

**PASA Consortium
Medications Under Study
February 2019**

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

- 1) a kappa opiate receptor (KOR) antagonist (CERC-501)
- 2) alpha adrenergic blockers (doxazosin and lofexidine)
- 3) a cortisol blocker (PT150)
- 4) a gamma amino butyric acid type B(GABA_B) receptor allosteric modulator (ASP8062) and a GABA receptor agonist (baclofen)
- 5) a complex anti-seizure medication (zonisamide)
- 6) a partial opioid agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor (buprenorphine)
- 7) an opioid antagonist (naltrexone)

Five medications are undergoing pre-clinical investigation (baclofen, doxazosin, zonisamide, ASP8062, and CERC-501) and four are undergoing clinical evaluations (PT150, zonisamide, buprenorphine and naltrexone). In order to broadly explore treatment of AUD and PTSD, we have selected compounds with a range of non-overlapping mechanisms of action (MOA) that have been shown relevant in these diseases. For example zonisamide is being clinically tested for its potential efficacy for PTSD, since two outpatient clinical trials have already shown efficacy for AUD. Other medications in this list are positive controls such as baclofen for its action in reducing alcohol use in animal models and humans, doxazosin for its efficacy reducing alcohol use and PTSD symptoms in animal models and humans, and naltrexone for its efficacy in reducing alcohol use in animals and humans.

Two medications deserving a special explanation are doxazosin and lofexidine. Doxazosin is a direct blocker (antagonist) of post-synaptic alpha 1 adrenoreceptors, while lofexidine is an agonist at pre-synaptic or auto- alpha 2 adrenoreceptors. The MOA for lofexidine reducing adrenergic activity in the brain is through feedback inhibition of norepinephrine release from these pre-synaptic neurons rather than directly blocking the effects of norepinephrine on the post-synaptic neurons. Thus, lofexidine has a much broader effect than doxazosin in reducing brain adrenergic activity because lofexidine not only reduces activity at alpha-1 receptors, but also reduces activity at all the four types of both alpha and beta adrenoreceptors.

Endogenous opioid systems in the brain are involved in regulation of mood, stress modulation, and cravings. Kappa opioid receptors are densely localized in limbic and cortical areas comprising the brain reward system, which play a role in modulating stress and in promoting addictive behaviors. The MOA for KOR antagonists like **CERC-501** involve blocking the increased dynorphin A (endogenous ligand for KOR) and increased KOR signaling in the amygdala with AUD. This excessive signaling in the dynorphin/KOR system during the stress response contributes to the anxiogenic and dysphoric responses to stress which directly produce negative emotional/mood states that accompany alcohol withdrawal and contribute to excessive alcohol consumption to avoid withdrawal. KOR antagonists block the actions of endogenous dynorphins and alleviate the negative mood states from AUD. Similar actions are

**PASA Consortium
Medications Under Study
February 2019**

postulated for reduction in PTSD symptoms. CERC-501 is currently unavailable for additional studies due to its being purchased by another pharmaceutical company that is pursuing its use in major depression as the first approved indication.

Alpha adrenergic blockers like **doxazosin** have an MOA that reduces the excessive adrenergic activity characteristic of PTSD and AUD and withdrawal. Doxazosin, an alpha-1 specific blocker is FDA approved for prostate hyperplasia and hypertension, and has been shown to reduce PTSD in clinical studies and reduce AUD in preclinical and clinical studies. It has a longer half-life than prazosin which is another alpha adrenergic blocker that has been shown to also reduce PTSD symptoms (nightmares). **Lofexidine** is in contrast an alpha2-adrenergic receptor agonist. Like doxazosin it can be used as an anti-hypertensive, but is mostly used to help relieve symptoms of heroin or opiate withdrawal in opiate dependency. It also has broader efficacy in reducing all types of adrenergic activity through feedback inhibition of adrenergic neurons, as explained above.

Cortisol blockers like **PT150** have an MOA that are relevant due to the significant dysregulation of the Hypothalamic-Pituitary-Adrenal (HPA) axis in both AUD and PTSD leading to elevated cortisol activity.

GABA systems have been implicated as targets for ethanol at the cellular, molecular and behavioral level. The MOA relevant to modulating the GABA_B receptor to increase its activity, which decreases alcohol responding and like the prototypic agonist, **baclofen**, reduces the self-administration of alcohol. The GABA_B receptor allosteric modulator, **ASP8062**, reduced voluntary responding for 10% ethanol in a dose-related manner in initial animal studies. Increased GABA activity can increase depleted dopamine levels and possibly reduce drug cravings. A reduction in GABA_B activity is also characteristic of PTSD and augmentation of this activity should reduce PTSD symptoms.

Zonisamide is an anticonvulsant that has a broad combination of complementary MOA as an antiepileptic agent. Chemically it is a sulfonamide. By altering the fast inactivation threshold of voltage dependent sodium channels, zonisamide reduces the sustained high-frequency repetitive firing of action potentials. Zonisamide also inhibits low-threshold T-type calcium channels in neurons, which may prevent the spread of seizure discharge across cells. Both alcohol and zonisamide regulate/modulate the activity of the same neuro transmitter systems. Zonisamide in repeated doses decreases the sensitivity of the hippocampus to ethanol. Its MOA for reducing PTSD symptom is less clear and will be explored in both rodent and human study.

Buprenorphine itself is an opioid, but the maximal effects are less than other more dangerous opioid agonists, like methadone and heroin, and is FDA-indicated for the treatment of opioid dependence, because it is a partial rather than full agonist of the mu receptors. More importantly for the proposed human studies, buprenorphine is the only clinically available medication that acts as an antagonist of the kappa opioid receptors. Kappa opioid antagonists

**PASA Consortium
Medications Under Study
February 2019**

in animal models and buprenorphine in preliminary human studies have reversed PTSD symptoms more effectively than the currently FDA approved selective serotonin reuptake inhibitors (SSRIs) used for treating PTSD (sertraline and paroxetine). These antagonists can also reduce alcohol use.

Naltrexone reverses the effects of opioid analgesics by binding to the various opioid receptors in the central nervous system, including the mu, kappa and delta-opioid receptors. This leads to an inhibition of the typical actions of opioid analgesics, including analgesia, euphoria, sedation, respiratory depression, miosis, bradycardia, and physical dependence. Naltrexone is longer-acting and more potent compared to naloxone (Narcan). Naltrexone is used to block cravings for both opioids and alcohol (FDA-indicated for the treatment of alcohol dependence) but naloxone is not. Both drugs block the analgesic and respiratory depressant actions of exogenous opioids and the pleasure response of endogenous endorphins, which are released when drinking alcohol. However, to treat an overdose naltrexone does not act quickly enough, while naloxone is both quick and short acting for opioid overdose treatment. While naltrexone cannot be used to rescue someone from an opioid overdose, it can help people who are addicted to opioids have less craving for them (FDA-indicated for the prevention of relapse to opioid dependence following detox).

RFA1 – Preclinical - Discovery

AS140026-A1 *“Preclinical Analysis of a Combined GABA B PAM modulator and Doxazosin Treatments in Stress-Alcohol Drinking Models”* - Howard Becker, Medical University of South Carolina

Objective and Study Design:

The overall objective of this study is to employ two well-established mouse models of alcohol dependence and stress/PTSD exposure to evaluate the ability of medications to reduce excessive alcohol consumption and, in particular, the exacerbating effects of stress that perpetuate hazardous and harmful drinking associated with dependence. The study will employ two well-established mouse models of alcohol dependence and stress/PTSD exposure to evaluate the ability of medications to reduce excessive alcohol consumption and, in particular, the exacerbating effects of stress that perpetuate hazardous and harmful drinking associated with dependence. Based on clinical and preclinical evidence, two promising medications, a GABA B PAM modulator and doxazosin, will be evaluated alone and in combination to assess the effectiveness of the drugs on stress facilitation of drinking in alcohol dependent vs. nondependent male and female mice and on drinking in a PTSD-alcohol dependence model in male and female mice. Carisbamate was originally planned for this study, but it was suddenly withdrawn by the supplying pharma company prior to study start. Thus, we determined that zonisamide would be an appropriate replacement compound worthy of study.

Two medications, zonisamide and doxazosin, will be evaluated alone and in combination to assess the effectiveness of the drugs on stress facilitation of drinking in alcohol-dependent vs. nondependent male and female mice and on drinking in a PTSD-alcohol dependence model in male and female mice.

Collectively, these studies will provide valuable information regarding potentially new and more effective treatment strategies for AUD and PTSD comorbidity.

Aim 1 (Alcohol Disorder Model). Examine the effects of:

- zonisamide alone
- doxazosin alone (positive control for the PTSD and alcohol models)

**PASA Consortium
Medications Under Study
February 2019**

- zonisamide and doxazosin in combination on stress facilitation of drinking in alcohol-dependent vs. nondependent male and female mice.

Primary outcome: alcohol drinking during Forced Swim Stress procedure using the Chronic Intermittent Ethanol-Forced Swim Stress (CIE-FSS) Drinking Model

Aim 2 (PTSD and Alcohol Disorder Model). Examine the effects of:

- zonisamide alone

- doxazosin alone (positive control for the PTSD and alcohol models)

- zonisamide and doxazosin in combination on drinking in a PTSD-alcohol dependence model in male and female mice.

Primary outcome: alcohol drinking using the PTSD-CIE Drinking Model Chronic Intermittent Ethanol-Forced Swim Stress (CIE-FSS Drinking Model)

At a Glance Info:

Study Type: preclinical trial

Population: Transgenic male and female mice

Number of Participants: 640 mice

AS140026-A2 - *“Assessing pharmacotherapies in animal models of post-traumatic stress disorder and alcohol use disorder”* - Colin Haile, University of Houston

Background: Recent evidence shows the endogenous opioid dynorphin and its receptor (kappa opioid receptor, KOR) play a significant role in stress reactivity and alcohol reinforcement. In particular, KORs modulate noradrenergic (NE) in brain stress circuits important in animal relapse models. KOR antagonists block the reinforcing effects of alcohol, and stress-induced increases in alcohol consumption. KOR antagonists have been shown to reduce stress in preclinical studies. KOR antagonists also possess potent antidepressant effects. Thus, for this application we are collaborating with Cerecor Inc. to assess CERC-501, a centrally penetrant, orally active, high-affinity and selective KOR antagonist in animal models of PTSD and AUD. Subsequent to the commencement of this project, CERC-501 was purchased by a large pharmaceutical company (Johnson and Johnson) that is pursuing its use in major depression and PTSD as an FDA approved indication based in part from Dr Haile’s successful pre-clinical study. We consider this a highly successful outcome, since the medication has moved to a BIG pharma company, which has the resources to conduct the necessary Phase 3 FDA studies and file the New Drug Application (NDA), which cost about \$100 million and is well beyond the resources of PASA.

Doxazosin, another off-patent generic drug, is already being used effectively for reducing adrenergic activity in both alcoholism and PTSD as supported by several outpatient clinical trials, and is acting as a positive control in this study examining kappa opioid antagonism and now GABA-b agonism as other MOAs for reducing PTSD and AUD. Moreover, pursuing a different mechanism of action (MOA) as a treatment option makes better scientific and commercial sense for a pre-clinical discovery study, and the MOA of Astellas’ GABA-B PAM (ASP8062) provides this option, as well as the BIG pharma support to move this medication forward into Phase 2 and 3 clinical trials for an NDA filing under these two indications. Its MOA as an allosteric modulator of the gamma amino butyric acid type B (GABA-B) receptor is unique and different from all the other agents being examined for AUD and PTSD. This particular compound is being commercially developed by Astellas, a large Japanese pharmaceutical company through its USA branches, for use in affective (mood) disorders. Because of this parallel investment by Astellas, a successful FDA Phase 2 clinical study in our DoD PASA consortium pipeline following a successful preclinical discovery study would lead Astellas to develop this GABA-B PAM

**PASA Consortium
Medications Under Study
February 2019**

through a New Drug Application (NDA) filing with the FDA. Thus, this GABA-B PAM offers both a unique MOA for discovery and commercial potential for being marketed and made available for AUD and PTSD.

PTSD and AUD are linked to dysregulated noradrenergic (NE) function, altered Hypothalamic Pituitary-Adrenal (HPA) axis stress reactivity, and underactivity of the GABA-b system. The endogenous opioid dynorphin and its receptor (kappa opioid receptor, KOR) as well as the GABA-b system 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

Objectives and Study Design:

The experiments to be conducted in this preclinical trial will provide essential information for identifying the most efficacious medications to be translated to Phase 1 human clinical trials. Specifically, within the context of this preclinical trial, the study team will 1) evaluate whether the study drugs will alter PTSD-like symptoms in a rodent model of PTSD; 2) evaluate whether the study drugs will alter alcohol self-administration; and 3) determine whether the study drugs will alter PTSD-induced increases on alcohol self-administration when administered alone and in combination.

This study will look at four compounds:

- (1) doxazosin (α 1-selective alpha antagonist) (positive control)
- (2) ASP8062 (allosteric modulator of the GABA-B PAM receptor)
- (3) Baclofen (derivative of the neurotransmitter (GABA). Its MOA is by activating (or agonizing) GABA receptors) (positive control)
- (4) CERC-501 (kappa opioid antagonist)

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.

At a Glance Info:

Study Type: preclinical trial

Population: Sprague-Dawley rats

Number of Participants: ~600 rats

RFA2 – Clinical – Proof of Concept

AS140026-A3a - "Efficacy and Safety Study of PT150 (formally ORG34517) in Veterans with Co-morbid PTSD/AUD" - Dewleen Baker, UCSD

Background:

Proven safe, effective treatments for PTSD alone, AUD alone or co-occurring illness are severely limited; the FDA has given approval to two drugs for the treatment of PTSD, and three for treatment of AUD, but

**PASA Consortium
Medications Under Study
February 2019**

in neither of these disorders are these pharmacotherapies fully effective. Recently, an emerging awareness of the overlap in PTSD/AUD phenomenology, as well as genetics, neurobiology and neural circuitry has driven efforts to exploit these mechanistic overlaps for pharmaceutical development for treatment. The overlapping neural circuitry offers a number of potential molecular targets, in particular stress-signaling pathways converging at glucocorticoid receptor (GR) signaling. There is substantial pre-clinical and clinical evidence for the dysregulation of pathways involving corticotropin releasing factor (CRF) and GR signaling in AUD development and maintenance as well as in fear learning (FL) and PTSD. Antagonism of GR, which modulates brain CRF, has been shown to be a potentially effective pharmaceutical in both alcohol dependent rodents and humans. In alcohol-dependent rats, GR antagonists were shown to be effective in reducing compulsive-like alcohol intake, diminishing withdrawal behaviors (e.g. aggression), and preventing elevations in blood cortisol levels

We propose PT150, a novel, selective GR antagonist as a candidate for a proof-of-concept trial for treatment of co-occurring PTSD/AUD. This study is innovative and potentially of high impact in that it tests a novel compound (PT150) on common co-occurring conditions (PTSD and AUD) using a collection of well-validated, objective biological and behavioral measures in conjunction with subjective symptom measures as a first-step in assessing efficacy and safety of this compound as a pharmaceutical agent for PTSD and AUD.

PT150

- Glucocorticoid receptor antagonist that targets modulation of HPA-axis function
- Shown to reduce AUD in preclinical & clinical studies There is substantial pre-clinical and clinical evidence for the dysregulation of pathways involving corticotropin releasing factor (CRF) and GR signaling in AUD development and maintenance as well as in fear learning (FL) and PTSD. Antagonism of GR, which modulates brain CRF, has been shown to be a potentially effective pharmaceutical in both alcohol dependent rodents and humans. In alcohol-dependent rats, GR antagonists were shown to be effective in reducing compulsive-like alcohol intake, diminishing withdrawal behaviors (e.g. aggression), and preventing elevations in blood cortisol levels
- IND held by PoP test oncology

Objectives and Study Design:

This proof of concept study is aimed at examining a novel drug compound (PT150), a Glucocorticoid Receptor (GR) antagonist, in Veterans with co-occurring PTSD and AUD to test the efficacy, safety, and tolerability of this drug for PTSD and AUD dual diagnosis treatment. The three main objectives are to:

- To test the effectiveness of PT150 to significantly enhance extinction recall tested as previously described, and alcohol consumption, measured by blood phosphatidylethanol levels
- To test the effectiveness to improve PTSD symptoms, measured by the Clinician Administered PTSD Scale (CAPS), and AUD symptoms, i.e. alcohol craving, measured by the Yale Craving Questionnaire (YCQ)
- To determine PT150 safety, as measured across safety endpoints, adverse event (AEs), vital signs and laboratory measures

We hypothesize that veterans taking PT150 compared to placebo will show significantly greater extinction recall, an improvement in PTSD and AUD symptoms over the time course of the study and that PT150 will be safe and well tolerated.

The FDA requires an in-patient alcohol/PT-150 interaction study (10 subjects) and an alcohol/PT-150 PK study prior to the Proof of Concept study

**PASA Consortium
Medications Under Study
February 2019**

The *primary outcome* measures are potentiated startle to the CS+ during the first block of extinction training (to measure cued fear response 15) and the extinction recall index (to measure 24 hr retention of extinction learning). The *secondary outcomes* include:

- Change from baseline in Clinician-Administered PTSD Scale V (CAPS-V) scores
- Change from baseline in the percent of heavy drinking days (%HDD)
- Severity and numbers of AEs
- Treatment retention and medication compliance
- Physiological measures including vital signs and ECG abnormalities
- Breath alcohol content
- Subjective and psychometric effects of alcohol (e.g. mood, urge/craving)
- Alcohol use measures including but not limited to alcohol craving, days of abstinence, drinks per day and biochemical tests.
- Presence and symptom assessments for PTSD, depression and anxiety
- Serum concentrations of phosphatidylethanol (PEth)

At a Glance Info:

Population: This study population (n=40) will be drawn from adult veterans (all sites) of any race or ethnicity; males and females who are post-menopausal, or are infertile females and not hormone cycling. Potential enrollees will be drawn of those seeking treatment or enrolled in VA San Diego Healthcare System (SDVAHS) clinics.

Phase: Phase 2 Clinical Proof of Concept Trial

Number of Sites enrolling participants: All study assessments and procedures will take place at VASDHS main hospital (1 site).

Participant Duration: This outpatient clinical trial consists of 14±4 days of treatment with 900-mg/day (6 pills) of study drug, followed by a 14-day follow-up drug-free observation period, so approximately 28 days total duration.

AS140026-A3b - "Efficacy and Safety Study of PT150 (formally ORG34517) in Veterans with Co-morbid PTSD/AUD - Alcohol Interaction Study" - Dewleen Baker, UCSD

Study Type: Phase I, single center, alcohol interaction 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).

Objective: The objective of this study is to compare safety endpoints following an alcohol challenge prior to and concurrent with PT150 treatment in 10 non-treatment seeking healthy participants by evaluating pharmacodynamic and safety endpoints during alcohol challenge prior to, and after 5 days of PT150 treatment, when PT150 has reached steady state.

- Safety will be assessed via a multitude of assessments including mean changes from both post alcohol challenge pre-treatment (day 1) to post-alcohol challenge with concurrent treatment (day 5) and pretreatment (baseline) to post-treatment (days 5 and 6)
- After completion of the screening period, the remaining study duration for each participant will include a 7-day in-patient stay. For females, a follow-up visit will be scheduled to occur at least 14 days after the final dose of PT150 is administered to ensure pregnancy does not occur.

At a Glance Info:

Population: Veterans with co-occurring PTSD and AUD

**PASA Consortium
Medications Under Study
February 2019**

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| <p><i>Number of Participants:</i> 10 veterans and/or civilians <i>Participating Site:</i> Michael E. DeBakey VAMC, Houston, TX <i>Principal Investigator:</i> Christopher Verrico PhD, and Dewleen Baker, M.D. <i>Duration:</i> 7 day in-patient</p> |
| <p>AS140026-A3c - "Efficacy and Safety Study of PT150 (formally ORG34517) in Veterans with Co-morbid PTSD/AUD – Alcohol Pharmacokinetic (PK) Study" - Dewleen Baker, UCSD</p> |
| <p>In design phase</p> |
| <p>AS140026-A4 - "Zonisamide as a New Treatment for PTSD & Co-Occurring AUD" - Christopher Verrico Baylor College of Medicine</p> |
| <p>Background: Of the nearly 1.2 million Operation Enduring Freedom (OEF)/Operation Iraqi Freedom (OIF)/ Operation New Dawn (OND) Veterans who utilized VA health care services between 2002 and 2015, 31% were identified as having potential post-traumatic stress disorder (PTSD). Not only does PTSD decrease overall health, it also frequently leads to hazardous drinking. Alcohol use disorder (AUD) poses a significant risk of physical and behavioral health issues related to combat service. AUD is the most prevalent substance use problem in the military and is considered to be the substance use concern of greatest significance to the military. In fact, nearly half of OEF and OIF Veterans who screen positive for PTSD symptoms also report alcohol misuse. Because of the negative impact PTSD and AUD have on military readiness, psychological fitness, VA health care costs, and psychosocial function, effectively treating PTSD and AUD is important for the nation as a whole. To this end, this study will evaluate the efficacy of zonisamide as a treatment for Veterans with combat-related PTSD and coexisting AUD.</p> <p>Compared to individuals with PTSD or AUD alone, those with PTSD and coexisting AUD exhibit greater severity of PTSD and AUD symptoms. Comorbid PTSD and AUD is also associated with poorer quality of life, poorer recruitment and retention in treatment programs, poorer treatment outcomes, poorer treatment adherence, and shorter periods of abstinence post-treatment compared to either disorder alone. Although treatment of co-occurring AUD is vital for the effective management of PTSD, there is a lack of evidence on how best to treat for comorbid PTSD and AUD. In fact, PTSD treatment research has predominantly excluded patients with co-occurring AUD. Nonetheless, recent studies underscore the feasibility and importance of treating PTSD and AUD concurrently to facilitate improvements in PTSD symptoms and reductions in comorbid alcohol use.</p> <p>The study proposes to test the safety and effectiveness of zonisamide for comorbid PTSD and AUD in veterans. Zonisamide has undergone considerable clinical studies to investigate its efficacy and safety in the adjunctive treatment of epilepsy. Zonisamide is FDA-approved as an adjunct treatment for partial seizures. Zonisamide enhances GABA function, blocks voltage-sensitive sodium channels and T-type calcium channels, and inhibits carbonic anhydrase. The most common side effects of zonisamide are somnolence, anorexia, dizziness, headache, nausea, and agitation/irritability. Zonisamide is similar to topiramate (which recommended first line therapy for AUD in DoD/VA CPG), and has been shown to reduce AUD in preclinical studies. Zonisamide has promising clinical data in alcoholism and there is no need for further alcohol interaction studies in order to obtain an IND for this study. Additionally there is a study that indicates its potential use for anxiety disorders such as PTSD.</p> |
| <p>Objective and Study Design: The objective of this study is to determine if, compared to placebo, zonisamide (up to 400mg/day, PO) is a safe and efficacious treatment for PTSD and AUD in veterans with PTSD and co-occurring AUD. Researchers hope zonisamide will be a better drug for treating patients with AUD and reducing the</p> |

**PASA Consortium
Medications Under Study
February 2019**

symptoms of PTSD. This is a short term clinical trial 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.

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 study drug and another which will get a placebo. Both groups will be treated with either the drug or placebo for 4 weeks and then tested to see if the drug had any effect on the symptoms of PTSD and AUD. The primary outcomes are a change from the baseline in scores on the Clinician-Administered PTSD Scale V (CAPS-V) and fear-potentiated startle (FPS) response as well as percentage of heavy drinking days (%HDD). The secondary outcomes include treatment retention, medication compliance, severity and number of adverse events (AEs), physiological measures including vital signs and ECG abnormalities, breadth alcohol content (BAC), alcohol craving, days of abstinence, drinks per drinking day, and biochemical tests for alcohol use.

At a Glance Info:

Participating Site: Michael E. Debakey Veterans Affairs Medical Center (MEDVAMC)

Number of Participants: 60 male and female Veterans with PTSD and AUD

Principal Investigator: Christopher Verrico, Ph.D., Baylor College of Medicine

Study Type: Phase 2 randomized controlled trial

Statement of Compliance: This was exempted from IND requirements on 31 Oct 2017.

Design: A randomized, double-blind, placebo-controlled study to examine the ability of 4-weeks treatment with zonisamide, up to 400 mg/day, per os (PO, by mouth).

Objective: The objective of this study is to determine if, compared to a placebo, zonisamide (400mg/day) is a safe and efficacious treatment for PTSD and AUD in Veterans with PTSD and co-occurring AUD.

Study Duration: 49±4 days (participants will receive either zonisamide (up to 400 mg/day) or placebo for 35±4days, followed by a 14-day down-titration period with follow-up).

RFA#2

AS140026-A5 - “Kappa Opioid Receptor Antagonist for the Treatment of Alcohol Use Disorder and Comorbid PTSD” – PI: Lori Davis; UAB School of Medicine

Background: The use of medication that result in kappa opioid receptor (KOR) antagonism represents a novel potential treatment for veterans and Service members with comorbid AUD and PTSD. KOR antagonists may be beneficial in the treatment of addictions, PTSD, and major depressive disorders. 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, and thus, is an excellent alternative study medication to ALKS-5461 and CERC-501. There is clinical evidence that buprenorphine is effective in attenuating some PTSD symptoms among those with opioid use disorder. 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.

**PASA Consortium
Medications Under Study
February 2019**

Objectives and Study Design:

A Phase II Randomized Controlled Trial to evaluate the efficacy and physiological effects of sublingual buprenorphine (SL-BUP; Subutex) combined with extended-release injectable naltrexone (XR-NTX; Vivitrol) which yields a pharmacologically net effect of kappa opioid receptor (KOR) antagonism in the treatment of comorbid AUD and PTSD.

- Aim 1: To evaluate the efficacy of SL-BUP + XR-NTX in the treatment of comorbid moderate-to-severe AUD and PTSD based on a response in both AUD and PTSD outcomes.
- Aim 2a: Examine the baseline association between fear extinction and PTSD symptom severity in Veterans/service members with comorbid AUD and PTSD.
- Aim 2b: Examine the baseline association between Psychophysiological Reactivity to a Trauma-Relevant Stimuli and PTSD symptom severity.
- Aim 2c: Examine the baseline association between Psychophysiological Reactivity to Alcohol-Cues Stimuli and measures of alcohol craving.
- Aim 3: Examine the association of baseline fear extinction, stress reactivity, and treatment outcomes.
- Aim 4: Examine whether the degree of change from baseline to 2-week psychophysiological measures are associated with AUD and PTSD outcomes at week 8. An early indication of s

The *primary outcome* is a reduction of both AUD and PTSD symptoms at 8 weeks such that lowering both will be coded success and any other outcome will be failure.

The *secondary outcomes* examined both between group and over time include:

- Examine association between baseline psychophysiological measures, severity of PTSD and AUD, and treatment outcomes.
- Examine whether low dose or high dose SL-BUP + XR-NTX improves psychophysiology measures at 8 weeks.
- Examine whether the degree of change from baseline to 2-week psychophysiological measures are associated with AUD and PTSD outcomes at week 8.

At A Glance:

Study population: 135 male and female, treatment-seeking veterans and active duty service members with comorbid AUD and PTSD.

Participant Duration: 14 weeks from the time of randomization

Number of Sites: (3):

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

RFA#3

AS140026-A6 – “Lofexidine Combined with Buprenorphine for Reducing Symptoms of Post-Traumatic Stress Disorder and Opioid Use Relapse in Veterans” - PI: Christopher Verrico; Baylor College of Medicine

**PASA Consortium
Medications Under Study
February 2019**

Background: The overall objective of the proposed study is to determine if lofexidine (LFX) as an adjunct to buprenorphine (BUP) treatment improves symptoms of both opioid use disorder (OUD) and PTSD. Our central hypothesis is that LFX as an adjunct to BUP treatment will reduce opioid use relapse and symptoms of PTSD in Veterans more effectively than treatment with BUP alone. Our hypothesis is based on the distinct yet complimentary mechanisms by which each medication reduces symptoms of both disorders. BUP is a μ -opioid receptor (MOR) partial agonist and a K-opioid receptor (KOR) antagonist. Because BUP has a high affinity for, and slowly dissociates from the MOR it also attenuates the surge in noradrenaline (NA) release and thereby suppresses symptoms of opioid withdrawal. On the other hand, BUP-induced blockade of KORs is thought to mediate its observed antidepressant effects in opioid users, anxiolytic effects in healthy adults and therapeutic effects on symptoms of PTSD in Veterans.

Aim 1. To determine the proportion of veterans who achieve 30-days of sustained abstinence from illicit opioid use at the end of treatment with either PLB or LFX (up to 3.2 mg/d) as adjuncts to BUP.

Aim 2. To determine change from baseline scores on the PTSD Checklist (PCL-5) at the end of study.

At a Glance info:

This is a randomized, double-blind, placebo-controlled, single-site, parallel groups, 8-week study to compare the safety, tolerability, and efficacy of BUP treatment alone, to BUP treatment with adjunct LFX, on measures of OUD and PTSD in Veterans with both disorders. 68 veterans with OUD and PTSD will be enrolled

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” – PI: Steve Batki; Univ of California San Francisco

Background: We will build on the encouraging results from our recently completed pilot clinical trial of N acetylcysteine (NAC) in the treatment of AUD in Veterans with TBI. We propose to conduct a larger confirmatory clinical trial testing the efficacy of NAC to reduce alcohol use, improve neurocognitive functioning, and reduce PTSD symptom severity in Veterans with TBI and AUD. If successful, the proposed study will advance the state of knowledge about the use of pharmacotherapy for AUD in patients with TBI and AUD. This trial will meet the following Primary Aim, with lesser aims in the secondary, tertiary and exploratory positions.

Primary Aim: To conduct a confirmatory test of the efficacy of NAC in reducing alcohol use in Veterans with TBI and AUD.

Secondary Aim: To conduct a confirmatory test of the efficacy of NAC in improving neurocognition in TBI and AUD.

Tertiary Aim: To conduct a confirmatory test of the efficacy of NAC in reducing PTSD symptom severity.

Exploratory Aim: To explore potential mediators and moderators of outcome, including the role of improvement in cognitive function as a mediator of alcohol use reduction

At a Glance info:

A prospective, parallel groups, randomized, double-blind, placebo-controlled confirmatory clinical trial of NAC treatment of AUD in 80 Veterans with TBI and AUD.

AS140026-A8 – “Novel Strategies for the Treatment of Opioid Use Disorder and Post-Traumatic Stress Disorder: Anti-Fentanyl Vaccine and Buprenorphine Combination Therapy” – PI: Colin Haile; Univ of Houston

**PASA Consortium
Medications Under Study
February 2019**

Background: Fentanyl is a highly potent μ opioid receptor agonist indicated for the treatment of moderate to severe pain. Fentanyl and fentanyl-analogs (e.g. carfentanil, sufentanil, alfentanil, and lofentanil) are highly lipophilic and rapidly penetrate the CNS which can be lethal. The standard medication to reverse fentanyl's effects is the mu antagonist naloxone. Because of fentanyl's potency however, very high doses of naloxone are needed in a timely manner to avert overdose. A novel treatment strategy that could potentially avert overdose and prevent relapse in individuals with OUD trying to remain abstinent is by vaccination with an anti-fentanyl vaccine. Buprenorphine is an approved medication for treating opioid use disorder, and blocks all of the available opioid analgesics except the fentanyl drugs. Thus, the vaccine is essential. Buprenorphine as a prototypical kappa opioid antagonist, has also shown efficacy in some human studies for reducing PTSD symptoms more effectively than the currently approved SSRIs for treating PTSD. Thus, will also be examined in the animal models for reducing PTSD, which the fentanyl vaccine is not expected to impact.

Objective: to provide essential information for identifying efficacious medications to be translated to phase 1 human clinical trials

Aim 1. Assess anti-FEN antibody levels in combination with 3 doses of BUP administered chronically via osmotic mini-pumps.

Aim 2. Determine whether the functional effects of fentanyl are blocked in rats vaccinated with TT-FEN alone and in combination with BUP.

Aim 3. Ascertain whether BUP will attenuate predator-odor induced place aversion in an animal model of PTSD.

At a Glance Info:

Study Type: preclinical trial

Population: Sprague-Dawley rats

Number of Participants: 480 rats

AS140026-A9 – “Preclinical assessment of PT-150 for opioid use disorder and PTSD” – PI: Michael Bardo; Univ of Kentucky

Background: Selective blockade of glucocorticoid receptors (GRs) in brain with PT-150 will serve as an effective pharmacotherapy for opioid use disorder (OUD) and co-morbid post-traumatic stress disorder (PTSD).

Objective: The goal of this preclinical project is to provide initial proof-of-principle evidence that PT-150 ameliorates stress-induced escalation of fentanyl self-administration and stress-induced reinstatement, thus offering a potential new avenue for treating co-morbid OUD and PTSD.

Aim 1: Determine if PT-150 reduces stress-induced reinstatement of fentanyl seeking: This aim will use a reinstatement model of relapse. Rats will first be trained to self-inject escalating doses of the potent opioid fentanyl using a standard 2-lever operant conditioning procedure. Following this, rats will be treated daily with either PT-150 or placebo while undergoing response extinction (abstinence). Stress will then be applied either environmentally (mild footshock) or pharmacologically (yohimbine) and reinstatement of fentanyl seeking will be measured. This procedure is intended to model the use of PT-150 as a pharmacotherapeutic to prevent relapse. Endpoint: The primary endpoint for this experiment will be the number of responses on the previously active following stress. This measure will be compared to the number of responses on the last day of extinction. The primary hypothesis is that PT-150 will reduce stress-induced reinstatement of fentanyl seeking. Positive results from this experiment

**PASA Consortium
Medications Under Study
February 2019**

will form the scientific premise for determining if PT-150 blocks fentanyl craving in human participants with OUD who are abstinent.

Aim 2: Determine if PT-150 reduces fentanyl self-administration in individuals with co-morbid PTSD: This aim will use two different models of stress: (1) chronic social isolation and (2) acute stress induced by restraint/swim, which have been used to model PTSD. Previous work has shown that these stressful manipulations increase drug self-administration behavior. This aim will determine if oral PT-150 reduces the effects of chronic social isolation and acute stress, either alone or in combination, on fentanyl self-administration. Rats will be raised in either social isolation or in group housing and then will receive acute restraint/swim stress or control treatment. Plasma corticosterone will be measured immediately before and after the acute stress. On the day after the acute stress treatment, rats will be treated daily with either PT-150 or placebo and then will be trained to voluntarily self-administer i.v. fentanyl using a standard 2-lever operant conditioning procedure. Endpoint: The primary endpoint for this experiment will be the number of fentanyl infusions across sessions. A secondary measure will be plasma corticosterone levels. We expect that chronic social stress and acute stress will both increase plasma corticosterone and fentanyl self-administration. The primary hypothesis is that PT-150 will reduce the stress-induced increase in fentanyl self-administration. If this latter result is obtained, it will form the scientific premise for conducting a clinical trial with PT-150 in patients with co-morbid OUD and PTSD.

At a Glance Info:

Study Type: preclinical trial

Population: Sprague-Dawley rats

Number of Participants: 80 rats