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PRINCIPAL INVESTIGATOR: John D. Roache, Ph.D.

CONTRACTING ORGANIZATION: University of Texas Health Science Center
San Antonio, TX

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John D. Roache, Ph.D.
Email: roache@uthscsa.edu

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14. ABSTRACT

We propose two experiments addressing the effectiveness of SSRI's for the treatment of PTSD in OEF/OIF veterans with combat-related trauma. First we will collaborate with Dr. Young who is conducting a Fluoxetine vs. placebo comparison for the treatment of PTSD among OEF/OIF active-duty personal stationed at Fort Hood after their return from deployment in the Middle East. For this study, we will add to the ongoing clinical trial, assessment of drinking behavior and four other measures necessary to derive patients' alcohol-related subtype. Second, we will conduct a prospective study comparing the effectiveness of Sertraline vs. Placebo to treat PTSD in OEF/OIF veterans who have a PTSD + Alcohol Dependence dual diagnosis and are seeking treatment within the VA. For Both studies we hypothesize that alcohol-related subtypes can be derived from amongst the subject population which will predict the outcomes of treatment with the SSRIs. Also, both studies will collect DNA for the assessment of genetic polymorphisms pertinent to the prediction of treatment outcome.

15. SUBJECT TERMS

None provided.

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INTRODUCTION:

As part of the STRONG STAR Consortium, this project proposes to study the assessment and treatment of alcohol dependence comorbidity among OEF/OIF military personnel and separated veterans who have PTSD and were exposed to combat-related trauma. A particularly important aspect of this study is to evaluate the hypothesis that there are subgroups of patients who have different phenomenological presentations of alcohol dependence comorbidity; and further that these subgroups have fundamental differences in their serotonin biology that cause them to respond differently to medication treatment with selective serotonin reuptake inhibitors (SSRI's). These objectives are being approached in two different ways. First, we plan to conduct a randomized clinical trial evaluating the efficacy of sertraline (an SSRI) in the treatment of Dual Diagnosis PTSD-Alcohol Dependence patients who are OEF/OIF veterans seeking treatment in the Texas Veterans Health Care System. Second, we plan to develop a protocol to assess the drinking behaviors and phenomenological characteristics of active-duty military personnel receiving treatment for psychiatric symptoms at Fort Hood. In the first year of the project funding, we have focused our work on developing the research protocol to examine sertraline efficacy in different subgroups of Dual Diagnosis PTSD-Alcohol Dependence veterans seeking treatment in the South Texas and Central Texas Veteran's Health Care Systems.

The study is a two-site, randomized, placebo-controlled, double-blind parallel-group treatment of 240 male and female veterans of OEF/OIF campaigns who have PTSD and Alcohol Dependence. All patients will receive 12-weeks of an integrated, manualized cognitive and behavioral psychotherapy as the standard of care and will be randomized to receive either sertraline (150 mg) or placebo as an adjunct to treatment. Randomization will be stratified based upon the Onset Precedence (before vs. after) of Alcohol Dependence symptoms (i.e., were symptoms of alcohol dependence preceding or subsequent to battlefield-related trauma exposure). *Post-Hoc* clustering techniques will be used to derive two subgroups of patients and data will be analyzed for the hypothesis that patients classified as Type-A will respond favorably to sertraline whereas patients classified as Type-B will do less well with sertraline than with placebo.

BODY:

- Preparation and Review of the Research Proposal for Multiple IRB Approvals. We have developed the final study protocol to evaluate the efficacy of sertraline in OEF/OIF veterans seeking treatment for PTSD-Alcohol Dependence Dual Diagnosis in the South Texas (STVHSC) and Central Texas (CTVHSC) VA systems. The Protocol was developed by Dr. Roache to assess patients for serotonin biological factors and to assess them for their phenomenological classification as to validated sub-type of alcohol dependence. The protocol also was developed with the collaboration of Drs. Sudie Back and Kathleen Brady who are experts in Dual Diagnosis treatment at the Medical College of South Carolina (MUSC) and who have developed an evidence-based, integrated psychotherapy for Dual Diagnosis. The therapy known as COPE, integrates standard CBT for alcohol dependence with Exposure Therapy for PTSD. We have established an excellent collaboration with Sudie Back, Ph.D. and Kathleen Brady, M.D., Ph.D. who are experts with Dual Diagnosis treatment of PTSD and who have developed the COPE Therapy manual which will be used as the standard of care for the research treatment study. We also have established a collaboration with John Klocek, Ph.D. who will be the primary psychologist at the

CTVHSC. Dr. Crystal Pearson at the STVHCS has given notice of her departure from that position, and we have worked closely with Drs. Flynn and Kearney who are the Mental Health Product Line Chief and Director of Psychology at the STVHCS to recruit in a new psychologist to replace Dr. Pearson. Final protocol approval at the STVHCS is pending identification of this new psychologist. The protocol was approved by the University of Texas Health Science Center at San Antonio (UTHSCSA) Institutional Review Board (IRB) 3 Mar 2009. This IRB is the primary IRB of record for Dr. Roache and the STRONG STAR Consortium and the STVHCS. The STVHCS Research & Development Office also has given contingent approval pending identification of clinically-responsible VA personnel. Dr. Klocek at the CTVHCS has only just now submitted the protocol to the CTVHCS IRB in Waco and approval there is expected by the end of Sep 2009. The study protocol was submitted to U. S. Army Medical Research and Materiel Command (USAMRMC) Human Research Protection Office (HRPO) 15 Aug 2009 and that submission is pending review at the time of this report.

- Hiring and Training of Research Staff. Drs. Roache and Ms. Benson have been working to develop the study procedures for the treatment protocol and Dr. Javors for the biological assessments required for the study. Mr. Jonathon Polanco has been appointed as the Study Coordinator and Jeslina Raj, Psy.D. has been hired to provide psychotherapy at the San Antonio site. Dr. Raj is applying to the VA for WOC (without compensation) status to conduct therapy on site. Dr. Klocek has been appointed to the PTSD Center of Excellence and given protected time to work on and develop the study site at the CTVHCS. Dr. Back has visited the San Antonio site and trained study personnel in the COPE psychotherapy manual.

- Participant Recruitment, Therapy, Participant Evaluation. The SOW planned no patient accrual in the first three quarters. Delays in regulatory approval predict there will not be patient accrual in the last quarter either – however, we do expect that all regulatory approvals will enable the San Antonio site to begin patient accrual in the 5th quarter of the contract period.

- Data Analysis. Pending participant recruitment and treatment.

- Administrative Tasks. Dr. Roache and members of the Research Team attended the STRONG STAR Investigators Kick-Off meeting in San Antonio, TX in Sep 2008. Dr. Roache and members of the Research Team participated in weekly STRONG STAR teleconferences. Dr. Roache and members of the Research Team also attended the first annual meeting for STRONG STAR investigators in San Antonio on July 20-21, 2009.

KEY RESEARCH ACCOMPLISHMENTS:

- No research patient accrual has been achieved.
- The final study Protocol and study procedures have been developed and the protocol has received final IRB approval from the primary study-site IRB of record.
- The Protocol has been submitted to HRPO for final regulatory approval.
- Personnel have hired and trained in study procedures.

REPORTABLE OUTCOMES:

- A Poster has been developed for presentation at the Military Health Forum in Kansas City (see Appendix B).

CONCLUSION:

The proposed research is focused upon the OEF/OIF veteran-population within the VA Health Care system. However, the hypotheses, study design, and treatments are not unique to the VA and the results are extremely important to the DoD and approaches to enhance warrior resilience. It is important discover the biological basis for behavioral disorders such as alcohol dependence and PTSD. It is perhaps even more important to understand the biological basis of individual differences in treatment response so that we can predict who will respond in what ways. Given our hypothesis that some patients actually may not respond well to SSRI's, it is critical to gain this information as soon as possible and to get it out into the VA/DoD and public domain so that doctors will not make the mistake of producing iatrogenic complications in their treatments. The notion that SSRI treatment can actually exacerbate drinking problems is not generally recognized by the treatment community and needs to be better understood so that iatrogenic harm can be avoided.

Thus, the proposed research has potentially great impact upon the health care of OEF/OIF veterans, but equally so for the general public and the general medical practice in the U.S. and the world. In order to facilitate this information, the results will be published in major medical journals and press-releases will be issued to popular media outlets

REFERENCES:

None

APPENDICES:

Appendix A: See Attached Study Protocol

Appendix B: Study Poster from the Military Health Research Forum in Kansas City

A. BACKGROUND

A.1 Problems of PTSD for the VA

Military personnel exposed to combat may be the most high-risk population for the development of Posttraumatic Stress Disorder (PTSD) because of their recurrent exposure to extreme trauma (Harvey et al., 2003; Jones, 2004; Lamberg, 2004). Since the September 11, 2001 terrorist attacks on the United States nearly 1 million U.S. military personnel have deployed on missions in Afghanistan (OEF=Operation Enduring Freedom) and Iraq (OIF=Operation Iraqi Freedom). Recent studies by Hoge et al., (2004, 2006) found that 5-13% of Soldiers and Marines who returned from a deployment in Iraq had symptoms of (PTSD). Similar results were reported in a May 2006 report by the Government Accounting Office (GAO) which indicated that about 5% of servicemen returning from Iraq and Afghanistan were at risk for developing PTSD. This report also noted that only 22% of these individuals were referred on for further evaluation and possible treatment. PTSD is a common illness within the Veterans Administration (VA) system (Wilson & Kizer, 1997) and the most common psychiatric condition for which veterans seek VA benefits (Schnurr et al., 2000). The disorder is a maladaptive response to the acute stress of having experienced a traumatic event perceived as threatening the life or physical integrity of oneself or someone else close to oneself. Substantial distress and dysfunction occur in someone with PTSD because of the chronic re-experiencing of intrusive thoughts, feelings, and memories of the trauma which cause avoidance and hyperarousal. For both men and women in a national sample (Kessler et al., 1995), the most common types of trauma include accidents, natural disasters, witnessing the unnatural death of others, and among women, rape and molestation. The traumatic experience which is most often reported often among male veterans is being threatened with a weapon and/or being in mortal combat. Despite efforts to control exposure to trauma, military service remains inherently dangerous. The experiences of troops in times of war continue to grow more stressful and demanding (Keegan, 1976). In peacetime, the demands of training for war can exact a high psychological toll (Grossman, 1995). Even apart from military conflict, service-women are at risk also for sexual abuse. In one study, 70.9% of servicewomen's applications for VA disability included in-service sexual assault as an inciting trauma (Murdoch et al., 2003). These facts ensure that PTSD will be an ever present consequence of military service.

A. 2 Treatment of PTSD in the VA

Among patients with PTSD, there is a high incidence of comorbid conditions that present special demands to the DoD and VA health care systems. A survey of all male patients receiving clinical care (medical and psychiatric) at Boston area outpatient VA clinics revealed that 20% had a diagnosis of PTSD (Hankin et al., 1999). Of those with PTSD, 82% had a comorbid major depression and 24% had an alcohol use disorder. While the high prevalence of PTSD/alcohol dependence comorbidity and the special treatment demands it requires presents a burden to the DoD and VA mental health systems, the true cost is even greater. PTSD patients show increased use of mental health services compared to veterans with major depression or alcohol dependence alone (Hankin et al., 1999) and increased use of medical treatment services as well (Schnurr et al., 2000). In addition, treating patients with comorbid PTSD and alcohol dependence requires more services since they show poorer social adjustment and have reduced social resources compared to those with PTSD or alcohol dependence alone (Riggs et al., 2003).

Although other types of medications have been used, serotonin-selective reuptake inhibitors (SSRI's) have been the medications of choice for the treatment of PTSD (Albucher & Liberzon, 2002; Stein et al., 2002; Ursano et al., 2004) both within the VA and in the field in general. Sertraline was the first medication approved by the FDA for PTSD treatment based upon randomized, double-blind, placebo-controlled studies showing sertraline to be superior to placebo in treating active PTSD symptoms (Brady et al., 2000; Davidson et al., 2001b), and in preventing relapse after remission (Davidson et al., 2001a). Paroxetine also received FDA

approval for treating PTSD based upon randomized, double-blind, placebo-controlled trials (Marshall et al., 2001; Tucker et al., 2001). Although not registered with the FDA for the treatment of PTSD, fluoxetine also has been effective in randomized, controlled trials (Connor et al., 1999; Martenyi et al., 2002b; Van der Kolk et al., 1994). Despite these findings, a recent Institute of Medicine report suggested that the evidence for efficacy of SSRI's in the treatment of PTSD is not as strong as it is for cognitive behavioral therapies including exposure therapy (IOM, 2007). That report further concluded that the best evidence for SSRI efficacy was in cases of civilian trauma and that little research had been done so show efficacy in combat-related trauma. Nonetheless, SSRI's are "strongly recommended" by the VA/DoD Clinical Practice Guideline for the treatment of PTSD (http://www.oqp.med.va.gov/cpg/PTSD/G/Interv_Sum508.pdf) and they continue to be used frequently in veteran populations.

VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF POST TRAUMATIC STRESS

Interventions Module Summary

B. Post Traumatic Stress Disorder (PTSD) Pharmacotherapy

Table B1: Summary Table

R	Significant Benefit	Some Benefit	Unknown	No Benefit/Harm
A	SSRIs			
B	RECOMMENDATIONS			
C	**MONOTHERAPY:**			
I	1. Strongly recommend selective serotonin reuptake inhibitors (SSRIs) for the treatment of PTSD.			
D				Benzodiazepines Typical Antipsychotics

Cognitive-behavior therapy (CBT) has been demonstrated to be the most effective non-pharmacological treatment for PTSD (Nemeroff et al., 2006; Office of Quality and Performance, 2006). CBT is a broad term that encompasses several different variants of CBT treatment approaches including Prolonged Exposure Therapy (Cigrang et al., 2005; Cooper & Clum, 1989; Foa et al., 1991, 1995, 1999, 2004, 2005; Marks et al., 1998; Paunovic & Ost, 2001; Rothbaum et al., 2005; Tarrier et al., 1999), Seeking Safety Therapy (Najavits, 2002, 2004, in press; Najavits et al., 1998, 2004; Ouimette et al., 1998; Zlotnick et al., 2003), Eye Movement Desensitization and Reprocessing (Shapiro, 1989, 1995, 1996, 1999), and Cognitive Processing Therapy (Resick et al., 2002; Resick & Schnicke, 1992, 1993). The research data are very limited when evaluating CBT treatments for co-morbid PTSD and alcohol. One notable exception is a form of CBT called Seeking Safety Therapy (Najavits et al., 1998, 2004; Ouimette et al., 1998; Zlotnick et al. 2003). Second, Triffleman, Carroll, & Kellogg (1999) have developed Substance Dependence PTSD Therapy (SDPT), a manualized treatment for substance use and PTSD symptoms. Both of these treatments have shown promising results in preliminary studies. Last, Concurrent Treatment of PTSD and Cocaine Dependence (CTPCD), was developed to treat comorbid PTSD and cocaine dependence. CTPCD incorporates two empirically supported treatments—a cognitive behavioral intervention for substance dependence (Carroll, 1998) and Prolonged Exposure Therapy (PE) (Foa & Rothbaum, 1998). CTPCD has also been adapted to address alcohol dependence, known as Concurrent Treatment with Prolonged Exposure (COPE) and preliminary results are promising (Brady et al., 2001).

A.3 Subtypes of Alcoholism

There has been a long-standing interest in sub-grouping types of alcoholism (Bowman & Jellinek, 1941). The "delta" and "gamma" species described by Jellinek (1960) represented the two most common subtypes who were distinguished based upon the psychopathology, severity of drinking, and psychosocial disruption. In a series of adoption studies examining the inheritance of vulnerability, Cloninger (1987) and colleagues (1981) proposed a dichotomous classification of "milieu-limited" (Type I) and "male-limited" (Type II) alcoholism where Type II alcoholics were considered to have inherited personality characteristics, usually from alcoholic fathers, that caused antisocial behavior, and heavy, problem drinking at a young age. More recently, Babor et al. (1992a,b) proposed a dichotomous classification of alcoholism (Type A vs. Type B) based upon an empirical clustering method involving 17 defining patient characteristics in 228 male and 85 female (n=321) alcoholics. Babor described that **the Type B cluster is "...characterized by early onset, a more rapid course, more severe symptoms, greater psychological vulnerability, and poorer prognosis**." (Babor et al., 1992b). Schuckit et al. (1995) applied the k-means clustering approach to 1539 alcohol-dependent participants in the Collaborative Study on the Genetics of Alcoholism (COGA) and replicated Babor's Type A/B classification and further described the **Type B subgroup as having an earlier onset and more severe disease**. Carpenter and Hasin (2001) compared Cloninger's Type I/II and Babor's Type A/B classification amongst a group of non-

severe "problem drinkers" from a general population sample (n=8643) and a selected community sample (n=664) and found a dichotomous classification resembling Babor's Type A/B. The authors further stated that clustering techniques were "…stronger for the A/B subtype model that incorporates dimensions of alcohol use and/or the frequency of negative consequences". Thus the post-hoc sorting of patients into categories has reproducibly dichotomized a subgroup of alcoholics is characterized by an earlier onset of more severe symptoms and worse prognosis.

The Type A/B classification scheme roughly divides alcoholics by severity (Schuckit et al., 1995; Kranzler et al., 1996; Carpenter & Hasin, 2001). Descriptions of Type B alcoholism are consistent with suggestions that inherited biological vulnerabilities, are revealed by an early onset, rapidly developing disease state that results in more severe psychiatric and psychosocial pathology (Buydens-Branchey et al., 1989a,b; Johnson, 2000a; Johnson et al., 2000b,c; von Knorring et al.,1987). A problem with the empirical clustering techniques of multi-dimensional classification is that they must be done post-hoc. It is difficult to prospectively classify one individual who exhibits certain, but not all classification characteristics. However, "Age of Onset" of alcoholism appears to do this. Individuals who have "biological" vulnerabilities that dispose them to psychopathology including alcoholism are more likely to have an earlier onset and more severe course of the illness (Johnson, 2000a, 2004; Johnson & Ait-Daoud, 2000; Johnson et al., 2000b,c). Thus, alcoholics have been classified as Early Onset Alcoholics (EOA) or Late Onset Alcoholics (LOA) based upon the age at which they began experiencing the problems of alcohol dependence. While different ages of onset (i.e., < 20, <25 yrs, etc.) have been proposed as the cut-off for discriminating between EOA and LOA (Babor et al., 1992a,b; Irwin et al., 1990), our own results (Johnson et al., 2000b) showed primarily quantitative (not qualitative) differences in psychopathological frequency and severity as a result of using different cut-off ages. Comparisons of different typologies have confirmed "Age of Onset" to be a critical parameter for segregating subgroups of alcoholics (Penick et al., 1999; Irwin et al., 1990). A survival analysis of age to first use of alcohol and other drugs across seven international sites demonstrated substantial country differences in prevalence but a remarkable consistency in the ages of onset of first use (Vega et al., 2002). That study concluded that in each ethnically and culturally diverse population, there is a vulnerable group of individuals who begin using substances at a younger age than the majority and these individuals also have a more severe course of the dependence syndrome.

We previously have used age of onset to classify subgroups of alcoholics prospectively (Johnson et al., 2000b,c). In a study of the effects of ondansetron, a 5-HT3 receptor antagonist, alcohol dependent outpatients were classified a priori as EOA (onset < 25 yrs) vs. LOA (onset > 25 yrs) and this classification was used as a stratification variable prior to randomization to ondansetron vs. placebo (Johnson et al., 2000c). Importantly, ondansetron was shown to be significantly better than placebo to reduce drinking in EOA patients but not the LOA subgroup who did just as well with placebo in a treatment using CBT as the standard of care. That EOA subjects respond to ondansetron better than LOA subjects also was replicated in an open-label study with ondansetron (Kranzler et al., 2003). Recently, we reanalyzed the original ondansetron study (Johnson et al., 2000c) using cluster techniques to classify subjects as Type A/B (Roache et al., 2008), and found a 70% concordance between the Type A/B and LOA/EOA classification schemes as well as differential treatment response in the Type A/B subgroups. As with the LOA/EOA distinction, ondansetron was superior to placebo in the treatment of subjects classified as Type B and was not effective in subjects classified as Type A.

A.4 SSRI Treatment Efficacy Depends upon Alcoholism Subtype

Sertraline and other SSRI's. A number of different studies have reported beneficial effects of SSRI's to reduce alcohol drinking amongst heavy problem drinkers. Using an outpatient procedure to monitor the drinking of heavy social drinkers participating in medication research projects, a series of studies have reported that SSRI's including zimelidine, citalopram, viqualine, and fluoxetine each reduced alcohol intake in

comparison to placebo (Naranjo et al., 1984, 1987, 1989, 1990). However, the general use of the SSRI's fluvoxamine and fluoxetine given to alcohol dependent outpatients has not worked (Kranzler et al., 1993; 1995). In the latter of these studies (Kranzler et al., 1995), fluoxetine was superior to placebo at improving the depressive symptoms in a subgroup of patients with comorbid depression, but was of no overall benefit to reduce alcohol consumption. These investigators (Kranzler et al., 1996) subsequently reanalyzed their data after a cluster analysis divided their subjects into the Babor Type A/B groupings and found that while fluoxetine was no different than placebo in n=60 Type A alcoholics, it was significantly worse than placebo in n=35 Type B alcoholics. Because CBT was a standard of care in that study and all subjects showed drinking reductions from pre-study levels, the authors concluded that "fluoxetine reduced the beneficial effects of CBT" and that **"...fluoxetine not be used to maintain abstinence or reduce drinking in high-risk/severity alcoholics"**. Following up on that study, Pettinati et al. (2001) compared the effects of 200 mg sertraline vs. placebo in n=53 alcohol dependent patients with lifetime histories of depression vs. n=47 without histories of depression. She failed to detect antidepressant effects of sertraline at all, but did find that sertraline only reduced the drinking of subjects who had no lifetime history of depression. In order to try to understand this paradoxical finding, their data were reanalyzed by cluster analyses (Pettinati et al., 2000) after which **sertraline treatment was shown to be substantially superior to placebo to reduce drinking only in n=55 Type A alcoholics but not in n=45 Type B alcoholics**. At six month longitudinal follow-up of these patients after completing the study (Dundon et al., 2004), those Type A patients previously treated with sertraline continued to do better than those treated with placebo. In contrast, among the Type B alcoholics, those previously treated with sertraline drank significantly more over the follow-up period than did those treated with placebo. More recently, Chick et al. (2004) published the results of a reanalysis of a one-year long study in a large sample of alcohol dependent patients that originally was not published because fluvoxamine was poorly tolerated and associated with high drop-out rates, and the study found no difference between fluvoxamine vs. placebo on drinking outcomes. However, a reanalysis of those data divided subjects into Type I and Type II subgroups and also into EOA and LOA groupings based upon age of onset. Placebo treated subjects showed no differences amongst subgroups divided as Type I vs. Type II or divided as LOA vs. EOA. However, for subjects treated with fluvoxamine, the subgroups classified as Type II or EOA did worse than the subjects classified as Type I or LOA. Thus, data from three different studies of three different SSRI's, published in six different analyses, have all uniformly demonstrated that the classification of alcoholism subtype predicts response to SSRI's. All three studies have shown that **SSRI treatment can worsen the prognosis and increase drinking relative to placebo in the Type B, Type II, or EOA classified subgroup of alcoholics** that are characterized as more severe and more vulnerable, and more biologically determined. Beneficial effects of SSRI's to treat alcohol dependence only have been found in one study (Pettinati et al., 2000) where sertraline was superior to placebo in Type A alcoholics. Thus, **the typological classification of an alcoholic appears to be critical to predict response to treatment with SSRI's**.

SSRI's for the treatment of PTSD with comorbid Alcohol Dependence

Alcohol dependence is not uncommon among veterans (Hankin et al. 1999). It is characterized by continuing problems controlling one's consumption of alcohol despite medical, legal, or psychosocial problems brought on by or exacerbated by drinking. The chronic condition of alcohol dependence often results in psychosocial dysruption, increased prevalence of other mental illness including anxiety, depression, and PTSD, and an increase in the prevalence of other medical illnesses, especially hypertension, heart disease, and in the end stages, liver disease. Adding to the impairment attributable to either a substance use disorder or to PTSD, 50% of men and 30% of women with PTSD have a comorbid substance use disorder, most often involving alcohol or sedative drugs (Brown et al., 1995). Both PTSD and alcohol use disorders greatly increase a patient's likelihood of seeking mental health treatment within the VA system (Hankin et al., 1999).

If one considers the frequency of comorbid PTSD + Alcohol Dependence and the fact that SSRI's are "strongly recommended" by the VA/DoD Clinical Practice Guideline for the treatment of PTSD (http://www.oqp.med.va.gov/cpg/PTSD/G/Interv_Sum508.pdf), then the importance of differential effects of SSRI's in various subtypes of alcohol dependence becomes apparent. This fact has been shown, in a recent study of 94 subjects with civilian trauma-related PTSD and comorbid alcohol dependence (Brady et al., 2005). In that study, subjects were treated with CBT focusing on alcohol dependence and were given 150 mg sertraline vs. placebo under double-blind conditions for the treatment of PTSD. Although most subjects showed study-related decreases in drinking, sertraline was not different than placebo overall to decrease alcohol consumption in whole study cohort and there was only a non-significant trend for PTSD symptoms to be improved by sertraline. Given these equivocal results, a secondary cluster analysis identified three different subgroups of subjects based upon responses to treatment. Sertraline was superior to placebo in reducing the drinking amongst the smallest cluster (n=14) of patients although no sample sizes were reported for the drug vs. placebo groups within the cluster of 14 patients. A larger cluster (n=27) of subjects, who were heavier drinkers at baseline, showed that sertraline was worse than placebo in drinking outcomes. Finally, the largest cluster (n=53), who were the majority of the sample, showed no differential effect of sertraline. The marginal improvements in PTSD symptoms were seen uniformly across all three clusters indicating no subtype relationship to PTSD outcomes. Clearly, this study result a concern given previous research by the same group (Brady et al., 2000; Davidson et al., 2001a,b) showing effectiveness of sertraline for the treatment of primary PTSD. For the dual diagnosis study (Brady et al., 2005), it is not clear why the medication standard of care didn't improve PTSD symptoms to a greater extent, and it is not clear why sertraline didn't show more beneficial effects to reduce drinking in a larger proportion of subjects. Although the sample sizes of the clusters were too small to draw any meaningful conclusions, the authors suggested that Cluster 1, who showed benefits of sertraline, were Type A-like in character and had the least severe alcohol dependence and had an age of onset for PTSD which clearly preceded the onset of alcohol dependence. Similarly, among the Cluster 3 subjects, who were said to be Type B-like in having an earlier age of onset of more severe alcohol dependence, sertraline was less helpful than placebo in subjects receiving targeted CBT.

The current proposal is to systematically expand these findings and determine whether or not alcohol dependence subtyping may explain differential treatment outcomes in the use of the SSRI sertraline. Specifically, we will examine the efficacy of sertraline vs. placebo in a large sample of OEF/OIF veterans who have a PTSD and alcohol dependence dual diagnosis and who are receiving CBT for PTSD symptoms. Prior to randomization, subjects will be stratified into two groups based upon whether or not signs of alcohol dependence preceded or followed military-trauma exposure and after the study, multidimensional clustering techniques will be used post-hoc to classify subjects into Type A vs. Type B prior to the efficacy analysis. We hypothesize that sertraline will be superior

A.5 Role of the Serotonin Transporter and Serotonergic Hypotheses related to Alcoholism

Vulnerability Due to Low Serotonin. Strong evidence shows that the **biological vulnerability of EOA patients may be related to a serotonergic dysfunction** (Johnson, 2000; Johnson and Ait-Daoud, 2000; LeMarquand et al., 1994). EOA have been reported to have a lower cerebrospinal fluid levels of 5-HIAA than do LOA, and this effect was particularly great in those having a family history of alcoholism (Fils-Aime et al., 1996). Reduced plasma ratios of tryptophan to other neutral amino acids have also been related to alcoholism in general (Branchey et al., 1981) and to EOA more specifically (Branchey et al., 1984; Buydens-Branchey et al., 1989a,b). In particular, those studies found that alcoholics with the most reduced tryptophan ratios also had the greatest problems with aggression and depression. These findings directly tie together the affect and impulse control problems of EOA with a large literature on the role of reduced serotonin function in the comorbid symptoms of depression and impulse-control problems (Buydens-Branchey et al., 1989a,b; Linnoila, 1997; Linnoila & Virkkunen, 1992, 1994; Linnoila et al., 1993; Virkkunen and Linnoila, 1990). Reduced

serotonin function also is associated with impulsive aggression and excessive alcohol intake in monkeys (Heinz et al., 1998b).

Serotonin Transporter Polymorphisms - Genotype effects. The biological risks of alcoholism are undoubtedly determined by a multivariate interplay of genetic and environmental factors though it is well established that alcoholism is a heritable disease (Pickens et al., 1991; Schuckit and Smith, 2001). Molecular genetic studies of candidate genes or genetic linkage have identified possible chromosomal genes associated with alcoholism at higher frequencies than in control populations (Goldman, 1995; Edenberg and Kranzler, 2005; Kreek et al., 2005). The short (S) and long (L) polymorphism of the serotonin transporter promoter region (5-HTTLPR, genetic locus SLC6A4) has long been of interest as a potential risk factor for alcohol dependence as well as for other psychiatric disorders (Johnson, 2000; Schuckit et al., 1999). Recently a meta-analysis of 17 studies examining the serotonin transporter (Feinn et al., 2005) has shown that the S-allele is significantly associated with the risk of alcohol dependence among individuals with either a co-morbid psychiatric condition or an early-onset and more severe type of alcoholism. In contrast, the L-allele has been associated with risk of conversion to alcohol dependence among adults who showed a low level of alcohol responsiveness in college (Schuckit et al., 1999, Schuckit and Smith, 2001). Among 16-year old adolescents who currently reported using alcohol, those who were homozygous for the L-allele (i.e., LL) drank more heavily and reported experiencing a low-level of response to alcohol (Hinckers et al., 2006). While no alcoholism gene(s) has been found, it is becoming clear that complex diseases such as "alcoholism" are unlikely to be simply associated with one or even a few gene candidates (Moffitt et al., 2005). For this reason, our group has **focused efforts on the behavioral phenotypes of early ages of onset of alcoholism so as to study the biological correlates** of this behavior and the genetic factors influencing that biology.

The serotonin transporter gene is found on chromosome 17p12 and is regulated by the 5' regulatory promoter region (5'-HTTLPR) which has a 44 base pair insertion/deletion polymorphism creating a short (S) form which confers reduced gene expression and functionally reduced transporter levels (Heils et al., 1996). In normal subjects, the long (L) form, in comparison to the S-form of the 5'-HTTLPR promotor, results in greater SERT expression as seen in binding assays in brain imaging (Heinz et al., 2000), in lymphoblasts (Lesch et al., 1996), and in platelets (Greenberg et al., 1999). The S-allelic genotype has been linked to depression (Lotrich and Pollack, 2004) and anxiety-related traits (Lesch et al., 1996; Mazzanti et al., 1998) and greater fear activation of the amygdala in fMRI studies (Hariri et al., 2002). A recent study found that patients with generalized anxiety disorder who were L-carriers responded better to SSRI treatment than did the SS-homozygotes (Stein et al., 2006).

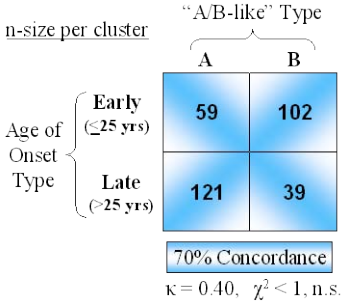
In most studies, the S-allele appears dominant amongst heterozygotes and therefore, compared to LL homozygotes, S-carriers show reduced binding in the brain (Heinz et al., 1998b, 2000, 2001). However, a platelet study of L and S carriers was able to assess both binding and function (Greenburg et al., 1999) and reported that found that the LL homozygotes showed only an increased functional uptake (Vmax) of 5-HT into the platelets, without changes in content or paroxetine binding (Bmax). In contrast to these findings of LL-associated increases in SERT in normal subject populations, Heinz and colleagues (2001) have reported that alcoholics, homozygous with the LL-form of SERT, show reductions in brain binding potential compared to normal controls while the S-carrier alcoholics are no different that S-carrier controls (Heinz et al., 1998b, 2000). This finding has been interpreted as a neurotoxic effect of alcohol in the LL genotype (Heinz et al., 2000) although an equally-likely possibility is that there is some other trait characteristic of the LL-carrier alcoholic phenotype that alters the normally-increased expression of SERT in the LL genotype.

Several allelic association studies have suggested links between polymorphic variation in serotonin transporter function and alcoholism, although the data are somewhat contradictory. The S-allele was nearly two times more common in 104 alcohol dependent patients than in controls in a French study (Hammoumi et al.,

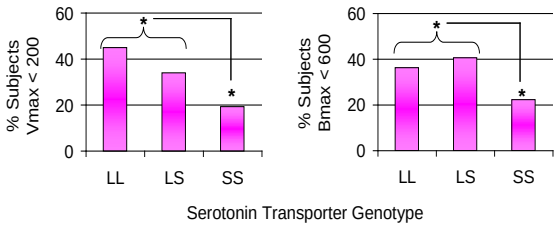
1999). In a study of alcohol-dependent males of Finnish ethnicity, SS homozygotes were more common in EOA than LOA or control subjects (Hallikainen et al., 1999). In a German study of forensic blood samples, the odds ratio of the S-allele was 2.82 times that of the L-allele in subjects whose blood alcohol levels evidenced "high tolerance" to alcohol as compared to "low tolerance" individuals (Turker et al., 1998). However, an American study contradicts these findings. When 41 sons of alcoholic fathers, who were originally tested for their sensitivity to alcohol challenges, were followed up 15 years later, 14 subjects homozygous with LL variant showed historically low responses to alcohol and a greater probability of current alcohol dependence (Schuckit et al., 1999). The relationship to alcohol sensitivity and SERT polymorphism is interesting because greater serotonin uptake has been associated with lower 5-HIAA, reduced alcohol sensitivity, and more aggressive behavior in monkeys (Heinz et al., 1998a).

Studies on platelet serotonin transporter biology have been valuable because unlike the brain binding studies, on can measure function as well as binding potential. Compared to control subjects, alcoholics have been shown to have both an increased (Daoust et al., 1991) and a reduced platelet serotonin uptake (Heinz et al. 1998b) although greater serotonin uptake has perhaps been more consistently seen with abstinence (Faraj et al., 1997). Our own studies on this subject have found that abstinent EOA may have greater platelet uptake of serotonin (Javors et al., 2000), but that actively drinking LL homozygotes have a dramatically reduced 5-HT uptake (Javors et al., 2005). Another study examined platelet binding in 72 control and 72 alcoholic subjects genotyped for the LL, LS, and SS variations and reported no population differences, no genotype effects, and no relation to self-reported impulsivity (Preuss et al., 2000). However, that study failed to measure 5-HT uptake function (i.e., Greenburg et al., 1999 showed functional, but not binding differences in normal population platelets) and all but five of the 72 alcoholics were of the Type 1 (LOA) typology (i.e., LOA may look more "normal" than EOA).

A.6 Preliminary Studies

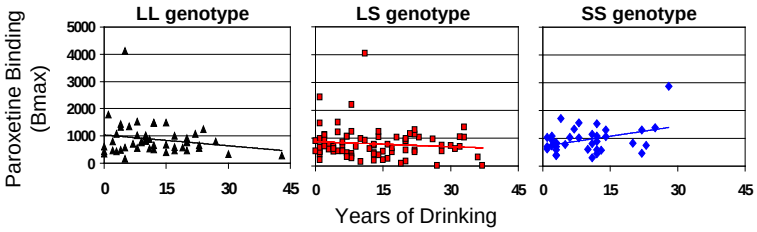


Alcoholism Treatment and Serotonin Biology. Our group previously has shown that the 5-HT_3 antagonist, ondansetron, was effective in the treatment of early onset (EOA) but not late onset (LOA) alcoholism (Johnson et al., 2000c). A reanalysis of the data of n=321 alcoholics and showed that the *a priori* classification of subjects by age of onset was about 70% concordant with a Type A/B classification from a *post hoc* cluster analysis (Roache et al., 2008). These data suggest **that using the EOA/LOA classification *a priori* has about a 70% chance of classifying subjects similar to the *post-hoc* Type A/B clusters**. Interestingly, despite the high concordance between age of onset and A/B typology, response to ondansetron in that analysis was predicted better by age of onset than by A/B classification.



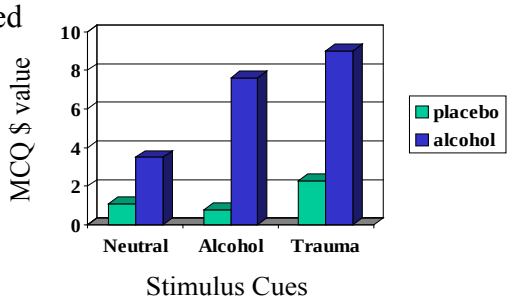
Another study of alcohol dependent outpatients by our group examined the serotonin biology of alcoholism and its relationship to the "long" vs. "short" diallelic polymorphism of the serotonin transporter. Previously, we reported (Javors et al., 2005) that compared to SS homozygotes, alcohol dependent subjects with the L-allele were more likely to have a reduced maximum uptake (Vmax < 200) of serotonin into blood platelets. These data have now been expanded to include n=198 patients wherein we find that compared to the SS homozygotes, L-carriers also are more likely to have reduced paroxetine binding (Bmax < 600) to the serotonin transporter (Johnson et al., 2008). These findings of reduced serotonergic functioning in L-carriers is contrary to previous data indicating that the L-allele is associated with increased transporter activity (Heinz et al., 1998b, 2000, 2001) but is consistent with the hypothesis that alcoholic drinking is "toxic" to the transporter activity and causes reduced functioning in L-carriers (Heinz et al., 2000).

In a recent study (Johnson et al., 2008), we found that this "down-regulation" (decreased paroxetine binding) of the serotonin transporter in LL-homozygotes is related to years of heavy alcohol drinking.



Studies in PTSD and Alcohol Dependence.

We previously have conducted one study in PTSD patients who reported a self-medication motive for the use/abuse of alcohol (Casada and Roache, 2002). This was a not for benefit research study where research volunteers were given trauma-related cues on some occasions and alcohol-related or neutral cues on other occasions to see how these factors provoke craving and alcohol use in the dual diagnosis population. The Multiple Choice Questionnaire (MCQ) was used to quantify alcohol-seeking behavior as the dollar value of a drink. The figure shows that an alcohol-containing beer was preferred by and more valuable than a placebo beer. More importantly, the presentation of both alcohol-related and trauma-related cues increased the dollar value of the alcohol compared to placebo. This is interpreted as "drug-seeking" behavior indicating that alcohol and trauma –related stimulus cues increased the reinforcing or reward value of alcohol. This finding has important implications for the current study proposal wherein we would hypothesize that successful reduction of PTSD symptoms should reduce drinking in the dual diagnosis population.



B. HYPOTHESIS

Study Rationale. Both PTSD and Alcohol Dependence are devastating disorders that each destroy lives and disable affected individuals. When PTSD and Alcohol Dependence are combined in the same patient, the dually-diagnosed individual has a worse prognosis and combined treatments are complicated. Selective Serotonin Reuptake Inhibitors (SSRI's) are a commonly used, standard of care medication treatment for PTSD. However, a recent Institute of Medicine Report (IOM, 2007) concluded that the evidence for SSRI efficacy is not strong – especially for combat-related trauma. SSRI's also are commonly prescribed for patients with alcohol dependence, but again their efficacy is limited. Now, there is strong evidence that different subtypes of alcoholics respond differently to serotonergic treatments (Roache et al., 2008). Specifically, those classified as Type A show benefits of SSRI treatment over placebo (Pettinati et al. 2000) while those classified as Type B, Type II, or Early Onset Alcoholics (EOA) show evidence that SSRI treatment is worse than placebo (Chick et al., 2004; Dundon et al., 2004; Kranzler et al., 1996). Within a group of dually-diagnosed patients having PTSD and Alcohol Dependence, Brady et al. (2005) reported that different subgroups of dually-diagnosed patients showed differential effects of sertraline treatment. Specifically, they reported one subgroup of n=27 patients (characterized as EOA/Type B-like), for whom sertraline was inferior to placebo, but another subgroup of n=14 patients having Type A-like characteristics, for whom sertraline was superior to placebo in the treatment of both PTSD and alcohol symptoms.

Hypothesized Effects	Alcohol Subtypes	
	Type B	Type A
PTSD symptoms:	Sert = placebo	Sert > placebo
Alcohol Drinking:	Sert ≤ placebo	Sert > placebo

We hypothesize that the same clustering and subtyping techniques found useful to predict alcoholism treatment outcome also can be employed in the dually-diagnosed PTSD-Alcohol population to identify clinically meaningful subgroups who will benefit from SSRI treatment as well as those who will not benefit from this treatment. Because the Early Onset/Type B form of alcohol dependence is believed to indicate a biological vulnerability related to serotonin deficiency, we further speculate that genetic and biochemical studies of serotonin transporter biology will help us to identify the

biological vulnerability that makes dual diagnosis patients differentially-responsive to the effects of SSRI's. We propose a study to confirm these hypotheses and to further understand the biological and psychosocial characteristics that distinguish SSRI responders and non-responders.

C. Technical Objectives

Specifically, we propose to conduct a clinical trial to evaluate sertraline treatment efficacy in a large sample of OEF/OIF veterans with dual diagnosis PTSD and Alcohol Dependence who are receiving Cognitive and Behavioral Therapy as part of the VA-system's new dual diagnosis program. The study is designed as an efficacy trial of sertraline used as an adjunct to Cognitive Behavioral Therapy (CBT) in the treatment of PTSD/Alcohol dual diagnosis. There are two outcomes of interest, namely PTSD symptom improvement and also decreased alcohol consumption. We are interested to know whether or not sertraline is superior to placebo in improving the symptoms of either one or both of these two disorders. Even though sertraline is a treatment of choice for PTSD, we expect that the comorbid condition of alcohol dependence will complicate the treatment of PTSD and that the clustered subgroups will show differential treatment response with sertraline. The primary objective of the present study is to identify subgroups of alcohol dependent persons with PTSD who will either benefit or not benefit from treatment with SSRI's. The proposed study will enroll veterans with PTSD and dually-diagnosed alcohol dependence in a 12-week treatment providing sertraline vs. placebo medication as an adjunct to manualized CBT and will specifically test the hypothesis that **subtypes of alcohol dependence can be used to predict which patients respond well and which subgroup responds poorly** to SSRI treatment. This study will address the following **Specific Aims:**

1. To determine whether multidimensional baseline measures can be used to classify Type A/B clusters of OIF/OEF veterans with dual diagnosis PTSD + Alcohol Dependence. *We hypothesize that two dichotomous subgroups having Type A-like and Type B-like clinical profiles will be classified from dual diagnosis veterans.*
2. To examine whether sertraline efficacy differs as a function of the Type A/B subtype classification. *We hypothesize that sertraline will:*
   - *i) not be different than placebo among the dual diagnosis population as a whole;*
   - *ii) will be less than or equal to ($\leq$) placebo in benefit to reduce either PTSD symptoms or alcoholic drinking among the Type B subgroup; but*
   - *iii) will be superior to (>) placebo to reduce both PTSD symptoms and alcohol drinking among the Type A subgroup.*

We expect that the CBT will have benefit to reduce both drinking and PTSD in OIF/OEF veterans and therefore compared to baseline, most study patients will show some improvement. **Aim #2 really is a standard efficacy trial of sertraline treatment for dual diagnosis** but with the *a priori* hypothesis that different subgroups of patients will respond differently to adjunctive medication treatment. The problem is that we are uncertain as to our ability to predict in advance, which patient is a member of which subgroup. Therefore **Aim #1 seeks to cluster subjects into clinically meaningful subgroups that will predict medication treatment response.** We expect to show that one subgroup of subjects (Type A) is benefited by sertraline treatment while the other subgroup (Type B) does not respond well to sertraline and may actually do worse than placebo-treated subjects. For the Type A subgroup, we expect that both PTSD and alcohol symptoms will show improvement. In contrast, we expect that sertraline will be significantly worse than placebo treatment to reduce drinking in the Type B group. This we expect to be true whether or not there is evidence for benefits of sertraline in the treatment of PTSD symptoms in the Type B subgroup.

We also have an exploratory aim to evaluate the possibility that the differential SSRI responsiveness of these clinically distinguishable subgroups (A vs. B) may be explained by differences in serotonin biology. This

aim is related to psychiatric literature showing that individuals with low serotonin functioning are vulnerable to psychiatric disturbance and that genetic polymorphisms of the serotonin reuptake transporter may account for vulnerability to disease. Since SSRI's work through the serotonin transporter, it is plausible that these same genetic variations also may explain differential treatment responses to SSRI's. Therefore, we seek to collect genetic and phenotypic expression data which might identify the serotonin biology associated with the subgroups who differentially respond well or poorly to treatment with sertraline.

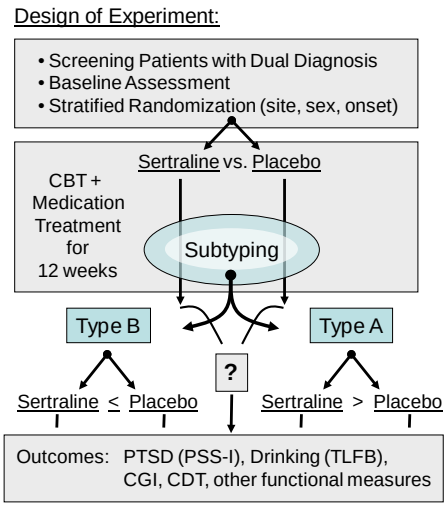
D. METHODS

D.1 Experimental Design

The study design is a parallel group, double-blind, placebo-controlled, stratified, randomized medication treatment trial of male and female OEF/OIF veterans who experienced "in-theater" trauma and meet DSM IV criteria for both **PTSD and Alcohol Dependence**. All subjects will receive manualized **Cognitive Behavior Therapy (CBT)** as a standard of care. Additionally, subjects will be randomized 1:1 to receive double-blind treatment with **Sertraline vs. Placebo** as an adjunctive treatment. The manualized therapy provides standard cognitive-behavioral treatment to address alcohol dependence and state-of-the-art behavioral exposure therapy targeting PTSD. Sertraline is a common treatment for PTSD and alcohol dependence but is hypothesized to have differential efficacy in different subtypes of alcohol dependent patients. A post-hoc clustering approach will be used to determine which subgroups of dual diagnosis patients may benefit from sertraline vs. placebo treatment.

As part of the STRONG STAR Consortium on PTSD, two VA sites in Texas – the South Texas Veterans Health Care System (STVHCS) and the Central Texas Veterans Health Care System (CTVHCS) – will enroll a total of n=240 treatment-seeking patients entering into the VA's Dual Diagnosis program. After providing written-informed consent, subjects will be screened for eligibility, and eligible subjects will begin the 12 week treatment protocol and follow-up assessments at one and six months post-treatment. Treatment includes manualized CBT for dual diagnosis and randomized study drug treatment with either sertraline (150 mg) or placebo, administered orally, under double-blind conditions. Prior to randomization, subjects will be stratified by site (two sites) to control for possible site differences, sex (M,F) to control for sex differences, and also by Onset Precedence (Pre/Post) to control for whether or not drinking-related problems occurred before or after service-related trauma exposure.

Weekly outcome assessments of PTSD symptoms and drinking patterns will utilize standard procedures to track changes over time. Drinking will be estimated for the 60 days prior to screening and subjects will be considered "evaluable" if they continue in study and comply with medication for at least four weeks post-randomization. Drinking will be assessed by validated Time-Line Follow-Back (TLFB) self-reports and by objective laboratory tests of Carbohydrate Deficient Transferrin (CDT) and Phosphotidyl-Ethanol (PE). PTSD symptoms will be assessed by the clinician administered PTSD Symptom Scale (PSS-I) and Clinician Assessment of PTSD Symptoms using the PCL-M.



Post-hoc clustering techniques will be used to classify phenomenological subgroups into Type A vs. Type B using dimensional measures similar to those employed in previous studies of primary alcohol dependence, but adapted to the dual diagnosis military-veteran population. Section D.4.3 describes ten baseline characteristics that will used for the cluster derivation. Basically, these include Age of Onset and Onset

Precedence (Pre vs. Post PTSD) factors, drinking and PTSD severity factors, other psychiatric or mood disturbance, personal trauma history, and family history of alcoholism. The efficacy of sertraline vs. placebo to reduce drinking and PTSD symptoms will be examined within each of these two empirically-derived clusters (Type A and Type B).

D.2 Subjects

Subject Population. Subjects will be 18-65 year old male or female veterans seeking treatment for service-related PTSD and who also have a dual diagnosis (DSM-IV criteria) of both PTSD and Alcohol Dependence. Subjects will be recruited from the VA Hospital. For study inclusion, subjects must meet diagnostic criteria for PTSD as determined by the clinician administered PTSD Symptom Scale (PSS-I) and minimum PTSD severity ($\geq$ 30 on the PCL) and currently be drinking heavily ($\geq$ 5 drinks per drinking day for men and $\geq$ 4 for women) on at least 50% of the past 30 days.

Inclusion Criteria

1. Male or female volunteers aged 18-65 years who are seeking treatment for PTSD and have an alcohol dependence dual diagnosis and meet DSM-IV criteria for PTSD and Alcohol Dependence.
2. Subjects must sign written informed consent after providing a 0.00 mg/dl breath alcohol sample and currently (within past 30 days) be drinking heavily (> 5 drinks per drinking day for men and > 4 for women) on at least 50% of the 30 days.
3. Subjects must have experienced trauma related to military deployment in OEF or OIF theater and have a PCL score $\geq$ 30;
4. Females must provide negative pregnancy urine tests at study intake and at during study participation; and also must not be nursing babies. They also must have a proven medical history of infertility or be practicing accepted methods of birth control including hormonal contraceptives, diaphragm, or condoms with spermicide;
5. Subjects must be healthy and have no medical illnesses which would preclude study participation (see exclusions);
6. subjects must be able to abstain from using any psychoactive drugs except for nicotine, caffeine, alcohol, and marijuana and be able to provide urine samples free from all drugs of abuse except cannabis;
7. Subjects taking prescription psychoactive medications (see exclusion criteria below) must be willing and able to discontinue the medication without serious risk and to do so for two weeks or five elimination half-lives (whichever is longer) prior to beginning the study.

Exclusion Criteria

1. Inability to tolerate sertraline;
2. Inability to commit to a regular schedule of clinic visits;
3. Inability to provide a 0.00 mg/dl breath alcohol sample without signs of withdrawal (withdrawal is defined as CIWA scores $\geq$ 10 in the presence 0.00 breath alcohol samples).
4. Physiological dependence on alcohol necessitating medical detoxification;
5. Lifetime history of bipolar disorder or psychotic disorder or current (within 1 year) diagnosis of a primary major depression requiring treatment;
6. An anxiety disorder unrelated to PTSD, which complicates treatment in the opinion of the investigator;
7. Current enrollment in psychodynamic or cognitive-behavioral therapy addressing PTSD or any substance abuse treatment outside of the study;
8. Any unstable medical illness, medical illnesses treated with psychoactive drugs (e.g. beta-blockers), medical illness complicating psychiatric symptoms (e.g. thyroid disease), or contraindications for treatment with sertraline or use of alcohol;

9. Current use of prescribed psychotropic medications including, but not limited to anticonvulsants, antidepressants, antihistamines, antipsychotics, anxiolytics, beta-blockers, hypnotics, and stimulants;
10. Any current or past history of illicit substance dependence excepting marijuana abuse or dependence;
11. Failure to provide a urine sample free from the presence of drugs of abuse (except cannabis);
12. Current suicide or homicide risk meriting crisis intervention.

D.2.2 Subject Recruitment and Screening

Subject recruitment Subjects will be recruited through self-referral from flyers posted in the psychiatric triage service, and in the PCT and Dual Diagnosis clinics at the VA and by psychologist or physician referral from VA clinics. Any subject reporting symptoms of PTSD and alcohol use disorder and interest in receiving treatment for dual diagnoses will be invited for written informed consent and eligibility screening.

Subject Screening: Subjects providing consent will be screened by structured clinical interviews and patient-completed questionnaires. Physical health will be screened by medical history, physical examination, and laboratory tests. PTSD diagnoses will be established using the clinician-administered PTSD Symptom Scale (PSS-I) and severity of symptoms must be $\geq$ 30 on the PTSD Checklist – Military Version (PCL-M) a 17 item self-report measure that evaluates the severity of PTSD symptoms in the last month (Weathers, Litz, Herman, Huska, & Keane, 1993). Other Axis I diagnoses will be determined using the SCID (First et al., 1998), a structured clinical interview designed to diagnose Axis I disorders according to criteria set out in the Diagnostic and Statistical Manual (DSM)-IV (APA, 1994). Recent and lifetime patterns of drug use will be determined by gathering quantity and frequency information on all major classes of prescription drugs and licit and illicit drugs of abuse. Alcohol use over the past 90 days will be determined using calendar-based timeline follow-back techniques (Sobell & Sobell, 1992).

Subject Health Status. All subjects must be medically healthy as indicated by laboratory tests and physical examination and free from the use of other psychotropic agents for a minimum of two weeks before screening commences. Subjects must be able to provide drug free urine samples (excepting marijuana), and the non-pregnant health status of women will be verified by urine pregnancy tests. Urine drug screens will test for the presence of cocaine, methamphetamine, opiates, THC, and benzodiazepines using NIDA standard cut-off values. Urine drug screens and pregnancy tests will be conducted at screening and then repeated monthly throughout the study.

Management of Excluded Subjects and Drop-Outs. Any consenting subject who is excluded from study participation or who elects to discontinue the study at any point during the screening or randomized treatment portions of the study will be eligible to receive usual care from the VA Dual Diagnosis clinic.

D.3 Justification of Design and Consideration of Alternatives

Justification of stratification for randomization. To account for possible site differences in subject population or procedure variables, we must stratify randomization within site. Because a previous study of sertraline treatment in dual diagnosis patients reported significant sex differences in response, (Sonne et al., 2003), we will stratify on sex to assure a balanced distribution of females across dosage groups. The Type A/B typology is based upon a multidimensional clustering technique that is only done in a post-hoc manner after study enrollment is closed. However, the Type B subtype is associated with an early age of onset of problem drinking and age of onset has been used previously to classify subjects on an *a priori* basis prior to randomization (Johnson et al., 2000b,c; Roache et al., 2008). Though age-based classifications of alcoholism previously used $\leq$ 25 years of age as a cut-off for "early onset", that age cut-off may not be useful for the military population where new recruits are sent into battle and experience combat trauma at younger ages. We

considered whether to include only subjects who experienced PTSD-first before the onset of problem alcohol drinking. However, that may very well exclude the early age Type B subgroup who may begin experiencing problem drinking before trauma exposure and for whom we hypothesize a differential response. In a small sample of dual diagnosis patients (Brady et al., 2005) sertraline was in fact reported to be beneficial to the few cluster 1 subjects who had an onset of PTSD prior to the alcohol dependence but was less helpful than placebo to cluster 3 subjects who were Type B-like with a younger age of onset of alcohol dependence (see Sec.A.4). Thus, whether or not alcohol dependence precedes PTSD may be predictive of clustered subgroups of the A/B type. This suggests the possibility that young military recruits who exhibit problem drinking prior to combat exposure may be the same subgroup as the Type B/early onset alcoholic who also is more vulnerable to psychiatric disturbance. Therefore, in an attempt to stratify-balance sertraline vs. placebo groups for probable subtype membership, we will us Onset Precedence to stratify subjects by whether or not (Yes/No) drinking preceded military trauma.

Justification of Drinking criteria. The drinking criteria (drinks per day of drinking $\geq$ 5 for males and $\geq$ 4 for females) are based upon NIAAA research definitions of heavy drinking (http://www.niaaa.nih.gov) which have now become standard definitions of "problem drinking". We have required that included subjects drink that amount or more on at least 50% of the days to define a minimal amount of baseline drinking which should be amenable to change. DSM-IV diagnosis of alcohol dependence is based primarily on loss of control of problem drinking and so an outpatient treatment population can be selected who can come in for clinic visits without being intoxicated or in withdrawal and still meet criteria for dependence because they can't stop drinking regularly or excessively when they do drink. Patients who may be physically-dependent and require medical detoxification, will be excluded and referred to alternative treatment by the study exclusion criteria requiring subjects to provide a 0.00 mg/dl breath alcohol level without showing signs of withdrawal (i.e., CIWA scores < 10)

Justification of Trauma Criteria. We have included in the study, OEF/OIF veterans with service-related PTSD, but without specification of the types of experience meeting the Criterion A traumatic event. The two most likely types of trauma seen in the veteran population are combat-trauma (especially now due to the continuing Iraq war) and for women, sexual abuse. A recent Institute of Medicine Report (IOM, 2007) concluded that most studies of SSRI efficacy had been done with civilian trauma and that there was no evidence for efficacy amongst veterans of combat trauma. For example, one study (Van der Kolk et al., 1994) noted that the fluoxetine vs. placebo differences in PTSD symptoms were larger in the non-combat clinic than in the combat clinic. Another study (Zohar et al., 2002) found only a non-significant tendency for sertraline vs. placebo differences in 42 Israeli military veterans. However, both of these studies are extremely limited by small sample sizes and short-term periods of treatment (i.e., 5-10 weeks). In open-label extension studies (Brady et al. 2000; Davidson et al. 2001b; Londborg et al. 2001) sertraline response rates have been observed to increase with longer periods of treatment. And though combat veterans may be expected to have a greater chronicity of illness or a greater number of traumatic events, in fact, Martenyi et al. (2002b) reported that subject age and combat trauma were predictors of increased response to fluoxetine. We considered whether or not to exclude subjects who may have experienced traumatic events in childhood or prior to military service. However, some of these experiences may in fact be associated with an Early Age of Onset of alcoholism and so excluding those subjects would be counter-productive to the hypothesis test. We expect that by recruiting only veterans with service-related PTSD, we will be including into the study only those persons who were not so disabled by earlier life PTSD or alcohol dependence so as to be excluded from military service. Further, the study of war-related PTSD among veterans is the target population of military-relevance regardless of whether or not patients experienced earlier-life trauma.

Selection of Sertraline. SSRI's are the medications of choice for PTSD (see Sec.A.2). Of the available SSRI's, only sertraline and paroxetine are approved by the FDA for treating PTSD, though fluoxetine also has

been reported to be effective. Though we probably could have selected any SSRI, we selected sertraline because: 1) it was the first medication approved for PTSD treatment and it has been well studied; 2) it has been shown to have differential effects in the Type A/B subtypes of alcoholism; and 3) it is the only SSRI that has been tested in dual diagnosis PTSD + Alcohol Dependence. Even though the previous study of sertraline effects in dual diagnosis was negative overall, a subsequent analysis showed subgroups who may differentially respond to sertraline treatment (Brady et al., 2005). Additionally, the same group of investigators previously reported beneficial effects of sertraline in single diagnosis PTSD (Brady et al., 2000; Davidson et al., 2001a,b). This is all the more reason to study sertraline in the current larger sample using a design which will allow testing the hypothesis that treatment response is determined by alcoholism subtype.

D.4 Clinical Assessments

Our selection of variables was guided by the need for thorough and valid content coverage across multiple domains while keeping in mind time and effort constraints. In particular, we must: i) assess PTSD and Alcohol dimensions for diagnosis and treatment outcome; ii) evaluate trauma history and its relationship to drinking history; iii) assess psychosocial variables of potential value in subtyping alcohol dependence; and iv) assess other variables important to characterize the study population and measure other factors important to aid in understanding our results or predicting treatment outcome. Some of these assessments have been specifically selected because they also are being used in active duty populations in other STRONG STAR Consortium studies and therefore serve to characterize how the Veteran dual diagnosis population may or may not differ from the active duty PTSD population. The study assessments are described below in four groupings.

D.4.1 Measures of PTSD and trauma history

The STRONG STAR Consortium is using two instruments (the PSS-I and PCL-M, see below) as standard and validated methods for PTSD assessment. Though these have not been used in previous medication trials, it is nonetheless appropriate to use them as the standard outcomes assessment within the OEF/OIF veteran population.

PTSD diagnoses. The PTSD Symptom Scale, Interview Version (PSS-I): PSS-I is a 20-minute, 17-item clinical interview that evaluates DSM-IV PTSD symptoms on a frequency/severity scale (Foa et al., 1993). The PSS-I is comparable to the gold standard employed in studies of veterans (the Clinician Administered PTSD Scale; CAPS) yet takes considerably less time to administer (Foa & Tolin, 2000). The scale has excellent internal consistency ($\alpha = .91$), test-retest reliability (.80), and inter-rater reliability (kappa = .91). This measure will be administered monthly by a blinded Independent Evaluator at each study site.

PTSD symptom scores. We will use the PTSD Checklist-Military Version (PCL-M) (Weathers et al., 1993), a 17 item self-report measure that evaluates the severity of PTSD symptoms in the last month. The PCL has excellent psychometric properties (e.g., Blanchard et al., 1996). Based on the recent report by Terhakopian et al. (2008), we will use a score of > 30 on the PCL as a minimum score for enrollment screening. Symptom severity assessments will be done weekly throughout the study.

Trauma history. The *Life Events Checklist* (LEC) will be used at screening to assess exposure to trauma/traumatic events that may have occurred prior to military duty. It includes a list of 17 different potentially traumatic life events that that are commonly associated with PTSD symptoms. Individuals are asked to respond whether an event happened to them personally, they witnessed, or they learned about happening to someone close to them. The LEC has been shown to have good temporal stability, convergent validity with other measures such as the TLEQ and to be significantly correlated with psychological distress and PTSD symptoms among combat veterans (Gray et al., 2004). We have added a two-item screen to the LEC which asks

about military-related sexual trauma. The VA uses this screen with everyone who seeks services at the VA. The *Psychiatric Epidemiology Research Interview Life Events Scale* (PERI-LES) (Dohrenwend et al., 1978) is a self-report checklist designed for repeated assessment to detect periodic changes in stressful life events that can affect the emotional and behavioral well-being of subjects during the study. The original scale is 100-items but the abbreviated version we will be using, consists of only 11 of the items from the original scale. Items were chosen based on their relevance to military members. This assessment will be completed once monthly during the study.

D.4.2 Drinking Measures

Alcohol Dependence Diagnoses. Alcohol dependence diagnoses will be established by *Structured Clinical Interview for Diagnoses (SCID)* using DSM-IV criteria (First et al., 1998). The **Age of Onset** for each subject will be determined during the SCID interview. For each of the seven the DSM-IV criterion symptoms of alcohol dependence that a subject endorses, we will ask the subject "…at what age did you first begin having this problem". Then at the end of the drug abuse section of the SCID interview, the diagnostician will review these self-reports and make a clinical judgment of the age, in years, that the subject began experiencing symptoms that ultimately led to their alcohol dependence diagnosis. For **Onset Precedence**, the psychologist will make a determination of whether or not (Yes/No) any of these drinking-related problems occurred prior to exposure to service-related trauma. For consistency with the rest of the STRONG STAR Consortium, we will use the Alcohol Use Disorders Identification Test (AUDIT; Babor et al., 2001). This AUDIT is a 10-item screening measure with three subscales (alcohol consumption, drinking behavior, and alcohol-related problems) that are scored on a 4-point scale for a highest possible total score of 40. Among those diagnosed as using alcohol in a harmful manner, 92% had scores of 8 or more. The AUDIT has good internal consistency (α = .65-.93) as well as sensitivity and specificity (Saunders et al., 1993). The AUDIT will be completed at the baseline visit and repeated at the final study visit.

Timeline Followback Measures of Drinking. The Timeline Follow-back procedure (Sobell and Sobell, 1992) uses a calendar-based structured interview to obtain valid estimates of the number of standard drinks consumed each day. Following the convention of the Form90 (Miller and Del Boca, 1994), we will collect data at Intake for the previous 90 days leading up initial screening. From that point forward, timeline follow-back procedures will be used on each weekly visit to obtain information on drinking that occurred during the past week. From the timeline data, we will calculate two primary measures of drinking as the percentage of days on which drinking occurred and the mean number of drinks consumed on those days (drinks per drinking day). From these data, we will use NIAAA **research definitions of heavy drinking** (http://www.niaaa.nih.gov) to calculate the percentage of days on which heavy drinking occurred ($\geq$5 drinks for males or $\geq$ 4 drinks for females). For *a priori* specification of hypothesis tests, we will use identify mean weekly *drinks per drinking day* and *percent days of heavy drinking* as the two primary outcome drinking measures. These same two drinking measures were examined and shown responsive in the previous dual diagnosis trial (Brady et al., 2005).

Laboratory Measures of Drinking. Percent Carbohydrate Deficient Transferin (%CDT) has been approved by the Food and Drug Administration (FDA) as a laboratory measure of alcoholic drinking (Anton et al., 2001). We have used it in previous clinical trials to validate self-report and as an objective laboratory measure of drinking outcomes (Johnson et al., 2000a,c; Miller et al., 2006). Phosphatidylethanol (PE) is a non-oxidative metabolite of ethanol that gets incorporated into red cell membranes that can be used to estimate the level of alcohol consumption in humans. Varga and Alling (2002) demonstrated that PE is formed in human red cells at physiologically relevant ethanol concentrations. Aradottir et al (2006) reported that PE concentrations in blood are correlated to reported alcohol intake in alcohol-dependent patients. CDT levels will be measured in plasma

samples collected at baseline and monthly (i.e., 4, 8, and 12 weeks) thereafter. These samples will require one 10 ml blood draw.

D.4.3 Measures used for Typological Classification

Although we stratified the randomization based upon Onset Precedence (i.e., whether or not problem drinking preceded service-related trauma), we intend to classify subjects based upon *post-hoc* assessments using a multidimensional Type A/B classification scheme which is adapted to the dual diagnosis military-veteran population. As done previously, clustering dimensions include measures of alcohol disorder severity, psychiatric symptoms, and childhood risk factors. Baseline characteristics used for the cluster derivation include:

i) **Onset Precedence** – did problem drinking begin prior to (Pre) vs. after (Post) trauma exposure determined by the SCID (Sec.D.4.2);
ii) **Age of Onset (years)** of alcohol-related problem drinking determined by the SCID (Sec.D.4.2);
iii) **Mean drinks per drinking day and % heavy drinking days** in past 30 days determined by the TLFB (Sec.D.4.2);
iv) **AUDIT**- dependence and harmful use subscale scores (Sec.D.4.2);
v) **Relief-Drinking** assessment score (a clinician rating scale – see below)
vi) **PTSD Checklist** – Military version (PCL-M) scores (Sec.D.4.1);
vii) **Life Event Checklist** (Sec.D.4.1);
viii) **Beck Depression Inventory (BDI)** score (Sec.D.4.4);
ix) **POMS** Tension/Anxiety and Depression/Dejection Scores (Sec.D.4.4);
x) **Parental family history** of alcoholism (see FIGS, Sec.D.4.4).

Item v) "Relief Drinking" will be a single item 7-point Likert rating scale (-3, 0 +3) wherein the SCID clinician scores the extent to which they perceive the subject "…*to be drinking to relieve the subjective discomfort of sobriety*".

The efficacy of sertraline vs. placebo to reduce drinking and PTSD symptoms will be examined within each of the two empirically-derived clusters (Type A vs. Type B).

D.4.4 Other Assessments

Demographics and Combat Experience. The Demographics and Military Service Characteristics Form measures standard demographics (race, gender, age) and military service information (e.g., rank). High- and low-intensity deployment stress exposure will be assessed using scales from the Deployment Risk and Resilience Inventory (DRRI; King et al., 2006). The DRRI was developed and tested in three separate national samples of veterans of the first Gulf War. It has very good internal consistency (á = .85 to .89) and construct validity. It is currently being revised and tested with OEF/OIF returnees. High intensity stressor exposures will be assessed using the DRRI Combat Experiences, and Aftermath of Battle subscales. Low-intensity deployment stress will be assessed with the DRRI Deployment Environment subscale.

Medical History & Laboratory Tests The medical history of subjects will be collected for evidence of illnesses and concurrent medication use which might exclude participants. Standard hemotology and chemistry tests will be used to assess medical health status.

Family History of Psychiatric Illness. The Family Interview for Genetic Studies (FIGS) will be used to obtain genetic history information for the genomics core. The FIGS has been shown to have an internal consistency, as measured by Cronbach's alpha coefficient, of 0.92 for depression, 0.99 for mania, 0.94 for psychosis, 0.94 for alcohol and drugs and 0.97 for personality disorders. Additionally, Pearson's correlation

coefficient varied from 0.41 to 0.99 for the lists of symptoms and all were statistically significant ($p<.0001$) (Diaz de Villalvilla T et al, 2008).

The Temperament and Character Inventory (TCI) is an 240 item true-false self-report questionnaire (Cloninger, 1994) used to assess temperament and personality variables previously found to be associated with the Type I/II alcoholism subtype discrimination (Chick et al., 2004). The TCI measures individual differences on seven dimensions of temperament and character and has been extensively evaluated in both normative and clinical samples (Cloninger, 1994).

Beck Depression (BDI) and Anxiety (BAI) Inventories. The Beck Depression Inventory (BDI) will be used to assess depression and the Beck Anxiety Inventory (BAI) will be used to assess anxiety. This is a 21-item measure that asks participants to rate the severity of their symptoms of anxiety within the past week on a 4-point scale, with anchors Not At All to Severely. The BAI has been shown to have high internal consistency ($\alpha = .92$) and test-retest reliability and to reliably discriminate between anxious and non-anxious diagnostic groups (Beck et al., 1988).

Aggressive behaviors. We will also use an abbreviated version of the State-Trait Anger Expression Inventory (STAXI; Spielberger, 1988), a 44-item scale that evaluates dimensions of anger. Specifically, participants will be asked to respond to the 10 items related to the State-Anger (S-Anger) subscale on a four-point scale that assesses the intensity of anger felt at a particular moment in time. Internal consistency of the subscale was found to be strong ($\alpha = .90$), as was its convergent validity with measures of hostility and other personality scales.

Profile of Mood States (POMS) We will employ only the Tension-Anxiety and Depression-Dejection subscales of the POMS as brief self-report rating scale highly sensitive to mood changes (McNair 1970)

Social Functioning. Limitations in role functioning will be assessed using the SF-12v2, an abbreviated version of the Medical Outcomes Study Short Form Survey (SF-36; Ware et al., 1994). The SF-12 is recommended for use in larger samples when monitoring overall physical and mental health outcomes (Ware et al., 1996).

Somatic Symptoms. The Patient Health Questionnaire-15 (PHQ-15; Kroenke, Spitzer, & Williams, 2002) is a brief, self-administered questionnaire that assesses somatic symptom severity. Participants rate the severity of 15 somatic symptoms as 0 (not bothered at all), 1 (bothered a little) or 2 (bothered a lot). The scale has strong psychometric properties in terms of internal reliability, convergent validity, and discriminant validity (Kroenke, et al., 2002), and has been used in recent research using an active duty military sample (Hoge, et al., 2008).

D.5. Biological Measurements of Serotonin

Previous brain imaging studies have shown that alcoholics homozygous for the L-allele (i.e., LL) demonstrate non-normal reductions in central serotonin transporter binding (Sec.A.5). We have demonstrated the same phenomena in platelets and further demonstrated that this is associated with reduced binding and function (Sec.A.6). Since we hypothesize that the normally elevated transporter activity of LL alcoholics is deficient, we need a measure of binding of the transporter in these individuals. **Thus, an assay of serotonin transporter binding is critical to the interpretation of our genotype data.** Each participant will provide a blood sample at screening which can be used to describe their both their transporter polymorphism genotypes and also their transporter binding during the study. Standard receptor binding assays will assess serotonin transporter density and serotonin content.

Platelet Preparation. 30 ml of whole blood is drawn by standard procedures into three 10 ml vacutainer tubes. From these collective samples, a platelet rich plasma (PRP) preparation is prepared for platelet measures of serotonin content and transporter binding and DNA will be extracted from the white and red blood cells.

D.5.1 Measurement of Serotonin Transporter Binding in Platelets.

Platelet Studies of Serotonin binding. PRP (platelet rich plasma) is prepared by centrifugation of whole blood at 150 *g* for 20 min at 23°C in a Beckman TJ-6 centrifuge. The PRP is then centrifuged at 10,000 *g* for 10 min at 4°C to obtain a platelet pellet. Each pellet is washed twice in 8 ml of washing buffer (50 mM Tris-HCl, 150 mM NaCl, 20 mM EDTA, pH 7.4) and sonicated with two 5 second bursts (10% max) in 8 ml of lysis buffer (5 mM Tris-HCl, 5 mM EDTA, pH 7.4). The final pellet is suspended in 2 ml of incubation buffer (50 mM Tris-HCl, 3 mM KCl, 120 mM NaCl, pH 7.4) and kept at -80°C until analysis.

[^{3}H]-Paroxetine Binding. [^{3}H]-paroxetine binding is performed according to Arranz *et al.* (1999). Platelet membrane homogenates are incubated at 6 concentrations of [^{3}H]-paroxetine (0.015 to 0.5 nM) in incubation buffer in a total volume of 1.6 ml. Non-specific binding is determined in the presence of 100 μM 5-HT. After incubation for 60 min at 25°C, 6 ml of ice cold Tris-HCl incubation buffer is added to each tube, then the samples are filtered through Whatman GF/C filters using a Brandel Cell Harvester. The filters are washed with two 6 ml of ice cold incubation buffer, air dried, then placed in scintillation vials with 8 ml of Beckman Redi-Solv scintillation fluid for counting. Samples are analyzed in duplicate. Binding accounts for less than 10% of total radioactivity ([^{3}H]-paroxetine) added. The amount of membrane protein is determined using the BioRad protein assay. Specific [^{3}H]-paroxetine binding is calculated by subtracting non-specific binding from total binding and is expressed as fmoles/mg protein. K_d and B_{max} of [^{3}H]-paroxetine binding is determined using Prism 3 software by GraphPad. K_d is expressed as nM.

D.5.2 Genotypic Polymorphisms of the Serotonin Transporter.

The white and red blood cells are spun down and separated from the plasma and then they are resuspended and lysed. A phenol/chloroform/acqueous phase extraction process is used to separate the DNA into the aqueous phase. After two purifications, including an overnight exposure to proteinase K, DNA is precipitated by suspension in an ethanol solution. DNA is then re-suspended in TE-buffer and can be stored indefinitely in polypropyline tubes. DNA samples labeled by study and subject identification codes will be stored at -80 0C.

DNA genotyping. Genotyping of polymorphisms of candidate genes (described below), as well as genotyping of microsatellite markers, will be performed at the Genetics Core Laboratory for the STRONG STAR Consortium, where this type of genotyping is performed routinely. Repeat genotyping of samples in our laboratory has shown an error rate of less than 1%. For all studies that depend upon comparison of groups with and without a particular polymorphism, we will test for population stratification, using 20 microsatellite markers randomly chosen for the genome, which will be genotyped for all samples. These markers will be chosen from the ABI linkage mapping set, and include 2 chromosome X markers, which will also be useful for detection of sample mix-ups (see below).

Variable number tandem repeat (VNTR) and microsatellite markers: DNA from each of the subjects will be amplified by PCR using standardized reaction mixes and fluorescent-labeled primers. The amplified DNA products will be electrophoresed using a 3100 DNA analyzer (Applied Biosystems). Genotypes will be assigned using GENESCAN and GENOTYPER software (Applied Biosystems), with a combination of automation and actual visual scoring. Each run will be scored independently by two individuals and results will be compared electronically. After discrepancies are resolved, the final data will be imported into the PEDSYS program to check for inconsistencies

SNP genotyping: Genotyping will be performed using the Applied Biosystems Taqman Allelic Discrimination assay (Foster City, CA). The Taqman assay is a high-throughput system that allows for genotyping of 384 individuals simultaneously. The method uses the 5' nuclease assay, which allows direct detection of the PCR product by the release of a fluorescent reporter. Two fluorescent probes, one for each SNP allele, that hybridize to the target sequence are used in the assay. Each probe consists of an

oligonucleotide with a 5'-reporter fluorescent dye (either FAM or VIC) and a 3' non-fluorescent quencher. When the probe is intact, the proximity of the reporter and quencher results in suppression of fluorescence. As the Taq polymerase cleaves the probe with its 5' to 3' nuclease activity, the reporter dye is separated from the quencher, resulting in increased fluorescence. The fluorescence intensity is read and quantified by the ABI Prism 7900HT, allowing for immediate availability of the genotype information. Primers and probes for each SNP will be obtained using the custom assay-by-design service offered by ABI.

There are three known polymorphisms of the serotonin transporter, each of which has been variously studied or reported to be functional and have significant predictive value in understanding the behavior of psychiatric conditions including affective illness and/or alcohol dependence (see Sec.A.5). The serotonin transporter gene is found on chromosome 17p12 and is regulated by the 5' regulatory promoter region (5'-HTTLPR). The most widely studied polymorphism (a.k.a. L/S) is a 44 base pair insertion/deletion polymorphism creating a short (S) and long (L) form of the promoter which confers differential gene expression rates (Heils et al., 1996). The second polymorphism is a 17 base pair variable number tandem repeat in the second intron of the gene (a.k.a. vntr-2) (Lesch et al., 1996). Most recently, there is a third polymorphism (Parsey et al., 2006) (a.k.a. L_A/L_G) which produces variation in the Long form of the 5'-HTTLPR such that L_G alleles are claimed to act more like S-alleles. Beginning first with the L/S polymorphism, we propose to analyze the allelic genotypes of all study participants so as to determine if any of these transporter polymorphisms predict sertraline response in the study.

D.6 Timeline for Experimental Assessments

Timeline of Experimental Measures

	Measure	Screening Visit -1	baseline Visit 0	Wk1 Visit 1	Wk2 Visit 2	Wk3 Visit 3	Wk4 Visit 4	Wk5 Visit 5	Wk6 Visit 6	Wk7 Visit 7	Wk8 Visit 8	Wk9 Visit 9	Wk10 Visit 10	Wk11 Visit 11	Wk12 Visit 12
Screening	Demographics	X													
	Medical History	X													
	SCID	X													
	PSS-I	X													X
	TLFB-90	X													
	safety labs	X													
	UDS	X							X						
	pregnancy		X						X						
Baseline	FIGS		X												
	Genotype		X												
	Platelet		X												
	LEC		X												
	Audit		X												
	TCI		X												
Treatment	Randomization		X												
	Dose		X	X	X	X	X	X	X	X	X	X	X	X	
	CBT		X	X	X	X	X	X	X	X	X	X	X	X	X
Outcomes	TLFB		X	X	X	X	X	X	X	X	X	X	X	X	X
	PCL-M		X	X	X	X	X	X	X	X	X	X	X	X	X
	AE's		X	X	X	X	X	X	X	X	X	X	X	X	X
	Biomarker		X				X				X				X
	BDI/BAI		X				X				X				X
	POMS		X				X				X				X
	STAXI		X				X				X				X
	SF-12		X				X				X				X
	Peri-LES		X				X				X				X
	PHQ-15		X				X				X				X

E. Cognitive Behavioral Therapy for Dual Diagnosis

The non-pharmacological treatment portion of the study will consist of 12 sessions of manualized cognitive-behavioral therapy (CBT). The manual chosen for the study is the Concurrent Treatment with Prolonged Exposure (COPE) manual developed for the treatment of patients diagnosed with current PTSD and a substance

use disorder. This therapy was designed to integrate two established empirically supported treatments—a cognitive behavioral approach to treat drug dependence (Carroll, 1998) and an exposure-based treatment for PTSD (Foa & Rothbaum, 1998). COPE is designed to integrate these two approaches in order to address those issues specific to trauma victims while still remaining sensitive to those issues experiences by individuals with substance dependence. The PTSD component incorporates prolonged imaginal exposure and in vivo exposure techniques. The substance use component incorporates cognitive behavioral techniques, such as, cognitive restructuring, recognizing and coping with cravings, managing thoughts about substance use, problem solving, planning for emergencies and a possible lapse, and stimulus control.

The treatment will be delivered by a doctoral-level therapist in twelve weekly, 60-90 minute individual sessions. Therapists will receive training in implementation of the manualized therapy according to guidelines established by its developers (Brady et al., 2001; S. E. Back, personal communication, October 2, 2008). All therapists will be required to meet therapy certification requirements prior to treating study participants. Therapists will audiotape treatment sessions and 10% of randomly chosen tapes will be reviewed by an individual designated to monitor treatment fidelity. This CBT treatment program will ensure that an evidence-based behavioral intervention is provided to all participants.

F. Medication Dose, Blinding, Randomization

Sertraline Dose. We propose to dose subjects with a fixed dose of 200 mg sertraline per day as was done previously for alcohol dependent subjects (Pettinati et al., 2000). Brady et al., (2000) used a flexible dose up to 200 mg per day for PTSD patients and a fixed dose of 150 mg/day for dual diagnosis patients (Brady et al., 2005). Doses will be prepared by the research pharmacist by over-encapsulation of 50 mg tablets with gelatin capsules filled with lactose. Matching placebo capsules will be prepared and filled with lactose only. Sertraline/capsule Dose will be adjusted for all subjects by varying the number of capsules (50 mg/capsule). As described by Pettinati et al., 2000, all subjects will begin with 1 capsule per day and dose will be increased by one capsule every 3-5 days as clinically tolerated. After completing the study, subjects will be given an additional two week supply of medicine to gradually taper down (1 capsule every 3-5 days) their dose so as to minimize any withdrawal discomfort.

Randomization and Blinding. Randomization schemes will be prepared by the research pharmacist within four different stratification groups. Three stratification variables are necessary for this study. Separate randomizations will occur within each site to assure randomization balance across sites. Within each site, strata will be four categories based upon **Sex** and **Onset Precedence**. The study coordinator will provide the research pharmacist with a notification of enrollment of a new subject. This notification will list the subject name, study ID, and subject number, and a date for the clinic visit. The form also will identify the sex as male or female and the Onset Precedence as Pre or Post. The pharmacist will randomize the subject 1:1 to receive sertraline vs. placebo within one of the four Sex vs. Onset strata. Doses will be labeled with the patient name and subject ID number and week number with dose labeled as “sertraline/placebo study medication” so that dosing is blinded to the investigator and the subject.

G. Statistical Analysis

The primary study objectives and hypotheses relate to the efficacy of sertraline in treatment of PTSD and/or alcohol dependence. To determine efficacy, subjects must take medication and outcome must be assessed. Thus, only subjects who took medication and provided at least two weeks (14 days) of self-reported drinking and PTSD symptom assessment post-randomization will be considered “evaluable” for this study.

All data will be analyzed using Proc Mixed from SAS Release 9.1 (SAS Institute). Proc Mixed uses a random regression approach to repeated measures designs so that drop-out and missing observations (assuming missing at random) are properly accounted for.

G.1 Analysis to Satisfy Aim #1

Satisfaction of the first Specific Aim will be to conduct the post-hoc clustering of study subjects to confirm that a dichotomous classification scheme indeed produces clusters of the TypeA-like and Type B-like profiles.

1. To determine whether multidimensional baseline measures can be used to classify Type A/B clusters of OIF/OEF veterans with dual diagnosis PTSD + Alcohol Dependence. *We hypothesize that two dichotomous subgroups having Type A-like and Type B-like clinical profiles will be classified from dual diagnosis veterans.*

After enrollment in the study is closed, SAS procedures for clustering (i.e., Proc CLUSTER, MODECLUS, SAS Release, 9.1) will be used to assign cases to one of two clusters using scores from the ten items used for cluster derivation (see Sec.D.4.3). These SAS procedures provide algorithms and diagnostic statistics to assess the appropriateness of specifying two clusters. Type A/B differences in baseline clinical characteristics will be examined ($p<0.05$) with t-tests and $\chi 2$-tests as appropriate. An additional approach to assure the structural integrity of the cluster, we will use decomposition approaches to principal components analysis to remove cluster derivation factors systematically to determine the extent to which the cluster identity remains intact with the use of fewer items having primary influence upon the cluster.

G.2. Analysis to Satisfy Aim #2

The primary outcome variables are PTSD Symptoms measured by the PSS-I and PCL-M and the drinks per drinking day and % days of heavy drinking measures from the timeline follow-back assessment as well as the %CDT biomarker of alcohol consumption. Primary outcomes will be analyzed for the intent to treat (ITT) population having two weeks of post-randomization data available. Data analysis will use mixed effects regression (Proc MIXED) with a 2 (Type A/B cluster) x 2 (Treatment with sertraline vs. placebo) factorial design for the two between-groups factors and repeated measures for time (treated as a linear effect with df=1), measured weekly for PTSD symptoms and alcohol drinking and monthly for laboratory tests of alcohol consumption. Baseline measures of PTSD or alcohol drinking will be considered as covariates. Sex and it's possible interaction with cluster type and Treatment also will be considered for inclusion in the final model. Separate analyses will be performed for PTSD and alcohol outcomes using unadjusted $p=.05$ criteria since these outcomes are theoretically distinct dimensions assessed at different frequencies by different methods. In addition to ANOVA model main effects and interactions, a priori-specified contrasts will test between group differences at study endpoint. The linear growth model (random regression) allows use of cases with incomplete data, tests significance of slopes across and within groups, and permits specification of the covariance matrix for the repeated measure. The primary study hypothesis will be supported by finding an interaction of Type A/B cluster x Treatment.

2. To examine whether sertraline efficacy differs as a function of the Type A/B subtype classification. We hypothesize that sertraline will:
   i) not be different than placebo among the dual diagnosis population as a whole;
   ii) will be less than or equal to ($\leq$) placebo in benefit to reduce either PTSD symptoms or alcoholic drinking among the Type B subgroup; but
   iii) will be superior to (>) placebo to reduce both PTSD symptoms and alcohol drinking among the Type A subgroup.

Power analysis. We propose a sample size of n=240 subjects randomized to treatment. Previous experience suggests that the Type A/B cluster derivation should dichotomize the study population into approximately equal groups with no worse than a 40/60 split, yielding effective cell sizes no smaller than about 50 even with unequal cells. Power analyses used the SPSS SamplePower2 ANOVA module, and RMASS2 for mixed effects

regression (Hedeker et al., 1999). Based upon previous sertraline findings from other investigators (Brady et al., 2005; Pettinati et al., 2000) we estimated the effect size for the interaction of cluster x treatment to be medium (Cohens $f = .25$). At two-tailed $\alpha=.05$, power is .93 to detect the hypothesized treatment by subgroup interaction effect which would support the primary study hypothesis.

G.3 Analysis to Satisfy an Exploratory Aim to Examine Serotonin Biology

Specific Aims #1-2 are the primary Aims of the study. There is good evidence that genotype and low serotonin function may be possible causes or correlates of psychiatric disorder including alcoholism and PTSD and may explain subtype-related treatment response. However, there still is a great deal of uncertainty about the directional hypothesis of how these variables may affect treatment. Specifically, is the individual with low serotonin function going to be more responsive or less responsive to treatment with an SSRI like sertraline. Thus, exploration of the serotonin biological variables may help us to understand if serotonin biology can explain the phenomenological findings. Regardless of the result, we will learn whether or not differences in genotype or transporter binding or function can be used to predict treatment response; especially under those conditions where the treatment response can be widely divergent ranging from inferiority to superiority over the benefits of taking placebo while in treatment.

Analysis of Serotonin Binding. We have strong reasons to believe that differences platelet in serotonin transporter binding may predict response to sertraline. Normally, hypotheses predict that low transporter binding or functional uptake of serotonin will be associated with more psychiatric pathology, however, reduced transporter activity may also predict minimal effects of SSRI's like sertraline. Thus, we really don't know whether or not high levels of Paroxetine binding potential or high levels of serotonin uptake may be correlated with high sertraline response or low sertraline response and in either case, we still need to know whether or not high sertraline response is beneficial or harmful to changes in drinking behavior. Thus, it is critical to simultaneously examine both the baseline characteristics of transporter activity and also how patients respond to treatment. The statistical analysis of these data requires a bidirectional hypothesis determining whether or not sertraline-related changes in drinking are correlated with transporter binding and uptake. We will use the mixed-effect model to determine the sertraline vs. placebo differences drinking behavior over weeks of the study as we did above for the previous two aims. For this aim, we will determine whether or not the baseline platelet measures of transporter binding (Bmax or Kd) or functional activity in serotonin uptake (Vmax or Km) are significant ($p<0.05$) covariates predictive of drinking outcomes between sertraline vs. placebo The significance (p-value) and direction of effect ($\pm$) will be determined. Both the main effect of the covariate and its interaction with the "Treatment" factor will be examined in the ANOVA model. Consistent with the Specific Aim, the primary dependent variables will be the two drinking measures (DDD and PHDD) though we also are interested in knowing whether other outcomes (i.e., PTSD symptoms) are predicted by these same variables.

Genetic Analysis. A major focus of much psychiatric research is the vulnerability associated with polymorphisms in the serotonin transporter. The primary genotype of interest is the long (L) vs. short (S) allele of the promoter region where we (Sec.A.6) previously have shown that SS homozygotes differ from L-carriers (LL and LS) in several psychiatric vulnerabilities. In our own studies of patients with primary alcohol dependence, L-carriers were different than the SS homozygotes in their functional serotonin uptake into platelets and in the relationship between paroxetine binding and years of alcoholic drinking behavior. We now hope to determine whether or not the L-carriers differ from the SS homozygotes in their response to sertraline. Thus, we will divide the subjects into two groups, by SS vs. Lx (i.e., LL and LS) genotypes and determine whether their outcomes differ. Because only about 20% of the sample are likely to be SS-homozygotes, we will do two things to enhance the SS sample size. First, we will examine the A to G variant of the L-allele which makes L_G alleles act as if they are S-alleles. According to the recommendations of Parsey et al., (2006) subjects

having the L_GL_G and L_GS genotypes will be reclassified as if they are S'S' homozygotes. This may be expected to increase the proportion of S'S' to be about 30-35% of our sample. Next, we will include in the analysis, all subjects who provided at least two weeks (14 days) of drinking data before drop-out. This may have only a small effect on sample size, but it is important to know whether those early drop-outs may be the ones showing increases in drinking behavior. This will require a simplified drinking outcome which analyzes drinking at end-point without requiring the weeks factor. Therefore, for this analysis, we will determine the mean drinking (DDD and PHDD) collected from the last week of study participation for each subject, which is at that subject's "end-point" two or more weeks after randomization.

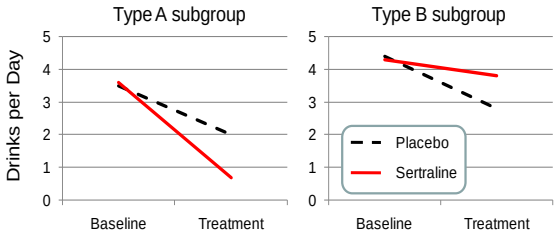
After the enhancement of S'S' sample size, we will evaluate the interactions of genotypes (S'S' vs. L'x) with treatment in the linear model to test the effect of genotypes. To simplify the analysis, we will either use the "endpoint" minus "before" difference scores with number of weeks in treatment as a covariate to weight the observation and/or will include time (before vs. endpoint) as a factor in the model. The null hypothesis of no difference will be rejected by a 2-tailed test since we are not certain whether to expect greater or lesser effects of sertraline in the S'S' homozygotes vs. the L'-carriers. In either case, the hypothesis that serotonin transporter genotype influences sertraline response will be supported if sertraline is greater than placebo in one genotype group and/or less than placebo in the other genotype group.

H. Risks and Safety Monitoring

The STRONG STAR Consortium has established a DSMB to provide annual review of subject safety and study progress for this study as a part of the Consortium. There also is a DSMP prepared as a protocol attachment which describes basic plans for data and safety monitoring.

Common Risks of Sertraline Treatment. Sertraline may produce the risk of side effects and these risks for sertraline are not different than the risks of taking other SSRI's. Risks include: Diarrhea (loose stools); Nausea (upset stomach); Dry mouth; Insomnia (can't sleep); Drowsiness or sleepiness; Muscle tremors or shakiness; Feeling nervousness or anxiety; Feeling hot or sweaty; Headache; Fatigue or feeling worn-out; Decreased appetite; and Decreased sexual interest or performance. None of these known side effects are considered serious and all are temporary.

Risk of Exposure Therapy. All patients enrolled in treatment will receive Exposure Therapy for PTSD. During exposure therapy, the symptoms and distress of PTSD can be exacerbated temporarily before benefits are experienced. Most patients completing treatment will experience benefits of therapy.



Hypothesized Risk of Differential Treatment Effects. Most alcohol dependent patients engaging in treatment will experience some benefit of reduced drinking by coming into the clinic regularly and monitoring their drinking levels. Patients treated with placebo may experience these benefits. We hypothesize that sertraline treatment may produce beneficial effects above placebo in Type A subjects but and reduce the benefits of placebo in Type B subjects. Thus, we hypothesize a statistical difference from placebo and a group difference in Sertraline effects but do not expect to see a clinical worsening of drinking relative to baseline – -i.e. most subjects will show some improvement, but some more than others.

Monitoring for adverse events. The Principal Investigator and all study staff understand their responsibilities to assure protocol compliance and quality and safety monitoring during the conduct of this study. Patients receiving double-blind medication will be seen by a Physician's Assistant on each weekly visit to be assessed

for any adverse events. Standard procedures exist to record and document adverse events (AE's) when and if they occur and to bring those to the attention of Psychiatrist associated with the VA Dual Diagnosis programs of the STVHCS and CTVHCS. As Principal Investigator, Dr. Roache will assure that all AE's are evaluated as possible Unanticipated Problems Involving Risk to Subjects and Others (UPIRSO's) and that serious UPIRSO's will be promptly reported to the performance site IRB. As a standard part of their clinical assessment on each patient visit, the Psychologist conducting therapy for this study will make global mental health assessment in general and suicide risk assessment in particular. Patients who show clinically-significant deterioration during the study will be clinically evaluated by the PTSD-Dual Diagnosis treatment team for alternative treatments patients may need. Patients will be discontinued from the study if alternative psychotherapies or medications are required to address their needs.

Study Stop-Point Criteria. Patients who show clinically-significant deterioration of their PTSD, alcohol, or other mental health in the opinion of the patient, the therapist, or the psychiatrist, - and who need an alternative psychological therapy or psychotropic medication treatment will be discontinued from the study and given that alternative treatment. Patients who are unable to tolerate the sertraline/placebo medication in the opinion of the patient or the psychiatrist will be discontinued from the protocol and given alternative treatment.

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SSRI Treatment of Dual Diagnosis PTSD and Alcohol Dependence: A Test of the Serotonergic Hypothesis.

JD Roache[1], T Benson[1], J Klocek[2], S Back[3], K Brady[3], and J Potter[1]

[1]Univ. Texas HSC – San Antonio, [2]Central Texas Veteran's Health Care System (Waco), and [3]Medical College of South Carolina (Charleston).

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The STRONG STAR Multidisciplinary PTSD Research Consortium is a multi-institutional consortium of military, civilian, and VA institutions and investigators.
STRONG STAR (South Texas Research Organizational Network Guiding Studies on Trauma and Resilience) implements several studies, such as this one, to investigate the diagnosis, causes, treatment, and rehabilitation of PTSD and other trauma-related disorders.

Dual Diagnosis of PTSD and Alcohol Dependence

Among DoD and VA patients with PTSD, there is a high incidence of comorbid conditions. A survey of all male patients receiving medical and psychiatric care at Boston area outpatient VA clinics revealed that 20% had a diagnosis of PTSD (Hankin et al., 1999). Of those, 82% had comorbid major depression and 24% had an alcohol use disorder. The high prevalence of PTSD and alcohol dependence comorbidity, along with the special treatment demands it requires, presents a burden to the DoD and VA mental health systems. Dual Diagnosis patients have increased use of mental health (Hankin et al., 1999) and medical treatment (Schnurr et al., 2000) services compared to veterans with single diagnoses. In addition, patients with comorbid PTSD and alcohol dependence require more services, since they show poorer social adjustment and have reduced social resources compared to those with PTSD or alcohol dependence alone (Riggs et al., 2003).

Use of SSRIs in the Treatment of PTSD

Although other medications have been used, serotonin-selective reuptake inhibitors (SSRIs) have been the medications of choice for the treatment of PTSD (Ursano et al., 2004) both within the VA and in the field in general. Sertraline was the first medication approved by the FDA for PTSD treatment based upon randomized, placebo-controlled studies showing its efficacy in reducing PTSD symptoms (Davidson et al., 2001b), and preventing relapse (Davidson et al., 2001a). Paroxetine also is FDA-approved to treat PTSD (Tucker et al., 2001) and, though not FDA-approved, fluoxetine also has shown efficacy (Martenyi et al., 2002). Despite these findings, a recent Institute of Medicine report (2007) suggested that the evidence for efficacy of SSRIs in the treatment of PTSD is not as strong as it is for cognitive behavioral therapies (CBT) and that most of the evidence was with civilian rather than combat-related trauma. Nonetheless, SSRIs are "strongly recommended" by the VA/DoD Clinical Practice Guideline for the treatment of PTSD, and theycontinue to be used frequently in VA and DoD populations.

Importance of Alcohol Subtyping

There has been a long-standing interest in sub-grouping types of alcoholism (Bowman & Jellinek, 1941). In adoption studies, Cloninger and colleagues (1981) proposed a dichotomous classification of "milieu-limited" (Type I) and "male-limited" (Type II) alcoholism. More recently, Babor et al. (1992a,b) proposed a Type A vs. Type B typology based upon an empirical clustering method wherein **the Type B cluster is "...characterized by early onset, a more rapid course, more severe symptoms, greater psychological vulnerability, and poorer prognosis."**

Sertraline and other SSRIs. Although many studies have shown that SSRIs reduce alcohol drinking among heavy problem drinkers, they have not worked for alcohol dependent outpatients. Kranzler et al. (1995) found that fluoxetine improved depressive symptoms in a subgroup of alcoholics with comorbid depression but was of no value in reducing alcohol consumption. A subsequent reanalysis of those data divided subjects into the Babor Type A/B groupings and found that fluoxetine was no different than placebo in *n*=60 Type A alcoholics, but it was **significantly worse than placebo** in *n*=35 Type B alcoholics (Kranzler et al., 1996). Pettinati et al. (2001) failed to detect antidepressant effects of sertraline in a subgroup of alcoholics with depression but did find that sertraline reduced drinking in subjects without a history of depression. A reanalysis of those data (Pettinati et al., 2000) found that **sertraline was superior to placebo to reduce drinking in n=55 Type A alcoholics but not in n=45 Type B alcoholics.** A six-month follow-up of these patients (Dundon et al., 2004) showed that Type A patients previously treated with sertraline continued to do better than those treated with placebo, while the Type B alcoholics previously treated with sertraline drank significantly more over the follow-up period than did those treated with placebo. Chick et al. (2004) came to similar conclusions about the potential harmfulness of SSRIs when he found that, for alcoholics treated with fluvoxamine, those classified as Type II or early onset did worse than subjects classified as Type I or late onset.

Thus, data from three different studies of three different SSRIs have all uniformly demonstrated that the classification of alcoholism subtype predicts response to SSRIs. All three studies showed that **SSRI treatment can worsen the prognosis and increase drinking relative to placebo in the Type B, Type II, or Early Onset classified subgroup**, who have increased vulnerability and alcoholism that is more severe and more biologically determined. Beneficial effects of SSRIs to treat alcohol dependence only have been found in one study (Pettinati et al., 2000) in which sertraline was superior to placebo in Type A alcoholics. Thus, the typological classification of alcohol dependence appears to be critical to predict response to treatment with SSRIs.

SSRI Treatment of Dual Diagnosis

Given the frequency of comorbid PTSD + Alcohol Dependence and the fact that SSRIs are "strongly recommended" by the VA/DoD Clinical Practice Guideline for the treatment of PTSD, the importance of differential effects of SSRIs in various subtypes of alcohol dependence becomes apparent. The potential problems of dual diagnosis treatment are illustrated in a study of 94 subjects with civilian trauma-related PTSD and comorbid alcohol dependence (Brady et al., 2005). In that study, subjects treated with CBT for alcohol dependence were given 150 mg sertraline vs. placebo for the treatment of PTSD. The results found a large cluster (n=27) of subjects who were heavier drinkers at baseline and who showed that sertraline was worse than placebo in drinking outcomes. Sertraline was superior to placebo in reducing the drinking among a small cluster (n=14) of subjects, but the largest cluster (n=53) showed no differential effect of sertraline vs. placebo. The authors suggested that the small cluster of subjects who showed benefits of sertraline were Type A-like in character and had the least severe alcohol dependence with an age of onset for PTSD that clearly preceded the onset of alcohol dependence. In contrast, the large cluster of subjects in whom sertraline was less helpful than placebo appeared to be a Type-B-like cluster with an earlier age of onset of alcohol dependence symptoms.

COPE manualized Therapy for Dual Diagnosis

A 12-week manualized therapy (Concurrent Treatment with Prolonged Exposure, or COPE) has been developed to treat PTSD and Alcohol Dependence (Brady et al., 2001). This therapy integrates a cognitive behavioral approach to treat drug dependence (Carroll, 1998) and an exposure-based treatment for PTSD (Foa & Rothbaum, 1998). The PTSD component incorporates prolonged imaginal exposure and in vivo exposure techniques, while the substance-use component involves CBT techniques, such as, cognitive restructuring, recognizing and coping with cravings, managing thoughts about substance use, problem solving, planning for emergencies and a possible lapse, and stimulus control.

Subject Population

Subjects will be 18- to 65-year-old male or female veterans seeking treatment for service-related PTSD who also have a dual diagnosis (DSM-IV criteria) of both PTSD and Alcohol Dependence. For study inclusion, subjects must meet diagnostic criteria for PTSD as determined by the clinician administered PTSD Symptom Scale (PSS-I) and minimum PTSD severity (> 30 on the PCL) and currently be drinking heavily (> 5 drinks per drinking day for men and > 4 for women) on at least 50% of the past 30 days

Specific AIMS

We plan to conduct a clinical trial evaluating sertraline treatment efficacy in OEF/OIF veterans with dual diagnosis PTSD and Alcohol Dependence. Even though sertraline is a medication of choice for the treatment of PTSD, we expect that the comorbid condition of alcohol dependence will complicate treatment and that clustered subgroups (i.e., Type A vs. Type B) of alcoholics will show differential treatment response with sertraline. The hypothesis of the study is that subtypes of alcohol dependence can be used to predict which subgroup of dual diagnosis patients respond well and which subgroup responds poorly to SSRI treatment. This study will address the following Specific Aims:

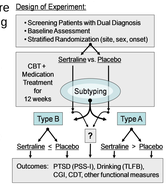
We hypothesize that sertraline will:

i. *not be different than placebo among the dual diagnosis population as a whole;*
ii. *be less than or equal to (<) placebo in benefit to reduce either PTSD symptoms or alcoholic drinking among the Type B subgroup;*
iii. *be superior to (>) placebo to reduce both PTSD symptoms and alcohol drinking among the Type A subgroup.*

Study Design

The study design is a parallel group, double-blind, placebo-controlled, stratified, randomized medication treatment trial of male and female OEF/OIF veterans who experienced "in-theater" trauma and meet DSM IV criteria for both **PTSD and Alcohol Dependence.** All subjects will receive manualized CBT (COPE) as a standard of care. Additionally, subjects will be randomized to receive double-blind treatment with **Sertraline vs. Placebo** as an adjunctive treatment. The manualized therapy provides standard cognitive-behavioral treatment to address alcohol dependence as well as state-of-the-art behavioral exposure therapy targeting PTSD. A post-hoc clustering approach will be used to determine which subgroups of dual diagnosis patients may benefit from sertraline vs. placebo treatment.

As part of the STRONG STAR Consortium on PTSD, two VA sites – the South Texas Veterans Health Care System (STVHCS) and the Central Texas Veterans Health Care System (CTVHCS) – will enroll a total of n=240 treatment-seeking patients entering into the VA's Dual Diagnosis program.



Study Procedures

Weekly outcome assessments of PTSD symptoms and drinking outcomes will utilize standard procedures to track changes over time. Drinking will be assessed by validated Time-Line Follow-Back (TLFB) self-reports and by objective laboratory tests of Carbohydrate Deficient Transferrin (CDT) and Phosphotidyl-Ethanol (PE). PTSD symptoms will be assessed by the clinician-administered PTSD Symptom Scale (PSS-I) and Clinician Assessment of PTSD Symptoms using the PCL-M.

Post-hoc clustering techniques will be used to classify phenomenological subgroups into Type A vs. Type B using dimensional measures similar to those employed in previous studies of primary alcohol dependence but adapted to the dual diagnosis military-veteran population. Ten baseline characteristics will used for the cluster derivation. These include Age of Onset and Onset Precedence (Pre vs. Post PTSD) factors; drinking and PTSD severity factors; other psychiatric or mood disturbance; personal trauma history; and family history of alcoholism. The efficacy of sertraline vs. placebo to reduce drinking and PTSD symptoms will be examined within each of these two empirically derived clusters (Type A and Type B).

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