

A. BACKGROUND AND SIGNIFICANCE

A1. Significance: PTSD is a debilitating disorder that is common among veterans returning from Iraq and Afghanistan (OIF/OEF) due to the high risk of exposure to combat and other trauma. Recently, emerging evidence suggest a strong link between PTSD and ADHD. The co-occurring ADHD symptoms are likely to reflect the impairment in cognitive function, which often expressed as reduced attention span, concentration difficulties, impaired decision-making abilities, and memory problems (LaGarde et al, 2010). Co-occurring ADHD cognitive impairments add another layer of complexity to the disease process and pose more severe impairments in daily function. While treatments for the avoidance, arousal, and re-experiencing symptoms associated with PTSD for military personnel are readily available, substantial gaps exist in the treatment of the cognitive deficits associated with PTSD. Further, ADHD cognitive symptoms are associated with poorer patient attendance to medical appointments, poorer medication compliance and increased risk for psychotherapy resistance and medication abuse or diversion (Kolar et al., 2008). Consistent attendance is the best predictor of patient functional recovery from PTSD (Tarrier et al., 2000). Subsequently, untreated co-occurring ADHD cognitive symptoms that increase the risk for problems in patients' PTSD treatment engagement, PTSD treatment responses, functional impairment, and quality of life have tremendous negative impact on treatment outcome. However, in so far, studies have not examined the impact that treating ADHD cognitive symptoms have on PTSD treatment engagement, outcome, and functional recovery. The proposed study directly addresses this knowledge gap by testing the feasibility and preliminary efficacy of atomoxetine (ATX) in treatment of ADHD cognitive symptoms among those with comorbid ADHD/PTSD. Our research is directly responsive to the mission of RR&D-SPIRE "to maximize functional recovery" of cognitive function in PTSD. The outcome of the proposed research will be significant, because it will provide a knowledge base to help determine who is at risk for developing problems with treatment engagement among PTSD patients, thereby allowing for development of early intervention strategies before drop-out. More importantly, the new knowledge may lead to discovering new targets for novel and more effective treatments for PTSD. This novel clinical trial may have immediate benefit to Veterans by enhancing their cognitive function, reducing ADHD symptom related disabilities and further improving quality of life for veterans with comorbid ADHD/PTSD.

A2. Review of the Literature Relevant to This Application

Cognitive Impairments in Comorbid ADHD/PTSD: Combat Veterans with PTSD often show cognitive impairments in attention, working memory, executive functions, and inhibitory control (Vasterling, 2007), a cluster of symptoms overlapping with symptoms of adult ADHD. It has been proposed that the cognitive deficits in PTSD may be related to the same disturbance of fronto-temporal systems observed in ADHD. This hypothesis has been supported by several imaging research findings that indicate functional alteration in the medial frontal and lateral prefrontal cortex in PTSD (Nee et al 2007, Shin et al 2006). Further, impaired response inhibition task, Go-NoGo (GNG), a measure of executive function has been observed both in ADHD and in PTSD patients (Fisher et al 2011; Swick et al 2012). Finally, there is substantially higher rates of PTSD development in individuals with ADHD (Hanson et al 2012), suggesting that both may share common biological risks. Although the exact mechanisms of co-occurrence of cognitive symptoms in both ADHD and PTSD is not yet fully known, research has suggested that this cognitive impairment plays an important role in PTSD development, treatment response, and prognostic outcomes (Aupperle et al, 2012). **Cognitive Function and PTSD Treatment Outcome:** Many cross-sectional studies have documented strong evidence that PTSD is associated with significant cognitive impairment, and the presence of cognitive impairments is related to poorer treatment outcome (Verwoerd et al, 2009; Wild and Gur, 2008; Walter et al, 2010). As a result, the DSM-5 diagnostic criteria for PTSD have expanded the cognitive symptom criteria associated with PTSD. In the past 2 decades, extensive psychological and pharmacological treatments have been developed for PTSD, but as many as 50% of individuals with PTSD do not fully respond to the standard interventions and drop-out rates are often cited around 30%. Many of these standard treatments are developed predominantly to address re-experiencing and avoidance symptoms, but not cognitive impairment. However, in patients with PTSD, the impairment in occupational, academic, and social functioning often persists after receiving specialized treatment, including successful treatment of PTSD symptoms of avoidance and re-experiencing (Westphal et al, 2011). It is well documented that intact cognitive function is essential for activities of daily living, including self-care. However, problematic treatment behaviors commonly associated with impaired cognitive functioning are not targeted as part

of PTSD interventions but are regularly indicated as the best predictors of outcome for exposure-based PTSD treatment (Tarrier et al., 2000). Given that up to 50% of patients do not respond well to first line treatments for PTSD, it is imperative to identify potential risk factors for poor outcome and seek novel treatment strategies to improvement rehabilitation. The standard treatments do not directly target cognitive deficits, which may account for poor treatment compliance as well as the failure of functional recovery even after successful treatment in PTSD. **Cognitive Deficit and Risk of PTSD:** Recent prospective longitudinal studies have started to emerge and have documented evidence that pre-trauma subtle cognitive deficits were related to the development of PTSD (Vasterling et al, 2006). A veteran twin study suggests that lower pre-trauma cognitive function may constitute a risk for the development of PTSD after trauma exposure (Gilbertson et al, 2006). In summary, the cognitive deficit is at least partially responsible for PTSD susceptibility, treatment resistance, and poor functional recovery. The proposed study will investigate the potential mechanisms of cognitive function in the initiation, maintenance, and recovery of combat and other trauma related PTSD, in an effort to inform approaches to improve in primary, secondary, and tertiary treatment of PTSD in Veterans.

A3. ATX and Treatment of Cognitive Impairment in ADHD/PTSD: ATX is a selective norepinephrine reuptake inhibitor (SNRI). By blocking norepinephrine transporters (NET), ATX enhances noradrenergic and dopaminergic signaling in the pre-frontal cortex (PFC), but not striatum (Bymarster et al 2002). This feature explains why ATX reduces ADHD symptoms and improves PFC cognitive function but has no abuse potential. Therefore, it becomes more preferred therapeutic agent in patients where substance abuse is a problem or concern. Given the increased risk for substance abuse documented in patients with PTSD (Terriar et al, 2000), the reduced risk for abuse poses a substantial benefit to this drug. Currently, ATX is the only non-stimulant medication approved by FDA for treatment of ADHD. Studies have shown that ATX is safe, effective, and well tolerated with mild side effects profile in acute and long-term treatment of ADHD in children, adolescent, and adult (reviewed by Vauphan et al, 2009). Compared to MPH, ATX showed similar efficacy in the improvement of ADHD symptoms (Wang et al, 2007). In addition, ATX also exhibited beneficial effect on comorbid anxiety and depression in ADHD patients (Geller et al, 2007; Deviss, 2008), both of which are highly comorbid with PTSD. Further, the ATX may have potential to improve PTSD as similar SNRI, reboxetine, has shown efficacy in reducing PTSD symptoms in motor vehicle accident related PTSD (Spivak et al 2006). The above literature review provides strong rational for choosing ATX to treat cognitive symptoms in Veterans with ADHD/PTSD.

A4. Relevance to Veterans Health: PTSD is a debilitating condition that develops following exposure to traumatic events. Exposure to potentially life threatening events increases dramatically in military service, particularly for those directly engaged in combat. As such, PTSD is highly prevalent in military personnel and Veterans, estimated at between 11 and 18% of those returning from wars (True et al, 1993; Hoge et al, 2004). The primary mental health symptoms and secondary comorbid disorders associated with PTSD create a tremendous burden for the Veteran, their families, and for the VA health care delivery system, as well as incurring great society burden due to lack of workforce productivity that can result from this condition. Despite numerous efforts to develop effective treatments, many patients do not or only partially respond to current treatment or withdraw from treatment (Fontana and Rosenheck 1997; Johnson *et. al.* 1999; Prigerson *et. al.* 2001). The evidence from our research and others indicates that comorbid ADHD cognitive impairment is an additional additive risk for the development and maintenance of PTSD symptoms (Aupperle et al, 2012). However, as yet, the mechanism for this is unknown. This study serves to be the first to both address the lack of research on both the shared mechanism of cognitive dysfunction and preliminary trial of a treatment for improving PTSD treatment response. The proposed study will conduct a novel clinical trial to assess efficacy of ATX to improve treatment outcome and compliance as assessed by patient 1) functional impairment and quality of life and 2) reduce the cognitive impairment symptoms observed in both ADHD and comorbid PTSD. The outcome of this study will improve the understanding how cognitive deficit influence PTSD symptoms after exposure to trauma, and will provide the means to intervene through either primary preventive or secondary treatment strategies. The trial will immediately benefit Veterans and military personnel who suffer from comorbid ADHD/PTSD, since they will provide more direct treatment of cognitive symptoms that will improve their occupational and academic function more immediately, improve efficacy of PTSD treatments, and help prevent long-term disability. A long-term benefit of this research is that once an association is established among cognitive function and

ADHD/PTSD, methods can be developed to target the early intervention and treatment strategies and treatment retention enhancements. As a result, the approaches of prevention or early intervention may increase individual resilience to traumatic events, and enhance Veteran's ability to continue their performance and engagement in the workforce.

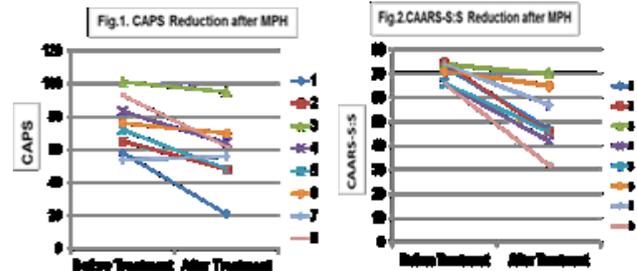
B. PRELIMINARY DATA

B1. Experiences: PI, Dr. Wang and Co-investigators, Dr. Hamner, Dr. Sallee, and Dr. Acierno have extensive experiences in genetic and treatment research in PTSD and ADHD. Dr. Wang has conducted numerous candidate gene research studies in various psychiatric disorders. Dr. Wang moved to Charleston VA Medical Center in 2007, and that same year he was awarded a Merit Review Award to study monoamine genotypes in Veterans with and without PTSD. He recruited 388 subjects and performed. The project found an association between homozygote short (S) genotype of 5-HTTLPR and PTSD (Wang et al, 2011). Recently, Dr. Wang's research has been focused on identifying biomarkers for various psychiatric disorders (Wang et al, 2006; Gilbert et al, 2006; Wang et al, 2007). In 2011, he won another Merit Review Award titled "Cortical Excitability: Biomarker and Endophenotype in Combat Related PTSD". The on-going project provided essential preliminary data for this application. Dr. Kirstin Gros, co-investigator, has extensive history as co-investigator and researcher on social impact on the etiology and course of externalizing disorders and modification of interventions to reduce barriers to engagement, will help to develop psychological assessments and with statistical analysis. Dr. Mark Hamner, Dr. Sallee, and Dr. Acierno have recently joined this research team as co-investigators to aid in pharmaceutical trial design, cognitive assessment, diagnostic assessment, and recruitment. Combined, the PI and co-investigators are well prepared to undertake the proposed research, as they have the scope, breadth of expertise, and resources needed to complete the research successfully.

B2. Preliminary Data:

B2.1. PTSD, Cognitive Deficit, and ADHD: In our on-going project, we evaluated combat veterans with and without PTSD with Clinician Administered PTSD Scale (CAPS), Conners' Adult ADHD Rating Scales–Self Report: Short Version (CAARS–S:S, score > 65 is regarded clinical significant cognitive impairment; Conner et al 1999). We included 47 participants, 29 PTSD subject (13 with CAARS > 65, 45%) and 18 controls (2 with SAARS > 65, 11%). The results indicated PTSD diagnosis is associated with significantly higher self-reported attentional and executive dysfunction symptoms ($\chi^2 = 5.81, p = 0.16$). This was also evident in the significant correlations between CAPS and CAARS-S:S scores ($R=0.497, p < 0.01$), and CAPS PTSD symptoms ($\beta=.26, t=1.88, p=.05$), and PTSD patient cognitive deficit severity as measured by the CAARS-S:S ($\beta=.59, t=4.81, p<.001, R^2=.34$). These findings further support available literature suggesting that cognitive symptoms associated with PTSD diagnosis are highly correlated with patients' functional outcome.

B2.2. MPH Improves Cognitive Function: Further, we conducted additional preliminary analyses with 8 PTSD individuals with cognitive symptoms who were treated with MPH. Analyses conducted on clinical assessments of patients' PTSD and ADHD symptoms (CAPS and CAARS-S:S) before and after MPH treatment revealed significant reductions in both PTSD and self-reported cognitive deficit symptoms (see Fig1 and Fig2; $F(1, 7) = 22.39, p = .002$).



C. RESEARCH DESIGN AND METHODS:

C1. Overview: The proposed project is a pilot, feasibility double-blind crossover study to investigate the efficacy and safety of ATX with comorbid PTSD/ADHD patients to reduce cognitive symptoms, improve treatment retention and response, and improve patient's activities of daily living. A prospective, 10-week, fixed-dose, randomized, double-blind, placebo-controlled, and cross-over trial of ATX as an adjunctive medication to other therapies will be conducted among veterans with comorbid PTSD/ADHD. The short-duration, crossover design, and blind enable the study to be feasible in both time and funding level. **The Primary Objective** is to assess the efficacy of fixed dose of ATX (80mg) (compared with placebo) in reducing cognitive symptoms in comorbid ADHD/PTSD such that functional

impairment and treatment retention are both improved, while **The Secondary Objective** is to replicate the our preliminary finding of negative impact of cognitive symptoms of ADHD on PTSD clinical outcomes. **The Tertiary Objective** is to assess the efficacy of ATX in reducing broad spectrum of PTSD symptoms. The proposed study will take 10 weeks and include two phases (**Phase I**: Initial Phase, 5 weeks; **Phase II**: Crossover Phase, 5 weeks). The crossover design was employed to both achieve study objectives while minimizing costs. Each phase consists two periods: **Period I** (week1 in Phase I and week6 in phase II) consist of psychological and physical assessments and placebo lead-in/wash-out, in which subjects take 6 days placebo; **Period II** (weeks 2-5 in Phase I and week7-10 in Phase II) consist of treatment with either atomoxetine 80mg daily or placebo daily). This project will take advantage of established on-going PTSD assessment and treatment clinical trials currently performed at the Ralph H. Johnson VA Medical Center (RHJVAMC) to facilitate recruitment. The proposed 50 veterans with ADHD/PTSD will be recruited from these on-going trials enabling both comprehensive assessment and evaluation of patients' engagement in ongoing PTSD treatments. Subjects will be randomized and assigned by the study investigator (Dr. Floyd Sallee) into crossover group 1 (ATX at Phase I, then placebo at Phase II) or 2 (placebo at Phase I, then ATX at Phase II) with both placebo and medication administered through pharmacy. Subjects and other investigators are thus able to remain blinded to the order of treatment assignment throughout the study. The 1-week interval was based on published pharmacokinetic data for 4 week doses of ATX (*Witcher et al, 2003*). After crossover, patients will be unblinded and data will be cleaned and analyzed. Final follow up will be 30-days after last visit.

C2. Investigational Agent: ATX is a non-stimulant, FDA approved agent for treatment of ADHD. ATX 80mg is the most common adult dose used in ADHD with and without comorbid condition (Adler et al, 2009). In this project, 80 mg ATX and placebo will be prepared in capsules with identical appearance and similar taste by Eli Lilly and Company, Indianapolis, Indiana.

Adverse effects (AE): Typical adverse events reported significantly more frequently with atomoxetine than placebo included dry mouth, insomnia, nausea, decreased appetite, constipation, dizziness, sweating, dysuria, sexual problems and palpitations. Modest increases in heart rate and blood pressure were well tolerated and gradually decreased on cessation of treatment.

Contraindications: ATX is contraindicated in patients known to be hypersensitive to the drug and during treatment with monoamine oxidase inhibitors (hypertensive crises may result). Medication will be stored and dispensed from the Charleston VAMC investigational drug pharmacy. Records will be maintained of all doses dispensed, and Veterans will be asked to return all unused tablets and empty prescription vials to the clinic for assessment of treatment compliance.

C3. Method

Subject Recruitment: All the subjects will be recruited through Charleston VAMC Mental Health Service Line. The Charleston VAMC has a large base of potential comorbid PTSD and ADHD participants. Many clinical trials, including pharmaceutical and psychotherapeutic trials are currently conducted in conjunction with the Charleston VAMC PTSD Clinical Team (PCT) clinic and the PCT team receives numerous PTSD evaluation consults from OIF/OEF program and Primary Care. Currently the PCT clinic receives 200 to 250 new referrals yearly of OIF/OEF Veterans who meet full criteria for PTSD based on a comprehensive initial intake interview that includes CAPS and functional impairment assessments. PI, Dr. Wang currently manages pharmacological consults for OIF and OEF Veterans. A HIPAA waiver of authorization will be on file with the IRB giving the research team permission to recruit from prior study populations. Veterans with PTSD from OIF/OEF are uniquely suited for this study because statistically they have fewer confounding variables for this clinical trial, including medical conditions such as hypertension or glaucoma and cognitive impairments such as dementia. Interested veterans who participate in clinical trials are explained the nature, purpose, and procedure of the study and asked to sign an informed consent that will explain in detail the purpose of the study, potential risks and benefits of pharmacotherapy study participation and alternative treatments that may be available.

Inclusion Criteria: 1) OIF/OEF Veterans age 20 to 60 with PTSD and significant ADHD symptoms (CAARS-S:S > 65); 2) Good physical health. 3) Trauma exposure sufficient to meet Category A of PTSD criteria (Breslau and Kessler 2001)

Exclusion Criteria: 1) Age younger than 20 or greater than 60. 2) Known sensitivity to ATX. 3) Presence of disorders that could conceivably be exacerbated by atomoxetine (specifically, narrow

angle closure glaucoma, urinary outflow obstruction, hypertension, and neurological disorders, particularly tics and Tourette's syndrome, or a history of epilepsy or seizures). 4) use of concomitant medication that could potentially interact with atomoxetine including monoamine oxidase inhibitors (MAOI), antihypertensive medication, or any concomitant medication that was a cytochrome 2D6 inhibitor (CYP2D6) as atomoxetine's elimination involves the CYP2D6 system. 5) An active or lifetime major mental health diagnosis as determined by DSM-IV Axis I Disorders, including schizophrenia, schizoaffective disorder, psychotic disorder not otherwise specified, bipolar I disorder, bipolar II disorder, bipolar disorder not otherwise specified. The project will allow presence of depressive disorders if the depressive episodes are secondary to PTSD. 6) Current substance dependence and abuse (within 3 month). 7) Females who are pregnant or likely to become pregnant. 8) Active suicidal thoughts and behavior.

Suicide Screen: A screen for recent or current suicidal thought and/or attempts will be conducted before the interview. If a subject reports suicidal thought at the time of interview, his physician or psychiatrist will be informed and the subject will be escorted to the ER immediately for further evaluation and treatment.

Screening/Baseline Evaluation: During this visit subjects will review and sign the Informed Consent. Eligibility to participate in this portion of the study will be determined by a minimum 6-month duration of PTSD illness, CAARS-S:S score of 65 or higher as well as a positive ADHD score for the adult section of the Conners ADHD interview, a total CAPS severity score of 55 or higher at the baseline visit. If the subjects qualify, then a medical/psychiatric history will be obtained along with laboratory safety measures, including electrocardiogram (EKG), liver and renal panel (SMA-12), complete blood count with differential, urine toxicology screen and concomitant meds. If the veteran is female, urine pregnancy test will be obtained.

PTSD Medication Stabilization: Those patients meeting inclusion criteria will be asked to maintain medications at current dosages where medically possible. Participants who have not initiated new prescription medications in the previous 4 weeks will initiate treatment one week following the assessment battery. However, those potential participants who have recently begun trials of prescription medication will be required to wait 4 weeks post-assessment to ensure medication stabilization, at which point the assessment battery will be re-administered.

Efficacy Assessments and Outcome Measurement: Primary outcome measures will be conducted at baseline and all subsequent visits by a qualified research clinician using the CAARS-S:S, with the Barkley Adult ADHD Rating Scale-IV (BAARS-IV) and Adult ADHD Quality of Life-29 (AAQoL-29) conducted at follow up visits. Clinical Global Impression Severity (CGI-S, at baseline only) and Clinical Global Impression Improvement (CGI-I, at all visits except baseline and W1) will be done as well. Additional assessments for evaluating secondary outcomes will include the Clinician Administered PTSD Scale (CAPS), Hamilton Depression Scale (HAM-D). Quality of life will be assessed using the Veteran's version of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF36-V). In addition to subjective measures, the response inhibition task Go/NoGo (GNG) and Stop Signal (SST) will be used as objective assessments to measure ATX treatment outcomes.

Key Assessment Measures:

Mini-International Neuropsychiatric Interview (MINI, Sheehan et al., 1998): The MINI is an abbreviated structured psychiatric interview that takes approximately 10-20 minutes to complete. The MINI has shown good inter-rater reliability and test-retest reliability for screening psychiatric disorders.

CAADID Part II: Diagnostic Criteria (CAADID, Epstein et al., 2001) The CAADID is a structured interview that assists in the process of diagnosing adult ADHD. This assessment is appropriate for those 18 and older. It is most effective when used with other types of ADHD measures, such as the CAARS™.

Clinician Administered PTSD scale (CAPS, Weathers et al., 2000): The CAPS is a structured interview that assesses both frequency and intensity of PTSD symptoms according to DSM-IV criteria. It provides both a dichotomous index for PTSD diagnoses and a continuous index of PTSD symptom severity.

Conners' Adult ADHD Rating Scales-Self-Report: Short Version (CAARS-S:S, Conner et al, 1999): The CAARS-S:S is a 26-item questionnaire that assesses symptoms of ADHD in persons aged ≥18 years. T-scores above 65 indicate a likelihood of moderate to severe ADHD symptoms and impairment.

The Adult ADHD Quality of Life-29 (AAQOL-29, Brod et al, 2006): AAQoL-29 is a participant-reported outcome measure used to examine disease specific functional impairments and quality of life for adults with ADHD. The AAQOL-29 includes Life Productivity, Psychological Health, Quality of Relationships, and Life Outlook subscales. Higher scores on the AAQOL-29 indicate better functioning.

The Barkley Adult ADHD Rating Scale-IV (BAARS-IV, Barkley, 2011): BAARS-IV offers an essential tool for assessing current ADHD symptoms and domains of impairment and recollections of childhood symptoms. BAARS-IV is empirically based, reliable, and valid for diagnosis and cognitive evaluation of adult ADHD.

Response Inhibition Task: The Go-NoGo (GNG) and Stop-Signal Task (SST) are classical paradigm to investigate response inhibition and response execution (higher-order motor and attention control) processing, and a reliable marker reflecting medial prefrontal functioning (Fallgatter and Strik, 1999). Further, ATX has been found to improve GNG and SST performance in ADHD patients (Nandam et al 2014; Chamberlain et al, 2007). GNG/SST require participants to implement their response to one kind of stimuli (Go/Start) and to withhold the responses to the other kind of stimuli (NoGo/Stop). Therefore, GNG commission errors SST time are a reliable marker to examine individual executive function and to measure ATX treatment response. GNG and SST will be performed at Dr. Wang's TMS Laboratory.

Table 1: Outline of study procedures and assessments of the study.

Initial Assessments	Screening/ Baseline	Phase I Start	Phase I Treatment visit	Phase I Follow up, Crossover lead in	Phase II Start	Phase II Treatment visit	Phase II Follow up	Final Follow up visit
visit (week)	1	2 (W1)	3 (W2)	4 (W5)	5 (W6)	6 (W7)	7 (W10)	8 (W14)
Consent	X							
MINI	X							
CAADID Part II	X							
CES	X							
DTS	X							
CGI-S	X							
CGI-I			X	X	X	X	X	
CAARS-S:S	X	X	X	X	X	X	X	X
BAARS	X			X			X	X
AAQoL-29	X			X			X	
SF-36-V	X			X			X	
CAPS-IV	X			X			X	
Ham-D	X		X	X	X	X	X	X
Ham-A	X		X	X	X	X	X	
GNG/SST	X			X	X		X	
Vital Signs	X	X	X	X	X	X	X	
Labs, EKG	X		X			X		
UDS	X			X				
Dispense med		X	X		X	X		
Compliance			X	X	X	X		
Concom meds	X	X	X		X	X		
AEs			X			X		

Safety assessments: At each study visit, safety will be assessed by measuring: weight, sitting blood pressure, heart rate, adverse events (except baseline), and use of concomitant medications. Laboratory and EKG assessments will be performed at baseline, one and seven weeks. Anxiety, depression, and suicidal ideation will be assessed with Ham-A, Ham-D, and suicide screen in each of the visits. Compliance will be assessed by pill counts and appointment attendance. Referrals to the Charleston PTSD clinic will be conducted at the final study visit for any remaining PTSD symptoms and the CBT clinic for remaining ADHD symptoms.

Follow-up: The final visit, 30-days after study completion, will include safety assessments, along with follow-up of any unresolved adverse events. This visit will also provide assurance that veterans who participated in this medication study will have adequate follow-up care in the Charleston VAMC PTSD or Mental Health Outpatient Clinic either with continued medication or psychotherapy. This visit may be done over the phone or by mail.

Diagnostic Procedures: After obtaining the informed consent, a trained research assistant will perform the initial interview and administer all of the diagnostic scales to the participants. Dr. Floyd Sallee, Dr. Mark Hamner (MD, Co-Investigator) and Dr. Zhewu Wang (PI) will make the final diagnosis based on all the data collected. The DSM-IV diagnostic criteria will be used to ascertain each phenotype.

Database Management: All collected clinical, demographic, and geographic data will be stored in Research Database Storage in the Charleston VAMC PTSD Program. The genotyping data will be stored in Dr. Wang's laboratory Research Database. For each patient, the clinical database will provide information as following: age, gender, ethnic origin, medical and psychiatric diagnosis, family history, developmental history, and existence of comorbidity. The genotyping data will be separately entered without knowledge of clinical data. Strict confidentiality is maintained regarding database information, which is secured and for research purposes only. All the specimens from the subjects will be labeled by code at the clinic. Names will not appear on specimens, nor will they be available in the laboratory. The person conducting the genotyping is blind to the clinical profile of the subject. No names or identifiable information will be used in any data presentation.

Statistical Analyses and Power Estimation: As a pilot feasibility study with double-blind crossover design, the design affords greater power and need for enrollment of fewer subjects. Similar design with this medication has suggested sample size of 40 was sufficient for effect sizes typically observed with this medication in similar populations (Bain et al 2013). To account for patient dropouts, the study will enroll/consent up to 50 patients. This will ensure 40 subjects complete the entire study. This design will allow initial pilot feasibility data, improved control and testing of causation, and greater power in the allotted time-frame and funding level. The primary consideration is difference in outcome between baseline and endpoint with ATX treatment as compared to placebo. The primary outcome measure a priori will be the change in total CAARS-S:S scores, AAQoL-29 and BAARS-IV. Secondary measures include the remaining efficacy and safety measures as delineated above. The primary outcome of interest is the moderating impact of ATX treatment (medication \times ADHD TAU) on treatment response (pre- and post-treatment measures of cognitive symptoms of ADHD and PTSD, functional impairment in daily living domains, and global functioning). A mixed model, repeated-measures multivariate analysis of variance with pre- and post-ADHD TAU treatment ADHD symptoms, functioning, and global functioning entered as repeated measures; and ATX treatment entered as the between factors. Pre-treatment PTSD severity scores (CAPS) will also be entered into the model as a potential explanatory covariate. Simple slopes using repeated measures ANOVA will be used to probe significant interactions

C4. Expected Results, Potential Problems and Alternative Strategies: Upon completion of the two objectives, we expect to find treatment with ATX enhances cognitive function, improve quality of life and treatment outcome among Veterans with ADHD/PTSD. We predict that the GNG and Stop Signal correlate with self-reported cognitive function in PTSD and can be used as biomarkers to measure treatment response. Despite the consolidate design, there is a remote possibility that some of the measures might not reach to statistically significance in our small sample size, short treatment duration and slower action of atomoxetine. The length of treatment has varied in previous atomoxetine studies from 3 to 11 weeks. Spencer et al were able to show efficacy on a cognitive test after 3 weeks. Because this was a pilot crossover study, a treatment period toward the shorter end of the range was most cost-effective and most likely to maximize subject participation and retention, so 4 weeks was chosen. We strongly believe that the primary objective will be accomplished using our design, as literature support robust significant improvement of ADHD symptoms, cognitive function, and quality of

life even at 2 weeks of treatment with ATX 80mg daily compared with placebo (Spencer et al 1998; Durell et al 2013; Epperson et al 2011; Tsang et al 2011). Due to the funding and time-frame limits, some of the secondary measure may not reach to significance, but we believe the study will provide data showing the improvement and that will provide direction for future studies.

C5. Future Direction: The current available treatments for PTSD are not fully effective for cognitive symptoms of PTSD and have high drop-out and poor engagement, two factors found to be most indicative of overall return to functioning for patients with PTSD. Successful completion of this pilot clinical trial may build a platform for future large scale double-blind, placebo-controlled studies using either ATX or psycho-stimulants or other cognitive enhancing medications. The response inhibition related measurements are sensitive to psychotropic medications. Therefore it is advantageous for us to use GNG and Stop Signal approaches to investigate individual treatments response in our future research. We believe GNG and Stop signal approaches together with pharmacogenetic approach will provide valuable information to direct future individualized medicine.

HUMAN SUBJECTS RESEARCH

1. Protection of Human Subjects

1.1 Risks to Subjects

a. Human Subjects Involvement and Characteristics:

Totally, up to 50 veterans with comorbid ADHD and PTSD will be recruited for this pilot clinical trial. All subjects will be Veterans from Operation Iraq Freedom / Operation Enduring Freedom (OIF/OEF). Our record review showed age range from 20 to 60 in this OIF/OEF group, and statistically they have fewer confounding variables for this clinical trial, including medical conditions such as hypertension or glaucoma (described detail in exclusion criteria) and cognitive impairments such as dementia, which meet criteria for our research study. PTSD subjects with and without ADHD cognitive symptoms will be recruited from the Charleston VAMC Mental Health Service Line. Examining and treatment of ADHD cognitive symptoms among Veterans with PTSD is scientifically and ethically justified to further understand the mechanism of developing PTSD after trauma exposure, and what is the best treatment for Veterans with comorbid PTSD and ADHD. Specific inclusion and exclusion criteria are listed below:

Inclusion Criteria: 1) OIF/OEF Veterans age 20 to 60 with PTSD and significant ADHD symptoms (CAARS-S:S > 65); 2) Good physical health. 3) Trauma exposure sufficient to meet Category A of PTSD criteria (Breslau and Kessler 2001)

Exclusion Criteria: 1) Age younger than 20 or greater than 60. 2) Known sensitivity to ATX 3) Presence of disorders that could conceivably be exacerbated by atomoxetine (specifically, narrow angle closure glaucoma, urinary outflow obstruction, hypertension, and neurological disorders, particularly tics and Tourette's syndrome, or a history of epilepsy or seizures). 4) use of concomitant medication that could potentially interact with atomoxetine including monoamine oxidase inhibitors (MAOI), antihypertensive medication, or any concomitant medication that was a cytochrome 2D6 inhibitor (CYP2D6), since atomoxetine's elimination involves the CYP2D6 system. 5) An active or lifetime major mental health diagnosis as determined by DSM-IV Axis I Disorders, including schizophrenia, schizoaffective disorder, psychotic disorder not otherwise specified, bipolar I disorder, bipolar II disorder, bipolar disorder not otherwise specified. The project will allow presence of depressive disorders if the depressive episodes are secondary to PTSD. 6) Current substance dependence and abuse (within 3 month). 7) Females who are pregnant. 8) Suicidal thoughts and behavior.

b. Sources of Material

c. Potential Risks

Therapeutic Risk:

Pharmaceutical agent: Atomoxetine (ATX) is a norepinephrine reuptake inhibitor that blocks norepinephrine and dopamine transporters and increases dopamine and norepinephrine availability in the synaptic cleft at the pre-frontal cortex. ATX is one of the first line treatments for children and adult attention deficit hyperactivity disorder (ADHD). Efficacy and safety of ATX are well established by numerous clinic trials in the past 15 years. However, there have been no trials of ATX for treating ADHD cognitive complaints associated with PTSD, possibly because of the less awareness of high comorbid rate of ADHD and PTSD, and concern about the abuse potential of commonly used stimulant medications and concern about interventions that increase catecholamine release may exacerbate

anxiety symptoms. Currently, ATX is the only non-stimulant medication approved by FDA for treatment of ADHD. Studies have shown that ATX is safe, effective, and well tolerated with mild side effects profile in acute and long-term treatment of ADHD in children, adolescent, and adult (reviewed by Vauphan et al, 2009). Unlike psycho-stimulants, ATX does not show abuse potential (Bymarster et al 2002). A couple of studies have also shown efficacy of ATX in treatment of ADHD cognitive symptoms in patients with comorbid ADHD and anxiety and/or depression. ATX were very well tolerated in individual with comorbid ADHD and anxiety, or ADHD and depression (Geller et al, 2007; Deviss, 2008). There is not excessive anxiety or other symptoms among subjects with comorbid anxiety and depression, who were taking ATX. Although ATX has not been tested in PTSD, a similar selective norepinephrine reuptake inhibitor, reboxetine has been studied in PTSD and shown safety and efficacy in reducing PTSD symptoms in motor vehicle accident related PTSD (Spivak et al 2006). The above literature review provides strong rationale for choosing ATX to treat cognitive symptoms in Veterans with ADHD/PTSD.

Adverse Effects:

Common

- **Cardiovascular:** Increased diastolic arterial pressure (adult, 4.8% to 12.6%; pediatric, 9.3% to 21.5%), Increased systolic arterial pressure (adult, 4.2% to 12.4%; pediatric, 4.9% to 12.5%), Tachycardia (adult, 1.5% to 22.4%; pediatric, 0.3% to 23.4%)
- **Endocrine metabolic:** Weight decreased (adults, 2%; pediatric, 7.1% to 29.1%)
- **Gastrointestinal:** Abdominal pain (adult, 7%; pediatric, 17% to 18%), Constipation (adult, 8%; pediatric, 1% to 2%), Decrease in appetite (adult, 16%; pediatric, 16%), Nausea (adult, 26%; pediatric, 7% to 13%), Vomiting (adult, 4%; pediatric, 11%), Xerostomia (adult, 20%)
- **Neurologic:** Headache (pediatric, 19%), Insomnia (adult, 15%; pediatric, at least 2%), Somnolence (adult, 8%; pediatric, 11%)
- **Renal:** Delay when starting to pass urine (adult, 6%)
- **Reproductive:** Dysmenorrhea (adult, 3%), Erectile dysfunction (adult, 9%)
- **Other:** Menopausal flushing (adult, 3%)

Serious:

- **Cardiovascular:** Myocardial infarction, Prolonged QT interval, Sudden cardiac death
- **Hepatic:** Injury of liver (Severe), Liver failure
- **Neurologic:** Cerebrovascular accident, Dyskinesia, Seizure (adult, 0.1%; pediatric, 0.2%)
- **Psychiatric:** Mania, Psychotic disorder, Suicidal thoughts (pediatric, 0.4%)
- **Reproductive:** Priapism (rare)
- **Other:** Angioedema

Contraindications

- cardiac or vascular disorders, severe; at risk for deterioration with clinically important increase of blood pressure (15 to 20 mm Hg) or heart rate (20 beats per minute); monitoring recommended.
- hypersensitivity to atomoxetine or to other components of the product.
- MAO inhibitor use; do not administer atomoxetine during therapy with or within 2 weeks of discontinuing an MAO inhibitor; do not administer MAO inhibitor within 2 weeks of discontinuing atomoxetine.
- narrow angle glaucoma; increased risk of mydriasis
- pheochromocytoma, current or history of; increased risk for serious reactions, including tachyarrhythmia and elevated blood pressure.

Psychological Risks: There is a minor chance that participant will experience anxiety, discomfort or embarrassment during the data collection process, the investigational team will make every effort to minimize potential psychological risks by maintaining a pleasant and professional manner, conducting interviews and physical assessments in a private clinical office, encouraging dialogue regarding the research process, and allowing participants to discuss any reactions or feelings that they may have throughout study participation. Additionally, in order to avoid or minimize any further discomfort, the participants are allowed to take breaks during the interviews and assessment, or reschedule the

appointment for completion at a later time. Participants can refuse to answer any question during an interview or on the questionnaire if it makes the participant uncomfortable.

Legal, Social and Economic Risks: In order to prevent the risk of developing feelings of being “labeled” or “stigmatized”, participants will be ensured that confidentiality safeguards will be strictly maintained throughout the study. Such safeguards include the conduction of all interviews and clinical visits within private and secure areas or offices. Additionally, all study documents will be kept in a locked office or on a computer located in a secure area, with limited password access. Confidential hospital medical records will document participation in the study through mental health progress notes. Additionally, participants’ name will not be identified in the data analysis, publications, or presentations of the research results. A Health Insurance Portability and Accountability Act (HIPAA) authorization page is included with the informed consent to notify the participants of the use of identifiable personal health information. The informed consent and HIPAA authorization page provide a detailed outline of the provisions utilized to protect the confidentiality of research data. The methods used to obtain information about the participants include medical record review and assessments described above.

In order to minimize any economic risk related to having to miss work or having to pay for transportation to and from the research visits, the study team will coordinate with the participants to schedule appointments at the most convenient time, including seeing participant outside working hours and limiting the frequency of visits to those necessary to adhere to the protocol.

1.2. Adequacy of Protection Against Risks

a. Recruitment and Informed Consent

Subjects will be recruited from Charleston VAMC OIF/OEF Screening Clinic. Additionally, Veterans with or without PTSD may be recruited through Savannah CBOC referrals if Charleston VAMC does not have a sufficient number of participants. The study will be open to all Veterans from Iraq Freedom Operation and Afghanistan who meet eligibility criteria regardless of ethnicity, gender or socioeconomic status. No charge will be incurred for the participant for any aspect of this study. Written consent will be obtained for each participant who meets the inclusion criteria prior to assessment. Veterans will be given as much time as needed to make a decision whether to participate. All participants will be informed that their participation is voluntary, and that reluctance to participate will not compromise availability of care, or the eligibility to participate in other studies. Participants may discontinue assessment at any time during the study.

b. Protection against Risk

Potential risks involve loss of time at work and the psychological stress involved in assessment procedures. These risks will be minimized in several ways. Breaks and encouragement will be given as needed during testing procedures. There is some flexibility in the on site assessment schedule to allow for completion of measures not finished during the scheduled testing time. In addition, some weekend/holiday assessment times will be offered to minimize loss of time of participants.

ATX is a widely used treatment for ADHD. It is generally well tolerated clinically. Subjects who meet the contraindications for ATX listed in section “Therapeutic Risk” will be excluded. Common side effects of ATX are dry mouth, insomnia, nausea, decreased appetite, and sweating. Insomnia and sweating are of some concern for individuals with PTSD; however, as noted above the ATX has been safely used in comorbid ADHD and anxiety. Subjects can also withdraw at any time without penalty.

The risk of venipuncture is minimal. The mild discomfort of venipuncture and very low possibility of local infection will be minimized by using experienced phlebotomists and standard blood drawing techniques. Universal precautions for the handling of human blood developed by the Centers for Disease Control will be followed at all times when working with blood as well as DNA isolated from blood.

All assessment information will be considered confidential. Data will be organized in code-labeled binders and stored in locked cabinets. No participant will be identified by name in any presentation of the results. Identification numbers will code data entered for computer analysis, and the data coordinator will keep all names and code numbers. Findings will be made available to legitimate agents of the participants (parents, schools, treating psychologists, physicians), and only with the express, written consent of the participants.

1.3. Potential Benefits of the Proposed Research to the Subjects and Others

The immediate benefit is the treatment effect on cognitive function enhancement that may improve individual occupational, academic performance, and daily quality of life. The other anticipated benefits for participating Veterans include individual neuropsychological assessments and interpretation of the

results. Neuropsychological test information (including psychoeducational assessment) and written feedback will be provided to participants. This information may be shared by physicians, educators, and other professionals involved with the patients care, as needed. The importance of the results to the fields of PTSD neurophysiology, neuropsychology, and genetics are significant due to the large numbers of PTSD participants and even larger number of Veterans returning from the OIF/OEF theatres affected with PTSD.

1.4. Importance of the Knowledge To Be Gained

The findings from this proposed study will contribute to the understanding of the neurophysiologic and genetic basis of PTSD. The establishment of effective treatment will provide an advanced and viable approach for further PTSD diagnostic, genetic, and treatment studies. These physiological and genetic markers may be useful in pharmacological treatment selection, and can be used in vulnerability assessment for risk population. The procedures in the proposed study all involve minimal risk, and are therefore reasonable in relation to the importance of the knowledge that is expected to result.

1.5 Data and Safety Monitoring

All collected clinical, demographic, and geographic data, as well as genotyping data will be stored in Psychiatric Genetic Research Database, a branch of Psychiatric Data Management. We will use computerized systems to collect, create, modify, maintain, archive, retrieve, and transmit clinical data. The genotyping data will be separately entered without knowledge of clinical data. Data of cortical inhibition will be stored in Charleston VAMC TMS Laboratory data bank.

All assessment information will be considered confidential. Data will be organized in code-labeled binders and stored in locked cabinets. Identification numbers will code data entered for computer analysis, and the data coordinator will keep all names and code numbers in a separate locked area. Findings will be made available to legitimate agencies, such as local IRB, and related research personnel. No names or identifiable information will be used in any data presentation. Strict confidentiality is maintained regarding database information, which is for research purpose only. All the specimens from the subjects will be labeled by code at the clinic. Names will not be used on specimens nor available in the research laboratory. The person conducting the sequencing and genotyping is blind to the clinical profile of the subject.

2 Inclusion of Woman and Minorities

Charleston VA Medical Center has traditionally served Veterans both in Charleston as well as neighboring counties. With the exception of occasional out-of-state referrals, the population served reflects that of the Charleston metropolitan area. Participation in this research is open to all Veterans who meet eligibility criteria regardless of race, gender, ethnicity, or socioeconomic status. We expect PTSD to affect Veterans of all races and ethnicities across a range of socioeconomic status. We had approximately 35% African American participants in our previous recruitment, which is proportional to our surrounding area. As for male to female ratio, our previous studies have shown a higher incidence of PTSD in male Veterans because a higher percentage of male soldiers have participated in combat. We expect a greater percentage of female Veterans from Iraq Freedom Operation and Afghanistan given we have found that more female soldiers have participated in the two wars. All possible effort will be made to recruit female Veterans.

3 Inclusion of Children

The proposed research study will include Veterans from 20 to 60 (NIH definition of children), and will be conducted at Charleston VA Medical Center. We expect less than 10% participants will be under the age 21 since the majority of Veterans participating to the screening clinic are older than 21. We will assure that the percentage of Veterans age 20 to 60 who participate in this research will reflect the age of soldiers in proportion to those who participated in the Iraq Freedom Operation and Afghanistan War.