DEPARTMENT OF VETERANS AFFAIRS

CBT for PTSD in Veterans with Co-occurring Substance Use Disorders

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I. SPECIFIC AIMS

Approximately 30-40% of patients with substance use disorders (SUDs) meet criteria for current posttraumatic stress disorder (PTSD).[1, 2] In 2006 there were 46,429 SUD patients in VA with a chart diagnosis of comorbid PTSD.[3] Both PTSD and SUDs are associated with poorer physical health[3, 4] and functioning[5, 6] and the comorbid condition confers even greater risk. Co-occurring PTSD and SUDs add to greater problem severity in psychiatric, medical, social, and employment functioning.[7-9] These patients respond less favorably to standard treatment, incur higher costs, are more likely to relapse, use more treatment services, are more likely to drop out of treatment, and less likley to remain in continuing care.[10, 11] Further, although outcomes in substance use vary, psychiatric symptoms, health, and psychosocial functioning are consistently worse.[10, 12-15]

This proposal responds directly to CSR&D's RFA CX-09-006 to integrate treatment for PTSD with treatment for SUD. The VHA Handbook 1160.01 on Uniform Mental Health Services Handbook requires that when PTSD or other mental health conditions co-occur with SUDs, evidence-based psychosocial interventions for the other conditions need to be made available, and with appropriate coordination of care. Yet few treatments have been developed for patients with co-occurring PTSD and SUD. Additionally, these therapies were neither designed to be integrated within existing addiction treatment programs, nor delivered by typical addiction therapists. Only one therapy, Seeking Safety, has been tested within a randomized controlled trial but has yet to demonstrate efficacy over a manual-guided relapse prevention treatment[16] or women's health education.[17] Thus, there is a clear need for more effective interventions for PTSD in people with co-occurring PTSD and SUD that can be implemented in routine addiction settings.

The development of a model of integrated treatment for Veterans with PTSD and substance use disorders would represent a significant advance in the healthcare being provided to Veterans. Historically addiction treatment programs have not addressed PTSD out of concern that targeting the PTSD would exacerbate re-experiencing symptoms and jeopardize early and unstable periods of abstinence.[18, 19] The opposite argument has also been proposed. Evidence in support of the self-medication theory indicates that people use substances as a means to control their re-experiencing symptoms.[20, 21] Therefore ignoring the PTSD may lead to increased relapse and poorer outcome. Integrating PTSD treatment into an addiction setting could result in improved PTSD and substance use outcomes as well as improved physical health and functioning.[13]

We propose to conduct a randomized clinical trial to evaluate the effectiveness of a relatively simple, manual-guided cognitive behavioral therapy (CBT) for PTSD in patients with SUD. One hundred sixty outpatients with comborbid PTSD and SUD will be randomly assigned to receive either: CBT for PTSD in conjunction with standard treatment as usual (TAU) (n = 80) or TAU only (n = 80) without additional individual treatment.

Our hypotheses are as follows:

Primary Hypothesis

1. Patients who receive CBT will have greater improvements in PTSD symptom severity relative to patients who receive TAU only at both the conclusion of treatment and at the 6-month follow-up.

Secondary Hypotheses

2. Patients who receive CBT will have greater reductions in substance use severity (drugs and/or alcohol) than patients who receive TAU only at both the conclusion of treatment and at the 6-month follow-up.
3. Patients in the CBT condition will have better retention in the addiction treatment program relative to patients who receive TAU only.

Typically patients with co-morbid PTSD/SUD are required to have their SUD "under control" before they are referred for PTSD treatment. This puts these patients in a symptomatic "Catch-22:" If they stop using substances PTSD symptoms worsen, if they only try to address PTSD without clinical attention to their substance use disorder, their substance use worsens.

In summary, this study proposes a simple objective: To evaluate the effectiveness of CBT for PTSD in Veterans with co-occurring substance use and posttraumatic stress disorders. Our overarching goal is to increase the number of Veteran SUD patients who receive treatment for their co-morbid PTSD, and consequently improve their treatment and life outcomes.

II. BACKGROUND and SIGNIFICANCE

A. Background

1. Prevalence and consequences of PTSD in addiction treatment

PTSD is common among patients in addiction treatment. Approximately 30-40% [1, 10, 12, 22-24] of SUD patients meet criteria for current PTSD. The Program Evaluation and Resource Center (PERC) reported that in 2006, 34.7% of all VA SUD patients had a chart diagnosis of PTSD.[25] This number likely represents a conservative estimate of the actual number with comorbid PTSD and SUD as PTSD is often undetected in addiction settings.[26]

PTSD is associated with greater problem severity among patients presenting to addiction treatment, including: more severe problems with drugs and alcohol;[7, 11, 27] additional Axis I disorders;[7, 28] more employment problems;[7] more legal problems;[29] more psychiatric distress, including suicidality;[28] medical problems, including more chronic cardiovascular and neurological problems,[13, 28] and more physical pain and poorer health.[13, 28]

Relative to patients without PTSD, SUD patients have less favorable substance abuse outcomes. These patients have greater alcohol consumption and lower remission rates, more substance related problems, worse psychological symptoms, and worse psychosocial outcomes including higher arrest rates and unemployment and fewer friend resources than SUD patients without PTSD.[29] Few studies report on the effect of PTSD on treatment outcome for substance use. One found poorer adherence and greater substance use following treatment in the PTSD patients.[14] Another study conducted in Australia found similar treatment adherence but poorer treatment outcomes in terms of occupational functioning, overdose, and physical and mental health.[12]

2. *Models of the relationship between substance use and PTSD*

Two models have been proposed to account for the association between PTSD and SUD.[30] In one case the PTSD is primary and patients drink to cope with PTSD symptoms. In the other SUD is primary and patients' substance use places them in risky environments where they are more likley to be traumatized. Data support the first model,[20, 21] sometimes called the self-medication theory, where patients use substances to manage their PTSD symptoms. Then withdrawal symtoms may trigger and exacerbate PTSD symtoms initiating a cycle that precipitates poorer addiction outcomes.

In either model, it is clear that treating PTSD in patients undergoing treatment for substance use disorders is important given that greater problem severity and poorer outcomes are associated with PTSD in this population. The preponderance of evidence suggests that not addressing PTSD in addiction treatment risks negative outcomes for both substance use and PTSD. These findings stimulated development of interventions designed to improve these outcomes

3. Treatments for co-occurring PTSD and substance use disorder

Several clinical practice guidelines offer recommendations for the treatment of PTSD.[31, 32] The Institute of Medicine (IOM) also recently published a report evaluating the evidence on PTSD treatment.[33] The guidelines unanimously recommend cognitive behavioral therapies as the most effective treatment for PTSD and selective serotonin reuptake inhibitors (SSRIs) (e.g. sertraline, paroxetine) as the frontline medication. Comparative studies and reviews of medications vs. psychosocial treatments favor the psychosocial treatments in terms of clinical change (effect size) and durability of effects (positive response after discontinuation of treatment).[33]

a. Pharmacological treatments. Few treatments exist for the comorbid condition, particularly in the area of pharmacotherapy. In the rare study specific to comorbid PTSD and SUD, sertraline had modest effects on alcohol use and PTSD symptoms but only in non-severe cases.[34, 35] In a reanalysis of data from an addiction medication study, Petrakis et al [36, 37] reported reductions in alcohol craving and PTSD symptoms with disulfiram and naltrexone. Few conclusions can be drawn from these studies. Meanwhile, the more potent and durable effects of the behavioral therapies have been the focus of development and testing.

b. Cognitive behavioral treatments. There is unambiguous evidence for the efficacy of cognitive behavioral treatments for PTSD. VA is rolling out two cognitive behavioral treatments for PTSD as part of the Uniform Mental Health Services Handbook: Cognitive Processing Therapy and Prolonged Exposure. However, the vast majority of studies on cognitive behavioral treatments excluded patients with substance abuse[38] and none that

we are aware of included patients with substance dependence. While these treatments may prove to be effective with patients with co-occurring substance use disorders, there is no evidence available to date.

Four distinctive efforts have emerged to extend and modify existing psychosocial PTSD treatments for patients with co-occurring PTSD and substance use disorders. These interventions either are exposure-based (focused on past trauma), cognitive and coping skills based (focused on current adjustment), or a combination of both.

Exposure therapies. Exposure therapies typically involve in vivo or imaginal exposure to the traumatic or feared event. But the stress associated with direct exposure to feared memories and situations has been identified as a barrier to patients seeking or completing exposure-based approaches. Exposure treatments, although effective, may be intolerable to many patients and clinicians, and consequently may result in high attrition rates and low adoption by community treatment providers.[39, 40] There have been two specific exposure-based behavioral therapies studied among persons with co-occurring PTSD and substance use disorders: Substance Dependence PTSD Treatment (SDPT)[41] and Concurrent Treatment of PTSD and Cocaine Dependence (CTPCD).[42, 43] SDPT has been minimally researched; there is a single unpublished, uncontrolled trial on 19 patients. CTPCD was studied in an uncontrolled trial of 39 patients. Although improvement was significant for PTSD symptoms at the end of treatment, drop out was extremely high (62%) and results were marginal at 6 month follow up. No research has been conducted on CTPCD since 2000, but plans are underway for resuming its study.[44]

Seeking Safety and other non-exposure based therapies. There are two, non-exposure based therapies that are specific to co-occurring PTSD and substance use disorders, Transcend[45] and Seeking Safety (SS).[9, 46] In an open trial of Transcend with 46 patients, PTSD symptoms, and days of alcohol and drug use, decreased in treatment completers. However, this program is no longer being actively researched.

To date, SS has generated the most interest perhaps due to the absence of other therapies for comorbid PTSD and SUD and the availability of a treatment manual. It has an active program of research and its use in VA is widespread. Although no data are available on the fidelity to the SS model, PERC reports (personal communication) that in 2006, 41% of programs indicated using SS in their intensive outpatient programs (IOPs). SS is a present-focused therapy that focuses on teaching coping skills that are relevant to both PTSD and SUD. There are 25 topics that address cognitive, behavioral, interpersonal, and case management issues. Several uncontrolled pilot studies looked promising,[e.g.,9, 47] suggesting SS may be effective in reducing substance use and in some cases PTSD symptoms in women. A small, randomized controlled pilot study of 33 adolescent girls, conducted by the developer of SS, also found that SS improved general trauma symptoms (but not PTSD) and substance use compared to TAU.[48]

Findings from larger, more rigorous studies are inconclusive. There have been two studies of SS using pre-post nonequivalent control group designs. Both included women only (one in Veterans and one in non-Veterans) and found statistically significant, but not clinically meaningful, reductions in PTSD symptoms and either no difference or an increase in drug use relative to the comparison groups.[49, 50]

Two large randomized controlled trials of SS both demonstrated significant reductions in PTSD symptoms, but SS was no more effective than either control condition in reducing PTSD symptoms. In the first study,[16] 96 substance dependent women from the community were randomized to either SS or a manualized relapse prevention therapy. A non-randomized community sample of women in addiction treatment (n=75) was also included. The second study,[17] conducted as part of the National Institute on Drug Abuse Clinical Trials Network, randomized 353 women to receive a shortened version of SS (12 sessions) or women's health education. This study also found no discernable differences between SS and the control condition in reducing PTSD symptom severity.

In concluding a review of SS, two randomized controlled trials found clinically and statistically large reductions in PTSD symptoms but no differences versus the comparison conditions. This is unexpected given that neither relapse prevention nor health education includes treatment components shown to be effective in reducing PTSD. Outcomes related to substance use were inconsistent. While both SS and relapse prevention resulted in improved substance outcomes in the first study, there was no effect of SS or women's health education on substance use in the second study.

3. Summary

There are high rates of PTSD in patients with SUD. The comorbid condition results in greater problem severity and poorer addiction treatment outcomes. Effective treatments exist for PTSD, in particular Cognitive Processing Therapy and Prolonged Exposure, but no studies have included patients with co-occurring PTSD and substance dependence and many excluded abuse.

Of the treatments designed for this comorbid population, most were freestanding and not integrated within addiction treatment programs. SS, the most widely used treatment, looked promising in uncontrolled pilot trials, but more recent research indicates that it is no more effective than control conditions in reducing PTSD and has been shown to have inconsistent effects on substance use. Additionally, it was never intended to function as a PTSD specific treatment.

One possible solution is to refer these cases to PTSD treatment teams. However, many clinicians believe that the substance abuse must be treated first out of concern that the intense emotions aroused during PTSD treatment may lead to instability and relapse.[2] So, they may be hesitant to refer. In addition, although there are new PTSD/SUD clinicians assigned to every PTSD clinical team in the VA, they cannot provide the intensive substance abuse care found in addiction settings. Thus a referral to this clinician would not be appropriate for all SUD patients.

An unanswered question is whether a PTSD-specific treatment can be successfully delivered in an addiction setting. We believe by targeting the PTSD directly we can improve PTSD outcomes as well as substance use. A brief, cognitive behavioral treatment that does not incorporate exposure components is ideally suited to the population of patients with PTSD and SUD. A treatment focused on cognitive restructuring will be more likely to be utilized by clinicians who remain fearful of exposure. And, cognitive restructuring is a simple and easy to learn therapeutic skill that has been shown to generalize beyond PTSD to other areas of patients' lives.

B. Significance

Comorbid PTSD and SUD pose a tremendous burden to VA SUD treatment resources and to the VA Health Care System. Approximately 1/3 of patients with SUD have co-morbid PTSD.[2] In 2006, 354,507 VA patients were diagnosed with substance use disorders. Of these, 121,926 (34%) received specialized substance abuse treatment,[51] of which an estimated 40,000 (1/3 of the total) would be expected to have comorbid PTSD. If the PTSD remains untreated, these patients have a high probability for premature attrition and relapse. The burden of non-remitted disease not only includes continued problems with substance use and the demands on the system for continued SUD treatment, but also medical morbidity and higher medical costs associated with prolonged substance use disorders[52] that would likely have been offset by effective treatment.[52, 53]

Addressing PTSD in SUD patients can result in significant improvements. Patients with comorbid PTSD and SUD who receive PTSD-related treatment within a year of SUD treatment are 3.7 times more likely to be in remission from SUD 5 years later.[8] Therefore, the Uniform Mental Health Services Handbook requires that when PTSD or other mental health conditions co-occur with SUDs, evidence-based pharmacotherapy and psychosocial interventions for the other conditions need to be made available, with appropriate coordination of care, where there are no medical contraindications.

The development of a model of integrated treatment for Veterans with PTSD and SUD that could be implemented without major changes to SUD treatment delivery systems would insure that patients identified as comorbid could access effective treatment. CBT for PTSD is such an intervention. This treatment is designed for use in an addiction setting as an addition to usual care. The treatment does not involve exposure, which is believed by some to be so emotionally intense as to risk relapse. Therefore, it is safer to administer to patients who are not yet stably in remission from SUD and it may also increase addiction therapists' comfort in using the therapy. CBT for PTSD also teaches cognitive restructuring as a skill that can be applied to a range of upsetting situations, not just trauma related cognitions. As a result, it is well suited to address the multi-problem presentations of dual disorder patients. Because it does not require patients to be stably abstinent during treatment, it also provides a viable treatment option for those patients whose PTSD prevents them from abstaining.

III. PRELIMINARY STUDIES

Our research team is well suited to carry out the proposed research for several reasons. First, team members have been instrumental in conducting the background research on the impact of PTSD on SUD outcomes and in the development and validation of PTSD assessment measures for use with this population. Second, the team has considerable experience in the design, management, and analysis of clinical trials related to PTSD and substance use. Drs. Schnurr, McGovern, Mueser, and Kimerling have all been funded to conduct randomized controlled trials, most of which were multisite. Dr. Hamblen is currently funded under an NIMH center grant to conduct an RCT of CBT for postdisaster distress. Third, the research team leverages the strength of several large research infrastructures including the National Center for PTSD, the Dartmouth Psychiatric Research Center, and an HSR&D Center for Excellence. Finally, Dr. Hamblen can capitalize on her experiences as Deputy Director for Education at the National Center for PTSD. In that role, she has substantial experience designing and implementing multi-site projects, developing and administering large budgets, forming and working collaboratively with partners.

Below we review studies on the development of our model for treating PTSD and provide data in support of adaptations to the model for special populations. These studies will demonstrate our ability to implement the model under various conditions and our skill in conducting and managing clinical trials.

A. The model: Cognitive behavioral therapy for PTSD

Under the direction of Drs. Mueser and Rosenberg, Dr. Hamblen, along with other Dartmouth investigators, developed a CBT model for PTSD for persons with severe mental illness (SMI).[54] The treatment is flexible in its ability to both address the psychological effects of any traumatic event, and to accommodate to a broad range of individual differences, such as different co-morbid disorders, level of education and intellectual functioning, and ethnic or cultural background. Stress related to treatment is minimized by relying on cognitive restructuring as the main active ingredient. The CBT for PTSD model has been manualized, and for most special populations requires 10-16 weekly sessions to complete. The treatment also includes educational materials and worksheets that are readily accessible to all traumatized individuals. The model has been successfully implemented by a wide variety of clinicians with different backgrounds and in different settings.[55]

The CBT for PTSD model is based on modern theories of posttraumatic reactions that place a premium on the importance of individuals' appraisals of traumatic events, their own reactions and those of others, and the meaning of the experience in terms of oneself and one's place in the world. In addition, the model employs cognitive restructuring to teach individuals how to examine and challenge their trauma-related appraisals and does not include exposure therapy. This approach is based on research showing that cognitive restructuring is just as effective as exposure therapies for posttraumatic disorders[39, 40, 56] and more effective than any alternatives.[39, 57-59] Many clinicians believe exposure is contraindicated for PTSD patients with SUD[60] and may therefore be more likely to utilize a model based on cognitive restructuring. Consequently, a growing research base indicates that the model has high acceptability to both vulnerable individuals from special populations and clinicians, poses low stress, and is clinically effective.[18, 61, 62]

1. Pilot study

An initial pilot study of CBT for PTSD[63] was conducted with 12 SMI patients. Hamblen (PI) treated several of these patients, including one with substance dependence (in addition to PTSD and bipolar disorder).[64] The patient had a history of child physical and emotional abuse by his mother and sexual abuse by a priest. He was later raped while serving in the Navy. Following the rape he began drinking heavily and using intravenous drugs; he was eventually administratively discharged. The patient's longest period of sobriety was 2½ years following an inpatient substance abuse treatment program. He had two other inpatient psychiatric admissions as well. The patient responded will to the CBT for PTSD treatment. He was actively engaged and attended all sessions. At post-treatment and 3-month follow-up he no longer met criteria for PTSD. His score on the Clinician Administered PTSD Scale (CAPS) dropped from 57 at pretreatment to 8 at post treatment and 9 at 3-month follow-up. Although he did not attempt to quit drinking during the treatment his continued use did not prevent him from making significant treatment gains.

2. Randomized controlled trial

We recently completed a randomized controlled trial comparing our treatment model with TAU in 108 SMI

patients who also had PTSD. The participants, much like those from addiction settings, were complex, multi-problem patients with significant comorbidities. Primary diagnoses included schizophrenia or schizoaffective disorder (16%), major depression (61%), or bipolar disorder (23%). Secondary diagnoses included current substance abuse (41%) and borderline personality disorder (25%). Ninety percent of patients had at least one prior psychiatric hospitalization; the median was 4 admissions. In the patients who received CBT for PTSD there were high retention rates (81%) and significantly greater improvements than in the TAU patients in PTSD symptoms, depression, perceived health, and trauma-related thoughts at 3- and 6-month follow-ups.[62]

3. Generalizability of the model

The CBT for PTSD model is highly generalizable. As we describe below in Section III.B, we have successfully modified it for implementation in a range of PTSD populations, including substance users in addiction settings, adolescents, disaster survivors, and primary care patients.[55] There are several reasons why the model is well-suited for use in varying populations. First, because it initially was designed as a treatment for people with SMI (i.e., schizophrenia, mood disorders, and borderline personality disorder), considerable effort was applied to determining how to make an intellectually challenging concept, such as cognitive restructuring, as basic and understandable as possible. For example, the model focuses on only four major feeling states, includes supplemental training on identifying thoughts related to these feelings, and utilizes a basic cognitive restructuring worksheet. This simplified version of PTSD treatment is well suited for populations with considerable problems and comorbidity such as patients with PTSD and SUDs.

Second, the goal of the cognitive restructuring is not necessarily to modify cognitions but rather to teach a skill for evaluating one's thinking when negative emotions are experienced. If a thought is determined to be inaccurate, the individual is taught to replace it with a more accurate one. When thoughts are determined to be accurate, or beliefs are resistant to change, the model allows for brain storming and problem solving to address the situation. This is different from more traditional cognitive therapy models where patients are confronted with the assertion that their thinking is inaccurate and forced to change their thoughts. We believe this approach will be more acceptable to SUD patients who may initially be more resistant to changing their thoughts, especially those around how their substance use may be worsening their PTSD symptoms and putting themselves at risk.

Third, the cognitive restructuring is intended to be applied in any situation in which the person identifies negative affect; thus it can easily be extended to a range of situations that go beyond PTSD. The treatment is especially well suited to patients with comorbid conditions as the cognitive restructuring can be applied to those situations as well. For example, patients with PTSD and SUD may be concerned that they may relapse. The cognitive restructuring can easily be applied to this situation where patients can either develop a more accurate thought or problem solve around strategies to prevent relapse.

B. Adaptations to the model

Investigators from our research team took the lead on developing two primary adaptations, PTSD for disaster survivors and PTSD for people with co-occurring substance use disorders. Both retain the core cognitive restructuring component.

1. CBT for Postdisaster Distress

Under the direction of Dr. Hamblen, CBT for Postdisaster Distress (CBT-PD)[65] was developed for use by Project Liberty, the Statewide Crisis Counseling Program developed in response to the September 11th, 2001 terrorist attack in New York. Several modifications of the manual were necessary to adapt the model to the disaster context. For example, we needed to significantly expand the psychoeducation module to include information about common disaster related reactions in addition to PTSD. We also added a behavioral activation component (i.e., pleasant activities scheduling) to target the high rates of depression. The model was also shortened from 16 to 8-12 sessions.

The New York State Office of Mental Health conducted an evaluation of CBT-PD as part of the overall program evaluation of Project Liberty.[66] Crisis counseling participants who scored above a specified cut-point on a screening tool were offered a referral to either CBT-PD or a grief intervention program. Participants improved significantly in 3 of 5 functioning domains and had significantly fewer symptoms of depression and grief and marginally less traumatic stress compared to baseline levels.

We recently completed an evaluation of CBT-PD among survivors of Hurricane Katrina.[61] Trained community-based therapists provided CBT-PD to adult survivors as part of *InCourage*, a mental health program sponsored by the Baton Rouge Area Foundation. Participants (*n* = 88) who were assessed at referral, pretreatment, intermediate treatment, and posttreatment showed significant and large improvements. The overall pre-post effect size was 1.4 in intention-to-treat analyses. Improvements were comparable for persons with more severe distress and persons with moderate distress at referral. Benefits were maintained at follow-up for the 66 adults who have been assessed.[61]

We are currently conducting a randomized controlled trial of CBT-PD in survivors of Hurricane Ike from the Galveston Bay Area. One hundred fifty participants will be randomized to one of two conditions: CBT-PD (*n* = 75) or Education for postdisaster distress (*n* = 75). Consistent with the goals of CBT-PD, the range of assessed outcomes is broad, including psychiatric diagnoses, PTSD symptoms, depressive symptoms, functioning, and quality of life.

An important question was whether we could successfully recruit and train community clinicians to deliver the intervention with fidelity. We examined this question in a paper currently under review.[67] One hundred four therapists attended a two-day training in CBT-PD with on-going case consultation. Following training, therapists showed significant improvements in their ratings of the importance of various elements of CBT, their knowledge and understanding of those elements, and their confidence that they could use them effectively. Immediately following the training, 90% of therapists demonstrated excellent retention of CBT-PD. Self-report measures from both therapists and patients indicated that therapists delivered critical session elements. This work suggests that the CBT model can be used with therapists who are not trauma specialists and do not have doctoral-level training. This is particularly relevant given the therapists encountered in addiction settings.

In summary, there is growing support for CBT-PD. The treatment, an adaptation from the CBT for PTSD model, has been shown to be effective for disaster survivors with PTSD, depression, and other disaster related distress. We have had success in recruiting and training non-academic, clinicians in delivering the intervention and in retaining survivors in the treatment.

2. CBT for PTSD in patients with SUD

Under the direction of Dr. McGovern (co-investigator), the CBT for PTSD model was adapted for use in an addiction setting. The primary modifications involve formally integrating discussion and work that address the relationship between PTSD and addiction. The introduction of the treatment makes clear the nature of the relationship between the addiction treatment program and CBT for PTSD. For example, patients are required to be in "good status" in the addiction program for the CBT to continue. Patients are informed about the type of information that might be shared (substance use) or not shared (details of trauma) with the addiction program by the CBT therapist. The crisis plan focuses on relapse to substances, and not relapses of psychiatric symptoms. Psycho-education more thoroughly establishes the relationship between PTSD and substance use, such as use of substances to cope with re-experiencing and hyper-arousal symptoms, and as the primary manifestation of avoidance symptoms. Finally, since addiction can be conceptualized as a chronic condition, most people are encouraged to attend peer recovery support group meetings in the community for the foreseeable future. The last module on generalization training and termination addresses the weaving of skills learned in the CBT for PTSD model into these treatments.

a. Feasibility study. Initial feasibility was evaluated with 3 patients from a community addiction treatment program to determine the safety and practicality of the approach. All patients achieved substantial reduction in PTSD symptoms at post-treatment, and for 2 patients these reductions increased at 3-month follow-up (Fig.1). On average, there was a 40% reduction in PTSD symptoms (CAPS Baseline Mean=63, CAPS 3-month follow up mean=38). Using the PTSD diagnostic criteria cut-off score on the CAPS of 45, none of the cases met criteria for a PTSD diagnosis at post-treatment or follow-up. Two patients were abstinent at post-treatment (note that patient 1001's data is behind patient 1015's data), and 1 had reduced days of use by 50%. At follow-up, one patient had continued to use alcohol, one had maintained consistent abstinence and one had used cocaine for one day (Fig. 2). All patients completed both CBT for PTSD and the addiction treatment program.

Figure 1: CAPS Total Score

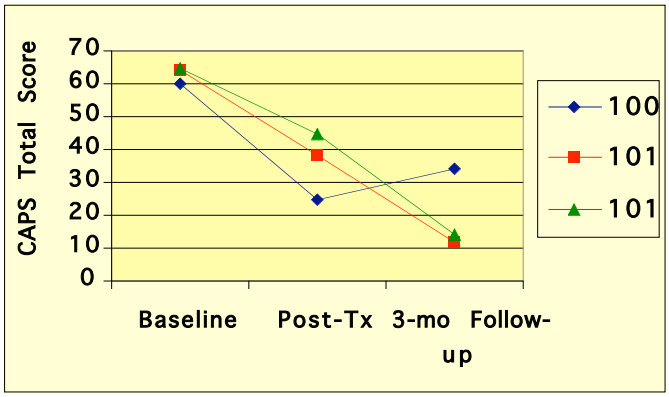
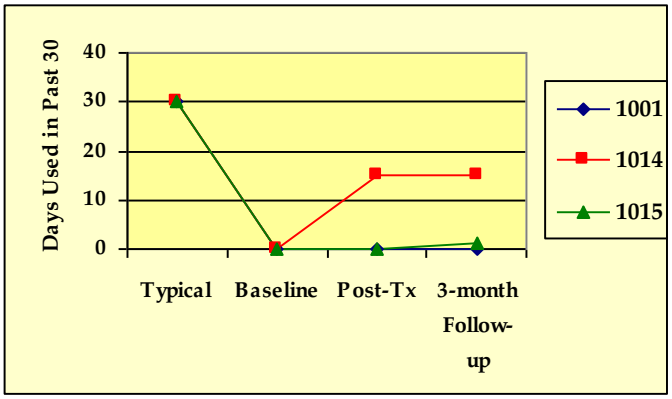


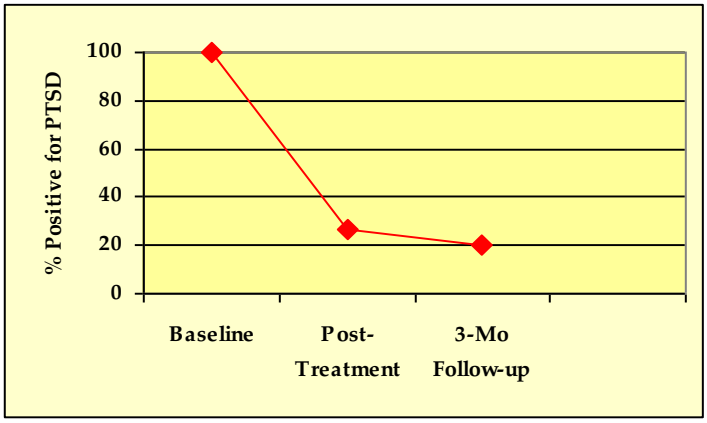
Figure 2: Substance Use



b. Uncontrolled trial. In the next phase, clinicians from 3 community programs were recruited to deliver the therapy: 1 psychiatric nurse practitioner, 1 masters' level and 1 bachelors' level counselor, 1 doctoral-level psychologist, and 1 addiction counselor intern. Only 1 had experience with CBT, PTSD, or manual-guided treatments. In addition to the didactic training, therapists received weekly supervision. Twice-monthly supervision was face-to-face, and twice monthly supervision was via telephone.

Eleven patients were enrolled in the treatment.[18] Their average age was 34.4 years, all were Caucasian, and 91% were women. All patients met criteria for current PTSD (past 30 day symptoms) and had an average CAPS score of 73.9 (SD=13.9), indicating significant severity. With respect to baseline substance use, most patients were negative on current toxicological screens (urine and breath), but reported use on an average of 25 out of the past 90 days. Drug and alcohol severity composite scores on the Addiction Severity Index (ASI) were within a moderate to severe range of problem level.

Figure 3: CAPS Diagnosis Over Time



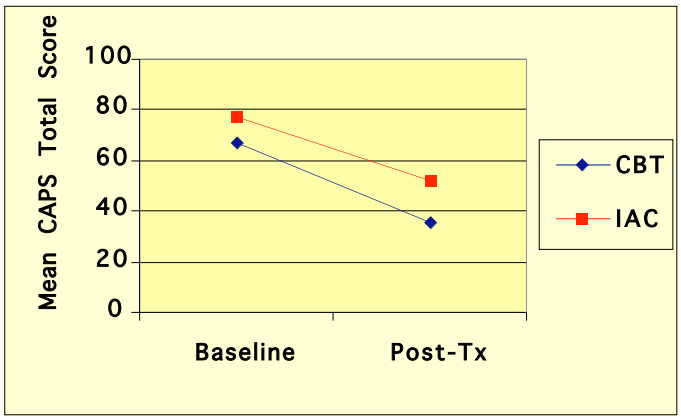
CAPS scores were significantly reduced from baseline to post-treatment ($p<.001$), and follow-up ($p<.001$). As seen in Figure 3, the number of cases who met criteria for PTSD dropped from 100% at baseline to 27% at post-treatment. At follow-up, 80% of cases no longer met diagnostic criteria for PTSD.[18]

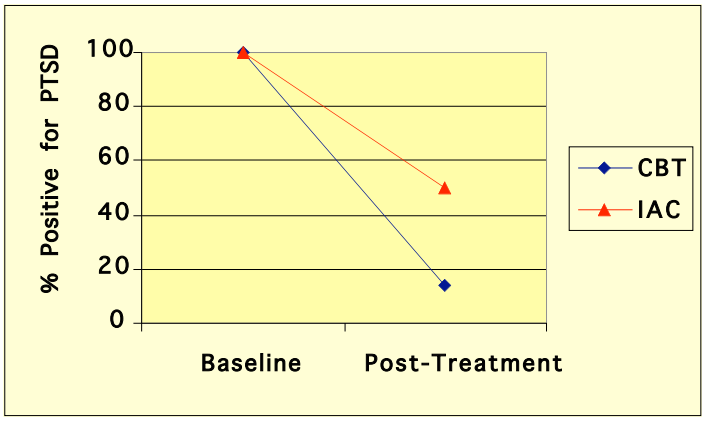
There were no changes in positive toxicological data or in days of drug or alcohol use. However, there were significant decreases in the ASI severity composite scores between baseline and the follow-up periods (alcohol, $p<.05$; drug, $p<.05$).[18] With respect to retention, 65% of patients completed at least 8 sessions.

c. Randomized controlled trial. We are now piloting the treatment in a randomized controlled trial comparing CBT for PTSD with Individual Addiction Counseling (IAC); all patients receive addiction TAU. IAC was adapted from the Individual Drug Counseling manual used in the NIDA Cocaine Collaborative Study. IAC is an intervention that does not directly address PTSD symptoms, but instead its mechanism of action is focused on addiction and recovery. We selected IAC because it has an evidence-base for effectiveness with drug use disorders, is matched in attention and frequency to CBT, and its mechanisms of therapeutic action should not directly affect PTSD but instead reduce substance use.

Two therapists from 4 sites volunteered. Therapists were staff members at the program from which patients were being recruited. The therapists include 6 masters' level counselors (2 of whom were licensed alcohol and drug counselors) and 2 bachelors' level counselors (1 a licensed alcohol and drug counselor). Thus, these clinicians might be considered representative of the community addiction treatment program clinical workforce. Therapists trained in CBT were also trained in IAC and therefore crossed in the delivery of treatments. Thus, each therapist was randomly assigned cases for delivery of CBT or IAC.

To date, we have gathered baseline and post-treatment data on 8 cases in CBT, and 4 cases in IAC (30% of planned enrollment). The following preliminary findings are available at the time of this application. The





average age of participants in the CBT group was 40 years, 87.5% are women, and all are Caucasian. Among the IAC group, the average age was 35 years, 50.0% are women, and all are Caucasian. At baseline, all of the participants had PTSD, with an average CAPS score of 67.3 (SD=16.5) in the CBT group and 77.0 (SD=23.5) in the IAC group. The majority of patients had negative breathalyzer and urine toxicological screens (100% and 87.5%, respectively in CBT; 75.0% and 75.0% respectively in IAC). The CBT group reported significantly more drinking than the IAC group (29 out of 90 days vs. 1 out of 90 days), whereas the IAC group reported significantly more drug use (48 out of 90 days vs. 9 out of 90 days). Alcohol and drug severity scores (on the ASI) were in the moderate to severe range at baseline.

CAPS total scores decreased over time in both groups (Figure 4). Although there was not a significant group X time interaction, there was a significant reduction in PTSD severity only in the CBT group (p=.05) and not in the IAC group. After treatment, only 12.5% of the CBT participants met criteria for PTSD, in comparison with 50% of IAC participants, but the difference was not statistically significantly, most likely given the small sample size (Figure 5).

Figure 4: CAPS Total Score in CBT (*n*=8) and IAC (*n*=4)

Figure 5: CAPS Diagnosis in CBT (*n*=8) and IAC (*n*=4)

In terms of substance use, CBT had the largest impact on alcohol use and IAC had the largest impact on drug use. This may have been due to the fact that most participants in CBT drank and most in IAC used drugs. For the CBT group, there was a significant reduction in the number of days of alcohol use (p=.01) and a reduction in alcohol severity on the ASI alcohol composite (p=.05). Participants in the IAC group significantly reduced the number of days of drug use (p=.05), but not alcohol use, and had no significant changes on the ASI alcohol or drug composite scores.

In terms of retention, 69.2% of the patients in the CBT group completed at least 8 sessions and 80.0% of the IAC patients completed at least 8 sessions. On average, CBT completers attended 10.0 sessions and IAC completers attended 10.5 sessions.

d. Summary. These findings suggest that CBT for PTSD is a promising treatment for patients with PTSD and SUD in an addiction setting. CBT for PTSD is yielding greater improvement in PTSD diagnoses than IAC. It is less clear how well CBT for PTSD affects drug and alcohol use because of the imbalance of these problems between treatment arms in our sample to date. Both treatments have equivalent retention. CBT retention (69.2%) is consistent with the findings in the feasibility study (65%) and indicates good patient acceptability. Data on therapist adherence and competence continues to be favorable. All therapists are consistently delivering adequate quality CBT and IAC.

4. Summary

Given the scientific literature on the prevalence and consequences of PTSD in standard addiction treatment and a synthesis of the evidence for the available research-based therapies, it is clear that there is a need for a PTSD treatment that can be integrated into existing addiction services. Currently, there are no PTSD specific

treatments that have been evaluated for use in an addiction setting. We believe that our CBT for PTSD model can respond to this need.

There is a strong program of research behind the CBT for PTSD model. CBT for PTSD has been tested in three different populations, SMI patients, disaster survivors, and individuals seeking treatment for substance use problems. In each population, research has progressed from small, uncontrolled studies to randomized controlled trials. The logical next step is to conduct a randomized controlled trial of the CBT for PTSD in a VA setting, the single, largest medical provider in the country.

Our team is well-suited to conduct the trial. We bring together key members of the initial PTSD treatment model development team (Mueser & Hamblen) with the investigator who took the lead on its adaptation for use in an addiction setting (McGovern). Additionally, we have brought in leaders in VA on both the impact of PTSD on SUD treatment outcomes (Ouimette) and the effectiveness of SS in a VA addiction setting (Kimerling).

IV. RESEARCH DESIGN AND METHODS

A. Design

1. Overview

The proposed research will evaluate the effectiveness of the addition of a relatively simple, manual-guided CBT for PTSD to TAU in patients with co-occurring PTSD and SUD. One-hundred-sixty outpatients with comborbid PTSD/SUD will be randomly assigned to receive either CBT for PTSD in conjunction with standard TAU (n = 80) or TAU (n = 80) without additional individual treatment. Recruitment will target participants at three VA intensive outpatient addiction programs as well as participants with SUD and PTSD in those facilities who are not in the IOP. Participants will be assessed at baseline, post-treatment (approximately 4 months from baseline) and 6 month follow-up (approximately 10 months from baseline). Consistent with the goals of CBT for PTSD, the range of assessed outcomes includes both PTSD and substance use. Clinician adherence to the manual will be evaluated. Primary analyses will focus on the hypothesis that CBT for PTSD is more effective in reducing symptoms of PTSD than TAU.

2. Design considerations

We proposed an additive design because we think it optimizes the internal and ecological validity of the study. We are interested in determining whether care as usual can be improved by adding CBT for PTSD. Specifically, we want to test whether it is desirable to add a new therapeutic regimen to TAU for substance abusing patients with the additional problem of PTSD. Thus, all participants must receive usual care for substance abuse treatment in addition to the new treatment. One concern that is sometimes raised with additive designs is that they do not control for the amount of treatment. To control for this, an alternative treatment can be offered to equate time. However, we do not think amount of treatment would be a plausible explanation for the expected difference between the CBT and TAU arms because the amount of CBT we propose to add is small relative to the amount of time in TAU treatment. Depending on the site, Veterans will receive between 87 and 225 hours of care in their intensive outpatient program, not including any mental health treatment Veterans may receive outside of the program. On average, CBT would only add 4-11% more treatment, depending on the program. We will carefully measure treatment services of the participants with SUD and PTSD who are not enrolled in one of the two intensive outpatient programs.

Another reason to consider comparing an active treatment to an alternative one is if the question focuses on whether the new treatment improves outcomes obtained by another standard of care. Currently there is no standard of care to use as a comparison. Although Seeking Safety appears to be the most widely used treatment in VA for patients with comorbid PTSD and SUD, the empirical evidence suggests it is no more effective in improving PTSD than control conditions such as relapse prevention and women's health education. Therefore, treatment as usual can serve as the control for whether observed outcome is due to any addiction treatment versus the addition of CBT specifically.

B. Sample and Recruitment

1. Inclusion criteria

Eligible subjects will meet the following inclusion criteria: (1) At least 18 years old, (2) Diagnosis of current substance use disorder, (3) Diagnosis of PTSD confirmed by the Clinician Administered PTSD Scale with a

total symptom score of 45 or more, (4) English speaking, (5) Agree to be audio recorded, and (6) Willing and able to provide informed consent.

2. Exclusion criteria

Only three exclusion criteria will be applied in order to maximize sample representativeness. (1) Individuals with acute psychotic symptoms will be excluded if they are not well-connected with appropriate mental health services. (2) Patients with a psychiatric hospitalization due to a suicide attempt or severe suicide risk or who made an attempt in the last month regardless of hospitalization will be excluded. (3) Individuals with unstable medical or legal situations that would make completion of the study highly unlikely will be excluded. Thus, as previously noted, the proposed research will attempt to recruit as heterogeneous and representative a patient sample as possible.

3. Expected participant demographics and diagnostic characteristics

Based on information provided by PERC on SUD outpatients seen in specialized care throughout VA,[51] about 95% of the patients are male, 24% are married, and the average age is 50 years old. About 52% are Caucasian, 41% African American, 7% Hispanic and 1% some other racial/ethnic group. Overall, 50% are Vietnam War era and 36% have a service-connected disability. With respect to diagnostic characteristics, 24% of SUD outpatients have a diagnosis of alcohol abuse/dependence only, 17% have a diagnosis of drug abuse/dependence only, and 45% have both disorders. Of the SUD outpatients seen in specialized care without alcohol or drug diagnoses, 4.5% had nicotine dependence as their only SUD diagnosis. About 60% had one or more other psychiatric disorders.

4. Sites

A search conducted by PERC identified 112 IOPs (i.e., SUD programs that offer at least 3 hours a day of treatment, 3 days per week). Of these 46 (41%) were excluded because they reported offering SS. We felt it was important to exclude sites that offered SS because it is not clinically indicated to have patients receive two trauma treatments simultaneously. From this search we selected, Tampa, FL and Syracuse, NY. These sites were selected because they treat more than 1,000 unique patients annually, were interested in conducting research at their sites, and were able to commit the necessary resources. We are also going to be using White River Junction VA as a site. White River Junction has the necessary resources, and will help bolster recruitment for the study.

5. Recruitment and enrollment

At least 1,000 unique Veterans were seen at each site over the last fiscal year. Thus we expect that each recruitment site will see at least 1,500 unique patients over the 18-month recruitment period. We used the VA performance measure on continuity of care to estimate the number of patients seen who have been actively engaged in the IOP for at least 3 days. This measure corresponds to the number of patients that have no SUD contact in the prior 90 days and then have at least 3 SUD visits within 30 days. Next we conservatively estimate that 30% of SUD patients will meet criteria for PTSD (see background). Finally, we included only those we believed will be interested. Randomized trials of brief interventions for SUD patients found that approximately 60% of patients eligible for study participation agreed to participate.[68-70] Assuming similar rates of participation, we expect that at least 60% of eligible participants will be interested. However, our study will have adequate power even if only 33% of patients agree to participate (See Table 1, Section B6 below, and the Inclusion and Enrollment Table included under Human Subjects).

Table 1. Recruitment and Enrollment

Site	# of SUD patients with SUD visit in 2008	Expected # of SUD patients available over 18 months	# SUD patients "successfully retained" based on continuity of care performance measure	Estimated # of PTSD cases (30%)	If 60% patients interested	If 33% patients interested
Tampa, FL	1000	1500	801 (53.4%)	240	144	80
Syracuse, NY	1200	1800	869 (48.3%)	267	160	88

Below is a revised recruitment table, assuming we are approved to recruit within the next two months through the end of the proposed study. These numbers show potentially eligible participants assuming we open recruitment up beyond the IOP in the two facilities. Numbers of veterans with comorbid PTSD and SUD were provided by PERC for FY 2012. (Note: numbers would be higher if we receive a one year no-cost extension)

Site	Estimated # of PTSD cases with SUD (25%)	If 60% patients interested	If 33% patients interested
Tampa, FL	1274	764	420
Syracuse, NY	901	540	270

In August of 2013, we made the decision to add a third site, White River Junction VA. This decision was made to boost enrollment and because of the cost-effectiveness of this particular site.

6. Power analysis

We aim to have a sample that would yield .80 power in longitudinal analysis with generalized estimating equations model (a type of generalized linear mixed models) to find a standardized detectable difference from .4 to .5 between intervention and usual care, assuming alpha = .05, two-tailed. We assume that the correlation between repeated measures will be .60. The outcome of treatments will be measured at two points in time (3-month and 9-month) for each individual. The sample size for our primary hypothesis (difference in slopes by treatments) is based on Diggle, Liang, and Zeger,[71] who developed a formula to calculate sample size for longitudinal studies with repeated measures to estimate the difference between slopes (or rate of change in CAPS as in this case) of two groups (m = size per arm):

$$M = 2(Z_\alpha + Z_\beta)^2 \sigma^2 (1-\rho)/(nS_x{}^2 d^2)$$

where $S_x{}^2 = \sum_j (x_j - \bar{x})^2 / d$, the within-subject variance of the x_j; type I error α= 0.05, power β = 0.8 and the smallest meaningful difference d = $\beta_{1B} - \beta_{1A}$ and $\sigma^2 = Var(\varepsilon_{ij})$ measures the unexplained variability in the response, $Corr(Y_{ij}, Y_{ik}) = \rho$ for all $j \neq k$, and n is the number of repeated measures per person.

Using this formula and based on these assumptions, we estimated the sample size needed. Table 2 shows how required total enrollment (both groups) would vary for a range of expected effects and if the true effect is larger or smaller than expected for a range of possible missing data scenarios.

Table 2. Enrollment Number N (total of two groups) as a function of effect size and rates of missing endpoints due to drop out and loss to follow-up

	Loss to Measurement		
actual effect size	10%	15%	20%
.40	160	169	180
.45	126	134	142
.50	102	108	115

We propose to enroll 160 subjects (80 in each treatment arm). The table shows we will have adequate power to find an effect as small as d = 0.4 if the percentage of missing data is 10%. And if the actual missing data is 20%, we still have enough subjects to detect an effect as small as .45. Because the primary analysis is intention-to-treat, we are basing our drop out on participants who are completely lost to measurement and not on those who do not complete treatment. We believe 20% is a conservative rate. Trafton et al (2003)[72] successfully tracked and interveiwed 270 subjects participating in a multi-site opiod substitution treatment study at remote sites with a 90% follow-up rate at 6-months.

C. Study Treatments

Participants will be randomized to TAU plus CBT or TAU alone. Therapists who provide CBT will not provide TAU services to study patients. Ratings of CBT recordings (adherence and competence indexes) will confirm therapy integrity and independence.

1. CBT for PTSD

CBT for PTSD in addiction treatment programs is a simple, manual-guided individual therapy.[54] It consists of 3 learning and skill components designed to improve PTSD symptoms and substance use: (1) Patient education about PTSD and its relation to substance use and treatment; (2) Breathing retraining: A behavioral anxiety reduction skill; and (3) Cognitive restructuring: A cognitive approach and functional analysis of the link among emotions, cognitions and situations.

CBT for PTSD has 8 modules and is delivered over 8-12 hour-long individual sessions. We have set the completion of 8 sessions as the criterion for completion. The modules are listed in Table 3. A patient workbook is used in conjunction with the therapist manual, and, as with most cognitive behavioral therapies, the approach includes homework between sessions, patient education and self-monitoring, skill acquisition, implementation and practice, and developing self-efficacy about more adaptive and alternative cognitions and behaviors.

The first session begins with an orientation to the treatment and is followed by the development of a crisis and relapse prevention plan. Breathing retraining is introduced as a skill for managing and decreasing anxiety. It involves teaching patients how to slow their breathing in order to reduce hyperventilation by taking in normal breaths and exhaling slowly often while saying a soothing self-statement such as “calm” or “relax.” Patients are reminded of the “fight or flight” response and how under threat people respond by taking in excess oxygen. Breathing retraining counteracts the automatic response and thereby slows down the intake of oxygen. After the therapist models the skill, the patient practices it first in session and then for homework under calm situations. Later, when patients become more proficient at the skill, they are encouraged to use the breathing skill to calm themselves when anxious.

Typically psycho-education is introduced in sessions 2 and 3. Psycho-education aims to provide patients with an understanding of PTSD symptoms and associated symptoms and is one way to normalize patients’ reactions and reduce stigma concerns. If done properly, it can also provide a rationale for why patients are experiencing their distress, instill hope, and improve engagement.

Table 3: Organization of CBT for PTSD therapist manual: Module, topic and therapeutic focus

Module	Session	Topic	Therapeutic focus
1	1	Introduction	Relationship between therapy and addiction treatment program, substance use.
2	1	Crisis & Relapse Plan Review	Identify relapse triggers, cues, alternative coping tactics, pre- and post-slip/relapse contact persons and numbers.
3	1	Breathing Retraining	Develop skills to reduce tension and anxiety as specific relapse antecedent.
4	1-2	Psycho-education Part I: Core symptoms of PTSD	Examine relationship among trauma, PTSD symptoms, and substance use, by historical and current coping strategies.
5	2-3	Psycho-education Part II: Associated Symptoms of PTSD	Educate on specific relationships between substance use, addiction treatment compliance, use of peer recovery support groups and associated symptoms.
6	3-4	Cognitive Restructuring Part I: Thoughts & Feelings	Introduction to cognitive restructuring: Situations, feelings, common styles of thinking
7	4-7	Cognitive Restructuring Part II: Challenging Your Thoughts & Feelings	Acquisition and practice of cognitive restructuring, including evaluation of evidence for thoughts (that lead to PTSD-related feelings) and development of alternative thoughts and actions.
8	8-12	Generalization Training & Termination	Focus on generalization of skill acquisition, integration with addiction treatment and peer recovery support groups, and minimizing re-traumatization potential.

Cognitive restructuring is taught over the next several sessions. First patients are introduced to the concept that people's emotional reactions to events are determined by their interpretations of those events. These interpretations may be influenced by other events the person has experienced, including traumatic events. Patients are informed that different types of negative feelings are associated with specific types of thoughts, which are often automatic and occur outside of their awareness. Patients identify upsetting situations and the associated thoughts and feelings.

Next patients are introduced to the cognitive distortions (called common styles of thinking) that may result from basing current thinking on past traumatic experiences. For example, patients who have experienced traumatic events often "catastrophize" or "overestimate risk" in situations in which there is no reason to suspect that something bad will happen. Patients are apprised of common problematic thinking styles and are helped to identify and correct distortions related to negative emotions.

Thereafter, patients are introduced to a five-step cognitive restructuring (CR) method for dealing with negative emotions. These steps are summarized on a worksheet, which is used both in the session with the therapist and practiced by the patient outside of the session on his or her own or with the help of another person. The five steps of CR are (1) Describe the situation, (2) Identify the negative feeling, (3) Identify the thought related to the feeling, (4) Challenge the thought, and (5) Take action. Patients practice CR for the remainder of the treatment sessions. The goal is to help patients move from learning CR as a skill to applying it to their disaster-related thoughts and from using the formal CR worksheet to completing the steps in their head when they are in an upsetting situation or immediately after it is over.

The last session focuses on generalization training and termination to ensure that the patient is able to use cognitive restructuring on their own outside of sessions, to review treatment gains, and discuss any plans to meet ongoing or potential needs that may arise.

2. TAU

Addiction treatment programs vary widely in VA. Data from PERC[51] provide a sense of typical IOP services. 95% of all SUD IOP programs report providing group and/or individual psychotherapy to their patients. Just over half of the programs (57%) report that their patients participate in on-site SUD-related self help groups, such as Alcoholics Anonymous. Only 11% of programs offered contingency contracting. The majority of programs conduct a psychiatric assessment of SUD patients (78%) and about half receive psychiatric treatment (54%) or medication (41%) for a co-morbid psychiatric disorder.

The Tampa Alcohol and Drug Abuse Treatment Program (ADATP) is a 3 week IOP that consists of a 7 day, 4 hours per day, program. Relapse prevention, aftercare groups, and family sessions are offered additionally in the afternoon and evenings. The philosophy of the ADATP is based on an understanding of alcohol and drug abuse/dependence as a complex biopsychosocial illness. The major thrust of the treatment approach is derived from the 12-step model of recovery with additional emphasis on educational and cognitive-behavioral approaches. Each patient's individual recovery program has its own structured aftercare component, which is an integral part of treatment. Patients are strongly encouraged to participate in voluntary substance recovery organizations such as Alcoholics Anonymous (AA), Al-Anon, Narcotics Anonymous (NA), Cocaine Anonymous, and Adult Children of Alcoholics (ACOA). The ADATP program includes a six week dual diagnoses treatment program for patients who have co-occurring substance abuse and mental health disorders. The focus is on evaluation, stabilization, and intensive treatment. This phase includes individual and group therapy, educational classes, therapeutic outings, and medication management.

The Syracuse Substance Abuse Treatment Service offers a six week IOP that consists of a 3 day, 4 hours per day, group treatment program based on a cognitive-behavioral treatment philosophy. The first hour of the program is focused on meditation and one time per week, patients receive acupuncture. The second hour is education; topics include education about cognitive-behavioral strategies (e.g., relapse warning signs) and other relevant topics (e.g., dealing with medical problems). The final 2 hours are group psychotherapy that are tailored to the needs of the group based on a CBT approach. Each patient is also required to attend an hour of individual counseling every other week. Twelve step participation is recommended depending on patients' needs but not required. The program also offers a dual-diagnosis group for patient who are mentally ill and chemically addicted and an aftercare program that teaches relapse prevention.

The White River Junction Residential Recover Center (RRC) program is offered as a six week intensive residential program specifically providing tandem evidence based treatments for co-morbidities such as PTSD, Major Depressive Disorder, and accommodation for either cognitive effects of PTSD or of traumatic brain injury.

To determine actual level of involvement in the IOPs, we will extract from the electronic medical record (i.e., Vista) days and types of SUD treatment received as well as additional services including mental health and primary care visits. We will also extract utilization records for participants who are not in IOP programs. In addition, all participants will provide information on a treatment services interview.

D. Therapist selection, training, supervision and quality monitoring

Therapists will be selected by the site principal investigator. We will not screen out therapists for this study based on any pre-existing criteria, experiences, or credentials. Several studies now demonstrate the feasibility of training community clinicians in manualized, cognitive behavioral treatments for trauma. Rape crisis counselors, community mental health clinicians, and school-based counselors have been shown to be able to learn specific cognitive behavioral interventions and to provide them with good outcome.[67, 73-75] Each site will work with the PI to identify therapists who are interested in learning CBT for PTSD and in participating in research. Each site will agree to commit 2 staff to serve as research therapists, even though only one is needed. In this way we can respond to any attrition of therapists without losing time.

All therapists will attend a two-day training in CBT for PTSD offered by Hamblen (PI) and McGovern (Co-I). This training, initially developed for the disaster treatment context, has been modified to include a specific module summarizing the research with co-occurring PTSD and substance use disorders and includes PTSD/SUD case examples. The training in CBT for PTSD includes a combination of modalities such as lecture, practice exercises, expert demonstration (including live and video demonstrations), and role plays. The

training begins by providing therapists with a solid rationale for the intervention. In presenting the rationale, trainers review empirical research on other PTSD/SUD treatments, such as Seeking Safety, and share the philosophy behind the development of this model. The goal is to establish the credibility of the treatment with the therapists. Next, therapists are taken step-by-step through each session of the intervention. Session goals are emphasized and suggestions for meeting those goals are provided. Therapists are shown how to use the manual during the session, how to integrate handouts into the teaching of the intervention, and how to address specific problems that may arise.

After a new technique has been described, the trainers demonstrate the technique and clinicians have an opportunity to participate in a role play to promote skill acquisition. For example, following a lecture on cognitive restructuring clinicians engage in a group practice exercise where they brainstorm typical trauma related cognitions and then try and identify alternative thoughts. Next the trainers demonstrate cognitive restructuring using a clinician volunteer and a real example. Finally, therapists actively practice the cognitive restructuring in small group role plays.

Barriers to implementation are openly discussed and debated throughout the training. Specific barriers addressed include the effects of manuals on the therapeutic relationship, therapists' concerns about manuals not being able to meet patients' individual needs, credibility of the manual, and therapist confidence. From the beginning, trainers emphasize the importance of the therapeutic relationship when using manualized treatments and encourage therapists to focus on the development of a therapeutic alliance. A second area of emphasis is on demonstrating the flexibility of the manual and showing how the manual can be tailored to meet individual patient needs.

Follow-up consultation is crucial to ensuring fidelity to the intervention. In this study each therapist will be assigned one CBT case at the outset, and be carefully supervised using audio recording of each session, and an hour of supervision for each hour of therapy. The first case will not be included in the research, and subsequent cases will not be included until the PI confirms the therapist is conducting the CBT to acceptable levels. A similar approach was used by Hien et al[76] in the study of SS. Once confirmed by the supervisor to deliver the therapy for the study, therapists will attend group supervision every other week by phone. Supervision will be provided by Hamblen (PI) and Bernardy (Co-I). McGovern will provide additional supervision as needed. Supervision includes a review of the status of all active cases followed by an in-depth presentation of 1-2 cases. Each therapist will be expected to prepare a case in advance and be able to provide a cognitive restructuring example for review. It is at the discretion of the supervisors to identify who will present.

In advance, therapists will be provided with the adherence and competence measures for CBT for PTSD (Adherence and Competence [ACI] Index) so they know how their audio recordings will be evaluated. In addition, therapists will keep a session-by-session "Therapist Session Tracking Form".

All sessions will be audio recorded. Digital recordings will be uploaded to the secure server at Research Services at the White River Junction VA. Dr. Mueser, one of the original developers of CBT for PTSD, will rate a random sample of 15% of all recorded sessions for each therapist by using the ACI and adherence and competence measures. From our earlier studies, we expect the therapists to be competent and adherent in delivering CBT.

E. Assessments and Data Management

The site coordinator will complete the screening assessment and the assessor will complete the eligibility, baseline, and follow-up assessments. Pilot testing indicates the baseline assessment will take 3.4 hours to administer and the follow-up interviews will take 2.1 hours to administer. Assessments will be done in person whenever possible. Assessments will occur by phone if necessary, so that data is not lost. The same assessors will be used for both methods.

All assessment instruments are described in detail below and summarized in Table 4.

1. Screening

The PC-PTSD[77] is a brief 4-item screen for PTSD. The PC-PTSD was developed with VA primary care patients, where the instrument detected PTSD diagnoses more accurately than did clinician diagnosis. In an

SUD population the PC-PTSD has a sensitivity of .90, and a specificity of .77. This screen has been adopted for use in all returning Iraq/Afghanistan Veterans and as a performance measure for primary care. The screen will be used to identify patients in need of full PTSD assessment to determine eligibility for the treatment trial prior to randomization.

2. Eligibility

Sociodemographics. Brief assessment of patient's social and demographic characteristics such as age, gender, marital status, and level of education. Measure includes questions on periods of service and disability status.

Life Events Checklist: The Life Events Checklist is used with the Clinician Administered PTSD Scale as a measure of trauma exposure. To be eligible for the study, patients need to endorse at least one Criterion A traumatic event. The Checklist will also provide descriptive information about the patients in the study.

Clinician Administered PTSD Scale (CAPS): The CAPS[78] is a structured diagnostic interview and is widely regarded as the gold standard for determining a diagnosis of PTSD. It has excellent reliability and validity[78, 79] PTSD diagnosis on the CAPS is based on meeting the DSM-IV symptom criteria, as well as having a minimum severity score of 45. Symptoms are considered to be present when they have a frequency rating of at least 1 and an intensity rating of at least 2.[79] Ratings will be based on current symptoms (past month).

Structured Clinical Interview for DSM-IV-Patient Edition with Psychotic Screen (SCID-P): Substance use disorders and other Axis I psychiatric diagnoses (other than PTSD) will be established using the SCID.[80-82] The SCID is a semi-structured interview that is widely accepted as the gold standard for establishing adult psychiatric diagnosis.[82] Our research center has extensive experience training research interviewers and using the SCID with a wide range of clinical populations, including patients with co-occurring psychiatric and substance use disorders.

3. Outcomes

Participants' treatment outcomes will be assessed at baseline, post-treatment for the CBT group (approximately 3 months after baseline) and 3 months after baseline for the TAU group, and at 6 month follow up (approximately 9 months after baseline).

CAPS: PTSD severity, as measured by the CAPS (see above) will serve as the primary outcome measure. CAPS severity is calculated by summing the frequency and intensity score for each item. We will also examine the percentage of patients who show clinically significant change on the CAPS, as defined as a decrease of 10 points or more[79].

PTSD Checklist (PCL): A secondary measure of PTSD will be the PCL.[83] The PCL is a widely used self-report measure that assesses the 17 DSM-IV PTSD symptoms. Responses to these questions are on a scale of 1 to 5 ("not at all" to "extremely"). The PCL has excellent psychometric properties. It will be administered at all assessments, and at every other treatment session to monitor symptoms.[83]

Addiction Severity Index (ASI): The ASI[84] is a multi-dimensional semi-structured interview that assesses lifetime and current use of all major classes of drugs of abuse plus history of substance related problems and history of SUD treatment. Five domains commonly associated with substance use are also assessed: medical, legal, employment, social/family, and psychological functioning. The ASI has good reliability and validity and has been used extensively with Veterans[84] We will utilize a brief, reliable and valid version of the ASI that derives current composite scores on alcohol and drug use which will serve as our primary outcome for measuring substance abuse.[85]

Time-line Follow-back interview (TLFB): The timeline follow-back interview method gathers self-report information about drug and alcohol use over the past 90 days.[86] Respondents provide information on the amounts and types of substances they have used. The TLFB has excellent psychometric properties[87, 88] and will enable us to measure variables used in the COMBINE trial such as "percent days abstinent," "heavy drinking," and "good clinical outcome."[89] Heavy drinking was defined as 5 (men) or 4 (women) drinks per day. Good clinical outcome was measured as moderate drinking without problems. Moderate drinking was defined as a maximum of 14 (men) or 11 (women) drinks per week, with no more than 2 days on which more than 4 drinks (men) or 3 drinks (women) were consumed. (Problems will be measured with the ASI).[89]

Toxicological data: Both urine screen and breathalyzer data will be collected to detect substance use. AlcoHawk ABI breathalyzer, a semiconductor oxide sensor, is Department of Transportation/ National Highway Traffic Safety Administration approved and FDA cleared for consumer use. Cannabis, cocaine, benzodiazepines, amphetamine, methamphetamine, and opiates will be tested for using the One Step Multi-Drug Screen Test Card with Integrated iCup, a rapid urine screening test that uses lateral flow chromatographic immunoassay for the qualitative detection of multiple drugs and drug metabolites in urine. It includes built-in validity/adulteration tests for temperature, and specific urine characteristics such as pH, gravity, nitrite, creatinine, and glutaraldehyde, as well as the presence of oxidants (e.g., bleach or hydrogen peroxide).

Patient Health Questionnaire-9 (PHQ-9):[90] The PHQ-9 is adapted from the PRIME-MD. It can be used as a screen for depression or as a severity measure. We will be using it as a measure of severity.

SF-12V:[91] The SF-12V is a measure of functioning health and well being from the patient's point of view. This version is for use in Veterans.

Penn Alcohol Craving Scale (adapted)[92]: The Penn Alcohol Craving Scale (PACS) is a self-report measure (5 items) that includes questions about the frequency, intensity, and duration of craving, resistance of drinking and drug use, and provides overall ratings.

Treatment Utilization and Retention: Data pertinent to service utilization and retention such as type and number of visits patients made to usual care SUD treatment services, as well as for other medical and psychiatric services, will be extracted from medical records using CAPRI or JLV and and placed into the VA Informatics and Computing Infrastructure (VINCI) study folder. VA TBI screening status will also be extracted in a similar manner.

Table 4: Summary of Assessment Measures

Domain	Measure	Time (minutes)	Entry	Post-treatment	6 month
SCREEN					
Probable PTSD	PC-PTSD	< 1	X		
ELIGIBILITY					
Inclusion					
Trauma	Life Events Checklist	5	X		
PTSD diagnosis & Severity	Clinician Administered PTSD Scale (CAPS)	45-60	X		
SUD	Structured Clinical Interview for DSM-IV (SCID)	60	X		
Exclusion					
Psychosis (unmanaged)	SCID (Psychotic Screen)	5-10	X		
Descriptives					
Sociodemographics	Demographic Measure	5	X		
PATIENT OUTCOMES					
PTSD	Clinician Administered PTSD Scale (CAPS)	45-60	From eligibility	X	X
PTSD	PTSD Checklist (PCL)	15	X	X	X
Substance Use	Addiction Severity Index (ASI)	20-30	X	X	X
	Time-line Follow-back (TLFB)	5-10	X	X	X
	Breathalyzer and Urine	Not counted	X	X	X
	Penn Alcohol Craving Scale	5	X	X	X
Functioning	SF-12V	3-5	X	X	X

Depression	PHQ-9	3-5	X	X	X
Treatment Utilization & Retention	Patient Records; brief interview questions	5	X	X	X
Total Time to Administer			3.4 hours	2.1 hours	2.1 hours

4. Assessor training and inter-rater reliability

Independent assessors will be trained to criteria on the CAPS and SCID. CAPS training consists of 80% agreement on all items, plus diagnostic agreement, on 2 consecutive cases. SCID training to criteria is exact diagnostic agreement on two consecutive cases. All sessions are audio-recorded and reviewed as necessary by the PI. Inter-rater reliability will be conducted on 10% of CAPS and 10% SCID at each assessment point and for each site.

5. Follow-up methods

Our research team has excellent experience and methods to successfully follow patients in community treatments. These methods include: documenting address and relevant phone number information, obtaining contact information on up to three locators (minimum of 2) who would be able to contact the patient, and at the baseline session establishing a working alliance between assessor and patient. To achieve high follow-up rates, we also follow the procedures recommended by Scott[93] and Twitchell et al,[94] such as patient education and motivation, collection of extensive and verified locator information, between assessments contacts via the mail and telephone, confirmation of follow-up appointments prior to follow-up date, standardized tracking procedures, and research team and site coordinator case review meetings. The same assessor who conducts the baseline assessment will (whenever possible) also conduct the post-treatment and 6 month follow up. We have found that conceptualizing the assessment process as a 3-part process (i.e., 3 assessment points) is helpful. For participants with travel difficulties, or for those who have left the area, telephone assessments will be used.

6. Data management and security

Data will be entered by the site-coordinator at each site. All forms will be reviewed for accuracy and completeness prior to data entry. Data will be entered electronically into an Access database specifically designed for the study and located on a VA protected server. Each item will be subject to range testing and validity checks as provided by the data system. We will use a double-entry method whereby data are entered twice and entries are matched against each other to flag inconsistencies, which are then corrected prior to data analyses. To maximize data accuracy, the project manager will carefully review all data prior to analyses, conducting several manual calculations, random spot-checking, and programmed range/validity checks on summary scores.

Data from the site databases will be transmitted either by synchronization with the central database at the VA in White River Junction, VT through a secure internet connection, or by a secure FTP of data files which are then loaded into the central database at White River Junction. We will work with our local ISO to determine what method is most secure.

Study site coordinators will extract data from the medical record. This will be transmitted to the White River Junction VA by means of the secure server at White River Junction's Research Services.

A participant will be identified in the central database by his or her unique subject identification number. Identifying information, such as name, address will not be stored electronically. It will be kept at the site in locked cabinets in locked offices at all times. All computer systems and programs will be password protected. Good computer security practice (shutting down of computers after work hours, restricting physical access to machines, prohibition of password sharing) will be required of all study personnel. Virus protection software will be installed on each study machine as required on all VA computers. Backups will allow for quick restoration of data in the unlikely event that a hardware failure or security breach should occur. Participant paper files will be stored in locked cabinets in locked offices at all times

F. Procedure

We will encourage sites to screen all patients with the Primary Care PTSD Screen (PC-PTSD) as a quality improvement measure. Participants will be recruited into the trial in 1 of 3 ways:

- Direct referrals from clinicians (the clinician talks to a client about the study, either because the client has a history of trauma, symptoms of PTSD, or a positive PC-PTSD screen. If the client is interested, the therapist contacts the site coordinator)
- Self referrals (the patient sees the posted study information, talks to his/her therapist or treatment team member, who contacts the site coordinator)
- Indirect referrals (Research therapists who participate in treatment team meetings hear of a case and suggest that the clinician talk to the client about the study. If the client is interested, the clinician contacts the site coordinator.)

The individual who approaches the participant about the study (the site coordinator or provider) will give a copy of the information sheet and the informed consent document to the patient for review. The site coordinator or other designated local site personnel will consent all participants and give participants the "Volunteering to Participate" brochure. The information sheet will also be posted at the site

Every prospective participant will receive the 4-question PC-PTSD and this information will be retained for study purposes. We are requesting an Informed consent waiver for recruitment purposes and a HIPAA Waiver of documentation for recruitment purposes to facilitate the transfer of this information (see Form 103).

For sites that do not wish to implement routine screening, we will ask clinicians to refer interested patients to the site coordinator who will conduct the brief screen and invite those with a positive screen to participate. We will ask clinicians to refer patients who are 18 or older and English speaking. We will ask clinicians not to refer patients with uncontrolled psychotic symptoms, suicide attempts in the last month, or unstable medical or legal problems. In cases where those doing the referring do not know the answers to our inclusion/exclusion criteria, we are asking for a HIPAA waiver to gather the inclusion/exclusion criteria from the medical record before informed consent. This will help us avoid approaching patients who would turn out to be not eligible. It will lessen patient burden, and help get participants into the study more quickly. The only information gathered at this time will be that needed for inclusion/exclusion. And this data will be retained securely double-locked at the site.

Once the screening is completed and informed consent is signed, a trained, blind, assessor will confirm a PTSD diagnosis with the CAPS. Patients who do not meet criteria for PTSD on the CAPS will be paid $20 (form of payment determined by site regulations) and will not be enrolled in the study. Patients with PTSD will be given the SCID to confirm their SUD and other Axis 1 disorders as well as the rest of the eligibility and baseline measures. Patients will receive an additional $30 for completing the baseline assessment, for a total of $50 for the baseline.

Individuals providing consent and meeting inclusion/exclusion criteria as confirmed by the baseline assessment will then be randomized. We will perform block randomization (block size of 2, 4, and 6) in allocating subjects to treatments. Moreover, stratified block assignment will be used, so that each treatment group will be balanced on type of substance use (alcohol only versus drug with or without alcohol, 2 categories), whether the patient has severe PTSD (2 categories), and the site of treatment (2 sites).

Patients who are randomized to CBT for PTSD will receive 8-12 individual sessions of CBT for PTSD. These sessions will be offered once or twice per week depending on patient and therapist availability. All participants will receive TAU. For patients assigned to CBT, approximately one week after the end of treatment patients will be given the post-treatment assessment. Patients in TAU will be assessed 4-5 months after the baseline. Six months from the post assessments all participants will receive the 6 month follow-up assessment. Assessors will be blind to treatment condition. Patients will be paid $30 for the post-treatment and follow up assessments. Patients will receive a reminder letter about their first appointment (and about subsequent appointments if requested.) Patients who miss a session of treatment or assessment may be sent a letter of contact, if study staff are unable to reach them by phone.

G. Data Analysis

This study is designed as a two-arm, parallel comparison of two therapies in the treatment of PTSD in patients who are receiving care in a VA intensive outpatient program for substance abuse or patients with comorbid substance use and PTSD. In designing this study, there are analysis issues that require special attention, such as handling of missing data, adjustment for loss-to-follow-up, and serial correlation for sample size calculation. The strategy for data analysis flows from the goals of the study, and in turn defines the statistical tests and sample size projections.

The unit of analysis is the participant. All analyses will be initially conducted according to intention-to-treat, i.e., participants' data will be analyzed according to their assigned group regardless of their actual exposure to treatment. Prior to analysis, we will carefully examine descriptive statistics and the distributional form of all variables. We will use appropriate transformations, recode or categorize skewed and abnormally distributed data, and use appropriate methods for outliers and missing data so that we do not violate assumptions of our statistical procedures. Imputation techniques for missing data, such as linear interpolation and multiple imputations will be examined to determine their effect on the results. It is recognized, however, that the best approach to missing data is to make all effort to minimize it, since imputation is difficult when the missing data are non-ignorable or not missing at random. Our aim is to use careful examination and planned procedures so that we minimize the number of statistical tests, thereby reducing the possibility of inferential errors. Therefore, for tests of hypotheses 1 and 2, we will not use a downward adjustment of alphas (from .05) as the analysis and hypotheses have been planned and stated a priori.

1. The effects of CBT on patient outcomes

Hypothesis 1 (primary): Patients exposed to CBT will have greater improvements in PTSD symptom severity relative to patients who receive TAU as measured by the CAPS total score, and secondarily by the PCL, from baseline to post-treatment and 6 month follow-up.

Hypothesis 2 (secondary): Patients receiving the CBT will have greater reductions in substance use severity (drugs and/or alcohol) relative to patients who receive TAU as measured by the ASI drug and alcohol severity composite scores, and secondarily by the TLFB, from baseline to post-treatment and 6 month follow-up.

Several steps will be taken in preparation for performing the primary analyses. We will evaluate the effectiveness of randomization by comparing CBT and TAU groups on demographics, baseline measures of key outcomes, and other important covariates such as psychotropic medication usage. Next we will perform simple end-point analyses of post-treatment and 6-month outcomes using t-tests (chi-square test for retention proportion) and use multiple linear and logistic regression models to examine predictors of outcome. Demographic variables, baseline severity, and medical and psychiatric comorbidities will be considered as possible covariates. Only covariates that significantly reduce variance will be added to the model.

Because the groups are randomized to be equivalent at baseline, the t-tests and end-point linear regression or logistic regression analyses are valid methods of comparison; however, patients who fail to provide any outcome data (at post-treatment and 6-months) measurement will naturally get excluded from the analyses, and this may introduce bias in the estimates. Furthermore, end-point analyses do not take into account the longitudinal nature of the data, time-varying covariates, or correlations among repeated observations.

For our main analysis, we will perform both cross-sectional and longitudinal analyses using Generalized Linear Mixed Model (SAS PROC MIXED) for continuous outcomes (for example, primary hypothesis) and PROC GLIMMIX for binary outcomes. We will model changes over time at population level. We will examine the

change in groups over time, i.e., change in treatment slopes over time, and the change in the difference between the slopes over time. We will fit a model that includes the fixed effects of PTSD severity at baseline, intervention, time, and the treatment by time interaction. We further plan to model changes over time at person-specific level by adding a random intercept and random slope to model the heterogeneity between individuals. We expect no significant site main effects or site by treatment interactions, but this will be examined. Although estimating the covariance structures is not a goal of the analyses, we will examine the model fit using different covariance structures as appropriate covariance structure is necessary for valid inferences about fixed effects. Once again, only those covariates that significantly reduce error variance will be added to the model. Demographic variables, baseline scores, baseline symptom severity, and site will be considered as possible covariates. We will plot predicted means for the groups over time, and for each site, along with confidence intervals.

Some simple parametric (e.g. linear or quadratic) curves will be used to describe the changes over time of the mean response. The fitting of parsimonious models for the mean response will result in statistical tests of covariate effect (e.g. treatment by time interactions) that have greater power than, for example, in analysis of response profiles.[95]

If the mean response changes in an approximately linear fashion over the duration of the study, we will adopt the following linear trend model

Hypothesis 1 and 2**:** $E(Y_{ij}) = \beta_1 + \beta_2 Time_{ij} + \beta_3\ Group_i + \beta_4 Time_{ij} * Group_i$

Where $Group_i = 1$ if the i^{th} individual was assigned to the CBT treatment, and $Group_i = 0$ otherwise; and $Time_{ij}$ denotes the measurement time for the j^{th} measurement on the i^{th} individual.

Our primary interest concerns a comparison of the changes in the mean response over time, which is a comparison of the slopes. The slope, or the rate of change in the mean response per unit change in time, is β_2 in the control group, and $(\beta_2 + \beta_4)$ in the treatment group. Thus, if β_4 is not significantly different from 0, then the two groups do not differ in terms of changes in their mean response over time.

Assuming that the changes in the mean response can be approximated by quadratic trends, the following model can be adopted:

$$E(Y_{ij}) = \beta_1 + \beta_2 Time_{ij} + \beta_3 Time^2_{ij} + \beta_3\ Group_i + \beta_5 Time_{ij} X Group_i + \beta_6 Time^2_{ij} X Group_i$$

Finally, we will contrast of the group population means across time points. For example, mean difference $\mu_1 - \mu_2$ is likely to be 0 at baseline if randomization is successful. With the different impact of treatments, mean difference might be 10 (on the CAPS scale) at end of study. We would like to test whether this change in mean difference is significant. This is our hypothesis 1 and 2.

2. The effects of CBT on retention

Hypothesis 3 (secondary): Patients who receive CBT will have better retention in the addiction treatment program relative to patients who receive TAU as measured by the proportion of expected days of treatment attended.

For patients in IOPs, we will calculate the proportion of substance abuse treatment completed as a percentage of the full treatment. Using this completion proportion as our dependent variable, we will conduct a multivariate linear regression analysis that includes variables such as treatment assignment, demographic information, and baseline symptom severity as potential covariates, for example:

$$E(Y_j) = \beta_1 + \beta_2\ Group_i + \beta_3 CAPS_{i0} + \beta_3 AGE_{i0} + \beta_4 SEX_{i0}$$

Where i0 stands for the i^{th} individual's measurement at baseline (time=0).If, for example, β_2 is not significantly different from 0, then the two groups do not differ in terms of completion proportion when adjusted for age, gender, and baseline symptom severity as measured by CAPS.

Data on utilization and retention will be extracted from medical records using CAPRI or JLV. The HIPPA Authorization and the Informed Consent both clearly state that this information will be obtained from their medical records.

3. Exploratory analyses

In addition to the hypotheses above we will also examine if patients in CBT show greater improvement in depression and functioning than patients in TAU as measured by the PHQ-9 and SF-12V, respectively, at baseline, post-treatment and 6 month follow-up. Other exploratory analyses will examine predictors of clinical response, including age, gender, race, era, severity of PTSD, TBI screening status, and PTSD disability status. We realize that causal inferences will not be possible as the groups will not be balanced with respect to important covariates and risk factors. We also realize that these analyses will require multiple statistical tests and are not grounded in specific hypotheses. This may require downward adjustment from the conventional alpha (.05) level to avoid an unacceptable experimental-wise Type 1 error rate. At the same time, we also recognize that statistical power for some of these analyses may be unacceptably low. Therefore, we will focus on reporting effect sizes in addition to p-values so that we do not infer causality and instead place the results in a practical context.

H. Project Management Plan

1. Management Plan

Dr. Hamblen will coordinate the management and oversight of the study. She works closely with Dr. Schnurr, who has agreed to meet weekly or more often to discuss study progress and problems. Dr. Schnurr's track record managing multi-site studies in VA and her close proximity to the PI enhances the likelihood of the trial being conducted successfully. Dr. Hamblen will meet weekly with site-PIs initially to monitor start up issues such as human subjects, hiring, and training and later to insure that patient recruitment goals are being met and that the study is being conducted in an effective and unintrusive manner. Dr. Hamblen will hold monthly calls with co-investigators to provide study updates and to troubleshoot. Together with Dr. McGovern, Dr. Hamblen will train therapists. She will then supervise them with the assistance of Dr. Bernardy. Dr. Mueser will provide overall fidelity monitoring.

2. Project Timeline

Table 5 depicts the timeline to realize the proposed study. The first 5 months will be devoted to preparation and training. We will recruit and hire site coordinators and obtain IRB approval. We will also finalize the operations manual. The next phase involves training therapists and the independent assessor. We will also set up the database. Beginning in month 6 and continuing for 18 months, we will recruit patients into the trial. Treatment and follow-up begins in month 6 as well, continuing 6 months past the end of the recruitment through month 29. The last year will be devoted to closeout, analysis, and report writing.

Table 5. Project Timeline (Updated with no-cost extensions)

Calendar Year	2010			2011								
Fiscal Year	**2011**											
Month	OCT	NOV	DEC	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP
Obtain IRB approval	X	X	X	X	X	X						
Develop Ops Manual							X	X	X	X	X	X
Site IRB approval							X	X	X	X	X	X

Calendar Year	2011			2012								
Fiscal Year	**2012**											
Month	OCT	NOV	DEC	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP
Hire research staff	X	X	X	X	X	X	X	X	X	X	X	X
Staff training	X	X	X	X	X	X	X	X	X	X	X	X
Site IRB approval	X	X	X	X								
Therapist training							X	X	X	X	X	X

Calendar Year	2012			2013								
Fiscal Year	**2013**											
Month	OCT	NOV	DEC	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP
Develop Ops Manual	X	X										
Hire research staff	X	X	X									
Staff training	X	X	X									
Site IRB approval										X	X	X
Recruitment				X	X	X	X	X	X	X	X	X
Treatment				X	X	X	X	X	X	X	X	X
Follow-up							X	X	X	X	X	X
Database mgmt	X	X	X	X	X	X	X	X	X	X	X	X

Calendar Year	2013			2014								
Fiscal Year	**2014**											
Month	OCT	NOV	DEC	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP
Recruitment	X	X	X	X	X	X	X	X	X	X	X	X
Treatment	X	X	X	X	X	X	X	X	X	X	X	X
Follow-up	X	X	X	X	X	X	X	X	X	X	X	X
Database mgmt	X	X	X	X	X	X	X	X	X	X	X	X

Calendar Year	2014	2015

Fiscal Year	**2015**											
Month	OCT	NOV	DEC	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP
Recruitment	X	X	X	X	X	X	X	X	X	X	X	X
Treatment	X	X	X	X	X	X	X	X	X	X	X	X
Follow-up	X	X	X	X	X	X	X	X	X	X	X	X
Database mgmt	X	X	X	X	X	X	X	X	X	X	X	X

Calendar Year	2015			2016								
Fiscal Year	**2016**											
Month	OCT	NOV	DEC	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP
Recruitment	X	X	X	X	X	X	X	X	X	X	X	X
Treatment	X	X	X	X	X	X	X	X	X	X	X	X
Follow-up	X	X	X	X	X	X	X	X	X	X	X	X
Database mgmt	X	X	X	X	X	X	X	X	X	X	X	X

Calendar Year	2016			2017								
Fiscal Year	**2017**											
Month	OCT	NOV	DEC	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP
Recruitment	X											
Treatment	X											
Follow-up	X	X	X	X	X	X	X	X	X	X	X	
Database mgmt	X	X	X	X	X	X	X	X	X	X	X	
Data analysis												X

Calendar Year	2017			2018	
Fiscal Year	**2018**				
Month	OCT	NOV	DEC	JAN	FEB
Data analysis	X	X	X	X	X
Manuscript preparations	X	X	X	X	X

3. Roles of Study Staff

a. Key Personnel. The study brings together an experienced team of investigators and research staff who have a history of collaboration. **Jessica Hamblen, PhD** (Principal Investigator), is the Deputy Director for Education at the National Center for PTSD located at the VA Medical Center in White River Junction, VT and an Assistant professor at Dartmouth Medical School. She has experience developing PTSD treatments and conducting clinical trials and, in her role as Deputy, overseeing national educational initiatives. Dr. Hamblen is responsible for the overall project management and for supervising staff at the Project Management office to ensure successful conduct of the study. She will insure that protocols for human subjects are maintained and followed. In collaboration with Drs. McGovern and Bernardy, she will train and supervise research and assessment staff as well as provide clinical supervision to the study therapists. Dr. Hamblen will donate 20% effort to the project.

Paula Schnurr, PhD (co-investigator) is the Deputy Executive Director at the National Center for PTSD and a Research Professor at Dartmouth Medical School. She is an expert in the management and methodology of clinical trials. She led 2 VA Cooperative Studies on PTSD treatment and is currently a PI on two PTSD treatment studies, including a multi-site trial of integrated primary care for PTSD that is being conducted in VISN 17. As the senior researcher on the project she will assist the PI on all aspects of implementing and managing the trial to ensure that the project is carried out effectively. She will advise on analyses and collaborate with the PI on the interpretation of findings, manuscript preparation, and dissemination of the findings. Dr. Schnurr will donate 10% effort to the project.

Mark McGovern, PhD (co-investigator) is an Associate Professor of Psychiatry and of Community and Family Medicine at Dartmouth Medical School. Dr. McGovern has conducted research and published in the field of co-occurring disorders, was the recipient of a NIDA K23 Career Development Award to translate evidence-based treatments for co-occurring disorders into typical community addiction treatment settings, and is the primary developer of CBT for PTSD in addiction treatment. Dr. McGovern will be involved in all aspects of this proposal from study design, to implementation, to dissemination. In addition he will participate in the training of study therapists. Dr. McGovern will work 10% on this research project

Kim Mueser, PhD, (co-investigator), is a Professor of Psychiatry and of Community and Family Medicine at Dartmouth Medical School. Dr. Mueser is a clinical psychologist and the primary developer of the CBT for PTSD among persons with severe mental illnesses. Dr. Mueser will be the primary treatment fidelity monitor. He will assist with the examination of CBT for PTSD and in interpretation of findings. Dr. Mueser will work 5% on this research project.

Rachel Kimerling, PhD (co-investigator) is a licensed clinical psychologist on the research staff at the National Center for PTSD in Palo Alto. She is currently conducting a randomized controlled trial of SS. Building on her experience with her current trial, she will advise the PI how to most successfully interface with the addiction staff so as to best integrate the CBT treatment into services as usual. She will also oversee our medical record data extraction plan.

Kyle Possemato, PhD (co-investigator and site PI) is a clinical research psychologist and Assistant Research Director of the VISN 2 Center for Integrated Healthcare at Syracuse. Dr. Possemato's research focuses on testing and implementing cognitive-behavioral and mindfulness interventions focused on increasing engagement in care and reducing PTSD symptoms and alcohol use among Veterans. She will assist the PI with subject recruitment and retention, help with data extraction required to measure utilization and retention, and serve in the additional role as Site-PI for Syracuse.

Nancy Bernardy, PhD (co-investigator) is a clinical psychologist and Program Director of the National Center for PTSD's Mentoring Program. Dr. Bernardy served as project coordinator on two of Dr. Schnurr's trials before accepting a clinical position with the Department of Defense in Europe where she worked for over four year with returning troops with primary substance abuse issues. Now back at the Center, Dr. Bernardy will provide supervision to study therapists and will assist with matters pertaining to coordinating clinical trials. Dr. Bernardy will donate 5% effort on the project.

Carole A. Lunney, MA and Bernard Cole, PhD will serve as biostatisticians. They currently work for the National Center for PTSD and have expertise in clinical trials research methods, and longitudinal data analysis. They will collaborate with the PI to develop optimal plans for study design and data analysis, will provide on-going consultation, and will randomize study patients to treatment groups.

Christopher Monahan, PhD (Site PI) is the PTSD-SUD staff psychologist at the Tampa, VA IOP. He will serve as site-PI. He will donate 10% effort on the project.

Project Manager (TBA). A 1.0 FTEE Project Manager will be recruited to oversee the day-to-day operations of the study, coordinate communication across all sites, and manage the budget. The project manager will ensure that all study materials are recorded, mailed, monitored, and reviewed in a timely fashion.

Assessment Fidelity Monitor (TBA). A .2 FTEE psychologist will serve as an Assessment Fidelity Monitor and will rate 10% of all SCID and CAPS assessments to assess inter-rater reliability.

Daniel Kivlahan, PhD (consultant) serves as Chair of the Research Review Committee and Director of the Center of Excellence in Substance Abuse Treatment and Education (CESATE). He is also Associate Professor at the University of Washington's Department of Psychiatry and Behavioral Sciences. He will provide expertise into VA's system of SUD care and will provide consultation on study design and implementation. Dr. Kivlahan will donate his time as needed.

Tracy Stecker, PhD (collaborator) is an Assistant Professor of Community and Family Medicine, Dartmouth Medical School. She is a NIMH and NIAAA funded principal investigator, with expertise in treatment access and engagement using cognitive behavioral approaches. She will assist in recruitment issues and guidance in approaches to engage patients. She will work 2.5% across all three years.

b. Other personnel

Each of the sites will have the following field staff:

Site-Coordinator (TBA) a .5 FTEE site coordinator will manage the day-to-day operations of the study and will stay in close communication with the project manager. They will recruit and consent patients, perform chart abstraction, be responsible for maintaining data in an approved, safe environment and entering it into electronic databases maintained on the VA Network.

Independent Assessor (TBA). A .2 FTEE independent assessor will be responsible for administering eligibility assessments to patients and conducting the initial and follow up assessments.

Therapist (TBA). A .2 FTEE therapist will be identified to provide the CBT treatment. This will be an unfunded position. However, an additional therapist will be trained at the outset in case the primary therapist is unable to deliver the treatment for any reason.

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