising	VAHOU Social Media
15-Feb-19	Advertising	Approved for placement of flyers in VAHOU Chapel
23-Apr-19	Advertising	TVs located throughout BCM and on BCM Social Media
25-Apr-19	Advertising	Advertised on StudyKik, Produced 13 leads
24-May-19	Provider Meeting	Drs. Verrico & Swann met with Drs. Marsh (Mental Health Care Line Director), Mathew and Jorge (providers/researchers) to integrate clinical care with research efforts
29-May-19	Provider Meeting	Drs. Verrico, Kosten, & Domingo met with Dr. Graham (PTSD Post-Deployment Clinic Director, Psychiatry)
12-Jun-19	Provider Meeting	Drs. Verrico & Swann met with Dr. Teng (Psychology Residency Director) who focuses on PTSD
24-Jul-19	Direct Recruitment	VAHOU PTSD Clinic
26-Jul-19	Provider Meeting	Drs. Verrico & Domingo presented to 24 practitioners under Dr. Smith (PTSD Post-Deployment Clinic Director, Psychology)
1-Aug-19	Advertising	Adetola Vaughan (RC) contacted 8 VAHOU outpatient clinics, 5 have posted study flyers

8-Aug-19	Direct Recruitment	Granted access to VA academic detailers clinical dashboards, which provides patient lists with specific disorders/medications, etc., including upcoming appointments
16-Aug-19	Provider Meeting	Dr. Verrico presented at the VA Neuroscience Addiction Summit 2019 to providers about SUDS and comorbidities generally, and specifically related to our studies

Despite efforts to ramp up recruitment and launch this study, it was decided, in conjunction with the GSC to terminate this study in September 2019. Details are presented in section 5.

3.4.c Training and professional development provided:

Baylor College of Medicine regularly provides training courses for research personnel. These training seminars are conducted by Baylor College of Medicine Office of Research and are SoCRA approved training programs.

3.4.d Dissemination to communities of interest:

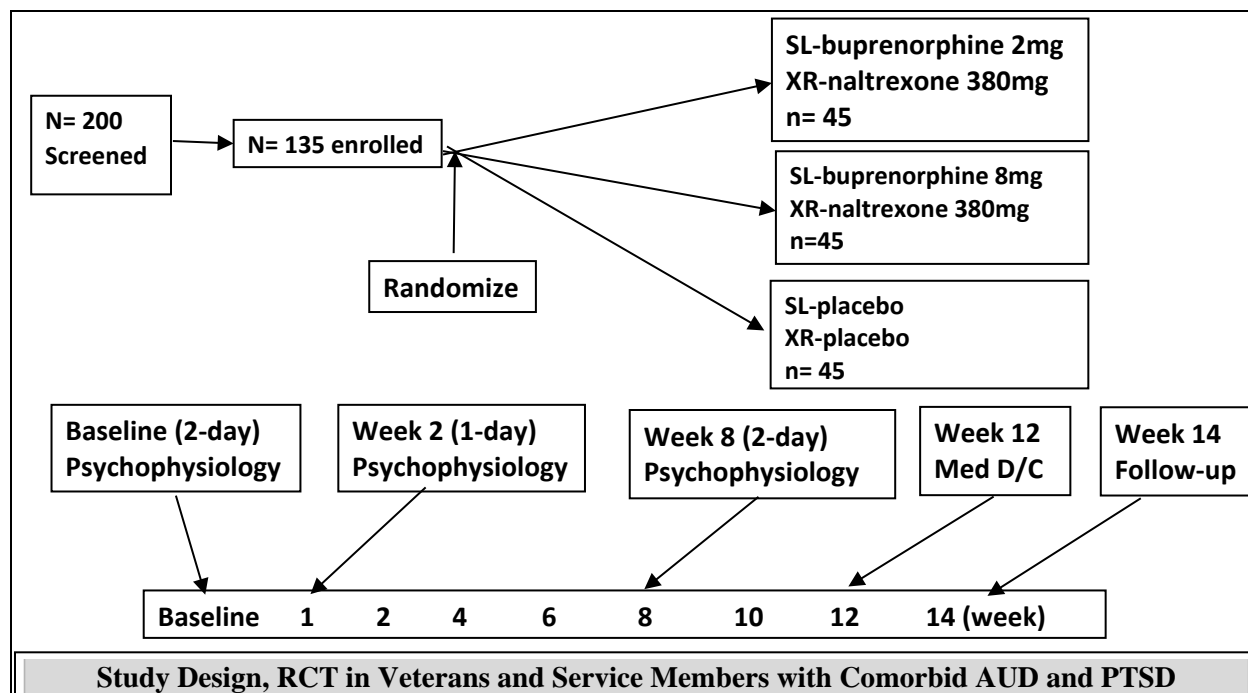
Not Applicable

3.4.e Plans for next reporting period to accomplish goals and objectives:

Not Applicable

3.5 AS140026-A5-Kappa Opioid Receptor Antagonism for the Treatment of Alcohol Use Disorder and Comorbid PTSD

The use of medications that result in kappa opioid receptor (KOR) antagonism represents a novel potential treatment for Veterans and Service Members with comorbid alcohol use disorder (AUD) and post-traumatic stress disorder (PTSD). The combination of buprenorphine, which acts as an antagonist at kappa and partial agonist of the mu receptors, and naltrexone, which blocks the mu receptor, yields a pharmacological net effect of a KOR antagonist. The use of buprenorphine in a non-opioid dependent population has ethical implications given its risk of addiction, which has led to the idea to combine it with naltrexone in order mitigate the potential for misuse. Further, preclinical studies suggest KOR antagonism is important for drinking behavior, stress induced reinstatement of drug and alcohol consumption. For these reasons, there is substantial interest in the development of KOR antagonists for indications such as AUD and PTSD and the combination of buprenorphine and naltrexone allows for a proof-of-concept study until a formulated KOR-antagonist becomes commercially available. Figure 1 provides an overview of the research design.



3.5.a Primary objectives and milestones for the fourth year were:

Goals for this year included CRADA between RTI and Tuscaloosa, completion of subcontracts, IRB approval, HRPO approval, study start-up activities, finalization of the protocol, recruitment and enrollment.

3.5.b Accomplishments under the goals include:

- a. CRADA between RTI and Tuscaloosa completed JAN-2019.
- b. Subcontracts between Tuscaloosa and both West Haven and Atlanta sites completed in JAN-2019.
- c. IRB approvals for all 3 sites, HRPO approval for 2 of the 3 sites.
 - i. Local Site IRB approvals obtained
 1. Tuscaloosa 01-Nov-2018
 2. West Haven 07-Nov-2018
 3. Atlanta 13-Feb-2019
 - ii. Final HRPO approval
 1. Tuscaloosa: 26-APR-2019
 2. West Haven: 15-MAY-2019
 3. Atlanta: Site transfer interrupted HRPO approval process.
 - Dr. Norrholm announced in AUG-2019 that he is relocating to Detroit (Wayne State University and Detroit and Ann Arbor VA Medical Centers) in OCT-2019.
 - Clinical research coordinator is also relocating to Detroit and will start IRB submission in OCT-2019.

- Tuscaloosa site will open satellite site at Birmingham VA to offset delays in enrollment due to Norrholm's move from Atlanta to Detroit. Additionally, Birmingham VA satellite site will continue to enroll participants for one year to catch up and keep up on enrollment goals.
- Re-budgeting and subcontracts between Tuscaloosa site and the Detroit and Birmingham sites are in process with goal to complete by 30-OCT-2019.

d. Study start up:

- i. Clinical Trials.gov registration approved and made public (22-Feb-2019)
- ii. NIH Certificate of Confidentiality approved (25-Feb-2019, revised for multi-site clarification on 18-Mar-2019)
- iii. Investigator meeting for study kick-off held in Tuscaloosa (28-MAR-2019).
- iv. Agreements in place for permission to use the MINI-5 (permission forms with Dr. David Sheehan) at no charge and to send the recordings of the CAPS instruments to external fidelity monitor (data use agreement with Dr. Frank Weathers 25-APR-2019).
- v. Certified Independent Assessors in Timeline Follow Back (TLFB) & Clinician-Administered PTSD Scale (CAPS-5) (April/May-2019).
- vi. Pharmacy Training for all sites (23-APR-2019)
- vii. Buprenorphine and Placebo Study Medication received (02-MAY-2019)
- viii. IM Naltrexone/ IM Placebo Study Medication received (22-APR-2019)
- ix. Laboratory Manual and Supplies including Urine drug test kits, urine pregnancy test kits, Breath Alcohol Testing equipment confirmed received by Tuscaloosa: 20-MAR-2019, West Haven: 22-APR-2019, and Atlanta: 22-APR-2019
- x. Psychophysiological Assessment equipment installed Tuscaloosa:27-MAR-2019, West Haven: 06-JUN-2019 and Atlanta: Existing prior to PASA study
- xi. Database and Case Report Forms finalized 03-MAY-2019
- xii. Electronic data capture (EDC) system, Medidata Rave, tested and in production 10-MAY-2019
- xiii. Recruitment began in Tuscaloosa on 16-MAY-2019 and West Haven on 10-JUN-2019
- xiv. DSMB Conference Calls held in JUN-2019 and AUG-2019

e. Protocol:

- i. Finalized to v1 OCT-2018
- ii. Revised to v2 DEC-2018 (incorporating initial IRB submission feedback)
- iii. Revised to v3 3-JUN-2019 (incorporating issues identified during start-up)
- iv. Revised to v4 30-SEP-2019
 1. Adjustments based on information obtained during first few subjects going through study assessments
 2. And information obtained from screening logs pertaining to eligibility roadblocks that could be changed without impacting safety or ability to detect treatment effect)

f. Enrollment numbers as of 30-SEP-2019:

- i. First subject enrolled: 20-MAY-19
- ii. Screened: 738
- iii. Approached for consent: 22

- iv. Consented: 13
- v. Randomized: 7
- g. Recruitment activities:
 - i. Daily reach out to clinicians, internal in-services done
 - ii. Chart reviews for clinic patients each week
 - iii. Press release approved by leadership, to be submitted with v4 protocol IRB submissions next quarter
 - iv. Advertising/Flyers placed in clinics, local VFW and American Legion, and AA meetings and Al-Anon meetings
 - v. Developing a study brochure (can be inviting and informative than a flyer)
 - vi. Mailing letters, from potential subject lists pulled for each site area
 - vii. Dr. Davis obtained VA Corporate Data Warehouse (CDW) list of Veterans (names and addresses) who have been seen at the local sites in the past 5 years with diagnosis of PTSD or alcohol use disorder under the age of 70 and excluding those with a diagnosis of psychotic disorder or dementia (>2000 people listed). Stepped mailout (by proximity to site) of IRB-approved letter of invitation has begun for Tuscaloosa and West Haven.
 - viii. In-services:
 - 1. Dr. Davis held an informational in-service with the Mental Health clinic providers in JUL-2019
 - 2. Dr. Davis attended staff meeting with the Comprehensive Outpatient Substance Abuse Team (COSAT) to give an informational in-service and discuss referrals in JUL-2019
 - ix. Future (and/or ongoing) meetings/contact with Veteran Advocacy Organizations (many listed on www. ALAvetnet.org) and local AA groups
 - x. Organize community outreach meeting with NAMI
 - xi. Advertise in the newspaper
 - xii. Distribute brochures at the American Legion hut
 - xiii. Study Site change (fall 2019):
 - 1. Both Birmingham and Detroit are larger sites and should be good settings for finding study subjects
 - 2. Staff will use government vehicle to transport participants from Birmingham to Tuscaloosa if needed
 - xiv. Considering recruitment services called "StudyKik" and "Trial Facts"

3.5.c Training and professional development provided:

Not Applicable

3.5.d Dissemination to communities of interest:

- a. Press releases have been approved and will be submitted to media outlets in OCT-2019.

3.5.e Plans for next reporting period to accomplish goals and objectives:

- a. Next Quarter:
 - xv. IRB approvals for v4 of protocol at all 3 sites

- xvi. Medidata migration with v4 protocol changes in next quarter
- xvii. IRB and HRPO approvals for Dr. Norrholm Detroit site
- xviii. IRB and HRPO approvals for Birmingham satellite site
- xix. Start enrollment at the Birmingham satellite site
- xx. Continue recruitment efforts (including implementing press releases and distribution of recruitment letters, at regular intervals, from list of >2000 potential study subjects that Dr. Davis obtained from the VA Corporate Data Warehouse (CDW))

Achieve a steady enrollment rate of at least 7 participants/month

3.6 AS140026-A6 Lofexidine Combined with Buprenorphine for Reducing Symptoms of Post-Traumatic Stress Disorder and Opioid Use Relapse in Veterans

Planning Grant Activities included: 1. Protocol development; 2. Populate protocol template and refine the protocol until finalized; 3. FDA application submitted for approval

3.6.a Primary objectives and milestones for the fourth year were:

- i. To submit an IND to the FDA for approval
- ii. To receive approval from the DSMB
- iii. To submit the proposal to the GSC for funding approval

3.6.b Accomplishments under the goals include:

All goals were accomplished, the IND was submitted to the FDA and returned with an exemption, the DSMB approved the study and the GSC funded the study. The study will be conducted under PASA2.

3.6.c Training and professional development provided:

Not applicable

3.6.d Dissemination to communities of interest:

Not applicable

3.6.e Plans for next reporting period to accomplish goals and objectives:

Not applicable

3.7. AS14026-A7 N-acetylcysteine Treatment to Reduce Alcohol Use, Cognitive Impairment and PTSD Symptom Severity in Veterans with Traumatic Brain Injury and Alcohol Use Disorder

3.7.a Primary objectives and milestones for the fourth year were:

The primary milestones for this past year included the kickoff meeting to go over reviewers' comments, discuss planning grant timeline, subcontracts and protocol. The team worked to explore options of collaborating with a pharma company, Promentis, and conducting the study at multiple sites. A DUA, budget, justification, and protocol draft were completed as a major milestone. RTI conducted final statistical data analysis and created a pilot data study report, including figures and tables to be included in the protocol. The draft of the protocol was

finalized and submitted to the PASA DSMB for review. Comments from the DSMB were discussed and revisions were made. The team created and presented abstract as a poster at the Research Society on Alcoholism's 42nd Annual Conference, titled "N-acetylcysteine Treatment of Alcohol Use Disorder in Veterans with Traumatic Brain Injury: A Pilot Controlled Trial". The protocol, budget, justification and Clinical Development Plan were submitted to the GSC; however, the study was not approved for funding.

3.7.b Accomplishments under the goals include:

Abstract presented as a poster at Research Society on Alcoholism's annual conference in Minneapolis, MN (June 26, 2019).

S.L. Batki, D.L. Pennington, B.A. Lasher, N. Vandergrift, T. Nolen, E. Herbst, T. Novakovic-Agopian, G. Abrams, F.N. Fong, N.A. Bautista, E.A. Harris, J. Bielenberg, L. Muquit, M. Cano. N-acetylcysteine Treatment of Alcohol Use Disorder in Veterans with Traumatic Brain Injury: A Pilot Controlled Trial. Poster presented at the Research Society on Alcoholism's 42nd Annual conference in Minneapolis, MN in June 22-26, 2019.

Published abstract:

Alcoholism: Clinical and Experimental Research, Vol. 43, No. 6, June 2019 online supplement; Abstract #887

3.7.c Training and professional development provided:

Not applicable

3.7.d Dissemination to communities of interest:

Abstract presented as a poster at Research Society on Alcoholism's annual conference in Minneapolis, MN (June 26, 2019). See details above.

3.7.e Plans for next reporting period to accomplish goals and objectives:

Not applicable

4. Impact

4.0 PASA Core

The work, findings and specific products of the projects sponsored through PASA are still early in their progress, but the most important impact during this reporting period has been with our pharmaceutical company partners. As noted above these partners have favorably noted our major accomplishments, innovations and successes for identifying promising new medications for substance use disorders and moved two of them directly from our pre-clinical models into clinical trials independent of PASA- DoD funding. We have refined our RFA and project award process to better identify viable projects and to make initial low-funded awards to allow for better determination of clinical trial needs for potential compounds. We continue to build our template library to allow for efficiency and consistency across studies. We have also established excellent working relationships with several VAMCs across the USA for conducting our PASA clinical studies. We have also used knowledge across studies conducted within the PASA consortium as well as knowledge of clinical trials conducted outside of the PASA consortium by

our established collaborators to help inform initial and continued funding decisions for compounds being studied within PASA.

4.1. AS140026-A1 Preclinical Analysis of Combined GABA B PAM and Doxazosin Treatments in Stress-Alcohol Drinking Models

Once analyzed and published this data will impact future studies of combined GABA B PAM and Doxazosin Treatments in Stress-Alcohol Drinking Models.

4.2. AS140026-A2 Assessing Pharmacotherapies in Animal Models of Post-Traumatic Stress Disorder and Alcohol Use Disorder

Results from the experiments conducted have had significant impact.

- Final report of AIM2 findings was submitted to Astellas which gave support to establish a research program to pursue ASP8062 as a potential treatment for AUD in humans.
- Manuscript containing the aforementioned data is being generated for publication.
- Based on the pre-clinical findings, Sr. Director, Global Development Project Leader has received full approval from Astellas to assess ASP8062 in clinical DDI (drug-drug interaction) studies. *The first patient was enrolled August 2019.*
- Astellas is continuing collaborations with NIAAA, NIDA and potentially Baylor College of Medicine, in planning Phase I (safety) and II (proof of concept) studies assessing ASP8062 as a potential treatment for AUD.

4.3. AS140026-A3 PT150 (formerly ORG 34517) as a Potential Treatment for Alcohol Dependence – Alcohol Interaction Study

Reports and manuscripts are being prepared.

4.4. AS140026-A4 Zonisamide as a New Treatment for Co-occurring Post-Traumatic Stress-Disorder (PTSD) and Alcohol Use Disorder (AUD)

No impact

4.5. AS140026-A5-Kappa Opioid Receptor Antagonism for the Treatment of Alcohol Use Disorder and Comorbid PTSD

The study is in early stage of enrollment, therefore there are no findings available to change practice. The investigators have worked through barriers to recruitment and by mailing letters directly to veterans have substantially pick up the pace of enrollment.

4.6. AS140026-A6 Lofexidine Combined with Buprenorphine for Reducing Symptoms of Post-Traumatic Stress Disorder and Opioid Use Relapse in Veterans

Not applicable

4.7. AS14026-A7- N-acetylcysteine Treatment to Reduce Alcohol Use, Cognitive Impairment and PTSD Symptom Severity in Veterans with Traumatic Brain Injury and Alcohol Use Disorder

Not applicable

5. Changes/Problems

5.0 PASA Core

A reduction in our research portfolio has been terminating the zonisamide study in alcohol and PTSD. The unspent funds will be reallocated to recently approved studies and/or planning grants.

5.1. AS140026-A1 Preclinical Analysis of Combined GABA B PAM and Doxazosin Treatments in Stress-Alcohol Drinking Models

Not applicable

5.2. AS140026-A2 Assessing Pharmacotherapies in Animal Models of Post-Traumatic Stress Disorder and Alcohol Use Disorder

No challenges

5.3. AS140026-A3 PT150 (formerly ORG 34517) as a Potential Treatment for Alcohol Dependence – Alcohol Interaction Study

a. Changes in approach and reasons for change

None

b. Actual or anticipated problems or delays and actions or plans to resolve them

The FDA required that all participants have an adrenocorticotrophic hormone (ACTH) stimulation test, which were initially completed at the VA; however, after 2 consecutive subjects failed the test, we could not resolve what the issue was with the VA. Hence, we outsourced this test.

c. Changes that have a significant impact on expenditures

The FDA required that all participants have an adrenocorticotrophic hormone (ACTH) stimulation test. Having an outside vendor complete these tests was not accounted for in the budget.

d. Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Not applicable

5.4. AS140026-A4 Zonisamide as a New Treatment for Co-occurring Post-Traumatic Stress-Disorder (PTSD) and Alcohol Use Disorder (AUD)

a. Changes in approach and reasons for change

The value of conducting the 5-week study of ZNS for alcohol use disorder (AUD) to the DoD and PASA is unclear for the following reasons.

1. Unlike carisbamate, which was originally proposed, there is no commercial partnership with a pharmaceutical company that would lead to eventual marketing of ZNS for AUD or PTSD.

2. The evidence supporting the efficacy of ZNS for AUD is not strong, with even less evidence of its potential utility for treating PTSD as has been discussed with RTI.

As such, in agreement with RTI and approved by the GSC, this study has been terminated for futility.

b. Actual or anticipated problems or delays and actions or plans to resolve them

Not applicable

c. Changes that have a significant impact on expenditures

Terminating the study stopped any further expenditures

5.5 AS140026-A5-Kappa Opioid Receptor Antagonism for the Treatment of Alcohol Use Disorder and Comorbid PTSD

- a. The relocation of a study site from Atlanta to Detroit for Dr. Norrholm is underway. Dr. Norrholm plans to be fully functional by Jan-2020 and will randomized 25 participants in the enrollment period remaining.
- b. Addition of Birmingham (satellite site to Tuscaloosa) to offset delays caused by Dr. Norrholm relocating to Detroit. The participants who are recruited from the Birmingham site will have the psychophysiological assessments and medications given at the Tuscaloosa site and all other follow-up visits at the Birmingham site.
- c. Protocol change to v4 will address issues found with screening, where eligibility criteria could be adjusted with impacting the safety or treatment effects of the study intervention.
- d. Enrollment goals adjusted to 7 subjects per month overall, to offset Atlanta never activated for screening, and subsequent move to Detroit for Dr. Norrholm.
- e. Budget adjustment: covered additional psychophysiological testing equipment expenses for West Haven.
- f. Budget adjustments: Tuscaloosa with Atlanta and Detroit to cover change in site location (no screening or enrollment took place in Atlanta; timeline is for Detroit site to begin enrolling next quarter). All adjustments are budget neutral.

5.6. AS140026-A6 Lofexidine Combined with Buprenorphine for Reducing Symptoms of Post-Traumatic Stress Disorder and Opioid Use Relapse in Veterans

The proposed trial in the planning grant will be funded under PASA2.

5.7. AS14026-A7- N-acetylcysteine Treatment to Reduce Alcohol Use, Cognitive Impairment and PTSD Symptom Severity in Veterans with Traumatic Brain Injury and Alcohol Use Disorder

The proposed trial in the planning grant was not funded.

6. Products

6.0 PASA Core

Specific products that have resulted from these projects during the reporting period include conference papers and presentations with several publications in progress. Two potential products also have moved into independent big pharma development for alcoholism and PTSD, as noted above.

Members of the PASA Consortium Core at RTI presented two abstracts at the Society for Clinical Trials in May 2019.

1. Surmounting Barriers with Targeted Solutions: Launching the Pharmacotherapies for Alcohol and Substance Abuse Consortium
2. Application of the Jira Software Technology in the Clinical Trial Case Report Form Development Process

6.1 AS140026-A1 Preclinical Analysis of Combined GABA B PAM and Doxazosin Treatments in Stress-Alcohol Drinking Models

This once analyzed, data from this study will produce a validated reference for future studies.

6.2 AS140026-A2 Assessing Pharmacotherapies in Animal Models of Post-Traumatic Stress Disorder and Alcohol Use Disorder

AIM 2 data were presented at the MOMRP meeting Ft. Detrick, MD, 09/11/2019 “Assessing Pharmacotherapies in Animal Models of Post-Traumatic Stress Disorder and Alcohol Use Disorder”

In coordination with Astellas (the pharmaceutical company that owns ASP8062) and RTI, a manuscript is in the process of being generated.

6.3 AS140026-A3 PT150 (formerly ORG 34517) as a Potential Treatment for Alcohol Dependence – Alcohol Interaction Study

- a. Presentation at MOMRP at Fort Detrick on 11-SEP-2019 by the PI. An abstract describing the study results was accepted and a poster will be presented at the annual meeting of the American College of Neuropsychopharmacology on 9-DEC-2019 by the PI.

6.4 AS140026-A4 Zonisamide as a New Treatment for Co-occurring Post-Traumatic Stress-Disorder (PTSD) and Alcohol Use Disorder (AUD)

The PI and study monitor recorded a podcast related to alcohol use disorder as a result of this study on 26-APR-2019, educating the broader public on an important topic. The podcast can be viewed here: [Whiskey Neat](#)

6.5 AS140026-A5-Kappa Opioid Receptor Antagonism for the Treatment of Alcohol Use Disorder and Comorbid PTSD

- a. Dr. Davis presented the study rationale and design at the annual meeting of the American Society of Clinical Psychopharmacology in Scottsdale, AZ (28-MAY-2019).
- b. Tuscaloosa investigators presented the study rationale and design during the local Tuscaloosa VA Mental Health Summit (27-AUG-2019).
- c. Press releases have been approved and will be submitted to media outlets in OCT-2019

6.6 AS140026-A6 Lofexidine Combined with Buprenorphine for Reducing Symptoms of Post-Traumatic Stress Disorder and Opioid Use Relapse in Veterans

Not applicable

6.7. AS14026-A7 N-acetylcysteine Treatment to Reduce Alcohol Use, Cognitive Impairment and PTSD Symptom Severity in Veterans with Traumatic Brain Injury and Alcohol Use Disorder

Not applicable

8. Participants and Other Collaborating Organizations

RTI International - Management Core

Nolen, Tracy	Principal Investigator	26%
Bilbrey, Hudson	Programmer/Analyst	15%
Bradley, Lauren	Research Coordinator	49%
Burd, Andrew	Clinical Data Manager	17%
Calabro, Meghan	Research Coordinator	14%
Carper, Ben	Statistician	14%
Crawford, Meg	Research Coordinator	32%
Fain, Katie	Research Coordinator	8%
Gblokpor, Agbessi	Programmer/Analyst	10%
Hirsch, Shawn	Statistician	42%
Kendrick, Amy	Research Coordinator	33%
LeGrow, Keith	Programmer/Analyst	39%
Nowack, Kayla	Statistician	47%
Riggs, Callie	Financial/Subcontracts Mgr	12%
Roberts, Cheryl	Clinical Data Manager	11%
Tang, Yan	Programmer/Analyst	17%
Turner, Gene	Clinical Data Manager	50%
Vandergrift, Nathan	Statistician	26%
Whitworth, Ryan	Statistician	24%
Williams, Rick	Co-Principal Investigator	19%

Baylor College of Medicine - Management Core

Kosten, Thomas	Co-Principal Investigator	25%
Domingo, Coreen	Site Coordinator	75%

Medical University of South Carolina

Preclinical Analysis of Combined GABA B PAM and Doxazosin Treatments in Stress-Alcohol Drinking Models

Becker, Howard	Principal Investigator	5%
Lopez, Marcelo	Co-Principal Investigator	12.80%
Reasons, Sarah	Research Technician	50%

University of Houston

Assessing Pharmacotherapies in Animal Models of Post-Traumatic Stress Disorder and Alcohol use Disorder

Haile, Colin	Principal Investigator	50%
Kosten, Therese	Co-Principal Investigator	10%
Miah Baker	Research Assistant	50%
Hailey Rodgers	Graduate Student	25%
Sergio Sanchez	Research Assistant	100%
Kate Koontz	Undergraduate Student	25%

Siaf Quadri	Undergraduate Student	25%
Kevin Winoske	Laboratory Manager	75%

Baylor College of Medicine

PT150 (formerly ORG34517) as a potential treatment for alcohol dependence – Alcohol interaction study

Verrico, Christopher	Principal Investigator	50%
Kosten, Tom	Co-Principal Investigator	55%
Choudhury, Aroteem	Study Coordinator	30%
Rojas, Cesar	Sr. Study Coordinator	37%
Johnson, Biju	Pharmacist	55%

Baylor College of Medicine

Zonisamide as a new treatment for post-traumatic stress disorder and co-occurring alcohol use disorder (Study 2016R1A5)

Verrico, Christopher	PI/PD	50%
Jacobsen, Christine	Study Coordinator L3	100%
Sarwar, Shafaq	Study Coordinator L2	75%
Van Sluis, Nicolette	Regulatory Coordinator	25%

Tuscaloosa Research & Education

Kappa Opioid Receptor Antagonist for the Treatment of Alcohol Use Disorder and Comorbid PTSD Planning Grant

Davis, Lori	Co-Principal Investigator	20%
Petrakis, Ismene	Co-Principal Investigator	20%
Norrholm, Seth	Co-Investigator	33%
Creel, Sandra	Support Staff/Coordinator	20%
Pilkinton, Patricia	Co-Investigator	10%
Brown, Ashley	Study Coordinator	100%
Estes, Sandra	Project Manager	50%
Newcomb, Jenelle	Study Coordinator	100%
Serrita, Jane	Independent Assessor	30%
Innocente, Brittany	Study Coordinator	100%
Weingast, Leah	Study Coordinator	25%
George, Renie	Independent Assessor	25%

Baylor College of Medicine

Lofexidine Combined with Buprenorphine for Reducing Symptoms of Post-Traumatic Stress Disorder and Opioid Use Relapse in Veterans - Planning Grant

Verrico, Christopher	PI/PD	50%
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Northern California Institute for Research and Education

N-acetylcysteine Treatment to Reduce Alcohol Use, Cognitive Impairment and PTSD Symptom Severity in Veterans with Traumatic

Brain Injury and Alcohol Use Disorder: A Confirmatory Study - Planning Grant

Batki, Steven	Principal Investigator	10%
Pennington, David	Co-investigator	10%
Lasher, Brooke	Research Project Manager	15%
Pothier, Holly	Study Coordinator	20%

7.

7.5.b Change in active support of the PD/PIs or senior/key personnel since the last reporting period:

There has been change in the active support of the PI in the last reporting period:

PETRAKIS, Ismene. L.

Dr Petrakis has a dual appointment at Yale University and the Veteran's Administration Medical Center. This is supported by a memorandum of understanding between the two entities and precludes the possibility of dual compensation. Under the current arrangement, 100% of Dr. Petrakis' TOTAL PROFESSIONAL EFFORT (TPE) is available as follows: Yale University 100% = 33% TPE, VAMC: 100% = 67% TPE

ACTIVE:

VACT:

MIRECC (Sofuoglu) (Role: Project PI) \$312,500 10/01/03–09/30/20
 Veterans Affairs 3 calendar, TPE 16.67%
 Effort provided by the VA

VISN 1: Mental Illness Research Education Clinical Center (MIRECC)

The purpose of this MIRECC is to improve the provision of biopsychosocial health care services to eligible veterans suffering from major mental illnesses and concurrent substance abuse or dependence (dual diagnosis patients).

VA Merit Award CSR&D (Petrakis) (Role: PI) 06/01/2018–5/31/2023
 1101CX001012-01A2 \$150,000 0.6 calendar TPE 3.33%
 Veterans Affairs Effort provided by the VA

Optimal Treatment of Veterans with PTSD and Comorbid Opiate Use Disorder (OUD)

The purpose of this study is to test whether CPT-C is more effective than *IDC in treating symptoms of PTSD* among Veterans with OUD maintained on buprenorphine. This study will also test whether CPT-C is more effective than *IDC in reducing opioid use* among Veterans with PTSD and comorbid OUD maintained on buprenorphine.

Merit Review Award CSR&D (Yoon) (Role: Co-Investigator) 7/1/2017–6/30/2021
 Department of Veterans Affairs \$146,319 0.6 calendar TPE 3.33%

Ketamine for The Rapid Treatment of Major Depression and Alcohol Use Disorder

The goal of the project is to evaluate whether ketamine is superior to placebo in treating depression in veterans with major depressive disorder (MDD) and alcohol use disorder (AUD) in

a double-blind, placebo-controlled trial.

Pharmacotherapies for Alcohol and Substance Use Disorders 10/01/2018–09/30/2021
(PASA) Consortium (Petrakis/Davis) Role: Co-PI \$ 523,775 1.2 CM/ TPE 6.67%
(West Haven VAMC Site)

Kappa Opioid Receptor Antagonist for the Treatment of Alcohol Use Disorder and Comorbid PTSD – Planning Grant

This study is testing a novel potential psychopharmaceutical treatment for Veterans and Service Members with AUD and comorbid PTSD. This study will test the safety and preliminary efficacy of BUP/NTRX in the treatment of AUD in military populations with comorbid PTSD.

Yale University:

R21 AA 024917 (Ralevski) (Role: Co-Investigator) \$118,750 04/01/18 – 03/31/20
NIH/NIAAA 0.18 calendar/ TPE 1.0%

Effect of Allopregnanolone on Stress-Induced Craving

We propose to explicate the role, and the mechanisms of allopregnanolone on alcohol effects by determining whether intravenous infusion of allopregnanolone attenuates stress-induced alcohol craving, stress-induced anxiety, and subjective stimulant/sedative effects of alcohol using a laboratory paradigm.

P01 AA027473-01 (PI McKee) (Role: Co-Investigator) \$298,506 9/30/2018–9/29/2020
NIH/NIAAA/ORWH 1.2 calendar/ TPE 6.67%

Sex-Appropriate Treatment Development for Alcohol Use Disorders

This cross-species, translational program project will bring together basic and clinical scientists to investigate new neurobiological targets for sex-appropriate therapeutics for AUD.

Pending:

U54AA027989 (PI McKee) 9/01/19 - 8/31/24

(Roles: Co-Investigator, Admin Core; \$86,642; .3 calendar/ TPE 1.67%;
Project Lead, Career Enhancement Core; \$150,000; .9 calendar/ TPE 5%;
Project Lead, Resource Support Core; \$100,000; .3 calendar/ TPE 1.67%;)
NIAAA/ORWH

YALE-SCORE on sex differences in alcohol use disorder.

Use a neurobiologically-informed approach focusing on the ‘dark side of addiction’ to inform and expedite the development of sex-appropriate therapeutics targeting stress and negative affect, which differentially maintain drinking in women, train the next generation of researchers to focus on sex and alcohol use, and provide a national resource on women and drinking.

Overlap: None

DAVIS, Lori L.

ACTIVE

DoD CDMRP PASA (Davis/Petrakis) 01/01/2019 – 12/31/2022 1.8 CM

Pharmacotherapies for Alcohol and Substance Abuse (PASA) Consortium \$1,893,454 total budget

KOR Antagonism for the Treatment of Alcohol Use Disorder and Comorbid PTSD

Role: Principal Investigator

This randomized, double-blind, placebo-controlled, multi-site study will evaluate the efficacy of sublingual buprenorphine combined with extended-release naltrexone in the treatment of comorbid AUD and PTSD. In addition to the primary clinical outcomes for AUD and PTSD, pre- and post-treatment psychophysiological correlates of fear and alcohol craving that include 1) measure of the extinction of fear-potentiated startle and 2) psychophysiological reactivity to trauma stimuli and alcohol cues will be measured.

VA HSR&D (Davis) 10/01/2017 – 09/30/2020 1.2 CM

VA Health Services R&D \$396,800 total budget

Health Care Utilization of Veterans Receiving Supported Employment

Role: Principal Investigator

The study evaluates the health service utilization of recently unemployed Veterans with a diagnosis of posttraumatic stress disorder (PTSD) who were prospectively randomized to receive either Individual Placement and Support (IPS) or Transitional Work Program (TWP) in the VA Cooperative Study Program #589.

VA-VACI-2016-01 (Social Finance/Davis) 04/01/2018-12/31/2021 1.8 CM

VA Center for Innovation \$6,000,000 total budget

Veterans Employment Pay for Success (Veterans CARE)

Role: Principal Investigator

Quasi-experimental multi-site dissemination study of Individual Placement and Support for Veterans with service-connected posttraumatic stress disorder to determine scalability and return on investment through Pay for Success financial structure.

D1489-I (Davis) 04/01/2015-09/30/2020 1.2 CM

VA Rehabilitation R&D \$1,037,532 total budget

Efficacy of Supported Employment within the OIF/OEF Patient Aligned Care Team

Role: Principal Investigator

A single site, prospective, randomized, controlled study to evaluate the efficacy of IPS when delivered within a primary care Patient Aligned Care Team (PACT) designated for Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn (OEF/OIF/OND) Veterans.

D1824-W (Hilgeman) 10/01/2015 – 09/30/2020 0.5 CM

VA Rehabilitation R&D \$920,100 total budget

Optimizing Dementia Care Through Collaborative Recovery Interventions

Role: Mentor

The primary research aims of this study are to develop a manual and conduct a randomized controlled pilot study of a telephone-based counseling and care consultation intervention for Veterans with dementia and their family caregivers.

SAMHSA (Albright) 01/01/2017- 10/31/2022 1 CM

Substance Abuse and Mental Health Services Administration \$750,000 total local budget

Alabama SBIRT Initiative

Role: Local Site Co-Principal Investigator Site

In collaboration with the University of Alabama Department of Social Work and the Alabama Department of Mental Health, Tuscaloosa VA Medical Center will be studying the implementation, integration, and impact of evidence-based substance abuse screening methods (Screening, Brief Intervention and Referral to Treatment - SBIRT) on veterans at TVAMC. This SAMHSA funded program seeks to enhance substance abuse detection and treatment in high-risk and underserved communities in West Alabama by partnering with care providers to integrate substance abuse screening into the primary care setting.

CX001068-01A1 (Norrholm) 01/01/2019 – 3/31/2020 1.2 CM

VA Clinical Science R&D

Neurobiological Correlates of Fear in Veterans with Military Sexual Trauma

Role: Local Site Investigator

The multi-site study will examine the association between fear extinction, dark-enhance startle, and posttraumatic stress disorder (PTSD) symptom severity and identify the effects of estrogen variation on these paradigms.

1 R61 AT010802-01 (Mumba) 10/1/2019 – 09/30/2024 1.2 CM

National Center for Complementary and Integrative Health (NCCIH)

A Mindfulness and Peer Mentoring Program to Improve Adherence to Medication Assisted Treatment for Opioid Use Disorders

Role: Mentor and Co-investigator

This two-site study will examine the efficacy of mindfulness relapse prevention combined with peer mentoring in improving adherence to medication assisted treatment for opioid use disorders.

PENDING

VA CSR&D (Lin) 07/01/2020 – 06/30/2025 1.2CM

VA Clinical Science R&D Career Development Award

A Randomized Placebo-Controlled Trial of Methylphenidate Augmentation of Aerobic Exercise in Veterans with a Diagnosis of Post-Traumatic Stress Disorder and Recent Cerebral Vascular Stroke

Role: Mentor and Co-Investigator

This Career Development Award application will test the efficacy of methylphenidate augmentation of aerobic exercise intervention in Veterans with a diagnosis of PTSD and recent stroke.

OVERLAP

There is no overlap in the budget, administrative aspects, or specific aims of the studies above.

7.5.c Other organizations that have been involved as partners:

None. However, the study team is planning to outreach to Alabama National Guard and Reserve units.