AD_____

Award Number: W81XWH-15-2-0077

TITLE: DoD Alcohol and Substance Abuse Consortium Award

PRINCIPAL INVESTIGATOR: Rick Williams

CONTRACTING ORGANIZATION: RESEARCH TRIANGLE INSTITUTE
RESTRIANGLE PARK, NC 27709

REPORT DATE: October 2018

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2018	Annual Report	30 Sep 2017 - 29 Sep 2018

4. TITLE AND SUBTITLE

DoD Alcohol and Substance Abuse Consortium Award

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-15-2-0077

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Rick Williams

E-Mail: rwilliams@rti.org

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Research Triangle Institute
3040 Cornwallis Road
Research Triangle Park, NC
27709

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

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 third year, the consortium continued progress on the three ongoing studies and launched two additional studies. Additionally, the consortium solicited new studies through the third RFA processes and are in the process of reviewing applications at the end of year 3.

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	21	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

- **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.

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

- **Accomplishments**

Our primary objectives for the third year were:

- To complete study design and launch for PT150-alcohol interaction study
- To initiate planning for the PT150-alcohol PK study
- Complete preparations to implement the Verrico outpatient study
- To monitor study progress and site performance and adjust protocols, budgets, and contracts as needed on the 2 pre-clinical studies being completed by Drs Haile and Kosten, and by Dr. Becker
- To issue another request for applications for small-cost and short-duration planning grants (RFA 3a) and basic science research or ready to implement human studies (RFA 3b).
- Complete Davis and Petrakis study planning and grant, gain approval for the full study from the GSC, make award of the study and begin study implementation activities.

3.1 Discovery Studies

3.1.1 "Assessing pharmacotherapies in animal models of post-traumatic stress disorder and alcohol use disorder" (Principal Investigators: Drs. Colin N. Haile, Therese A. Kosten)

PTSD and AUD are linked to dysregulated noradrenergic (NE) function, altered hypothalamic-pituitary-adrenal (HPA) axis stress reactivity, and the endogenous opioid dynorphin and its receptor (kappa opioid receptor, KOR) play a significant role in stress reactivity and alcohol reinforcement. Thus, the primary objective of this study is to test the ability of FDA investigational medications that target these systems on their ability to reduce PTSD-induced alcohol intake in a rodent model of PTSD/AUD comorbidity. Original study drugs include CERC-501, candesartan and perindopril. However, study drugs were recently modified to include ASP8062, a drug compound from pharmaceutical company, Astellas, as well as doxazosin and baclofen. These changes to study drugs have been modified accordingly in the study protocol and are approved under ACURO
The study has three aims to support this objective:

Aim 1 will evaluate whether medications (i.e. CERC-501, doxazosin, ASP8062) will alter PTSD-like symptoms in a rodent model of PTSD. The hypothesis is that all the drugs will decrease PTSD symptoms.

Aim 2 will evaluate whether medications (i.e., ASP8062 or baclofen) will alter alcohol self-administration. The hypothesis is that the drugs will reduce drinking.

Aim 3 will determine whether medications will alter PTSD-induced increases on alcohol self-administration. This aim is dependent on whether efficacy of ASP8062 is observed in at least one (and ideally both) Experiments 1 and 2. This experiment will include the most efficacious dose of ASP8062 alone (found in AIM 1) and the most efficacious dose of Doxazosin alone (found in AIM 1) and a vehicle control resulting in a total of 3 drug groups.
This study was selected for its alignment with the PASA Discovery aim to develop effective drug therapies for comorbid PTSD/AUD. The strengths of the study include (1) the proposed PTSD model in that, like humans exposed to traumatic stress, only a subset of rats that are exposed demonstrate enduring PTSD-like symptoms, representing a vulnerable population and (2) behaviors other than amount of alcohol consumed will be examined, such as anxiety-like behavior, sensitivity to pain and avoidance of an aversive stimulus all of which mirror human symptoms of PTSD.

3.1.1.a Accomplishments

1. AIM1: ASP8062 testing in male rats completed 8/03/2018.

2. AIM1: 75% of doxazosin testing in female rats completed 9/14/2018.

3. AIM2: Approximately 10 rats have acquired lever pressing for alcohol 9/30/2018. Testing is ongoing.

Behavioral Testing

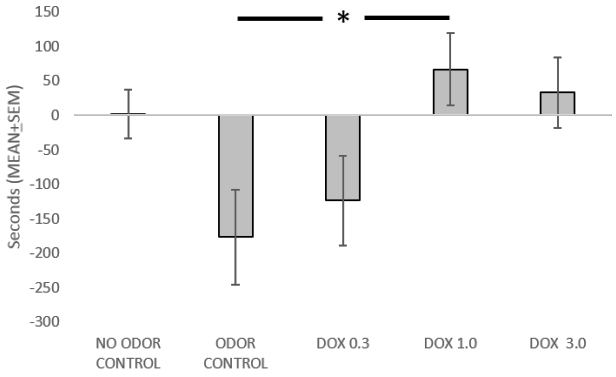
AIM 1: Evaluate whether medications (e.g. CERC-501, doxazosin, ASP8062,) will alter PTSD-like symptoms in a rodent model of PTSD.

General protocol description: To fulfill the objectives of AIM 1 of our proposal, we use the predator odor exposure stress model. In rodents, exposure to predator odor is associated with PTSD-like behaviors including increased anxiety and avoidance behavior. These behaviors are typically measured with elevated plus maze (EPM), open field test (OFT) and contextual avoidance conditioning procedures or conditioned place aversion (CPA). Overall, predator odor exposure decreases time spent on the open arms and increases time spent in the closed arms of the EPM. Predator odor exposure also decreases time spent in the center of the open field in the OFT. Finally, in the CPA tests predator odor exposure decreases time spent in the predator odor-paired context in the avoidance test. Results from these behavioral tests assessing doxazosin is presented below.

Testing protocol: Adult male Sprague-Dawley rats (Charles River Labs; Wilmington, MA, N=90, 60 males, 30 females) were used in the studies. Baseline measures were obtained first in all behavioral assays before predator odor exposure. Rats were then exposed to predator odor and tested again in all behavioral paradigms. On Day 6, rats were then administered various doses of doxazosin (0.3, 1.0, and 3.0 mg/kg, IP) for 5 days and their behavior again assessed in the behavioral assays on Days 9-10 Test2). The timing of the testing schedule was based on our preliminary data and previous studies. Individuals performing the behavioral tests were blind to the dose of medication administered. The testing procedure for each behavioral assay is detailed below.

Conditioned Place Aversion: The conditioning apparatus (MED Associates, St. Albans, VT) consists of two primary chambers that differ by floor texture (tactile, rods vs mesh), color (visual, white vs black) and lighting separated by a central compartment designed to provide a neutral starting position. Automatic Guillotine doors on either side of the center compartment allow doors to be opened simultaneously to both primary chambers without interference. Animal position is tracked by IR photo-beam detectors.

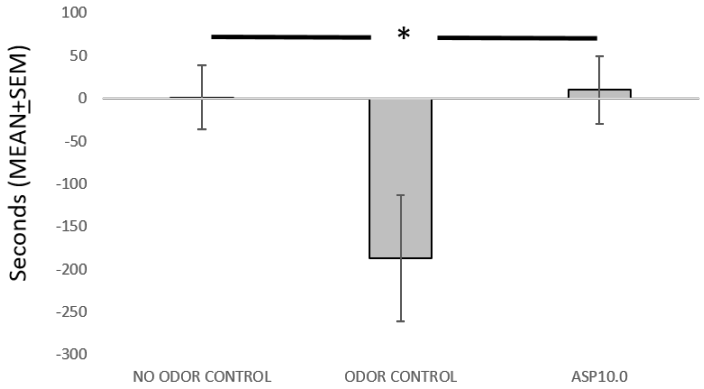
Figure 1. Effects of doxazosin on predator odor-induced conditioned place aversion day 10 test.



The central compartment and two primary chambers include a stainless-steel waste pan located directly beneath the floor. Rats were first exposed to the conditioning apparatus (MED Associates) for 15 min with full access to obtain baseline times spent in each chamber (baseline). The next day rats were randomly assigned to a compartment and exposed to predator odor or no odor for 15 min in the morning (AM session), then returned to their home cage. In the evening of the same day (PM session) rats were confined to the opposite compartment and exposed to bobcat urine (15 min) soaked filter paper in a disposable weigh-boat placed under the floor of the apparatus in the waste pan. The following day (Avoidance Test), rats were again allowed to explore the entire apparatus (15 min) and times spent in each chamber obtained. Avoidance of predator-paired context was quantified as post-conditioning time in predator context minus pre-conditioning time in predator context (change from baseline, seconds).

Results: Figure 1 presents preliminary data on the impact of various doses of doxazosin in male rats exposed to predator odor stress. “TEST1” was performed 24 hours after odor/no odor exposure whereas “TEST2” was performed 10 days after odor/no odor exposure. Additional rats have been

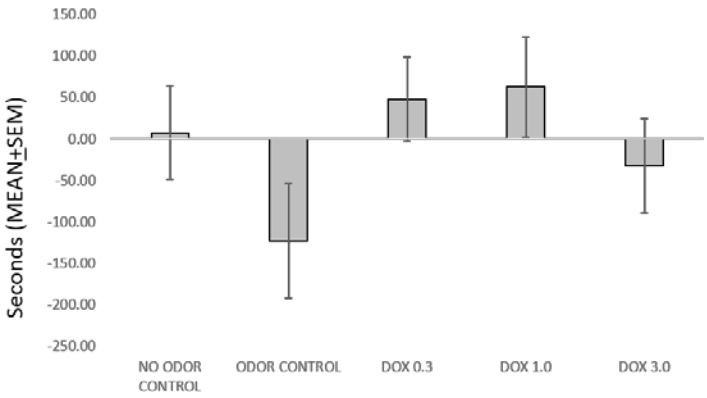
Figure 2. Effects of ASP8062 on predator odor-induced conditioned place aversion day 10 test.



added to the control groups as all tests have been completed for male rats. Figure 1 presents data obtained at baseline and on day 10 in male rats after being exposed to predator odor then administered various doses of doxazosin. Results revealed a significant treatment condition main effect ($F_{(4,47)}$=3.47, p=0.01). Post-hoc analysis indicated a significant difference between Odor Control and DOX 1.0mg/kg (p<0.05). Results suggests DOX blocked the enduring effects of predator odor-induced place aversion which is highly significant since our previous study showed DOX decreased PTSD symptomology in Veterans with PTSD (Rodgers et al. 2016). Overall, the results support the predator odor animal model of PTSD as a model of the human condition.

We have completed testing ASP8062 in male rats for AIM 1. Preliminary analysis of predator odor-induced conditioned place aversion is presented in Figure 2. Targeted statistical analysis revealed a significant main effect for treatment condition ($F_{(2,27)}$=4.32, p=0.02). Post-hoc analysis indicated a significant difference between Odor Control and the highest dose of ASP8062 (10mg/kg, PO, p<0.05). Results suggest ASP8062 significantly attenuated predator odor induced conditioned place aversion. Preliminary analysis of the impact of DOX on predator odor-induced conditioned place aversion is presented in Figure 3. Analysis did not reveal any significant differences between treatment groups (F(4,49)=1.58, p<0.19) likely due to the variability within groups. Nevertheless, data do suggest a trend for DOX to block CPA.

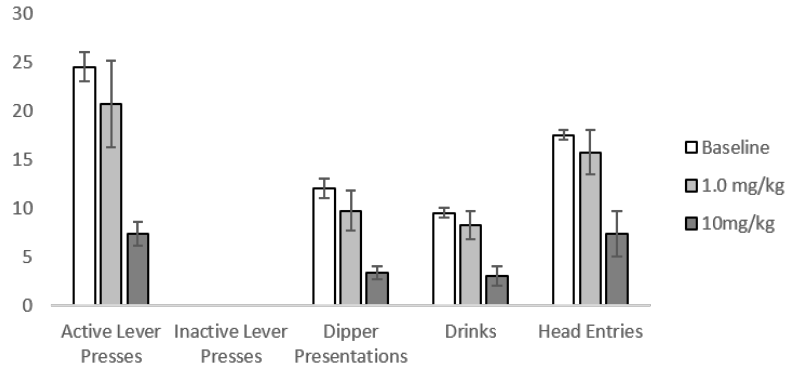
Figure 3. Effects of doxazosin on predator odor-induced conditioned place aversion day 10 test.



Experiments testing the impact of ASP8062 in elevated plus maze and open field test have been completed and data are being analyzed.

AIM2. Alcohol self-administration. Rats (male and female) are being trained to self-administer alcohol (10%) in one-hour sessions in standard operant chambers (Coulbourn Instruments, Allentown, PA) enclosed in sound-attenuating cubicles (Coulbourn Instruments). Each chamber is equipped with two levers located on either side of an access area into which a dipper (0.1 mL capacity) protrudes for the rat to orally self-administer the alcohol. Prior to activation, the dipper is maintained in a small reservoir of alcohol. When the active lever is pressed two times (FR2) the dipper is activated and made available to the rat. Three cue lights remain on above the active lever as well as the house light until the lever is activated. At that point, the cue and house light goes off and a light

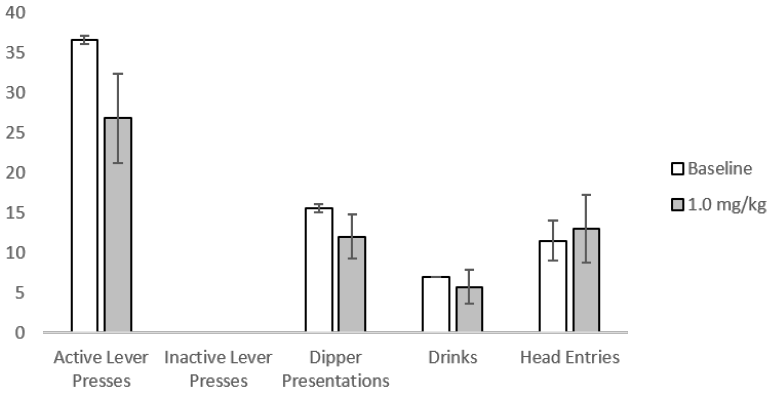
Figure 4. Effects of ASP8062 on operant alcohol self-administration in a representative male rat.



turns on above the dipper. Rats are trained until they meet acquisition criteria (>10 presses and not varying by ±20% across days. Following acquisition, rats are randomly assigned a test dose (Vehicle, ASP8062 or baclofen) that is administered for 4 consecutive days. A representative male rat that was administered two different doses of ASP8062 is presented in Figure 4. At least 5 days of washout was allowed between test dose administrations. Data suggest a dose dependent decrease in alcohol self-administration parameters.

Figure 5 shows data generated from a representative female rat following administration of a low dose of ASP8062 on operant alcohol self-administration. Data suggest a decrease in active lever presses for alcohol. Testing is ongoing.

Figure 5. Effects of ASP8062 on operant alcohol self-administration in a representative female rat



3.1.1.b What opportunities for training and professional development did the project provide?

Not applicable

3.1.1.c How were the results disseminated to communities of interest?

Preliminary results were presented at the MOMRP. Once all final data are available, a series of manuscripts will be prepared and submitted for publication. Additional discussions will also be held with the collaborating pharmaceutical companies about next development phase studies toward FDA approval and marketing.

3.1.1.d What do you plan to do during the next reporting period to accomplish the goals and objectives?

1) AIM1. Complete testing doxazosin in female rats.

2) AIM1. Assess the effects of ASP8062 in female rats.
3) AIM2. Continue to test the effects of ASP8062 and baclofen in male and female rats lever pressing for alcohol.
4) Continue to train rats to self-administer alcohol.

3.1.1.e Changes/Problems

1) Rats were inadvertently water restricted for a short period of time which artificially increased lever pressing. This event delayed testing.
2) Operant chambers have malfunctioned reducing our testing capacity by more than half. A technician was hired to look at the system. The problem was diagnosed, and parts sent to the company for repair. Estimated time the repairs will take, and system reassembled is 3-4 weeks.
3) A research assistant has started graduate school resulting in reduced staff.

3.1.2 "Preclinical Analysis of Combined Zonisamide and Doxazosin Treatments in Stress---Alcohol Drinking Models" (Principal Investigator: Dr. Howard C. Becker)

The primary objective of this study is to test the efficacy of zonisamide and doxazosin (independently or in combination) on a) stress-induced alcohol drinking and b) PTSD-induced alcohol drinking. The study has two aims to support this objective:

Aim 1: Examine effects of zonisamide and doxazosin treatments, alone or in combination, on stress-facilitation of drinking in alcohol dependent vs. non-dependent male and female mice.

Aim 2: Determine effects of zonisamide and doxazosin treatments, alone or in combination, on drinking in a PTSD-alcohol dependence model in male and female mice.

The study design initially included use of the drug compound carisbamate. Due to issues surrounding drug availability, it was decided that zonisamide be used in place of carisbamate, and the study protocol was modified to reflect this change in March of 2017, and the change was approved by ACURO on April 25, 2017.

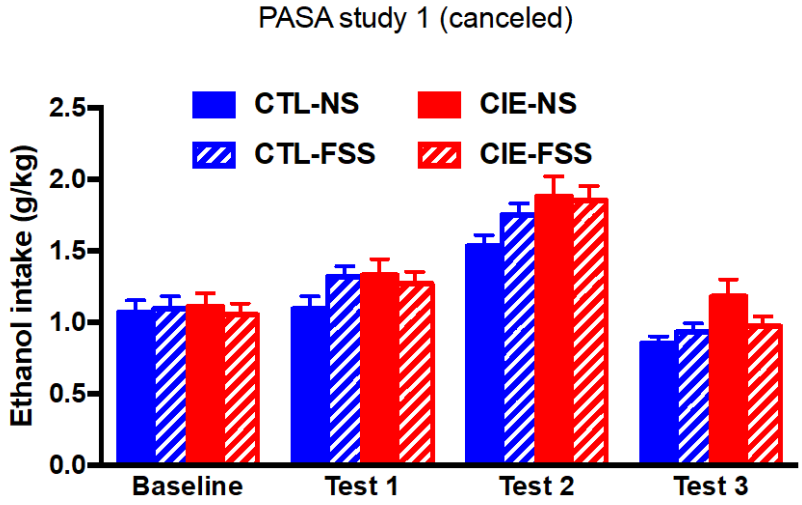
3.1.2.a Accomplishments

1. A pilot study conducted only with female subjects is ongoing to evaluate the optimal levels of ethanol vapor exposure that would result in enhanced voluntary ethanol intake after stress exposure. 30-MAR-2018
2. A new version of the ACURO was approved to reconciliate the number of subjects used in the first aim. 07-MAY-2018
3. A new set of female mice (n=128) was ordered to start a new study for Aim 1. 08-MAY-2018
4. This experiment is ongoing, and mice were randomized into four groups defined by the interaction between alcohol exposure (CIE, CTL) and stress (FSS, no-FSS). 25-JUN-2018
5. A new study with female subjects (n=128) started in May 2018 and was completed during this period. 30-SEP-2018

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**).

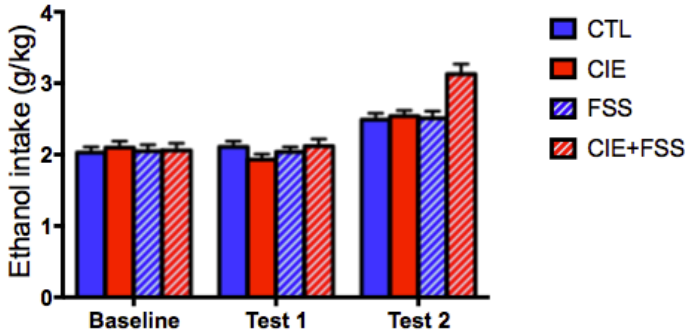
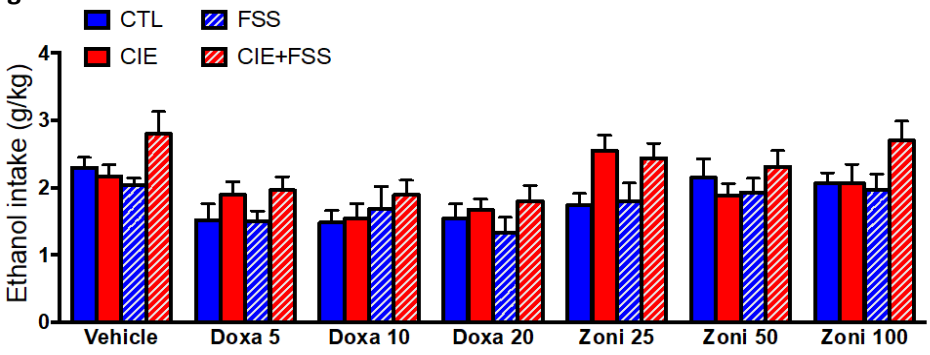


Figure 2

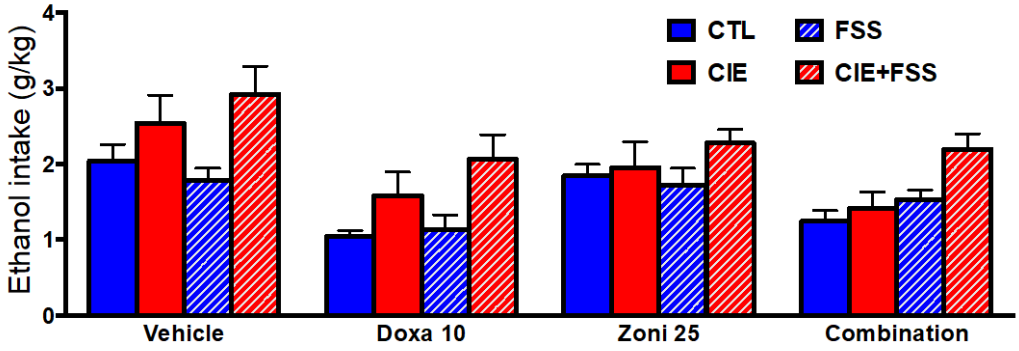
Data combined over test cycles 3 and 4 indicate that all the doses of Doxazosin were able to reduce voluntary ethanol intake particularly in mice that experienced CIE+FSS (**Figure 3**) while the three doses of Zonisamide evaluated did not reduce ethanol intake in any group (**Figure 3**).

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



3.1.2.b What opportunities for training and professional development did the project provide?

Not applicable

3.1.2.c How were the results disseminated to communities of interest?

Preliminary results were presented at the MOMRP. Once all final data are available, a series of manuscripts will be prepared and submitted for publication. Additional discussions will also be held with the collaborating pharmaceutical companies about next development phase studies toward FDA approval and marketing.

3.1.2.d What do you plan to do during the next reporting period to accomplish the goals and objectives?

The study to evaluate the effect of Doxazosin and Zonisamide alone and in combination using female subjects was completed and we plan to analyze this dataset along the data obtained with male subjects. The plan is to combine these datasets for publication.

3.1.2.e Changes/Problems

Nothing to report.

3.2 Proof of Concept Studies

3.2.1 "Efficacy and Safety Study of PT150 (formerly ORG 34517) in Veterans with Co-morbid PTSD/AUD" (Principal Investigator: Dewleen G. Baker, MD)

The primary objective of this study is to test the efficacy, safety, and tolerability of a novel GR antagonist PT150 (formerly ORG 34517) for AUD/PTSD dual diagnosis treatment in veterans. The study has two aims to support this objective:

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 is 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.

The study team and the PASA leadership jointly decided to remove Aim 2 as a component of this study and consider it as a separate study. The Aim 2 study, named "PT150 (Formerly ORG34517) as a Potential Treatment for Alcohol Use Disorder -Alcohol Interaction Study", will be conducted jointly between Dr. Baker and Dr. Verrico at the Baylor College of Medicine and will be completed before Dr. Verrico's study or the Aim 1 portion of Dr. Baker's study are initiated.

The Alcohol Interaction Study protocol is finalized and has been for some time. After briefly being put on clinical hold by the FDA (February 21, 2017) various study-related items were addressed and submitted in response to FDA, at which point the clinical hold was lifted (May 16, 2017). The study team also worked

diligently to address non-clinical hold-related items to be as thorough as possible, communicating with FDA between May and July 2017, to success. A Certificate of Confidentiality was also successfully obtained for the study. Study drug has also been received on site by the study team from PopTest, Oncology, the IND holder/pharmaceutical collaborator. The study launch was impeded by numerous regulatory delays experienced at the site IRB level. The study requires dual IRB approval from both the Baylor College of Medicine (BCM) IRB as well as the Veterans Affairs Research and Development Committee (the VA's version of the IRB) at the Michael E. DeBakey Veterans Affairs Medical Center. The process was also complicated due to the original PI, Dr. Thomas Newton, departing BCM in Summer of 2017. Protocol approval from the site IRBs was obtained in April of 2018, followed by HRPO approval that same month. Recruitment began shortly thereafter. The VA R&D had required the study team to restrict recruitment to veterans only at first (despite initial plans to include both veterans and non-veterans). After three months of unsuccessful recruiting among veterans, the study team petitioned the VA R&D to allow the study to open back up to recruitment of both veterans and non-veterans (which was the initial plan). This change received full approval from both the BCM IRB and VA R&D in July of 2018 (HRPO also approved of this modification). The study commenced recruiting under the new recruitment population guidelines in September of 2018 and is in the process of recruiting and screening subjects, with enrollment anticipated in late October/early November.

Additionally, the FDA suggested during its review of the IND application that a separate pharmacokinetic (PK) study also be conducted prior to carrying out Aim 1 of the originally proposed study. The study team and PASA leadership collaborated to devise the PK study design, and a detailed study protocol was drafted and has been disseminated for review and modification. Once finalized, this protocol will move through appropriate regulatory channels at the site, FDA, HRPO, etc. to ready it for implementation.

3.2.2 **"Zonisamide as a New Treatment for PTSD & Co-Occurring AUD"** (Principal Investigators**:** Drs. Christopher Verrico and Thomas Kosten)

This study initially set out to determine the safety and potential efficacy of carisbamate for treating PTSD and AUD symptoms in Veterans with PTSD and co-occurring AUD. However, due to issues pertaining to drug availability, the study drug was changed from carisbamate to zonisamide (in early 2017).

The study aligns with PASA aims for a proof of concept study to assess safety and surrogate markers of clinical efficacy in PTSD for treatment with an existing drug compound in veterans with AUD combined with PTSD. It is a short term clinical with outcomes including PTSD severity and alcohol use. There is ample safety data for zonisamide including its interactions with alcohol, and it has a similar therapeutic profile to FDA-approved Topiramate, but with a superior safety profile and longer half-life. The outcome measures are well justified and well validated (if not gold standard) with the populations (PTSD, AUD), and the inclusion of many PhenX toolkit measures is a methodological strength.

3.2.2.a Accomplishments

1. Fear potentiated startle (FPS) equipment purchased.
2. Fear potentiated startle (FPS) training has been completed.

3.2.2.b What opportunities for training and professional development did the project provide?

Not applicable

3.2.2.c How were the results disseminated to communities of interest?

Not applicable

3.2.2.d What do you plan to do during the next reporting period to accomplish the goals and objectives?

We expect to open the study for enrollment by the end of November 2018.

3.2.2.e Changes/Problems
Nothing to report.

3.2.3 "PT150 as a potential treatment for alcohol dependence – Alcohol interaction study" (Principal Investigators**:** Drs. Christopher Verrico and Thomas Kosten)

This study is a phase 1, single center, drug study. This within-subjects experimental procedure will assess the effects of PT150 (900 mg qd) on the subjective effects of alcohol in non-treatment-seeking alcohol-experienced volunteers (to include military service members, veterans and/or civilians). 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.

3.2.3.a Accomplishments

1. BCM IRB, VA IRB and HRPO approvals were received to initiate study.
2. All CRFs were finalized and implemented in the electronic data capture system.
3. A Manual of Operations was completed, and staff trained to implement the study.
4. Several subjects were recruited to initiate the study as the year ended.

3.2.3.b What opportunities for training and professional development did the project provide?

Not applicable

3.2.3.c How were the results disseminated to communities of interest?

Not applicable

3.2.3.d What do you plan to do during the next reporting period to accomplish the goals and objectives?

We expect to have the first cohort (1-2 people) of eligible participants complete study procedures. Following completion of chort-1, we expect to complete the site visit, and enroll the second cohort (3-4 people) of eligible participants complete study procedures.

3.2.3.e Changes/Problems

Every effort was expended to enroll veterans into the protocol, however, potential veteran subjects available typically did not meet inclusion due to pre-existing exclusionary comorbidities. The protocol was modified and approved on August 27, 2018 to extend enrollment to non-veterans. This led to delays in study implementation and loss of some staff members to conduct the study. Replacement staff are being recruited with medical staff working to conduct the study in the interim.

The only anticipated issue is subject retention. We will continue to make scheduling as easy for the participants as possible, with only the Research Pharmacy limiting when participants can be enrolled. That is, because alcohol is administered on Days 1 and 5 of the study, and the research pharmacy randomizes and prepares the alcohol beverages for participants we must schedule study participation such that alcohol is administered during a weekday.

3.2.4 "Kappa Opioid Receptor Antagonist for the Treatment of Alcohol use Disorder and Comorbid PTSD Planning Grant" (Principal Investigators**:** Drs. Lori Davis and Ismene Petrakis)

The overall objectives of the Planning Grant are:

- Conferring with the PASA Management Core and with leadership staff at Alkermes concerning the availability of support for the study and supply of study compound by Alkermes.
- Development of a protocol outline containing enough detail for the PASA Management Core and Alkermes to review and provide approval of the study concept.
- Provide a development plan and budget request to develop a full study protocol.
- In collaboration with the PASA Management Core, gain approval from the PASA Government Steering Committee to fund the development plan for a full study protocol.

3.2.4.a Accomplishments

1. The final revisions were made to the protocol and submitted to RTI PASA team on 25-May-2018 for submission to GSC. This protocol included revisions recommended by the DSMB, RTI Statistician, and GSC.
2. The project budget was submitted to PASA on 03-May-2018.
3. GSC approved the submitted protocol on 18-Jun-2018.

3.2.4.b What opportunities for training and professional development did the project provide?

Not applicable

3.2.4.c How were the results disseminated to communities of interest?

Not applicable

3.2.4.d What do you plan to do during the next reporting period to accomplish the goals and objectives?

1. This Planning Grant closed on 30-Jun-2018.
2. Approval has been received to proceed with the proposed study project.
3. Teams will move forward with project implementation.

3.2.4.e Changes/Problems

Not applicable

3.2.5 "Kappa Opioid Receptor Antagonist for the Treatment of Alcohol use Disorder and Comorbid PTSD Planning Grant" (Principal Investigators**:** Drs. Lori Davis and Ismene Petrakis)
Following completion of the planning grant, the protocol was approved to move forward to implementation. This study will Evaluate the efficacy and physiological effects of sublingual buprenorphine (SL-BUP; Subutex) combined with extended-release injectable naltrexone (XR-NTX; Vivitrol) in the treatment of comorbid alcohol use disorder (AUD) and post-traumatic stress disorder (PTSD). Subjects will be enrolled from three participating sites:

1. Tuscaloosa Research & Education Advancement Corporation (TREAC)/Tuscaloosa VA Medical Center (TVAMC)
2. Connecticut Research & Education Foundation (CREEF) / VA Connecticut Healthcare System (VACT)
3. Atlanta Research and Education Foundation (AREF)/Atlanta VA Medical Center

3.2.5.a Accomplishments

1. The protocol was drafted.
2. CRF development initiated.
3. Drug procurement procedures developed.

3.2.5.b What opportunities for training and professional development did the project provide?

Not applicable

3.5.3.c How were the results disseminated to communities of interest?

Not applicable

3.2.5.d What do you plan to do during the next reporting period to accomplish the goals and objectives?

We expect the three participating sites to obtain IRB approval. RTI will execute a subcontract and CRADA with TREAC. Agreements with the companies providing study drug will be executed.

3.2.5.e Changes/Problems

No changes or problems to report.

3.3 Administrative Deliverables

We executed the subcontract for Tuscaloosa Research Education and Advancement Corporation (TREAC) and closed the contract at the completion of work for the planning grant. We submitted all quarterly reports and continued to hold weekly meetings with PASA leadership and with CDMRP and distribute meeting minutes.

3.4 RFP Release and Review

The PASA Study Research Planning Program finalized and released two Research Funding Opportunities. The opportunities focused on:

- Request for Application (RFA) #3a: Small-cost and short-duration planning grants awarded to investigators concerning a specific compound or combination of compounds.
- Request for Application (RFA) #3b: Full study implementation awards for either:
    a. Conduct of proof-of-principle basic research to determine which compounds are most appropriate for human research trials; or
    b. Conduct of human proof-of-concept trials with promising compounds. The human trials must be ready-to-implement as defined in the RFA.

1. RFA #3a and #3b sent to GSC for Approval	15-Jun-18
2. Issue PASA RFA #3a and 3b	25-Jun-18
3. Letter of Intent Deadline	22-Aug-18
4. Full application deadline	03-Oct-18
5. Peer and Programmatic Review	7-Nov-18
6. Award Negotiations	30-Nov-18

- **Impact**

  Studies are still in planning or early implementation stages. Preliminary results for Drs. Haile and Becker's studies were presented at the Military Operational Medicine Research Program (MOMRP) meeting in September.

- **Changes/Problems**

  All problems have been described above in sections 3.1 and 3.2.

- **Products**

  Not applicable

- **Participants and Other Collaborating Organizations**

Name	Project Role	Person Months	Contribution to Project
Williams, Rick L	Principal Investigator	4	No change
Battestilli, Whitney	Clinical Data Manager	4	Maintained consortium website and related infrastructure; Developed CRFs for sponsored studies; Programmed Data Management Systems for sponsored studies; Developed data processing tools for aggregating, normalizing, and cleaning data; Created reports and dashboards to track study progress.
Bradley, Lauren	Public Health Analyst	8	No change
Collins, Doreen	Coordinator	1	No change
Crawford, Meg	Consortium Clinical Research Manager	3	Managed staff levels on protocol development and implementation of RFA 3; Led weekly leadership meetings; Monitored spending and participated in budget planning; Oversaw study development and implementation deadlines; Oversaw RFA 3 development and requests for applications.
Gatto, Gregory	Regulatory Affairs	2	No change
Hirsch, Shawn	Statistician	1	AIS: Reviewed data specifications for CDISC; Validation programming for SDTM and ADAM datasets; Reviewed and updated Statistical Analysis Plan; Drafted analysis shell tables, figures, listings; Created validation plan; Reviewed DMC report. D&P: Assisted with protocol, study design, CRFs and study timeline. Drafted randomization scheme.
Honeycutt, Emily	Statistician	2	Provided statistical support for protocol design, study implementation, data collection, data analysis and FDA submission.
Johnson, Madelyn	Administrative Coordinator	2	No change

Kendrick, Amy	Coordinator	1	Managed D&P study, working on CRADA and plans for acquiring drug and placebo. Prepared IRB submissions for initial lead site and working on items for IRB, VA, and HRPO approvals. Refined protocol, drafted MOP, worked on EDC and CRFs. Planned for equipment and procedures for testing, and plans for study procedures.
LeGrow, Keith	Programmer	1	Led PASA Jira team; Administered PASA website; Drafted documents for AIS, VOS and D&P studies; Develop and manage timeline for D&P study; Tested and documented Safety Gateway reporting system; Served on PASA leadership team.
Mendez, Angela	Programmer	2	Created, revised, and annotated CRFs for 3 PASA studies.
Nolen, Tracy	Senior Research Statistician	2	No change
Nowak, Kayla	Statistician	3	AIS: Assisted with CRF development; Assisted with CDISC implementation; Programmed DSMB reports; Contributed to Protocol, MOP, and SAP reviews. VOS: Assisted with CRF development. D&P: Assisted with CRF development.
Peeler, Russ	Human Subjects Protection leader	2	Managed IRB applications and communications with RTI IRB, and assisted with site IRB applications. Assisted with HRPO applications.
Pickett, James	Programmer	1	AIS and VOS: EDC system feature implementation; Study randomization scheme programming. D&P: Implementation planning and documentation support.
Riggs, Callie	Project Administration Specialist	2	No change
Tang, Yan	Programmer	3	Developed Medidata forms, conducted edit checks, tested systems.
Turner, Eugene	Programmer	6	CRF design, aCRF design, database testing, and created validation specifications for all studies.

Vandergrift, Nathan	Statistician	1	D&P: Reviewed proposal; CRF development; IRB submission and protocol revision; statistical analysis plan; randomization plan. RFA 3: Reviewed proposals; assisted with statistical sections for proposals; recruited external reviewers for proposals.
Whitworth, Ryan	Statistician	5	VOS: Finalized CRFs, tested DMS, developed randomization process, contributed to MOP, began drafting statistical analysis plan. AIS: Led CDISC effort. Overall: coordinated statistical team across all studies.

Baylor College of Medicine - Management Core

Kosten, Thomas	BCM Co-Principal Investigator	3
Domingo, Coreen	BCM Site Coordinator	9

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

Becker, Howard	Principal Investigator	1
Lopez, Marcelo	Co-Principal Investigator	1
Olsen, Anne	Research Technician	1

University of Houston
Assessing Pharmacotherapies in Animal Models of Post-Traumatic Stress Disorder and Alcohol Use Disorder

Haile, Colin	Principal Investigator	6
Kosten, Therese	Co-Principal Investigator	1
Walters, Hailey	Graduate Student	2
Winoske, Kevin	Research Coordinator	2

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

Verrico, Chris	Principal Investigator	6
Hoyer, Elisabeth	Study Coordinator	5
Isak, Rahel	Study Coordinator	5
Marzec, Alexander	Study Coordinator	5
Okoli, Ikechukwu	Study Coordinator	5

Baylor College of Medicine
Zonisamide as a new treatment for post-traumatic stress disorder and co-occurring alcohol use disorder

Verrico, Chris	Principal Investigator	3

Tuscaloosa Research Education and Advancement Corporation
Kappa Opioid Receptor Antagonist for the Treatment of Alcohol Use Disorder and Comorbid PTSD Planning Grant

Davis, Lori	Co-Principal Investigator	1
Petrakis, Ismene	Co-Principal Investigator	1
Norrholm, Seth	Co-Principal Investigator	1
Creel, Sandra	Support Staff/Coordinator	1

a. Has there been a change in the other active support of the PD/PIs or senior/key personnel since the last reporting period?

There has been no change since the last reporting period.

b. What other organizations have been involved as partners?

Not applicable

DoD Alcohol and Substance Abuse Consortium Award

Pharmacotherapies for Alcohol and Substance Abuse (PASA) Consortium

PI: Rick Williams, PhD & Thomas Kosten, MD **Org:** RTI International

Study Research Planning Program RFA #3

- Small-cost and short-duration planning grants awarded to investigators concerning a specific compound or combination of compounds.
- Full study implementation awards for either:
  - Conduct of proof-of-principle basic research to determine which compounds are most appropriate for human research trials; or
  - Conduct of human proof-of-concept trials with promising compounds. The human trials must be ready-to-implement as defined in the RFA.

The SRPP RFA process netted 13 applications. Programmatic review is ongoing and awards will be in Quarter 1 of Year 4.

Timeline and Cost

Activities	Q1	Q2	Q3	Q4
RFA 2 planning grant launched and completed				
Monitor animal study progress, site performance				
Clinical study development (MOPS, EDCs) completed and launched				
SRPP RFA 3a and 3b released				
Approximate Cost (k)	$356	$473	$436	$564

Year 3 Completed Objectives

- Complete study design and launch PT150 alcohol interaction study.
- Issue request for applications for short-duration planning grants and basic science research or human studies.
- Complete Davis and Petrakis planning grant and begin study implantation.
- Monitor study progress and site performance and adjust protocols and budgets as needed

Years 4 and 5 Objectives in Progress

- Ongoing study procedures/experimentation being carried out for 2 animal studies
- Ongoing study procedures being carried out for 2 human studies
- Launch Davis and Petrakis study.
- Design PT150 pK study.