2. SPECIFIC AIMS

We propose a randomized controlled trial to evaluate an integrated exposure-based treatment (Integrated Prolonged Exposure therapy; I-PE) for concurrent alcohol disorder and posttraumatic stress disorder (AD/PTSD). We will assess how well this evidence based treatment creates initial and sustained improvements in alcohol use and PTSD symptoms in 148 alcohol dependent adults with PTSD. I-PE integrates two evidence based treatments, Prolonged Exposure Therapy for PTSD (PE[1]), and Integrated Cognitive Behavioral Therapy for alcohol use disorders (ICBT[2,3]). I-PE will be compared to Seeking Safety (SS[4]), a widely used present focused psychotherapy for AD/PTSD that does not include exposure.

AD and PTSD frequently co-occur.[5] Individuals with AD/PTSD have worse AD treatment outcomes when they do not receive PTSD focused treatment.[6-8] Treating AD and PTSD in an integrated fashion is recommended.[9,10] Treatment guidelines for PTSD support exposure therapy as a first line treatment.[11,12] However, individuals with AD are generally not offered exposure therapy because of beliefs that exposure would lead to greater alcohol use and other dangerous behaviors (e.g.,[13]). Research has not supported such beliefs. In fact, a growing body of evidence, including data collected by this team of investigators, suggests that individuals with AD are able to tolerate and benefit from exposure therapy.[14-17] Coping skills therapies such as SS are the most widely disseminated treatments for AD/PTSD. However, in RCT's such treatments have neither shown sustained reductions in PTSD symptoms or alcohol use nor outperformed non-PTSD treatments (e.g.,[8,18,19]). The proposed trial would be the first to compare an integrated exposure-based psychotherapy to an integrated present-focused coping skills based psychotherapy for the treatment of AD/PTSD. In addition, mechanisms of change in both treatments, including sleep problems which are highly prevalent in both AD and PTSD, will be explored.

This project addresses a critical barrier in the field – the widely held belief that individuals with AD and PTSD cannot tolerate exposure therapy, although it is the best practice treatment for PTSD. If completed, this project will help change the practices that drive treatment for this highly prevalent and highly distressed Veteran population. The fundamental rationale for this study is to improve the evidence base that informs how patients with AD/PTSD can attain sustained recovery from these disorders.

The **primary aim** will be to evaluate the effects on alcohol use and PTSD symptoms of an exposure-based integrated AD and PTSD intervention when compared to a present-focused coping skills intervention in male and female Veterans with comorbid AD and PTSD. Hypotheses for the primary aim are:

- At post-treatment, both groups will show reductions in alcohol use, but I-PE will demonstrate greater reduction in PTSD symptoms than SS.
- At 5- and 8-month follow-up, I-PE will have significantly fewer percent drinking days than SS.
- At 5- and 8-month follow-up, I-PE will continue to have lower PTSD symptom scores.

The **secondary aims** will be to assess:

- The impact of the interventions on depression symptoms and quality of life at post-treatment and 5- and 8-month follow-up.
- Participant satisfaction with the interventions.

The **exploratory aim** of this study is to evaluate therapy process variables, affect-related, and sleep-related mechanisms of treatment outcomes for AD/PTSD patients. Specific hypotheses are:

- Reductions in negative post-traumatic cognitions will be a mediator of change in I-PE.
- Greater use of positive coping skills will be a mediator of change in SS.
- Therapy process variables (e.g., attendance) will be related to treatment outcome in both conditions.
- Changes in negative affect will be related to treatment outcomes for both conditions.
- Worse sleep latency and efficiency will be associated with worse PTSD outcomes in the PE condition.
- Worse sleep latency and efficiency, as well as increased %REM sleep, will be associated with greater risk of relapse in both conditions.

3. SIGNIFICANCE

3.A. Veterans Are at High Risk for AD and PTSD

Rates of alcohol use disorders (AD) are high among combat Veterans. Current AD is estimated at 16% in recently deployed Veterans seeking VA care.[20] AD is approximately four times as common among combat Veterans than in the general population (3.8% in the general population[5]). Moreover, prevalence of AD has increased more than two fold among Veterans seeking VA services since the start of the conflicts in Iraq and Afghanistan.[21]

Rates of PTSD are also high among combat Veterans. A recent reanalysis of the National Vietnam Veterans Research Study (NVVRS) data, using military records and data from clinical examinations found that 19% met lifetime criteria for the disorder and 9% currently met criteria for PTSD.[22] These rates suggest that PTSD is at least twice as common in combat Veterans as in the general population (3.5-7.8% general population).[5] Estimates of PTSD among Iraq and Afghanistan Veterans suggest that nearly 17% of active duty and over 24% of reserve service members screen positive for PTSD approximately 6 months after their return.[23]

3.B. Co-Occurrence of AD and PTSD Associated with Poor Treatment Course. Comorbidity of AD and PTSD is high both in the general population and among Veterans exposed to combat.[5,24] Prevalence of AD among those with PTSD has been shown to be up to 28% for women and 52% for men.[5,25] Rates of PTSD among patients with AD are 30-59% (e.g.,[26]). In a national sample of OEF/OIF Veterans using VA care, 62% of those with AD had a diagnosis of PTSD. Alcohol or substance use disorder was associated with a four-fold increase in likelihood of having a PTSD diagnosis.[27]

Individuals with AD/PTSD typically fare worse than those with either disorder alone.[28] Specifically, those with AD/PTSD have worse treatment outcomes and more psychiatric, medical, legal, and social problems than those with either disorder alone.[29,30] In addition, both VA and community clinicians report significant challenges in treating these individuals.[31] AD patients who receive PTSD treatment are less likely to relapse[10] and more likely to reduce alcohol use[32] than patients who do not receive PTSD treatment.

3.C. Why do Individuals Who Have Experienced Trauma Drink? Multiple pathways have been proposed for AD/PTSD. Avoidance of unpleasant PTSD-related affective states may take the form of alcohol use.[33,34] Alcohol use may begin during prolonged traumatic exposures (e.g., combat if alcohol is available, domestic violence) where individuals may drink to cope with ongoing trauma.[35] If AD precedes PTSD, individuals using alcohol may be more likely to find themselves in dangerous situations.[35] Alcohol use may interfere with natural recovery after trauma increasing the likelihood of PTSD development.[36] In addition, AD and PTSD share genetic and environmental vulnerabilities.[37] Regardless of the order of onset, the relationship between AD and PTSD can form a vicious cycle in which PTSD symptoms elicit drinking and drinking perpetuates and intensifies PTSD (e.g.,[38]). Unprocessed distressing trauma-related emotions and efforts to avoid such distress (e.g., avoiding trauma memories and reminders) can underlie both PTSD[1] and alcohol use in the context of PTSD.[34] In other words, unprocessed emotion drives PTSD symptoms (e.g., avoidance, intrusive memories) and drinking can be a method to facilitate avoidance and to cope with painful unprocessed emotions. Based on this model, two divergent treatment modalities for AD/PTSD have been proposed: exposure therapy to process trauma-related emotion, and coping skills therapy to learn alternative ways to cope with distressing emotion.

3.C.1. Exposure Therapy to Process Trauma-Related Emotion. Exposure therapy, in particular Prolonged Exposure (PE[1]; 3.C.), posits that emotional processing is necessary for recovery from PTSD and associated AD. In this model, exposure works through habituation/extinction and cognitive emotional processing changes occurring in tandem. When applying emotional processing theory to PTSD, Foa and Riggs[36] proposed two dysfunctional cognitions that are related to the development and maintenance of PTSD: 1) The world is completely dangerous, and 2) I am incompetent (e.g., my symptoms mean I am crazy). Through the process of repeated prolonged confrontation to trauma related stimuli, habituation of emotional responses associated with the trauma occurs. As trauma-related stimuli are repeatedly confronted without the occurrence of feared consequences (e.g., going crazy) and with lessening emotional activation, the patient experiences repeated evidence that disconfirms dysfunctional cognitions. A stronger sense of self-competence and control over negative affect and stimuli emerges which may allow patients to reduce trauma-related avoidance, leading to even more spontaneous exposure and continued reduction of PTSD symptoms. Treatment associated

reductions in negative thoughts about the self and the world have been associated with symptom improvement.[39] Early data from an RCT of PE with AD/PTSD show that PE was associated with both PTSD symptom reduction and reduction in alcohol cravings,[16] supporting emotional processing through PE as a method by which to treat AD/PTSD.

3.C.2. Learning Alternative Ways to Cope with Distressing Emotion. This modality posits that in order to alleviate PTSD symptoms and alcohol use, individuals must learn alternative "healthy" coping skills in place of avoidance and drinking. Positive coping skills including cognitive restructuring, behavioral skills (e.g., self-care, choosing safe alternatives to drinking), and interpersonal skills (e.g., getting others to support recovery, asking for help) are seen as the process by which PTSD symptoms and drinking are reduced. In support of this theory, several studies have found that coping motives for drinking were associated with problem drinking in individuals with PTSD.[40] Among coping skills therapies, Seeking Safety (SS[4]) for treatment of AD/PTSD has received the most attention. **The proposed study is designed to evaluate both emotional processing through PE and improved coping through SS as mechanisms of change for alcohol use and PTSD symptoms, with the hypothesis that emotional processing will be more effective in helping individuals make sustained improvements in PTSD symptoms and alcohol use.**

3.D. PE is the Best Practice Treatment for PTSD, Yet AD/PTSD Treatment Rarely Includes Exposure. Treatment guidelines for PTSD, including those put forth by the Institute of Medicine[12], support exposure therapy as a first line treatment.[12,41] Prolonged exposure therapy (PE[39]) includes psychoeducation, breathing retraining, repeated imaginal exposure to the trauma memory, and gradual in vivo exposure to trauma reminders. It is delivered in 9 to 12 90-minute sessions administered once or twice weekly. The efficacy of PE has been examined in seven studies and a variety of traumatized populations (e.g.,[11,42]) including Veterans (e.g.,[43]). **In six of the studies, the PE manual was adapted for the study, as will be the case in the proposed study.**

Although exposure therapy has been identified as the frontline PTSD treatment, integrated treatments for AD/PTSD rarely include exposure. AD/PTSD patients traditionally receive sequential treatment, first for addiction and then for PTSD.[13,16] This was based in part on the idea that individuals with AD could not tolerate trauma focused treatment and that such treatment would lead to an exacerbation of alcohol use or other unsafe coping. However, no research support for such clinical beliefs exist.[44] In fact, a recent temporal study of patients with AD/PTSD found that improvements in PTSD had a greater association with improvements in alcohol use than vice versa.[44] Consensus is mounting in favor of treatments that address both disorders in an integrated manner (e.g.,[45]). Most now advocate integrated or concurrent interventions (e.g.,[45]). In addition, both clinicians and patients have reported a preference for integrated treatment.[31,46] Existing studies of integrated SUD/PTSD treatments will be reviewed briefly here.

3.D.1. Pharmacological Treatment for Comorbid PTSD and Alcohol Use Disorders. In a study of 96 patients randomized to Sertraline or placebo, there were no differences in drinking outcomes between the two groups at post-treatment or follow-up. There was a trend toward decrease in PTSD symptoms in the Sertraline group.[47] Several other preliminary studies have been conducted as well; however, as of yet little can be concluded about effective pharmacotherapy for concurrent AD and PTSD.[48]

3.D.2. Non-exposure based integrated treatment for alcohol/substance use and PTSD. The psychosocial intervention for alcohol/substance use and PTSD that has been most widely disseminated is Seeking Safety (SS[4]). This 24 session treatment focuses primarily on three topics: improving safety, reducing PTSD, and abstinence. A theoretical basis of the therapy is that if participants are able to learn skills to maintain their safety, they will be better able to address their PTSD and substance use and better able to manage the triggers of each disorder. The therapy is integrated in that it focuses on the way the two disorders interact and maintain each other. The intervention is skills based and does not include exposure. For AD, the therapy draws most directly on cognitive behavioral coping skills therapy, relapse prevention and motivational enhancement. For PTSD, the therapy is based on cognitive behavioral principles.

Hien and colleagues[18,19] have conducted two RCT's of SS, one with 107 low-income urban women comparing SS, relapse prevention, or treatment as usual and the second comparing SS to health education in 353 women. Neither study showed much difference between SS and the comparison intervention in PTSD or SUD

symptoms and differences found were not sustained at follow-up. **Lack of SS effectiveness across the two completed RCT's is concerning given that SS is widely disseminated in VA and community settings.**

3.D.3. Evidence is Building that Integrated Exposure Treatments Help both AD and PTSD. There is one completed exposure-based psychotherapy RCT focusing specifically on AD and PTSD. Patients received PE for PTSD and a combination of naltrexone and psychosocial treatment for AD. The treatment was concurrent in that the patient met with a psychologist for PE and a nurse for pharmacotherapy and AD treatment. Exposure therapy was initiated by the second session as is standard PE protocol. Patients were asked to be abstinent through the course of treatment but were not terminated if relapse occurred. Preliminary results for the PE group were extremely promising, indicating overall significant reductions in alcohol intake, cravings, and PTSD severity using intent to treat (ITT) analyses. Importantly, patients who were treated with PE immediately after agreeing to abstain from alcohol benefited from the treatment and, contrary to clinical lore, did not show any exacerbation of alcohol use or cravings. In fact, patients who completed PE not only reported greater reductions in PTSD symptoms, but also greater reductions in alcohol cravings than other groups. **The proposed study will extend this research to comparing the efficacy of PE to a coping skills therapy (SS).**

Brady and colleagues[14,15] used PE to treat 39 individuals with PTSD and cocaine addiction. Their 16-session twice weekly therapy combined prolonged exposure with coping skills training. Relapse was not a cause for study discontinuation. Among study completers, cocaine use was reduced by 60% and scores on the Addiction Severity Index reduced by more than 50%. Clinician ratings of PTSD showed impressive reductions of 66%, 70%, and 47% on intrusion, avoidance, and arousal symptoms respectively.[14] Improvements were maintained through 6-month follow-up. It is important to note that most patients who dropped out did so prior to the initiation of treatment or exposure, suggesting that exposure was not the cause of drop-out.

3.E. Significance Summary for Primary and Secondary Aims: Relevance to the VA.

The findings from these studies coupled with our preliminary data (4.C.) provide evidence that exposure therapy is tolerated by individuals with AD/PTSD and can be used safely and effectively. The clinical notion that exposure would be deleterious to AD/PTSD patients has not been supported. In fact, not only did exposure not worsen patients' symptoms but significant improvements were seen in PTSD and alcohol/substance use.[16,44] Conversely, individuals with PTSD who complete coping skills therapies did not do better than those who receive no PTSD treatment and did not maintain their gains in alcohol use or PTSD at follow-up.[18,45,49] The simplicity of the PE protocol including just three therapeutic components (psychoeducation, in vivo and imaginal exposure) makes it amenable to dissemination and modification for AD treatment settings. Thus, if we can demonstrate that PE is better than coping skills for AD/PTSD treatment, it is more likely to be disseminated than other more complex therapies. **An essential next step is to test the best practice PTSD treatment, PE, against the best disseminated treatment, SS, to demonstrate that exposure therapy is more effective in treating AD/PTSD. The proposed study is designed to accomplish exactly this. The significance of this study will be to improve the evidence base that informs how Veterans and all patients with AD/PTSD can be treated effectively and which treatments should be considered for dissemination.**

3.F. Exploring Mechanisms of Change in integrated AD/PTSD Treatment

3.F.1. Understanding mechanisms of change in integrated AD/PTSD treatment will allow for the further refinement of treatment and will provide information to drive future research. This RCT will give us the opportunity to examine the mechanisms proposed for both PE and SS as well as additional mechanisms that may help or hinder treatment for this complex and challenging comorbidity. For PE, as trauma-related stimuli are repeatedly confronted without the occurrence of feared consequences and with lessening emotional activation, the patient experiences repeated evidence that disconfirms dysfunctional cognitions, and these dysfunctional cognitions are proposed to be replaced with more functional beliefs about the world and the self. In SS, individuals are expected to learn positive coping skills that they then use in place of alcohol or PTSD related behaviors (e.g., isolating, avoiding). In addition, certain factors such as therapy process variables (e.g., attendance, homework/commitment completion) and changes in negative affect have been shown to mediate psychotherapy treatment outcomes across psychiatric disorders (e.g.,[50]). **Thus, we hypothesize that changes in dysfunctional cognitions will mediate outcomes in the I-PE condition, that increased**

positive coping will mediate changes in the SS condition, and that therapy process variables and changes in negative affect will predict treatment outcomes for both conditions.

3.F.2. An important predictor of treatment outcomes for both AD and PTSD is sleep disturbance; however, sleep disturbance has received little attention in AD/PTSD treatment outcomes research. Sleep disturbance is a problem common to both AD and PTSD. Insomnia occurs in 36-72% of alcoholic patients.[51] Self-medication of sleep problems with alcohol is a leading hypothesis regarding why AD and sleep problems frequently co-occur. In addition, alcohol use, withdrawal, and chronic dependence are all associated with further sleep disruption.[52] Numerous studies examining biological predictors of relapse and/or treatment outcomes, including work from our research group (e.g.,[53]), have documented both subjective and objective sleep disturbance as a risk factor for relapse among individuals with AD and other substance dependence (e.g., for a review see[51,54]). Correlates of subsequent relapse among AD patients include prolonged sleep latency, decreased sleep efficiency and total sleep time, increased rapid eye movement sleep, and decreased slow wave sleep.[51] Anxiety and depressive symptoms place AD patients further at risk for sleep disturbance,[51] suggesting individuals with AD and PTSD are especially at risk for sleep problems and therefore likelihood of relapse. Sleep disturbance also increases the likelihood of mood changes, thus potentially worsening PTSD symptoms and placing AD patients further still at risk for relapse (e.g.,[51]).

There is a bidirectional relationship between sleep and PTSD. Among individuals with PTSD, 66-100% report significant sleep difficulties that correlate positively with PTSD symptom severity.[55,56]. Among returning Veterans with PTSD seeking VA treatment, PTSD, depression, and AD all increased the risk of sleep disruption. In the other direction, recent studies suggest sleep may be mechanistically linked to the development and maintenance of PTSD (e.g.,[57]). Sleep disturbances within a month of trauma exposure predict development of and/or symptom severity in PTSD 6-12 months later.[58] Sleep may interact with treatment differently than other PTSD symptoms, as well. For example, sleep related symptoms of PTSD (e.g., nightmares, insomnia) are less likely to respond to evidence based PTSD treatment such as PE than are "day time" symptoms of the disorder (e.g., our preliminary data, 4.D.). Moreover, the fact that sleep deprivation (which can result from chronic insomnia and nightmares) impairs consolidation of extinction memory implies the sleep symptoms of PTSD could potentially interfere with both natural extinction (thus maintaining PTSD) and treatment-induced extinction (thus reducing the effects of PE) of PTSD-related fear.[59]

Although few studies to date have examined AD/PTSD comorbidity in relation to sleep, literature on sleep problems in regard to each disorder would suggest that individuals with AD/PTSD would be highly likely to have sleep disturbance and that they would be at high risk of relapse because of the sleep disruption and mood symptoms associated with both disorders**. We will collect validated sleep measures pre- and post-treatment in this RCT to explore the function of sleep disruption as a mediator of treatment outcome for AD/PTSD treatment.**

3.G. Significance Summary for Exploratory Aims: Relevance to the VA.

Understanding mechanisms of AD/PTSD treatment will allow for the refinement and development of effective treatments for this challenging and complex population. As of yet, sleep as a predictor of treatment outcome has received little attention for AD/PTSD patients, yet given its high prevalence in these disorders among Veterans and given its negative relationship to treatment outcomes, exploring the role of sleep problems is timely and important.

4. PRELIMINARY STUDIES

The diversity of clinical and research experiences of our team of investigators is reflected in several preliminary studies. The first set of studies (4.A.) reflects our experience with integrated cognitive behavioral therapy for AD and Axis I disorders (depression and PTSD). The second set of studies (4.B.) reflects our research on treatment issues related to integrated AD/PTSD. Section 4.C. reviews our work with exposure based therapy both with concurrent AD/PTSD. The final section (4.D.) reviews our work documenting the importance of understanding the role of sleep problems in Veterans with PTSD.

4.A. Integrated Cognitive Behavioral Therapy for Alcohol/Substance Use Disorder (A/SUD) and Depression.

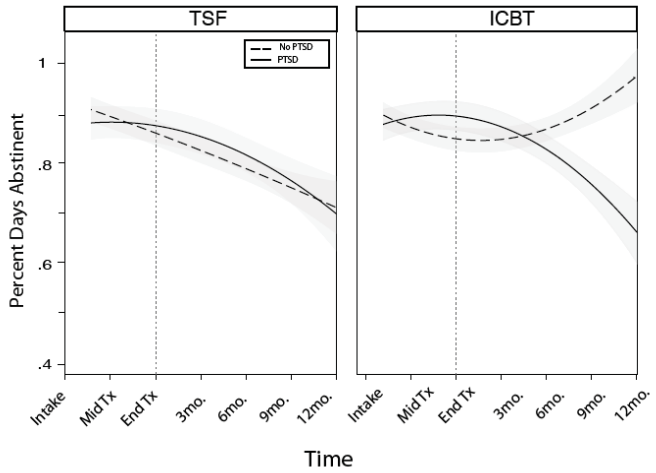
The results reported in the first studies below are findings from an integrated intervention study for co-occurring A/SUD and depressive disorders that has been conducted over an 11 year period (initial funding and renewal; PI: Sandra Brown; Co-I's Sonya Norman [on latest renewal] and Susan Tate; current PI: Susan Tate). Dr. Norman has led the work examining the impact of PTSD on ICBT treatment outcomes. Inclusion criteria were: (1) presence of a current DSM-IV diagnosis of alcohol, cannabis, and/or stimulant dependence, (2) DSM-IV depression diagnosis (major depressive disorder, dysthymia) with at least one episode independent of alcohol/substance use, and (3) recent alcohol and/or substance use and elevated depressive symptoms. **Although alcohol use disorder was not a requirement of the study, 85% of participants met criteria for an AUD.** The study was a randomized two-treatment group design. Integrated Cognitive Behavioral Therapy (ICBT) was developed for this study by integrating two well-validated cognitive therapies for addiction[60] and depression.[61] Both study interventions (ICBT and Twelve-Step Facilitation; TSF) were accompanied by monthly pharmacotherapy for depression and had two consecutive 12-week phases of treatment. Phase I involved twice weekly one-hour group sessions and the Phase II consisted of once weekly one-hour group sessions. Research assessments regarding alcohol and substance use and depression symptoms were conducted at intake, end of Phase I (12 weeks), end of Phase II (24 weeks), and quarterly thereafter until 18 months following treatment entry.

4.A.1. Integrated treatment for depression and substance use disorders: Outcomes of a randomized clinical trial (Lydecker et al., 2010).[3] These analyses compared longitudinal primary treatment outcomes (depression symptoms: Hamilton Depression Rating Scale: HDRS; substance use: percentage days abstinent: PDA) for 204 participants. All participants who completed the intake assessment and attended at least one session of the intervention were included in analyses. Primary outcome trajectories were created using linear mixed effects models. Predictor variables included treatment (ICBT versus TSF), time, number of sessions attended, early levels of depression and substance use, and interaction terms. Participants in both treatment conditions showed decreases in depression and substance use from intake. ICBT participants maintained improvements in substance involvement over time whereas TSF participant substance use increased more rapidly following treatment as evidenced by a significant interaction between time and treatment (p = .004). A marginally significant second order time by treatment interaction (p = .057) suggests that HDRS trajectories curved differently for the two treatment groups, with TSF showing more pronounced dips in the six months posttreatment although end points were similar. Although both treatments were associated with improvements in alcohol/substance use and depression, **ICBT led to more stable alcohol/substance use reductions compared to TSF, providing support for the efficacy of our newly developed ICBT manualized intervention. ICBT will be used in the current proposal integrated with PE for treatment of concurrent AUD and PTSD.**

4.A.2. Impact of PTSD on Treatment Outcomes for depression and alcohol/substance use disorders (Norman, Tate, et al., 2010).[62] The goal of this study was to explore the impact of PTSD on the treatment outcomes described above (N = 178). We included individuals with current PTSD (n = 68; 38%) at intake, and excluded individuals who met lifetime, but not current, criteria for PTSD (n = 11). Using linear mixed effects models, we created trajectories for primary outcomes (PDA and HDRS) for 18 months following intake. Predictors in the model were time, treatment type, PTSD diagnosis, and covariates for early treatment response PDA (first 90 days of intervention) and intake depression. PTSD was included with time and type of treatment in two and three-way interactions. Results indicated that PDA was similar across conditions during treatment. By contrast, in the year following end of treatment, a mixed effects model showed that a three way interaction of PTSD by time by treatment was significant (coefficient = -.064, p = .016). Participants in ICBT without PTSD had better PDA (M = 91% days abstinent) than those without PTSD in the TSF group (M = 76%) and those with PTSD in either group (ICBT M = 77%; TSF M = 75%). Participants with PTSD had higher depression levels across time points than those without PTSD, but benefited similarly to those without PTSD from both interventions (significant main effect, p < .004). Reductions in average HDRS were seen at 18 months in both those with PTSD (TSF = 29% decrease; ICBT = 23% decrease) and without PTSD (TSF = 17% decrease, ICBT = 21% decrease). In summary, despite reductions in alcohol/substance use during treatment, **poorer posttreatment abstinence trajectories were observed for individuals with PTSD compared to individuals in ICBT without PTSD.** Depressed, alcohol/substance dependent participants with PTSD had

higher levels of depression across time, but evidenced similar reductions in depression symptoms to participants without PTSD. **These findings highlight the need for research focused on preventing deterioration of treatment gains for those with comorbid A/SUD and PTSD and suggest that present-focused coping skills therapy alone is not enough for those with PTSD to sustain alcohol improvements.**

Figure 1. Substance treatment outcomes (PDA) for Veterans with PTSD (solid line) and without PTSD (dotted line).



4.A.3. Preliminary Findings on Individuals with PTSD Receiving ICBT: Treatment Utilization and PTSD symptoms. We examined predictors of ancillary healthcare services utilization in the year following end of treatment in our integrated intervention study, including inpatient services and outpatient mental health services (N = 236). There was a time by treatment group interaction trend for inpatient services: ICBT participants had decreases over the treatment and follow-up period while TSF had fewer days at the initial 6-months after treatment but more days in the following 6-months (6–12 months following end of treatment; $F(2,231) = 2.93$, $p = .055$). These findings again support the longer term benefits of ICBT. Also relevant to the current proposal, lifetime PTSD diagnosis was the most significant predictor of alcohol and drug treatment outpatient visits during the year after treatment: participants with A/SUD, depression, and PTSD attended fewer alcohol and drug treatment sessions in the year after study treatment ended relative to participants with A/SUD and depression but without PTSD. PTSD diagnosis was also the strongest predictor of attending PTSD outpatient sessions during the posttreatment year. Thus, **some individuals with PTSD are likely to access treatment for PTSD, but are less likely to access treatment for alcohol related problems. Without accessing this continued care when needed, individuals with PTSD may be at greater risk of relapse, again supporting the need for the availability of integrated treatment where alcohol related problems and PTSD are both addressed.**

4.A.4. ICBT Reduces PTSD Symptoms. The ICBT intervention study was designed to evaluate depression and alcohol/substance use outcomes, and was not designed to evaluate changes in PTSD symptoms over time. Thus, we do not have data on PTSD symptoms at each quarter. We report pilot data supporting a reduction in PTSD symptoms among a subset of participants receiving ICBT based on the Composite International Diagnostic Interview (CIDI) diagnostic assessment completed at intake, 12-, and 18-months. Nineteen individuals met DSM-IV criterion A for PTSD at intake (exposed to a traumatic event, and response involved intense fear, helplessness, or horror) and continued to endorse criterion A at the 12- and 18- month assessments. We examined whether these participants continued to endorse other PTSD criteria at later assessments. Of these 19, 13 met diagnostic criteria for PTSD at intake, which reduced over time as shown in the Table.

Table 1.

# Positive at:	Intake	12 months	18 months
A (trauma & response)	19	19	19

PTSD diagnosis	13 (68%)	8 (42%)	7 (37%)
B (re-experiencing)	18 (95%)	16 (84%)	14 (74%)
C (avoidance, numbing)	14 (74%)	12 (63%)	9 (47%)
D (arousal)	17 (90%)	13 (68%)	12 (63%)

Reductions in all three PTSD symptom clusters were observed in ICBT participants at the 12 month assessment and were maintained with additional slight reductions at 18 months. As noted previously, we also assessed healthcare services utilization in our study and thus were able to examine whether the participants with reductions in PTSD symptoms between intake and 12 months received PTSD treatment at the VA following completion of ICBT. Of the 19 participants meeting PTSD criterion A, only 4 participants attended more than a single outpatient visit for PTSD treatment following ICBT, receiving an average of 20 sessions. Of these 4 participants, 1 no longer met criteria for PTSD at the 12 month assessment and 2 no longer met criteria at the 18 month assessment. Both of these individuals continued to endorse symptoms meeting criteria for clusters B, C, and D above, but no longer endorsed criterion F: "The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning." Of note, 4 participants no longer met criteria for PTSD after the ICBT intervention without receiving PTSD treatment at the VA. This very preliminary finding suggests some benefit of the ICBT intervention in reducing severity of PTSD symptoms. It is important to note that dropout rates did not differ between PTSD participants and other participants, suggesting the intervention is acceptable to individuals with PTSD.

Based on our results indicating that ICBT is acceptable and helpful to individuals with PTSD, and given ICBT's focus on relapse prevention skills particularly in the context of experiencing negative affect, we have included ICBT as the AD treatment component of our integrated AD/PTSD psychotherapy.

4.B. Need for Integrated Care for AD/PTSD. We have also conducted several studies that support the need for evidence based integrated care for AD/PTSD.

4.B.1. Relapse Contexts Among Alcohol/Substance Dependent Veterans With and Without Trauma Histories.[63] Exposure to traumatic events is common among individuals with alcohol and substance use disorders (A/SUD), although not all go on to develop PTSD. We compared A/SUD treatment outcomes and relapse features in 3 groups of male Veterans receiving A/SUD treatment: 1) those without trauma exposure (A/SUD-only; n = 68), 2) those with PTSD (SUD-PTSD; n = 32), and 3) those with trauma exposure but no PTSD (A/SUD-trauma; n = 34). Participants were assessed regarding psychiatric symptoms, alcohol and substance use, and relapse features quarterly for 1 year. The groups did not differ on length of abstinence, relapse prevalence or severity. A/SUD-trauma participants reported more depression, anxiety, PTSD, and total psychiatric symptoms prior to relapse than A/SUD only. A/SUD-trauma participants also endorsed more PTSD and total symptoms following relapse than A/SUD-only. **PTSD symptoms were associated with greater risk of relapse in intrapersonal and negative physiological contexts, suggesting there may be expectancies that alcohol would be helpful in coping with such situations among individuals with PTSD.** Understanding relapse contexts for those experiencing PTSD symptoms can help us to understand one mechanism whereby those with both A/SUD and PTSD have a poorer clinical course. Additionally, this study highlights the risks associated with trauma exposure, even for those not meeting diagnostic criteria for PTSD.

4.B.2. Measuring PTSD-Specific Alcohol Expectancies (P-AEQ).[34] The P-AEQ differentiated alcohol dependent from non-alcohol dependent populations in a male Veteran sample consisting of Veterans who were alcohol dependent without PTSD, alcohol dependent with PTSD, diagnosed with PTSD without current alcohol dependence, and medical patients with no psychiatric diagnosis. **This newly developed assessment provides support for one mechanism connecting PTSD and alcohol use: expectations of symptom relief. Thus, interventions targeting PTSD-specific alcohol expectancies are included in I-PE.** We conducted a pilot study of Seeking Safety with combat Veterans who served in Iraq and Afghanistan.[49] Most participants in this present-focused treatment continued to score above the clinical cut-off on a PTSD symptom measure at the end of treatment.

4.B.3. Seeking Safety with Veterans who served in Iraq and Afghanistan (Norman, Wilkins, Lang, Tapert, & Najavits, 2010).[49] This pilot study with fourteen male OEF/OIF Veterans (9 treatment completers) suggests that SS may help to reduce alcohol use, PTSD, and depression in some participants at clinically significant levels, even when providing only ten sessions. However, most participants in this present-focused

treatment that did not include an exposure component continued to score above the clinical cut-off of 50 on the PTSD symptom measure (the PCL-M).[64]

Table 2. Study Completers Pre- and Post-Treatment Data

Participant	PCL-M Total			Drinking Frequency			#Drinks/Episode		
	Pre	Mid	Post	Pre	Mid	Post	Pre	Mid	Post
1	42	43	48	4+/week	2-3/week	2-3/week	7-9	5-6	5-6
2[a]	62	40	23	≤Monthly	≤Monthly	≤Monthly	5-6	5-6	5-6
3	73	64	72	4+/week	4+/week	4+/week	10+	10+	10+
4	77	61	67	2-4/month	Never	Never	1-2	[b]	[b]
5	44	30	30	2-4/month	Never	≤Monthly	1-2	[b]	1-2
6[a]	46	42	41	≤Monthly	≤Monthly	≤Monthly	1-2	1-2	1-2
7	72	71	66	2-3/week	2-3/week	Never	1-2	5-6	[b]
8	60	40	56	4+/week	2-3/week	2-4/month	3-4	7-9	3-4
9	59	56	47	4+/week	Never	4+/week	10+	[b]	7-9
Mean	59.4	49.7	50	--	--	--	--	--	--

Note: Dashes where means were not calculated.

[a]=Marijuana use disorder. [b]=Past month sobriety endorsed.

4.C. Trauma-focused treatment is Acceptable to Individuals with AD/PTSD.

4.C.1. Exposure to traumatic memories was found acceptable to a pilot group of 18 women with AD/PTSD. The clinical trial (final data analyses in progress) for the PI's K-award compares SS, integrated with one session of exposure to a traumatic memory, to supportive counseling. 15 of the women either dropped or maintained their amount of drinks per day. Percent days abstinent improved from 72% to 90%. Among those who completed, CAPS scores dropped an average of 18 points (a drop of 5 or more points is a clinically significant drop in PTSD symptoms). **Ratings for the exposure session were the highest (best) score on each satisfaction item** (how much did you learn from this session, how helpful was this information, how likely are you to use this information, and how satisfied are you with this session).

4.C2. Veterans with AD/PTSD are willing to engage in evidence based PTSD treatment. In our current ICBT study (Tate, PI; Norman, Co-investigator), Veterans with AD, depression, and PTSD who completes 16 weeks of group ICBT treatment are randomized to CBT or cognitive processing therapy (CPT). **Our recruitment rate, using the same methods that will be employed for this proposed study (see 6.D.), has been 5-6 Veterans per month**. To date, 47 Veterans have been enrolled in the study and 23 participants have been randomized to the CPT condition. Our drop-out rate from this 28 week intervention study has been 30% from treatment (15% if counting only those who are no longer available for assessment). In the proposed study, Veterans will attend only 16 sessions over eight weeks. We believe this shorter length of intervention will improve retention. Drop-out rates have not differed between the CBT and CPT conditions, suggesting trauma focused treatment has not been a reason for drop-out.

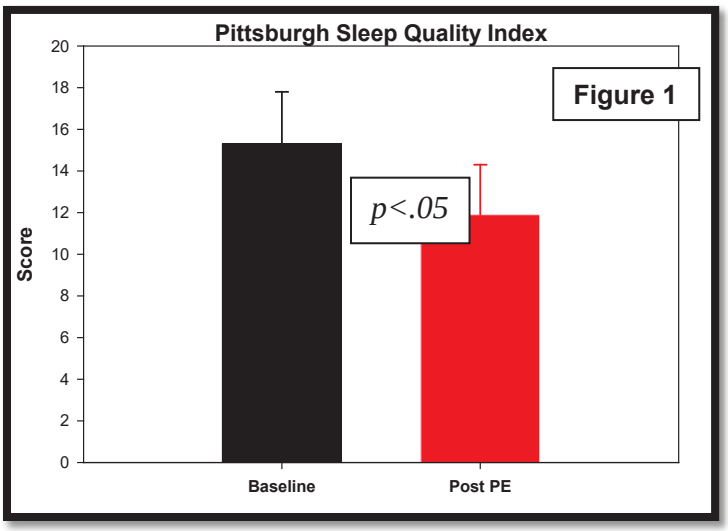
4.C.3. Dr. Norman has piloted one patient through I-PE with more in progress. A slightly modified version of the I-PE protocol proposed here was completed with a 34 year old Iraqi Army Veteran with AD/PTSD. At intake the Veteran reported drinking 25 ounces (1 bottle) of wine per day. His PCL-S was 64 and his BDI was 16. The Veteran agreed to abstinence during treatment. Following 12 weekly sessions of I-PE, his PCL-S dropped to 40 and BDI to 11. He maintained his abstinence through treatment. **This case documents our experience with the I-PE protocol as well as its tolerability to a potential target participant.**

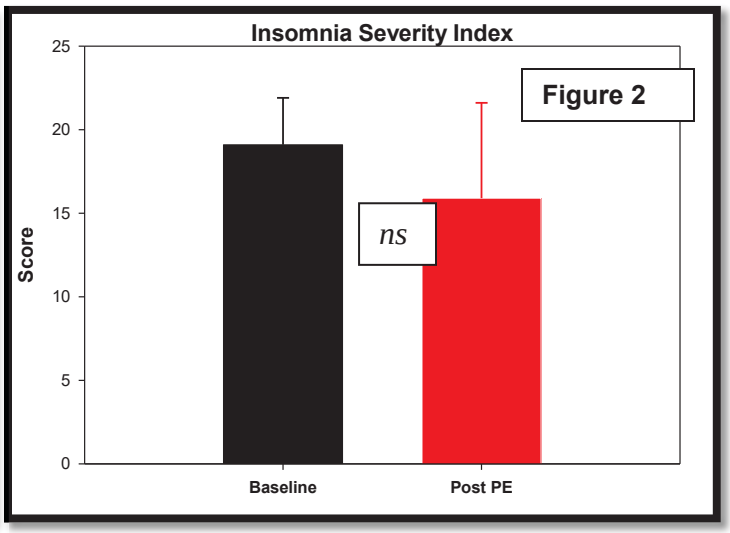
4.D. Sleep Disruption in PTSD.

In our ongoing NIH-funded clinical trial (RC1 NR011728-01), Project NITES, we are documenting the high prevalence of sleep problems among combat Veterans seeking PTSD treatment. We are also finding that sleep symptoms do not respond as well to PE as daytime symptoms. Briefly, Project NITES is a randomized clinical trial (RCT) designed to determine the efficacy of sequential PE and sleep-focused behavioral interventions (in that order; total treatment time = 18 weeks) upon PTSD symptoms, sleep, and quality of life. To be included in NITES, Veterans must: 1) have had at least one deployment as part of OEF/OIF/OND, 2) be diagnosed with PTSD related to a military event, 3) be experiencing clinically significant levels of insomnia and report at least 2 trauma-related dreams/week, 4) be free of an alcohol or other substance use disorder, hypnotic sleep medications and prazosin, and 5) be willing to participate in 18 weeks of psychotherapy.

4.D.1. Refractory Sleep Disturbance Following Prolonged Exposure: Preliminary Data from Project NITES.

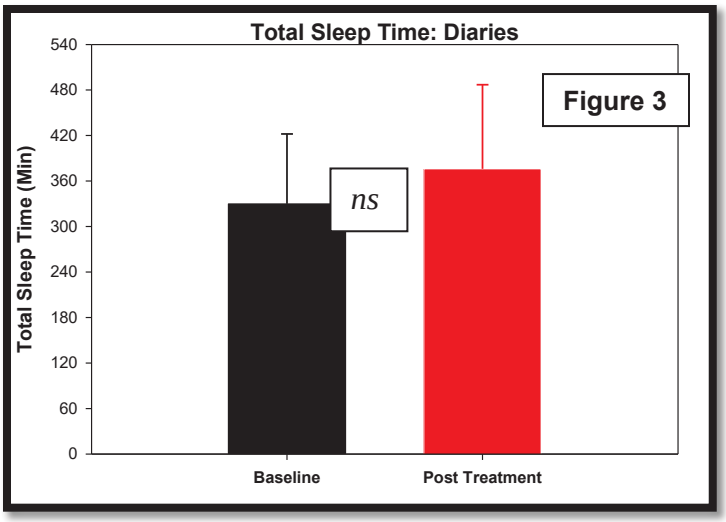
Data from the first 15 OEF/OIF Veterans who completed the PE segment of the trial shows that despite clinically significant and reliable decreases in overall symptoms of PTSD measured by the CAPS (mean pre-post change = 18.9, $p < .01$) and PTSD Checklist (PCL-S; mean pre-post change = 20.6, $p < .01$), Veterans remained in the clinically significant range of impairment on objective and subjective measures of sleep disruption. For example, on the Pittsburgh Sleep Quality Index (PSQI) and Insomnia Severity Index (ISI), Veterans reported mean post-treatment scores of 11.9 (*SD* = 2.4) and 15.6 (*SD* = 5.7), respectively (see Figures 1 and 2). To put this in context, patients scoring 5 or greater on the PSQI are categorized as "poor sleepers" and scores of 15 or higher on the ISI are indicative of moderately severe insomnia.

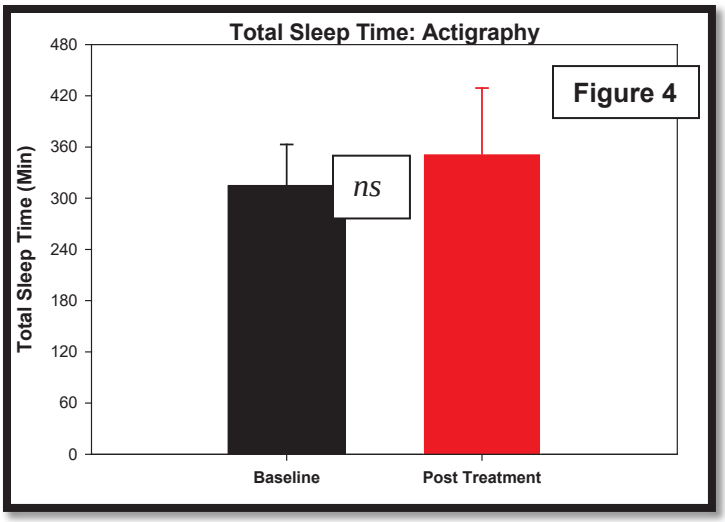




475

Findings from subjective and objective prospective sleep measures (daily diaries and actigraphy, respectively)





were similar. For example, on Total Sleep Time (TST;
the total quantity of time spent sleeping at night), Veterans demonstrated no significant improvements from pre to post PE (see Figures 3 and 4).

Post-PE TST means assessed subjectively (daily diary; *M* = 6.3 hours) and objectively (actigraphy; *M* = 5.8 hours) remained comparable to patients with Primary Insomnia and Major Depression and significantly impaired relative to healthy control subjects similar in age (See Figure 5).

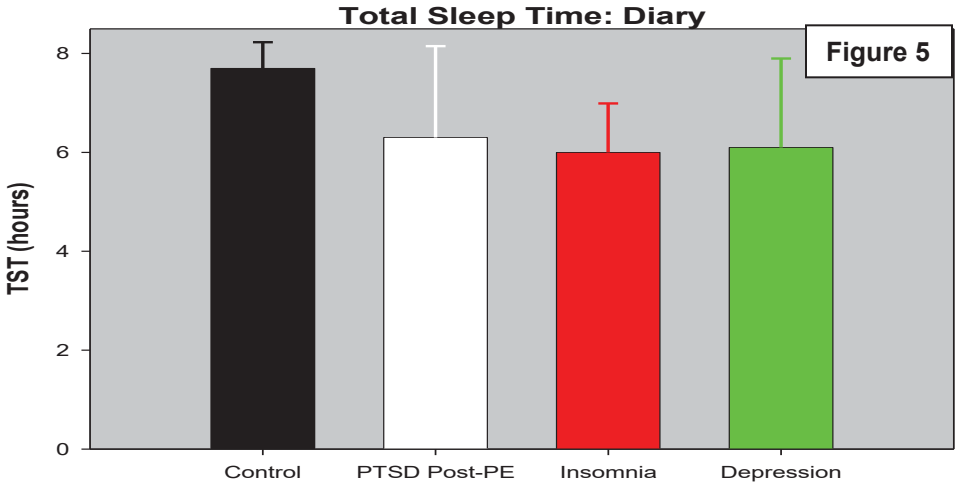


Figure 5

Finally, with regard to trauma-related dreams, daily diary data from Project NITES revealed no significant decrease in the number of distressing dreams or the mean level of distress associated with those dreams after PE. See Table 1.

Table 1. ***Weekly Values from Daily Sleep Diaries*****; n=15**	**Pre PE *M*(*SD*)**	**Post PE *M*(*SD*)**	***p***
Total # of Distressing Dreams (weekly)	**6.8(4.4)**	**5.5(5.1)**	**.19**
Associated Distress (0-10 scale)	**5.8(1.5)**	**5.8(1.9)**	**.92**

In sum, these data show that even when overall PTSD symptoms decrease after PE, the nighttime PTSD symptoms remain in the clinically significant range. This underscores the importance of understanding the role of sleep problems in PTSD treatment, as we propose to do in our exploratory aims with our AD/PTSD sample.

4.E. Conclusions and considerations from our preliminary work. Several conclusions can be drawn from our preliminary work. First, as seen in extant literature as well, PTSD impacts AD course and treatment outcome. Second, interventions that include exposure to a traumatic memory are an effective way to intervene on PTSD symptoms and we found such an intervention to be acceptable to pilot participants with AD/PTSD. Third, those with AD/PTSD appear to have PTSD-specific alcohol expectancies that can differentiate them from non-PTSD samples. As presented in the background section, the next theoretical step in AD/PTSD treatment research is to understand whether integrated exposure therapy is more effective than integrated present-focused coping skills therapy in reducing alcohol use and PTSD symptoms. **Our research team is ideally suited to carry out this work based on our clinical and research experience. Many decisions regarding the design of this proposed R01 were informed by our experience in conducting the PI's K23 research and our other RCT's of AD and/or PTSD. Our preliminary work supports that we have the theoretical and logistical experience to carry out the proposed work.**

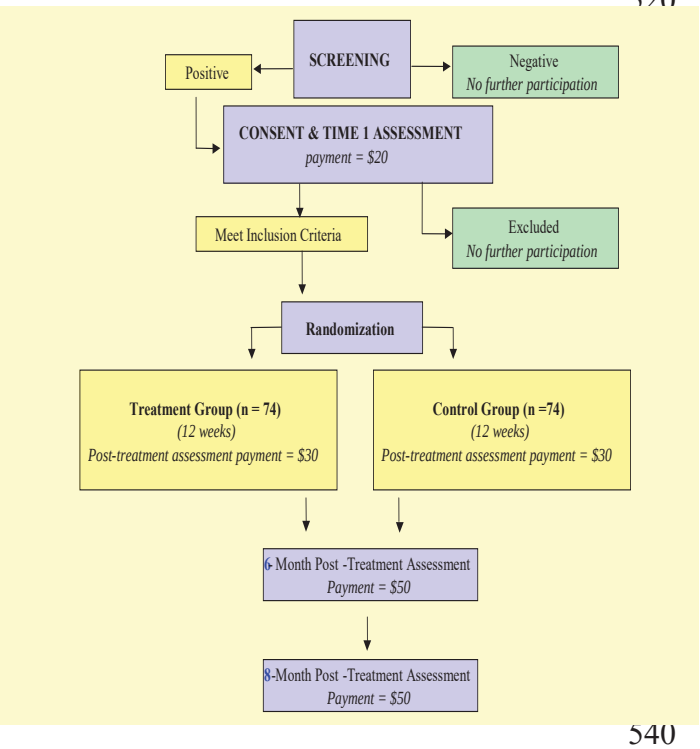
5. INNOVATION

This application challenges and seeks to shift current clinical practice paradigms (from coping skills therapy to treat AD/PTSD to integrated treatment that includes best practice PTSD treatment). We propose a refinement to exposure therapy and new application of exposure to AD in order to promote this paradigm shift away from a well disseminated form of treatment that has little empirical support for its effectiveness (coping skills for AD/PTSD) toward an evidence based practice that is far more promising in its potential for sustained recovery (integrated exposure therapy). The proposed trial would be the first to compare an integrated exposure

psychotherapy to an integrated coping skills psychotherapy for the treatment of AD/PTSD. In addition, we would explore the underlying mechanisms of AD/PTSD treatment to inform future treatment development and research.

5. APPROACH

Year	1				2				3				4				5			
Quarter	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Activity	Startup		Clinical Trial														Dissemination			
Final procedures																				
Hire and train staff																				
Recruit/Enroll																				
Collect Data																				
Clinical Trial																				
Data Analysis																				
Dissemination																				



6.A. Design. The proposed study will be a randomized controlled trial comparing Integrated Prolonged Exposure Therapy (I-PE) to Seeking Safety (SS) for the treatment of male and female Veterans with AD/PTSD. 148 participants will be enrolled through the San Diego VA and randomized at the individual level. Measures will occur at baseline, post-treatment, 5- and 8-month post-baseline follow-up.

6.B. Timeline. We propose a study lasting 5 years including:

Phase I Formative Research & Intervention Refinement (6 months): Start-up activities will include hiring and training of the research staff and therapists providing the study interventions, and setting up of data entry and management procedures with the statistician. Patient recruitment protocols will be developed, tested, and revised. Measurement will be largely the same as in Dr. Norman's NIAAA funded K-23 award and Dr. Tate's VA Merit.

Phase II RCT (42 months): Participant recruitment and enrollment will occur. Methods and procedures are consistent with CONSORT guidelines for conducting and reporting RCT's.[66] We will aim to recruit 3-4 participants a month for this study. We have recruited 4-6 participants per month in our prior ICBT studies that have had similar inclusion and exclusion criteria, thus a minimum of 3-4 participants per month is feasible. Data entry and management will begin in the following quarter with preliminary statistical analyses in the second year and continuing through the end of the study.

Phase III Dissemination (9 months): Assessments, data analyses, manuscript writing, and presentations to the scientific and clinical community will be completed.

6.C. Participants, Inclusion/Exclusion Criteria, and Rationale. Inclusion Criteria. Eligible participants will be Veterans who were victims of psychological trauma that occurred in childhood or adulthood; at least one month

post-trauma; age 18 or older; meet DSM-IV[67] criteria for current alcohol dependence and PTSD; literate in English; intend to stay in San Diego during study participation; willing to attend psychotherapy and measurement sessions; willing to stay abstinent during treatment. We are asking participants to be abstinent during the study period to be consistent with other studies on concurrent AD or SUD and PTSD treatment (e.g.,[16,17]). Also consistent with these other studies, relapse during treatment will not be a cause for study termination, but rather will be addressed in therapy (6.E.4). The study has relatively broad eligibility criteria for participation to capture the many types of manifestations of AD/PTSD among Veterans.

Exclusion criteria: Moderate or severe cognitive impairment on the Brief Neuropsychological (NP) Assessment Battery[68] as this may interfere with ability to benefit from treatment. Individuals with suicidal ideation will be included because it is important to explore how these patients respond to treatment; however, acutely suicidal individuals (assessed using the suicide items from the depression measures described below) will be referred for more appropriate treatment (see human participants section). Histories of psychosis or mania independent of substance use will be excluded because the presence of these disorders can impede therapy progress. Individuals who use intravenous drugs will be excluded. Participants who do not have adequate memory of the trauma (as assessed by the evaluator and confirmed by the PI during the first part of the CAPS which involves asking for a brief description of the traumas the individual has experienced) will be excluded because such memory is necessary for exposure. As long as the individual remembers at least the basic outline of what happened the memory is generally considered adequate. The evaluator will check with the PI and Dr. Thorp (both consultants on the VA PE roll-out and have ongoing research involving PE) if questions arise regarding whether the trauma memory of a particular individual is adequate. Only Veterans residing within 50 miles of the site will be included. Those with life threatening or unstable medical illness, documented neurological disorder, or inability to read will be excluded.

Who will not be excluded: Individuals with substance use disorder (SUD) other than IV drug use will not be excluded because of high comorbidity with ADs and PTSD.[7,32] Mild cognitive impairment will be included. Other anxiety and depressive disorders will not be excluded because of their high comorbidity with PTSD and AD.

Standard Pharmacotherapy. Participants will be asked to complete an initial medication evaluation and attend monthly follow-up appointments. Participants will receive psychiatric care in the Substance Abuse Mental Illness (SAMI) program at the VA San Diego Healthcare System under the oversight of Co-investigator and medical director of the SAMI program, Dr. Shannon Robinson. The pharmacological treatment will be provided at no cost to the proposed project. Medications will be prescribed in an open-label format. Standard VA pharmacology protocol for treatment of PTSD will be used with dosage determined by the psychiatrist (within protocol range) and altered as appropriate to meet the patient's needs at any given time according to the psychiatrist's judgment of good clinical care. The VA uses treatment guidelines that require standardized patterns of prescription for individuals with PTSD and suggests SSRIs as the preferred treatment. Based on these guidelines, we believe that this pattern of prescription will apply to at least 85% of participants and be comparable across treatment groups. To ensure that we are adequately accounting for medication, we will collect self-report information and receive permission from participants to track their medication prescription in CPRS. We considered recruiting participants who were not on medication or asking participants to be medication stable prior to study entry. However, psychotropic medications have well documented effectiveness for the treatment of anxiety and depression and withholding such medication would be inappropriate for this high-risk population. We recognize that prescription and changes in medications will be an uncontrolled source of variance but expect that any changes will be similar in the two groups and thus balanced by randomization. We will not include individuals who are taking benzodiazepines past the acute withdrawal phase (which would be prior to entering the study). However, we will include individuals if they otherwise meet criteria if they terminate the benzodiazepines under their psychiatrists' care prior to study initiation. The prescribing psychiatrist will not be blind to group assignment. Although this would be preferable from a scientific standpoint, our past experience has shown that attempting to maintain blind status is difficult. The SAMI psychiatrist views electronic patient records documenting study participation, type of treatment provided, and Veteran response to treatment. Although we could design a means of maintaining blinding, we decided it was best for the psychiatrist to be thoroughly informed of each Veteran's status and this safety concern took precedence over scientific design considerations.

6.C.1. Treatment Setting

All work will be carried out at the SAMI outpatient program of the Alcohol and Drug Treatment Program of the VASDHS. The SAMI program was established in 1991, with > 4500 outpatient visits per year. Referrals to SAMI come from ADTP (15,000 outpatient visits per year, and a 28 bed, 28 day inpatient program with > 360 inpatients annually), inpatient Psychiatric Unit (> 800 admissions/year), outpatient Mood Disorder Clinic (> 16,500 visits/year), and Primary Care (>12,000 Veterans/year). Services in the SAMI clinic have grown in recent years with a 33% increase in the number of Veterans receiving care. The staff includes a psychiatrist, clinical psychologist, social worker, program assistant, and trainees (psychiatry residents, psychology interns and postdoctoral fellows, social work interns).

6.D. Recruitment. Eligible participants will contact our study in response to 1) flyers posted in VA mental health, primary care, and alcohol and substance use treatment programs; 2) from advertisements in print and web-based media; and 3) by VA primary care, SAMI, PTSD, and other psychiatry clinics. Following oral consent, potential participants will undergo a telephone screening that takes approximately 30 minutes to complete. The screening, used in the PI's K-23 award and Dr.Tate's merit, is intended to detect clinically significant AD and PTSD symptoms. It consists of screening items from the SCID[69] and the Posttraumatic Stress Disorder Checklist-Specific Version (PCL-S[64]) for disorders that are part of the inclusion and exclusion criteria. Those who meet study criteria will attend an in-person interview where they will sign informed consent documents and take part in a baseline assessment (see measures in 6.F.). Following baseline assessment, participants will be randomized to the intervention or control condition. Random permuted blocks will be used which ensure exactly equal treatment numbers at certain equally spaced points in the sequence of patient assignment. A computer-generated randomization sequence will be provided by our statistical expert, Dr. Ryan Trim, and held by a colleague not otherwise involved with the study. Randomization will be stratified by gender to ensure a balanced number of males and females are in each treatment group. It is expected that randomization will balance out by PTSD and alcohol use severity. Dr. Allard, the Project Coordinator, and the therapists will know each patient's assignment; the PI and the rater will not have access to this information. The success of the blinding procedure will be evaluated by having the rater guess the patient's assigned treatment condition after each assessment. If indicated, participants will be asked to go through detoxification prior to beginning the study. Detoxification programs are available on inpatient and outpatient bases through programs funded by the San Diego VA. We will expect that participants will be 2-4 weeks post-alcohol use at the start of the study given that prior research has shown that it takes approximately this amount of time for cognitive skills to recover following cessation of alcohol use and given that participants will be expected to undergo detoxification prior to study entry if needed.

Study participants will be drawn from Veterans 18 years of age and older referred to the SAMI program or one of the PTSD treatment programs at the San Diego VA (e.g., OEF/OIF/OND PTSD clinic, PTSD Clinical Team, Military Sexual Trauma clinic). All Veterans referred to SAMI and the PTSD Clinical Team first attend an Orientation Group that meets once weekly where the services provided in the program are explained, and if the Veteran wants to receive services, consent for treatment in the clinic is completed. Following consent, an appointment is made for an in-depth clinical diagnostic intake. The Project Coordinator will attend the SAMI and PTSD Clinical Team Orientation Groups and briefly present information about the research study and provide a "Consent to Contact" form that gives research staff permission to contact the Veteran to describe the study and details of study participation to potential participants and to determine if the Veteran meets study criteria. Based on intake diagnostic interview and staff consensus, Veterans are assigned to appropriate treatment within the programs. As with our prior Merit studies, the interventions will be delivered within the SAMI program. Following clinical evaluation, Veterans determined to be appropriate for SAMI or PTSD Clinical Team interventions focused on PTSD and alcohol dependence will be approached individually, have the project explained by the Project Coordinator, and complete an informed consent. Of patients referred to SAMI, approximately 30% have been diagnosed with a PTSD. Veterans referred to the OEF/OIF/OND or MST services at the San Diego VA are scheduled immediately for an intake appointment. The study will be described during intake when discussing treatment options and interested Veterans will have the opportunity to meet with the study coordinator, the PI (who is the director of the OEF/OIF/OND clinic) or a Co-investigator (who are directors of MST, PTSD Clinical Team, and SAMI teams) to discuss study participation. Of patients referred to the PTSD clinics, about 15-20% have a current alcohol use disorder.

6.D.1. Feasibility. We will aim to recruit 3-4 participants per month for this study. It is important to note that for our current merit for AD/PTSD (PI: Dr. Tate), **we are enrolling an average of 4-6 Veterans per month**. The VASDHS has a very high consent to participate rate even when projects involve extensive FU (e.g., our study of dually diagnosed=90%). The proposed study would begin enrollment just as the current one phases out enrollment. In addition, please see letters of support from key VA clinic directors who will aid with recruitment. We will have access to eligible participants based on the following: 1) Relationships and approvals we have already secured as part of Dr. Norman's K-23 award and Dr. Tate's Merit award; 2) Drs. Norman and Thorp are Program Directors of two combat PTSD clinics at the San Diego VA, Dr. Allard is Program Director of the Military Sexual Trauma (MST) Clinic, and Dr. Trim is the program director of SAMI; Dr. Robinson is the medical director of SAMI; 3) The VA San Diego combat PTSD, MST, and SAMI clinics combined see over 3,000 patients annually. **Given our current recruitment successes with this target population and given the support we will have from relevant VA clinics, recruitment of 3-4 Veterans per month is feasible.**

6.D.2. Patient Retention Methods. The investigators have extensive experience in maintaining study cohorts over substantial periods of time. From Dr. Norman's K-23 award pilot, 100% women who began pilot treatment completed the treatment; 80% completed follow-up assessments to 9 months. In our ICBT research, the dropout rate was less than 28% (20% during treatment,10% post treatment to 18 months). Based on other AD/PTSD studies,[16] we have estimated our dropout rate at 35%. The following steps will be taken to insure high retention: (1) At all assessment points, participants will be asked to provide contact information for at least two close friends or relatives and permission to contact them. (2) A database accessible only to study staff will be maintained as a participant tracking system. (3) Computer public search engines (e.g., Accurint) will be used to locate those lost to follow-up. (4) During treatment, if a participant misses two consecutive sessions, we will conduct a brief motivational interviewing (MI) intervention by telephone. MI has been shown to enhance retention in longitudinal alcohol research (i.e.,[3]). Riggs and colleagues[28] compared patients with concurrent AD and PTSD to AD or PTSD only. A greater percentage of the comorbid sample was unemployed, low income, and living alone. Such patients may be more likely to drop out of treatment because they are unable to find transportation or childcare, because of an opportunity to earn money, or because they use the time to seek social services. We address these barriers by offering therapy at a centrally located site that is accessible by public transportation and offers free parking, by offering transportation reimbursement, and by offering therapy in individual format during daytime and early evening hours. We will encourage all participants to have a case manager through the VA so that case management issues are addressed in both treatment modalities.

6.D.3. Women and Minorities
Women comprise 11% (e.g., SAMI clinic) to 60% (Military Sexual Trauma clinic) of the Veterans seen in the clinics from which we will be recruiting and approximately 24% of Veterans in the program are minorities. Consistent with SAMI demographics as a whole, 11% of participants in our integrated intervention study over the past 8 years were women. We have been able to obtain 9% Hispanic, 16% African American, and 4% other ethnic groups, for a total of 29% from minority groups. Given that this study will include recruitment from the Military Sexual Trauma Clinic, the increasing numbers of women in the military, and increasing Hispanic proportion of the population in southern California, we will continue attempts to oversample these groups to obtain adequate recruitment of females and minorities to examine effect sizes for these groups relative to male and Caucasian counterparts. The inclusion of these groups is important to the current study given the disproportionately higher prevalence of PTSD diagnosis among women (56% of women; 40% of men) and minorities (38% of whites; 52% of minorities) observed in our previous studies.

6.D.4. Compensation. Participants will be compensated up to $150 for their time and effort for completing assessments: $20 baseline, $30 post-treatment, and $50 each for the 5- and 8-month post-baseline follow-ups.

6.E. Interventions. The experimental intervention augments PE with ICBT to enhance attention to alcohol use. The control condition will be SS. Below we describe the key features of each intervention, how PE and ICBT are integrated, and why these interventions were chosen.

6.E.1. Prolonged Exposure Therapy (PE).[1] PE is an exposure based therapy for PTSD (described in 3C.).

6.E.1.a. Why PE? Although several treatments have been found effective in treating PTSD, we have selected PE based on its particularly strong empirical record and its appropriateness given study aims. The evidence for PE efficacy is greater than that for any other PTSD intervention and treatment effects are generally maintained during follow-up. Six of the 20 RCTs of variants of exposure therapy utilized the PE manual that will be used in

this study. Thus, the safety and tolerability of PE is well documented and, because of their experience administering and disseminating PE, the study team is exceptionally well-prepared to utilize this intervention. The PI and Dr. Tate have preliminary data that trauma processing is acceptable and helpful to individuals with AD and PTSD (section 4C). Most importantly for the goals of this study, PE is among the purest of the exposure therapies in that others tend to include more cognitive or coping interventions (e.g., cognitive processing therapy) which would have more overlap with SS.

6.E.2. Integrated Cognitive Behavioral Therapy. ICBT includes interventions considered important to recovery from substance dependence including a learning theory based explanation of substance dependence, cravings awareness and management, etc.[60] ICBT is not a new treatment model, rather it consists of evidence based interventions for AD from Cognitive-Behavioral Coping Skills Training of Addiction combined with CBT for depression.[60] The thoughts module focuses on identifying maladaptive cognitions, generating alternative cognitions, and rehearsing thought challenging techniques in situations that could potentially lead to relapse. The activities module involves identifying, scheduling, and assessing effectiveness of activities for increasing positive affect and managing pressure to relapse. The social module consists of assertiveness and communication training to increase positive social interactions and efficacy in resisting pressure to use. We have strong data to suggest this intervention is acceptable and helpful to Veterans with AD and PTSD (see 4A).

6.E.2.a. Why ICBT? We considered using Cognitive Behavioral Coping Skills Training of Addiction[60] without the integrated cognitive behavioral therapy for mood. However, in light of literature suggesting individuals with PTSD use substances when they are experiencing negative affect, and because we did not want overlap with our coping skills based control condition, we chose ICBT to focus specifically on teaching coping skills for AD in the context of negative emotional states. PE and CBT have been combined and evaluated in previous RCT's.[41] Thus, we are using a combination of treatments (PE and cognitive behavioral skills) that has already been rigorously evaluated and found effective. The activities and social modules of ICBT are also consistent with PE in-vivo assignments. Finally, we chose ICBT because of our I-PE pilot data, our research team's many years of experience with it, and our positive outcomes in our VA research.[3]

6.E.2.b. Augmentation of PE with ICBT. The intervention will be delivered over 8 weeks in twice weekly sessions (16 sessions). From ICBT, managing cognitions is integrated into the first third of treatment, increasing healthy activities is integrated into the second third, and building social networks into the last third. These topics dovetail easily into PE where the first sessions focus on psycho-education about PTSD and PE, and in-vivo exposure is included in the remainder of treatment. In-vivo exposure includes both avoided items and behavioral activation items to increase pleasant activities and build healthy relationship. ICBT topics are integrated into each week with a focus on how to use these skills for addiction. As such, we are able to use both manuals with extremely minimal modification. We considered writing a developmental grant to augment PE with ICBT but our pilot data where successfully integrated the two treatments, our familiarity with these interventions, the fact that both are evidence based, that CBT and PE have been previously integrated and found effective, that the topics align such that integration is straight forward, and that we have several experts of both therapies involved in this study (PE: Thorp, VA trainer and consultant, Norman and Allard, VA consultants, ongoing research experience with PE; ICBT: Brown developer, Norman and Tate: co-I's or PI's of studies with ICBT) has allowed us to integrate these therapies easily. The I-PE outline is below:

Week*	Content
1	Establish rapport, motivational enhancement for AD and PTSD treatment, identify main trauma, introduce alcohol expectancies, overview of treatment
2	Learning theory-based model for PTSD and substance dependence, thought challenging techniques for situations that could potentially lead to alcohol use or PTSD symptoms, breath retraining, in-vivo exposure begins
3	Imaginal exposure begins, identifying and managing cravings; in-vivo exposure including pleasant activity scheduling continues
4	Imaginal & in-vivo exposure continued; focus in in-vivo on both reducing avoidance and increasing pleasant activities
5	Continued in-vivo and imaginal exposure; focus in in-vivo on both reducing avoidance and increasing pleasant activities
6	Continued in-vivo and imaginal exposure ; focus in in-vivo on both reducing avoidance and

	increasing healthy interactions
7	Continued in-vivo and imaginal exposure; focus in in-vivo on both reducing avoidance and increasing healthy interactions
8	Final imaginal exposure; review of progress; relapse prevention

*Each week is two sessions

6.E.3. Comparison Group. Seeking Safety (SS) is a present-focused integrated therapy that centers around several main ideas: 1) Establishing safety is often times one of the most important clinical needs of patients struggling with difficulties related to both trauma and alcohol use; 2) Integrating treatment for PTSD and alcohol/substance use; and 3) The utilization of cognitive, behavioral, interpersonal, and case management techniques. Seeking Safety consists of up to 24 modules that can be conducted in any order.[4] Each module includes safe coping skills pertaining to both AD and PTSD. The trauma is not addressed and exposure is not included in therapy. Although we will have 16 sessions we will include all 24 modules. In our preliminary work, we found that some sessions were shorter in length and overlap in content such that we were able to successfully cover two sessions in an individual 90-minute format.[49]

6.E.3.a. Why SS? SS is widely disseminated in community and VA settings and is the most researched integrated AD/PTSD treatment to date;[70] however, efficacy data on this intervention is still limited. SS is based on the model that patients must first achieve safety by learning coping skills to handle PTSD related distress and substance use before any form of trauma processing or exposure can be introduced. Thus, the therapy purposefully excludes any form of exposure. Because SS is widely used and specifically does not include exposure, it is ideally suited as a comparison condition for this study to allow us to examine whether exposure improves PTSD outcomes at post-treatment and AD and PTSD outcomes at follow-up.

6.E.4. If Participants Relapse During Treatment. Participants will not be discontinued, but rather a motivational interviewing protocol will be employed after any alcohol or substance use to help participants avoid further relapse. If a therapist or assessor identifies worsening substance use, the study investigators will evaluate whether best clinical care indicates a need for more intensive SUD treatment. Both ICBT and SS include asking about recent substance use. Therapists will be trained to contact the PI if a participant reports three or more days per week of alcohol use with more than four standard drinks or three or more days of illicit drug use in a week. If more intensive treatment is appropriate, we will assist the participant in establishing appropriate treatment, then discontinue study participation following a final evaluation.

6.E.5. Training for Intervention Delivery. We will follow the intervention training and integrity procedures established in our ICBT and NITES studies. Each study therapist will be trained to criteria by a certified trainer (Thorp and Tate for I-PE; Norman and Allard for SS), and will receive weekly supervision (Thorp and Tate for I-PE; Allard or Norman for SS). Therapists will deliver both treatments under conditions of careful ongoing supervision and fidelity assessment in order to avoid therapist effects. Audio recordings of sessions will be reviewed to ensure treatment integrity. In addition to review of audiotapes by clinical supervisors for clinical purposes, a random sample of audiotapes will be independently evaluated by research staff and rated for treatment fidelity and discriminability.

Therapists will be senior clinicians and post-doctoral psychology trainees in the PTSD and addictions programs at the VASDHS. All therapists complete detailed training in both interventions delivered. Therapists receive individual and group supervision and attend a weekly Biobehavioral Addictions Seminar led by Dr. Sandra Brown and other experts in addictions and a PTSD seminar led by Dr. Norman and other experts in PTSD treatment. Each study therapist receives weekly supervision by a senior investigator with expertise in the particular intervention. Drs. Susan Tate or Dr. Ryan Trim, Co-Investigators, will provide weekly supervision for the ICBT intervention. Dr. Tate and Dr. Trim have both served a therapists and supervisors for the ICBT intervention in our prior study. Dr. Thorp, VA PE trainer and consultant, and Dr. Allard, VA PE consultant will provide PE supervision. Drs. Allard and Norman (trained by Dr. Najavits, author of SS, and both with prior SS clinical and research experience) will provide SS supervision. Trainee rotations typically continue for 1-2 years. We will record changes in therapists to evaluate possible therapist effects. Participants will complete a brief questionnaire once monthly to assess therapeutic alliance and treatment satisfaction.

6.E.6. Other Personnel. We will hire, train, and supervise a study coordinator and research associate (RA) in reliable administration of clinical rating scales and outcome measures. The RA will have no connection to the

treatment to keep the person blind. An experienced statistician, Ryan Trim, will provide statistical support including data organization structure and reliability procedures that have been well established in Dr. Brown's prior studies. The study will pay for a portion of a research technician's time who is experienced in sleep assessment who will conduct all of the sleep laboratory-based and actigraphic assessments and data scoring. Funding for sleep measurement will be supplemented by the VA Center of Excellence and by a recent sleep equipment grant to Dr. Sean Drummond (co-investigator on this proposal), thus the sleep data will be collected at very low cost to this proposal relative to what it would normally cost.

6.F. Research Assessments

Dr. Norman and Dr. Allard will train the RA using video recordings, role plays, and jointly conducted interviews and will hold weekly ongoing supervision. A random sample of audio recordings will be independently evaluated by research staff and rated for treatment fidelity and discriminability. Dr. Norman will also view randomly selected audiotapes of assessment sessions to provide feedback and ensure interrater reliability. During each assessment, the RA will assess for any major changes in health (e.g., overnight hospitalizations), possible adverse events, suicidal ideation, and general well-being. Therapists will also assess for clinically significant worsening during therapy sessions. Any exacerbation of symptoms or alcohol/substance use will be reported and discussed with the supervising investigator so that appropriate action can be taken if necessary. Data collection staff and intervention staff will be strictly separate. We will have the support of Drs. Brown's and Stein's laboratories, each having over twenty years of experience in training and testing raters. All interviewers complete standardized training to criterion (instructions, training, manual, 5 videotapes) for the CAPS, NP, and TLFB assessments. The interviewer (RA) will observe a minimum of two assessments for each measure and then be observed for a minimum of two assessments. Additionally, the interviewer will be tested for reliability (once every six months), and participate in weekly staff meetings to address questions. Training is also provided on common issues associated with self-report measures. These training procedures are all in place and have been on-going for 11 years during the ICBT study; Dr. Norman, Dr. Tate and Dr. Brown have supervised this training and monitoring and Drs. Norman, Allard, and Tate will continue to do so.

As previously noted, intake diagnostics are completed by a trained research assistant within 1 week of entry into the SAMI or PTSD treatment program. In addition, a brief neuropsychological battery (approximately 30 minutes) will be completed at intake to allow evaluation of whether cognitive functioning is related to treatment response. Actigraphy data will be collected for one week pre- and post-intervention on all participants and polysomnography data will be collected for one night pre- and post-intervention (with a practice night included) for a randomly selected subset of 16 participants per year.

6.F.1. Measures. The primary outcome of interest will be reduction in PTSD symptoms and alcohol use at post-treatment and follow-up. We will examine percent days abstinent (PDA) and number of drinks consumed on drinking days. Other outcomes include depression symptoms and quality of life ratings, and mediators and predictors of outcomes such as process variables, affect, and sleep.

6.F.1.a. Alcohol and Substance Use Disorders Measures.

The Timeline Follow-back Procedure (TLFB[71]) will be employed at all assessment points to evaluate drinking and all drug use during the 30 days preceding each interview. The Quantity-Frequency Index[72] and maximal consumption will be calculated for alcohol use. Drug use indices will be similarly derived for stimulants, marijuana, and other drugs. The TLFB will be used at each follow-up to establish: percentage days abstinent, length of initial abstinence, length of use episodes, severity of relapse and current alcohol/drug use pattern. Using suggested theoretical guidelines, relapse severity will be classified as minor (lapse $\leq$ 4 days use and no major life problems followed by abstinence) or major (protracted episode, multiple episodes, continuous use). This system, developed in Dr. Sandra Brown's lab, has proven useful in previous alcohol and substance treatment research and is predictive of clinical course.

A self-report Substance Use Inventory[73] will be administered weekly at treatment sessions. The inventory asked patients on which of the preceding seven days they had used alcohol or any of seven major types of drugs. Participants will complete an initial toxicology screen at baseline and random screens will be conducted during 25% of the quarterly assessment.

Relapses will be classified using the Modified Contextual Cue[74] (MCC) system for precursors using transcribed verbatim reports of relapse episodes, and using Shiffman and Wills' framework of temptation, stress, or other.[75] Participants will be administered the AD and SUD sections of the Structured Interview for DSM-IV (SCID[69]).

6.F.1.b. PTSD and Other Axis I.

The Clinician-Administered PTSD Scale (CAPS[76,77]) is a standard semi-structured interview used to assess PTSD severity. As part of the CAPS, a list of potentially traumatic events is given to respondents. Using the list as a prompt, respondents select up to three of the most traumatic events they have experienced, and those events are used as the basis of assessing PTSD. The CAPS assesses each of the 17 items from the DSM-IV criteria B, C, and D, and it has demonstrated high levels of internal consistency, good interrater reliability, and excellent convergent validity. Importantly, the scale was not designed exclusively for use with combat Veterans.[78] The CAPS can be administered in 30-60 minutes, and it has the advantages of categorical (diagnostic) or dimensional scoring of PTSD plus items for assessing social and occupational functioning, dissociation, and the validity of the items. The F1-I2 method of scoring will be used in the current study.[79] A total severity score of 40 or higher indicates full threshold PTSD and a 15-point change in CAPS total severity score represents clinically significant change.[79]

The PTSD Checklist – Specific Version (PCL-S[64]) is a brief self-report instrument to measure the degree of PTSD symptoms related to a variety of traumatic experiences. It was chosen because it is so widely used. It consists of 17 items, scored on a 1-point (not at all) to 5-point (extremely) scale, that correspond to the DSM-IV symptoms of PTSD. The specific version was chosen to ensure that participants would answer the items in regard to their index trauma rather than in regard to general distress. Initial psychometric data include test-retest reliability (0.96) and validity, as indicated by a kappa of 0.64 for a diagnosis of PTSD from SCID. Alpha coefficients for internal consistency reliability have ranged from 0.89 to 0.92.

The Beck Depression Inventory II[80] is a 21-item self-report scale listing common symptoms of depression that. It is the most widely used self-report depression measure in clinical populations, again facilitating comparison between this investigation and others. Stem questions from the SCID are used during screening for initial screening of study inclusion and exclusion criteria.

6.F.1.c. Functioning.

The Brief Neuropsychological (NP) Assessment Battery targets neurocognitive skills previously associated with substance abuse treatment outcomes (e.g.,[68]) and is limited in length (30 minutes) to facilitate compliance. We included this brief evaluation of neuropsychological functioning at treatment entry as these neurocognitive skills have previously been associated with SUD treatment outcomes[68] and to understand potential impact on outcomes of mild levels of impairment related to traumatic brain injury. All NP measures will be administered by trained psychometrists in a standardized fashion designed to minimize fatigue and possible carryover effects (i.e., if a participant performed poorly on any one task). The NP battery will be initially administered approximately 3 weeks after the last date of alcohol or other drug use (i.e., no withdrawal symptoms are present). We will also take precautions to avoid possible contamination of NP performance by medications by insuring that patients are on stable doses of medications for at least two weeks at the time of NP testing. The measures, grouped by cognitive domain, include: 1) General Intelligence: American National Adult Reading Test (ANART); 2) Executive Functioning/Problem Solving: Wisconsin Cart Sort; 3) Attention: WAIS-III Digit Symbol. 4) Verbal Learning and Memory: Hopkins Verbal Learning Test (HVLT). Each raw test score will be transformed into a T-score (M=50, and SD=10) based on the degree of deviation from the normative age-referenced mean score. Then, domain T-scores will be calculated for each subject by averaging T-scores within that domain. This brief battery takes approximately 30 minutes and is a shortened version of the assessment utilized in our ICBT studies.

The Medical Outcomes Study 36-item short form self-report health survey (SF-36[81,82]) will be used to assess health-related quality of life. It has been validated in large, mixed-age medical and psychiatric samples.[81,82] With eight subscales, it provides a multidimensional assessment of quality of life related to both mental and physical health.

6.F.1.d. Measures of Mechanism and Mediation.

The Posttraumatic Cognitions Inventory (PTCI[83]) is a 36-item assessment of negative thoughts about the self, negative thoughts about the world, and self-blame that significantly distinguishes trauma survivors with PTSD from those without PTSD. The scale has good psychometrics and change in these thoughts has been related to change in PTSD symptoms with treatment.[39]

The Revised Ways of Coping Questionnaire (WOC[84]) is a well-validated measure that provides a variety of coping strategies and appraisal characteristics. WOC has been used in diverse populations and provides estimates of problem solving and emotion focused skills as well as several factor analytically derived subscales relevant to PTSD,[74] depression, and drinking/drug use situations (e.g. avoidance). At intake, participants respond to a standard high-risk drinking/drug use situations based on prior relapse studies, and at our two follow-up time points, participants generate one personal high-risk situation. Group differences in coping responses to the same situation and person consistency in coping with different stressors can be assessed. Patient generated situations will be grouped by conceptual areas,[74] and appraisal features (e.g. importance, controllability), will be used for further clarification. Situations will be categorized as changeable, having to be accepted, or requiring information. These characteristics have been found to produce different coping patterns. Coping response characteristics will be examined via cluster analysis to establish composite scores used in analyses.

The Expectancy of Therapeutic Outcome (ETO), a 5-item self-report scale to evaluate treatment credibility, will be administered by the therapist in Session 1 after the therapist has provided the overall rationale for the treatment program. Questions are rated on a 0 to 8 Likert-type scale, with total scores from 0 to 32.

The Additional Treatment Inventory (ATI) assesses additional treatment sought after the completion of study treatment. It asks about both psychiatric medications and psychotherapy.

The Client Satisfaction Questionnaire[85] is an 8-item self-report scale measuring satisfaction with treatment. It has excellent internal consistency and correlates with therapists' estimates of client satisfaction. This instrument will be used to measure participants' satisfaction with the interventions. Participants will also complete SS and I-CTT content specific questionnaires at the end of each session.

Participants will also complete SS (SS Content Form) and I-PE (Utility of Techniques Inventory) content specific questionnaires at the end of each session. Process measures including number of sessions attended, homework compliance, and lateness will be collected.

The Positive and Negative Affect Schedule (PANAS[50]) will be used to evaluate negative affect.

6.F.1.e. Home and Self-Report Sleep Assessment

All participants will have their sleep assessed for one week at home with sleep diaries and actigraphy both pre- and post-treatment.

Sleep Diaries. While the use of sleep diaries is ubiquitous in studies involving sleep, there is no universally accepted standard. Our particular form is briefly described here. The sleep diary is a 1-page form assessing seven days which includes measures of sleep continuity (sleep latency, number of awakenings, wake after sleep onset, total sleep time, and sleep efficiency). The sleep diary requires approximately five minutes per day to complete and participants will be asked to complete it in the morning.

Actigraphy. To obtain an objective measure of sleep, participants will wear an Actiwatch (Phillips) for one week before and after the intervention. The Actiwatch is a wrist-worn device that measures body movements and light. It is lightweight (17.5 g) and worn like a wristwatch. Data are downloaded onto a computer and customized software scores the data dichotomously as awake or asleep in 30 second increments. The methodology is commonly used to record sleep/wake patterns over several days and has reasonable

agreement with polysomnography in validation studies.[86] These data will provide standard sleep parameters: total sleep time, sleep efficiency, number of nocturnal awakenings, and length of awakenings.

The Insomnia Severity Index (ISI[87]) is a widely used measure of insomnia with well-established reliability and validity. The ISI consists of seven items, three of which assess severity of insomnia (i.e., degree of difficulty falling asleep, staying asleep, and waking too early). The remaining questions tap satisfaction with sleep pattern, effect of sleep on daytime and social functioning, and concern about current sleep difficulties. The Pittsburgh Sleep Quality Index (PSQI[88]) is a 19-item self-report measure intended to measure sleep quality and disturbances, and will be administered pre- and post- treatment. The PSQI has shown good validity and reliability, and is widely used as tool to measure sleep quality.

6.F.1.f. Laboratory Sleep Assessment

Sixteen randomly selected participants per year (eight in each condition) will be studied using polysomnographically (PSG) for two consecutive nights pre- and post-treatment. The first night will be used to acclimate participants to sleep laboratory environment and to rule out intrinsic sleep disorders other than insomnia, such as sleep disordered breathing. Participants will go to bed and be woken up at their habitual bed and wake times based on their sleep diaries. The recording montage will consist of a minimum 10 electrophysiologic signals. The basic montage includes 2 EOGs referenced to a single mastoid, 6 EEGs referenced to linked mastoids [F3, F4, C3, C4, O1 and O2], a bipolar mentalis EMG, and an ECG. The expanded EEG montage, although not required for sleep staging, allows for more precise identification of arousals or transient wakefulness. Several measures, in addition to our core montage, will be obtained. These include: 1 channel of nasal/oral airflow (obtained with pressure transducer monitors) and 2 channels of leg-related motor activity (right & left tibial EMGs). The airflow and tibial data are used to detect sleep apnea (OSA) and periodic limb movements (PLMs), respectively. While these additional clinical measures are insufficient to fully profile OSA or PLMs, they will provide a clinical screen for the presence of these disorders. In the morning following the PSG, participants will be free to leave and will return the next night for the second PSG. The record will be scored during the day so that participants who are found to have occult sleep disorders (apnea-hypopnea index ≥10/hour and/or PLM index ≥15/hour) will have their second night cancelled. These subjects will be replaced to maintain our sample size for this part of the protocol. The second PSG night will be used to characterize participants' sleep. The montage will be the same as for the first night except OSA and PLMs will not be measured. The PSG will be used to assess standard sleep continuity parameters (e.g. sleep latency, wake after sleep onset, total sleep time, sleep efficiency, and number and length of nocturnal awakenings) and sleep architecture parameters (e.g. time spent in each sleep stage), according to standard criteria.

6.F.1.g. Medication Adherence

The ACTG Interview of Antiretroviral Medication Use (AIAM) will be used to assess adherence to medication regimens. This interview was developed by the Adult AIDS Clinical Trials Group (ACTG) to assess in detail HIV medication adherence over the previous four days and takes about 10 minutes to complete.[89] The measure was modified for the current study to assess adherence for prescribed psychotropic medications by omitting references to HIV or AIDS and omitting the last item that lists side-effects that are common to HIV medications. Decreased medication adherence has been associated with substance use,[89] and in this study, we anticipate increased adherence following our SUD treatment. The accuracy of self-reports of medication adherence have been questioned, and more objective methodologies are available, such as unannounced pill counts and medication bottle caps containing microchips that record medication adherence. However, for the current study, we have selected this self-report measure that requires less time, effort, and costs and has been validated when compared with other methods. Additionally, based on our prior research with Veterans, there are substantial differences in number and types of medications prescribed, complicating alternative non-self-report assessment procedures.

	Baseline	2 months	5 months	8 months	Each Session
Primary Outcome Measures					
CAPS (PTSD)	X	X	X	X	
TLFB	X	X	X	X	

Other Alcohol and Substance Use Measures					
ASI	X	X	X	X	
SUI					X
Toxicology Screen	X	X (random)	X (random)	X (random)	
MCC	X	X	X	X	
SCID-IV (AD, SUD)	X	X	X	X	
Other Measures of PTSD and Other Axis I Disorders					
PCL-S					X
BDI					X
Measures of Functioning					
NP Battery	X				
SF-36	X	X	X	X	
Measures of Mechanism and Mediation					
WOC	X		X	X	
UTI		X	X	X	
ETO	In session 1				
ATI				X	
PTCI	X	X	X	X	
CSQ					X
SS content					X
Process Measures					X
PANAS	X	X	X	X	
Actigraphy (1 week)	X	X			
Sleep Diary (1 week)	X	X			
Polysomnogram (on subgroup)	X	X			
ISI	X	X			
PSQI	X	X			
Additional Measures for Initial Screening					
SCID stem questions for mania and psychosis					

6.G. Quality Control

6.G.1. Data Safety Monitoring (DSM). DSM will include periodic review and reporting of participant accrual, adverse event rates, treatment compliance, and drop-out rates. Study termination will be triggered by excessive drop-outs or adverse events. Adverse events includes 1) need to break confidentiality, 2) loss of data, 3) inadvertent harm caused by study participation, 4) patient suicidality. If treatment is needed during the follow-up phase due to increased alcohol consumption or serious psychiatric/medical symptoms, patients will be referred to appropriate treatment and followed by the PI and study psychiatrist until treatment is initiated. Adverse events will be reported to UCSD's IRB and the VA R&D (serious adverse events within 48 hours) and clinically managed as appropriate, including hospitalization if necessary. A summary of all adverse events will be submitted to the VA annually. The PI and a co-investigator (both licensed psychologists in the state of California) will be available by pager 24-hours a day. The PI will be responsible for initial determination of serious adverse events from non-serious adverse events.

Tammy Wall, Ph.D. will serve as the Data Monitoring Officer. Her functions include the following: 1) Review of research protocol and plans for data safety and monitoring, 2) Evaluation of the progress of the study every 6 months, including the quality of data collection, security and quality, participant recruitment/retention, participant risk and benefit, and any other factors affecting study outcome, 3) Consultation regarding continuation or termination or other modifications of the trial in the service of protecting safety of study participants, 4) Evaluation of study adverse events and consultation to maximize protection of participants. Progress evaluations every 6 months will be provided to UCSD IRB, VA R&D, and study investigators. The Data Monitoring Officer is not an investigator in the study and does not have any conflict of interest.

6.G.2. Data entry and management. Data will be collected on paper forms and checked for missing items at the time of collection. Patients will be queried immediately to complete or clarify blank or illegible responses. Refusal or inability to respond to items will be coded, with explanations documented. Data will be entered into Access databases using a double-entry system. This system incorporates checks for out of range values and requires all data to be entered twice, with discrepancies corrected at time of entry. Data will be stored in locked file cabinets.

Only approved study personnel will have access to study data, and all study personnel have been trained regarding privacy and security issues. In the event of a real or suspected breach of security, the VA Police, the VA Information Security Officer, and the VA Privacy Officer will be notified.

Secure information will be accessed, stored, and destroyed according to a data security plan that will promote security and privacy, including, but not limited to the following:

1. Hardcopy study data will be stored in the investigator's locked laboratory space in locked cabinets. Only approved study personnel, University of California, San Diego Institutional Review Board (IRB), and VA Research and Development will have access to this information. Hard copies will be retained for the amount of time specified by the VA (currently, permanently). Informed consent forms are kept in a locked office in a locked cabinet. The binder with these consent forms is in a separate cabinet from the de-identified case report forms. In addition, the code assigned to a specific participant exists only on two hardcopy documents that are stored separately from consent forms and case report forms.

2. All electronic study data is de-identified and stored electronically on VA research computer unless specifically designated otherwise and approved in advance by the Information Security Officer (ISO) and IRB. The computer is accessed only by approved study personnel, UCSD IRB, and VA R&D.

3. Study records entered into a computer system or on electronic media will be assigned code numbers and will not be individually identifiable. The key that relates the code numbers to the individuals will be kept in a locked cabinet in the research locked office and destroyed when data analyses for this study are completed.

4. All study recruitment, interventions, and assessments are conducted at the VA Medical Center in La Jolla and all study data remains at this site. No data is removed from the VA. All data analyses are conducted in the VA study research offices.

6.H. Statistical Considerations.

6.H.1. Power analysis. Sample size was determined to ensure adequate statistical power to detect between group differences in PTSD and PDA at end of treatment and 8-month follow-up. For both outcomes the effect size was estimated as **d** defined as [**d** = $| m_1 - m_2| / \sigma$] where m_1 and m_2 are change from intake in the outcome scores of the two conditions and σ is the common within-group standard deviation of the change score.[90] The effect size for the between group difference in PTSD CAPS scores from intake to end of treatment was estimated from several studies that have evaluated the effect of PE[36,42] or SS[45] on PTSD. Four studies of PE have demonstrated large within group effect sizes ranging from 1.3[42] to 4.1[91] with an average ES of 2.5. Hien et al.[18] found SS to have a within group effect size of .71 standard deviations. Using the average PE ES as an estimate, the between group effect size for the two treatments is about 1.79. This large effect size would require 6 participants per group to be detected with 80% power and a two-tailed test with alpha at .05. As a result of the large expected effect size for PTSD symptoms, study sample size was based on the second primary outcome of alcohol PDA at follow-up. This effect size is difficult to determine because exposure therapies have not been previously applied to individuals with AD and measured at follow-up time points, particularly after addressing PTSD symptoms. A recent study conducted by our group compared the effects ICBT to TSF on PDA and depression in a randomized trial of 178 Veterans.[3,8] By 12 months after treatment, participants without PTSD in the ICBT group maintained higher levels of abstinence at 18 months (adjusted M = 91% days abstinent) relative to participants without PTSD in the TSF group (adjusted M = 76%) and participants with PTSD in both groups (ICBT adjusted M = 77%; TSF adjusted M = 75%). Using a pooled standard deviation of σ = 26%, the estimated effect size d = (.91-.76)/.26 = .58. This effect size requires 48 participants per group to be detected with 80% power and a two-tailed test with alpha at .05. We increased the total sample size to N = 148 in anticipation of 35% study drop-out by the 8 month assessment. Overall, we

believe this sample size balances three needs: (1) sufficient power to compare the study groups; (2) the reality of recruiting a sample with dual AD and PTSD; and (3) project cost considerations.

6.H.2. Statistical Analyses. In the initial 3-6 months, data management procedures will be developed and put into practice. Data will be entered as it is collected and quality assurance checks conducted on an on-going basis (e.g., double entry and cross validation). Preliminary analysis with initial baseline data will examine data characteristics (outliers, distribution properties) and group characteristics to evaluate the success of group randomization and the potential utility of covariates (e.g. gender) or the need for more structured randomization procedures. Randomization will be stratified by gender. Analyses will be conducted on an on-going basis to assure strict adherence to important issues for clinical trials, such as treatment fidelity, therapeutic alliance, and therapist effects.

Preliminary analyses will include descriptive statistics of the study population, and assessment of randomization. Outliers will be assessed. Variables whose distributions depart significantly from normality will be transformed. Reliability of multiple item scales will be examined.

6.H.3. Primary Outcome Analyses. The first primary aim is to evaluate if I-PE demonstrated greater reduction in PTSD symptoms than SS at post treatment. The statistical model will be a random intercept regression model with treatment condition (I-PE, SS) and a linear term for time (0, 2 months). The primary test of the treatment conditions will be treatment x time interaction effect. We will also test the extent to which gender moderates treatment effect. The model can be expanded to determine an adjusted intervention effect by including additional covariates, (e.g., age, ethnicity). This model provides maximum likelihood (ML) parameter estimates; allowing modeling of the covariance error structure data across assessment points.[92]

The second primary aim is to evaluate if I-PE will result in greater percent days abstinent (PDA) from substance use at 5 and 8-month follow-up. The statistical model will be a random intercept regression model with treatment condition (I-PE, SS) and a linear term for time (0, 2, 5, 8 months). The primary test of the treatment conditions will be the treatment x time interaction effect. A quadratic effect of time will also be tested to model potential decaying treatment effects. We will test the moderating effect of gender on the treatment effect by testing a treatment x time x gender interaction term in the model. Additional covariates can also be added to the model to determine an adjusted intervention effect.

The primary outcomes will be tested using an intent-to-treat framework. If, the extent of missing data is small and the data appear to be consistent with a missing-at-random model (MAR), then the maximum-likelihood analysis using all randomized cases and the observed data is an appropriate method for handling the missing data. In the MAR model the missingness can be a function of the observed covariates and observed outcomes. The MAR assumption is plausible in treatment situations, even in studies such as substance abuse in adolescents.[93] The critical element when conducting MAR-based analyses is to include variables related to the missingness in the statistical model.[93] Potential variables we will measure that may be related to study drop out are group assignment, social and familial support, employment status, and income. As a check on the sensitivity of our conclusions to the assumption that the missing data are MAR we will conduct pattern-mixture modeling, which is appropriate with data that is likely MAR.[94] The distinction between ignorable (MAR) and non-ignorable missingness (missing not at random; MNAR) is generally not empirically testable and we acknowledge the possibility that data may be missing not at random. Therefore, we propose to perform MNAR sensitivity analyses using pattern mixture models. With 3 follow-up assessment points there are 9 potential missing data patterns that can emerge. Some patterns will likely have small numbers of cases precluding parameter estimation for these patterns separately. In this case we will apply the Hedeker and Gibbons (1997) approach that combines missing data patterns to estimates model parameters that are conditional on the missingness using a binary variable in the model to denote missing data at one or more time points.

5.H.4 Secondary Analyses. We will assess the impact of the intervention on PTSD symptoms at 5- and 8-month follow-up and the impact of the interventions on depression and quality of life at post-treatment, 5- and 8-month follow-up. The same random intercept regression model will be specified with data from 0, 2, 5, and 8 month assessments. A significant treatment x time interaction will indicate a differential slope effect between the groups over time. The quadratic effect of time will be tested to model potential decaying treatment effects.

We will compare participants' satisfaction between the two conditions. ANOVA models with satisfaction (post intervention) and attendance as dependent variables and treatment condition as the independent variable will be specified. The models can be expanded to determine an adjusted intervention difference by including additional covariates such as gender. A chi-square test will compare attrition rates between groups.

6.H.5 Exploratory Analyses. We will evaluate the extent to which psychosocial, intervention process factors, and sleep problems are related to treatment outcomes. We hypothesize that the I-PE intervention will result in greater reductions in negative post-traumatic cognitions, compared to the SS intervention; while the SS intervention will result in greater use of positive coping skills. We will also test effects of process measures such as number of therapy sessions completed, negative affect, and sleep disruption on treatment outcomes. The statistical model for the mediation tests will be a path analysis with regression paths from treatment condition to change in the mediator (α) and from change in the mediator to change in the outcome (β), along with the direct path from intervention to change in the outcome (τ). The statistical significance of the mediation effect ($\alpha\beta$) will be tested by dividing it by its standard error with critical values for the distribution of the product of the coefficients determined by PRODCLIN.[95] Standard regression models will be used when examining predictors that are not expected to have differential changes by treatment condition.

6.I. Strengths of this Proposal

Veterans with AD and PTSD are a highly prevalent population who are also highly distressed and clinically complex and challenging. Our team of investigators has both the clinical and research experience to further our knowledge of evidence based psychotherapy treatment for this population.

There are studies in progress through VA and NIH integrating CBT and exposure principles for the treatment of PTSD and alcohol or substance use disorder, but as of yet, outcomes are not available. The present study is unique in comparing the best practice therapy to the best disseminated therapy, and therefore, can directly address the question of what can and should be offered to individuals with PTSD and AD. In addition, this study is unique in that we integrate ICBT with PE. ICBT is not only a research-supported treatment for AD, but has a specific focus on negative affect which is highly prevalent among Veterans with comorbid PTSD and AD. PE is a best practice treatment for PTSD that is rarely offered to individuals with AD and PTSD. The strong data behind each treatment and the theoretical reasoning for combining these two treatments to reduce AD/PTSD suggests evaluating this integrated treatment is important.

Our VA recently received a grant for sleep equipment including polysomnography equipment (the PI, Sean Drummond, is a co-investigator on this proposal). Thus, we will be able to examine how sleep problems, which are highly prevalent among the AD/PTSD population, affect treatment outcomes, at very low cost to this proposal. This will give us important and novel data to help understand mechanisms of change in the treatments in the proposed trial. It will also give us an opportunity to collect pilot data to support future trials focused more primarily on sleep intervention.

As with other studies, the current project will generate data not related to the main aims, yet sufficient for testing secondary hypotheses and/or generating hypotheses for future studies. For example, we will be able to run moderator analyses to understand the role of mild cognitive impairment and gender on response to the treatments.

1. Foa EB, Hembree EA, Rothbaum BO. *Prolonged exposure therapy for PTSD: Emotional processing of traumatic experiences: Therapist guide*: Oxford University Press, USA; 2007.

2. Brown SA MJ, Granholm E, Laumakis MA, Tate S. Group Therapy Manual for Integrated Cognitive-Behavioral Treatment of Depression and Substance Dependence. *VA San Diego Healthcare System.* 2000.

3. Lydecker KP, Tate SR, Cummins KM, McQuaid J, Granholm E, Brown SA. Clinical outcomes of an integrated treatment for depression and substance use disorders. *Psychology of Addictive Behaviors.* 2010;24(3):453.

4. Najavits LM. *Seeking safety: A treatment manual for PTSD and substance abuse*: Guilford Press; 2002.

5. Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of twelve-month DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R). *Archives of General Psychiatry.* 2005;62(6):617.

6. Brown PJ, Recupero PR, Stout R. PTSD Substance abuse comorbidity and treatment utilization* 1. *Addictive Behaviors.* 1995;20(2):251-254.

7. Brown PJ, Stout RL, Mueller T. Posttraumatic stress disorder and substance abuse relapse among women: A pilot study. *Psychology of Addictive Behaviors.* 1996;10(2):124.

8. Wilkins KC NS, Tate SR, Cummins K, Brown SA. The Role of Ptsd in Depression and Substance Dependence Treatment Outcomes. *Research Society on Alcoholism.* Vol 33(6):195A. San Diego, CA2009.

9. Dansky BS, Brady KT, Saladin ME. Untreated Symptoms of PTSD Among Cocaine-Dependent Individuals:: Changes Over Time. *Journal of Substance Abuse Treatment.* 1998;15(6):499-504.

10. Ouimette P, Moos RH, Finney JW. PTSD treatment and 5-year remission among patients with substance use and posttraumatic stress disorders. *Journal of consulting and clinical psychology.* 2003;71(2):410.

11. Foa EB, Dancu CV, Hembree EA, Jaycox LH, Meadows EA, Street GP. A comparison of exposure therapy, stress inoculation training, and their combination for reducing posttraumatic stress disorder in female assault victims. *Journal of consulting and clinical psychology.* 1999;67(2):194.

12. Medicine Io. Treatment of posttraumatic stress disorder: An assessment of the evidence. In: Sciences NAo, ed. Washington, DC2007.

13. Becker CB, Zayfert C, Anderson E. A survey of psychologists' attitudes towards and utilization of exposure therapy for PTSD. *Behaviour Research and Therapy.* 2004;42(3):277-292.

14. Brady KT, Dansky BS, Back SE, Foa EB, Carroll KM. Exposure therapy in the treatment of PTSD among cocaine-dependent individuals:: Preliminary findings. *Journal of Substance Abuse Treatment.* 2001;21(1):47-54.

15. Coffey SF DB, Brady KT. Exposure-based, trauma-focused therapy for co-morbid posttraumatic stress disorder-substance use disorder. In: Ouimette P BJ, ed. *Trauma and substance abuse: Causes, consequences, and treatment of co-morbid disorders.* Washington, DC: American Psychological Association; 2003:127-146.

16. Riggs DS, Foa EB. Treatment for co-morbid posttraumatic stress disorder and substance use disorders. *Anxiety and Substance Use Disorders.* 2008:119-137.

17. Triffleman E, Carroll K, Kellogg S. Substance Dependence Posttraumatic Stress Disorder Therapy* 1:: An Integrated Cognitive-Behavioral Approach. *Journal of Substance Abuse Treatment.* 1999;17(1-2):3-14.

18. Hien DA, Cohen LR, Miele GM, Litt LC, Capstick C. Promising treatments for women with comorbid PTSD and substance use disorders. *American Journal of Psychiatry.* 2004;161(8):1426.

19. Hien DA, Wells EA, Jiang H, et al. Multisite randomized trial of behavioral interventions for women with co-occurring PTSD and substance use disorders. *Journal of consulting and clinical psychology.* 2009;77(4):607.

20. Affairs Vs. VHA Office of Public Health and Environmental Hazards. 2011; http://www.publichealth.va.gov/.

21. Seal KH, Bertenthal D, Miner CR, Sen S, Marmar C. Bringing the war back home: Mental health disorders among 103 788 US Veterans returning from Iraq and Afghanistan seen at Department of Veterans Affairs Facilities. *Archives of Internal Medicine.* 2007;167(5):476.

22. Dohrenwend BP, Turner JB, Turse NA, Adams BG, Koenen KC, Marshall R. The psychological risks of Vietnam for US Veterans: a revisit with new data and methods. *Science.* 2006;313(5789):979.

23. Milliken CS, Auchterlonie JL, Hoge CW. Longitudinal assessment of mental health problems among active and reserve component soldiers returning from the Iraq war. *JAMA: the journal of the American Medical Association.* 2007;298(18):2141.

24. Petrakis IL, Gonzalez G, Rosenheck R, Krystal JH. Comorbidity of alcoholism and psychiatric disorders: an overview. *Alcohol Research and Health.* 2002;26(2):81-89.

25. Thomas JL, Wilk JE, Riviere LA, McGurk D, Castro CA, Hoge CW. Prevalence of mental health problems and functional impairment among active component and National Guard soldiers 3 and 12 months following combat in Iraq. *Archives of general psychiatry.* 2010;67(6):614.

26. Jacobsen LK, Southwick SM, Kosten TR. Substance use disorders in patients with posttraumatic stress disorder: A review of the literature. *American Journal of Psychiatry.* 2001;158(8):1184.

27. Seal KH, Cohen G, Waldrop A, Cohen BE, Maguen S, Ren L. Substance use disorders in Iraq and Afghanistan Veterans in VA healthcare, 2001-2010: Implications for screening, diagnosis and treatment. *Drug and alcohol dependence.* 2011.

28. Riggs DS, Rukstalis M, Volpicelli JR, Kalmanson D, Foa EB. Demographic and social adjustment characteristics of patients with comorbid posttraumatic stress disorder and alcohol dependence: Potential pitfalls to PTSD treatment. *Addictive Behaviors.* 2003;28(9):1717-1730.

29. Driessen M, Schulte S, Luedecke C, et al. Trauma and PTSD in Patients With Alcohol, Drug, or Dual Dependence: A Multi Center Study. *Alcoholism: Clinical and Experimental Research.* 2008;32(3):481-488.

30. Tate SR, Norman SB, McQuaid JR, Brown SA. Health problems of substance-dependent Veterans with and those without trauma history. *Journal of Substance Abuse Treatment.* 2007;33(1):25-32.

31. Najavits LM, Norman SB, Kivlahan D, Kosten TR. Improving PTSD/substance abuse treatment in the VA: A survey of providers. *The American Journal on Addictions.* 2010;19(3):257-263.

32. Ouimette PC, Brown PJ, Najavits LM. Course and treatment of patients with both substance use and posttraumatic stress disorders. *Addictive Behaviors.* 1998;23(6):785-795.

33. VM. F, ed *Survivors of child sexual abuse: Treatment using a contextual analysis.* Reno, NV: Context Press; 1994. Hayes SC JN, Follette VM, Dougher MJ, ed. Acceptance and change: Content and context in psychotherapy.

34. Norman SB, Inaba RK, Smith TL, Brown SA. Development of the PTSD-alcohol expectancy questionnaire. *Addictive Behaviors.* 2008;33(6):841-847.

35. Norman SB WK, Baeressen K. *Drinking among female victims of intimate partner violence: Mechanisms and intervention.* Hauppauge, NY: Nova Science Publishers; 2010.

36. Foa EB, Riggs DS. Posttraumatic stress disorder following assault: Theoretical considerations and empirical findings. *Current directions in psychological science.* 1995;4(2):61-65.

37. McLeod DS, Koenen KC, Meyer JM, et al. Genetic and environmental influences on the relationship among combat exposure, posttraumatic stress disorder symptoms, and alcohol use. *Journal of traumatic stress.* 2001;14(2):259-275.

38. Coffey SF, Stasiewicz PR, Hughes PM, Brimo ML. Trauma-focused imaginal exposure for individuals with comorbid posttraumatic stress disorder and alcohol dependence: Revealing mechanisms of alcohol craving in a cue reactivity paradigm. *Psychology of Addictive Behaviors.* 2006;20(4):425.

39. Foa EB, Rauch SAM. Cognitive Changes During Prolonged Exposure Versus Prolonged Exposure Plus Cognitive Restructuring in Female Assault Survivors With Posttraumatic Stress Disorder. *Journal of consulting and clinical psychology.* 2004;72(5):879.

40. Grayson CE, Nolen Hoeksema S. Motives to drink as mediators between childhood sexual assault and alcohol problems in adult women. *Journal of traumatic stress.* 2005;18(2):137-145.

41. Ballenger JC, Davidson JRT, Lecrubier Y, et al. Consensus statement update on posttraumatic stress disorder from the international consensus group on depression and anxiety. *Journal of Clinical Psychiatry.* 2004;65:55-62.

42. Foa EB, Hembree EA, Cahill SP, et al. Randomized trial of prolonged exposure for posttraumatic stress disorder with and without cognitive restructuring: Outcome at academic and community clinics. *Journal of consulting and clinical psychology.* 2005;73(5):953.

43. Schnurr PP, Friedman MJ, Engel CC, et al. Cognitive behavioral therapy for posttraumatic stress disorder in women. *JAMA: the journal of the American Medical Association.* 2007;297(8):820.

44. Back SE, Brady KT, Sonne SC, Verduin ML. Symptom improvement in co-occurring PTSD and alcohol dependence. *The Journal of nervous and mental disease.* 2006;194(9):690.

45. Hien DA, Jiang H, Campbell ANC, et al. Do treatment improvements in PTSD severity affect substance use outcomes? A secondary analysis from a randomized clinical trial in NIDA's Clinical Trials Network. *American Journal of Psychiatry.* 2010;167(1):95.

46. Back SE, Brady KT, Jaanimagi U, Jackson JL. Cocaine dependence and PTSD: A pilot study of symptom interplay and treatment preferences. *Addictive Behaviors.* 2006;31(2):351-354.

47. Brady KT, Sonne S, Anton RF, Randall CL, Back SE, Simpson K. Sertraline in the Treatment of Co occurring Alcohol Dependence and Posttraumatic Stress Disorder. *Alcoholism: Clinical and Experimental Research.* 2005;29(3):395-401.

48. Norman S, Myers U, Wilkins K, et al. Review of biological mechanisms and pharmacological treatments of comorbid PTSD and substance use disorder. *Neuropharmacology.* 2011.

49. Norman SB, Wilkins KC, Tapert SF, Lang AJ, Najavits LM. A pilot study of seeking safety therapy with OEF/OIF Veterans. *Journal of psychoactive drugs.* 2010;42(1):83.

50. Watson D, Clark L. The Panas-X. *Manual for the Positive and Negative Affect Schedule–Expanded Form. University of Iowa. Retrieved June.* 1994;5:2003.

51. Brower KJ. Insomnia, alcoholism and relapse. *Sleep Medicine Reviews.* 2003;7(6):523-539.

52. Roth T. Does Effective Management of Sleep Disorders Reduce Substance Dependence? *Drugs.* 2009;69(S2):65-75.

53. Drummond S, Gillin JC, Smith TL, DeModena A. The sleep of abstinent pure primary alcoholic patients: natural course and relationship to relapse. *Alcoholism: Clinical and Experimental Research.* 1998;22(8):1796-1802.

54. Brower KJ, Perron BE. Sleep disturbance as a universal risk factor for relapse in addictions to psychoactive substances. *Medical hypotheses.* 2010;74(5):928-933.

55. Waldrop AE, Back SE, Sensenig A, Brady KT. Sleep disturbances associated with posttraumatic stress disorder and alcohol dependence. *Addictive Behaviors.* 2008;33(2):328-335.

56. Belleville G, Guay S, Marchand A. Impact of sleep disturbances on PTSD symptoms and perceived health. *The Journal of nervous and mental disease.* 2009;197(2):126.

57. Germain A, Buysse DJ, Nofzinger E. Sleep-specific mechanisms underlying posttraumatic stress disorder: Integrative review and neurobiological hypotheses. *Sleep Medicine Reviews.* 2008;12(3):185-195.

58. Spoormaker VI, Montgomery P. Disturbed sleep in post-traumatic stress disorder: Secondary symptom or core feature? *Sleep Medicine Reviews.* 2008;12(3):169-184.

59. Hussaini SA, Bogusch L, Landgraf T, Menzel R. Sleep deprivation affects extinction but not acquisition memory in honeybees. *Learning & memory.* 2009;16(11):698.

60. Kadden R. *Cognitive-Behavioral Coping Skills Therapy Manual: A Clinical Reserach Guide for Therapists Treating Individuals with Alcohol and Dependence*: DIANE Publishing Company; 1994.

61. Munoz RF MJ. *Group therapy manual for cognitive-behavioral treatment of depression*. Santa Monica, CA: RAND; 1996.

62. Norman SB, Tate SR, Wilkins KC, Cummins K, Brown SA. Posttraumatic stress disorder's role in integrated substance dependence and depression treatment outcomes. *Journal of Substance Abuse Treatment.* 2010;38(4):346-355.

63. Norman SB, Tate SR, Anderson KG, Brown SA. Do trauma history and PTSD symptoms influence addiction relapse context? *Drug and alcohol dependence.* 2007;90(1):89-96.

64. Weathers F, Litz B, Huska J, Keane T. PTSD checklist—military version. Boston: National Center for PTSD. *Behavioral Science Division.* 1994.

65. Sieber W, Groessl E, David K, Ganiats TG, Kaplan RM. Quality of well-being selfadministered (QWB-SA) Scale. *User's manual. Health outcomes assessment program. San Diego: University of California.* 2004.

66. Moher D, Schulz K, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. *BMC Medical Research Methodology.* 2001;1(1):2.

67. American Psychiatric Association. *Diagnostic criteria from DSM-IV-TR*. Washington, D.C.: American Psychiatric Association; 2000.

68. Morgenstern J, Bates ME. Effects of executive function impairment on change processes and substance use outcomes in 12-step treatment. *Journal of studies on alcohol.* 1999;60:846-855.

69. First M, Spitzer R, Gibbon M, Williams J. Structured Clinical Interview for DSM-IV Axis I Disorders: Patient Edition (SCIDI/P. Version 2.0. *Biometric Research, New York State Psychiatric Institute, New York.* 1995.

70. Najavits LM. An evidence-based model for substance abuse and trauma/PTSD. In: Witkiewitz KA MG, ed. *Therapists' Guide to Evidence-Based Relapse Prevention: Practical Resources for the Mental Health Professional*. San Diego, CA: Elsevier Press; 2007:141-167.

71. Sobell LC, Sobell MB. Timeline follow-back: A technique for assessing self-reported alcohol consumption. 1992.

72. Cahalan D CI. American drinking practices: summary of findings from a national probability sample. II. Measurement of massed versus spaced drinking. *Q J Stud Alcohol.* 1968;29(3):642-656.

73. Weiss RD HC, Najavits LM, Shaw SR. Weekly Substance Use Inventory. Boston, MA1995.

74. Marlatt GA GJ. *Relapse situations*. New York, NY: Guilford Press; 1985.

75. Wills TA, Shiffman S. Coping and substance use: A conceptual framework. *Coping and substance use.* 1985:3-24.

76. Blake D, Weathers F, Nagy L, et al. Clinician-administered PTSD scale (CAPS). Boston, MA: National Center for Post-Traumatic Stress Disorder. *Behavioral Science Division.* 1990.

77. Blake DD, Weathers FW, Nagy LM, et al. The development of a clinician-administered PTSD scale. *Journal of traumatic stress.* 1995;8(1):75-90.

78. Hovens J, Ploeg HM, Bramsen I, Klaarenbeek M, Schreuder J, Rivero V. The development of the Self Rating Inventory for Posttraumatic Stress Disorder. *Acta Psychiatrica Scandinavica.* 1994;90(3):172-183.

79. Weathers FW, Keane TM, Davidson JRT. Clinician administered PTSD scale: A review of the first ten years of research. *Depression and Anxiety.* 2001;13(3):132-156.

80. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Archives of general psychiatry.* 1961;4(6):561.

81. McHorney CA, Ware Jr JE, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Medical care.* 1993:247-263.

82. Ware Jr JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. *Medical care.* 1992:473-483.

83. Foa EB, Ehlers A, Clark DM, Tolin DF, Orsillo SM. The Posttraumatic Cognitions Inventory (PTCI): Development and validation. *Psychological Assessment.* 1999;11(3):303.

84. Vitaliano PP. The Ways of Coping Checklist: Revision and psychometric properties. *Multivariate Behavioral Research.* 1985.

85. Larsen DL, Attkisson CC, Hargreaves WA, Nguyen TD. Assessment of client/patient satisfaction: development of a general scale. *Evaluation and program planning.* 1979;2(3):197-207.

86. Kushida CA, Chang A, Gadkary C, Guilleminault C, Carrillo O, Dement WC. Comparison of actigraphic, polysomnographic, and subjective assessment of sleep parameters in sleep-disordered patients. *Sleep Medicine.* 2001;2(5):389-396.

87. Morin CM, Barlow DH, Dement WC. *Insomnia: Psychological assessment and management*: Guilford Press Nueva York; 1993.

88. Buysse DJ, Reynolds III CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry research.* 1989;28(2):193-213.

89. Reynolds NR, Sun J, Nagaraja HN, Gifford AL, Wu AW, Chesney MA. Optimizing measurement of self-reported adherence with the ACTG Adherence Questionnaire: a cross-protocol analysis. *JAIDS Journal of Acquired Immune Deficiency Syndromes.* 2007;46(4):402.

90. Cohen J. *Statistical power analysis for the behavioral sciences*: Lawrence Erlbaum; 1988.

91. Rothbaum BO, Astin MC, Marsteller F. Prolonged exposure versus eye movement desensitization and reprocessing (EMDR) for PTSD rape victims. *Journal of traumatic stress.* 2005;18(6):607-616.

92. Singer JD, Willett JB. *Applied longitudinal data analysis: Modeling change and event occurrence*: Oxford University Press, USA; 2003.

93. Graham JW, Hofer SM, Donaldson SI, MacKinnon DP, Schafer JL. Analysis with missing data in prevention research. *The science of prevention: Methodological advances from alcohol and substance abuse research.* 1997:325–366.

94. Hedeker D, Gibbons RD. Application of random-effects pattern-mixture models for missing data in longitudinal studies. *Psychological Methods.* 1997;2(1):64.

95. MacKinnon DP, Fairchild AJ, Fritz MS. Mediation analysis. *Annual review of psychology.* 2007;58:593.