**Background**

PTSD is a major public health concern and a growing problem for the VA and the DOD [1, 2]. Soldiers returning from Afghanistan and Iraq show PTSD rates of between 12 to 20% [3-6] with significant psychological, physical, and economic burdens for sufferers and society as a whole [7, 8]. Based on available treatment guidelines [9], the two first line treatments for PTSD include exposure therapy (such as PE) and selective serotonin reuptake inhibitors (SSRIs; such as SERT). To date, there have been no randomized, direct comparisons of medication, psychotherapy, and combined treatment among veterans or active duty troops. The current study aims to provide this critical data in a typical sample of OEF/OIF/OND returnees with significant combat-related PTSD. Further, emphasis is placed on continued, comprehensive collection of outcome data to assess the acceptability, adherence, compliance, and symptom change in each treatment arm throughout the study period. In addition, substantial morbidity remains in a high percentage of PTSD veterans [10, 11] even after PE or SSRI treatment are administered, suggesting that further treatment optimization and individual treatment matching are urgently needed if substantial personal and social costs are to be reduced. Identifying specific predictors, large effect size correlates of treatment response, or putative mechanisms involved in treatment response will be critical steps toward achieving the goals of treatment optimization and individual treatment matching. To inform treatment choices beyond what can be provided through standard clinical outcomes, we will examine neurobiological predictors and proximal correlates of effective treatment, and candidate mechanisms involved. Delineation of these factors and their specificity to medication or PE is a critical step towards treatment refinements, improved effectiveness and efficiency of PTSD treatment, enhanced dissemination, and individualized treatment. This is obviously an ambitious set of goals; however, the combined expertise of the research group involved, the synergy of the aims, and the efficient design, offer both a unique opportunity to examine multiple processes simultaneously, and to obtain the highest quality of critically needed data. To restrict the examination to just one system or one mechanism would be a missed opportunity to study these complex and interrelated systems, and their interacting in impacts on treatment.

**Why PE?** PE has proven effectiveness in the treatment of PTSD associated with a variety of traumas (see [9] for a review), including combat [12-16]. Recently, the Institute of Medicine (IoM) concluded that exposure therapy is the only treatment for PTSD with adequate evidence supporting efficacy and called for research comparing exposure therapy with medication alone and in combination [17]. In addition to direct effects on PTSD, PE has been found effective in reducing related psychopathology [general anxiety, depression, guilt, alcohol cravings, and anger (e.g., [18-22])]. Meta-analysis reported an impressive average effect size of 0.8 for studies among combat veterans indicating significant clinical change [23].

While PE is perceived by some as a challenging form of treatment, data demonstrates that it is as well tolerated as other effective psychotherapies for PTSD. In a meta-analysis of dropouts from 25 studies using various forms of cognitive behavioral therapy (CBT) for PTSD, Hembree et al. [24] found that dropout from exposure therapy alone was 20.5% compared to 22.1% for anxiety management or cognitive therapy alone and 26.9% for combination therapies. Rates of drop-out from medication trials for PTSD (SERT, paroxetine, and fluoxetine) range from 22% [25] to 38% [26]. Thus, PE is at least as tolerable for patients as other forms of CBT and SSRIs for PTSD. In addition, the simplicity of the PE protocol including just four main therapeutic components (i.e., psychoeducation, in vivo exposure, imaginal exposure, and emotional processing) makes it quite amenable to dissemination and modification for alternate populations and settings. Indeed, PE has been successfully modified for many uses, including as a preventative intervention [27], and as a PTSD treatment delivered in a primary care setting [28]. As such, this comparison is more relevant to standard clinical care than ever before. However, in spite of impressive effect size and good acceptability, 30% to 50% of patients still have significant symptoms and impairment following treatment (e.g. [29]) and even larger effect sizes have been seen with other trauma groups, suggesting that treatment refinements specifically targeting combat veterans and mechanisms may further enhance outcomes for this group. Finally, efforts are strongly underway in both the DOD and VA to disseminate PE for the treatment of PTSD making this treatment more widely available than ever before.

PE was founded in emotional processing theory of anxiety disorders [30]. However, little research has examined the theorized mechanisms of change, and their impact on the outcomes of PTSD treatment. Data

regarding the neurobiology of emotional processes hypothesized to be at the core of this intervention is lacking. Delineation of the underlying processes is a critical step towards the development of treatment refinements to improve effectiveness and efficiency of PTSD treatment, inform dissemination, and assist in identification of specific neurobiological factors that could guide optimal treatment selection for a given patient.

**Why SERT?** Of the available pharmacotherapies, SSRIs have been most extensively studied in double-blind, placebo-controlled randomized clinical trials (RCTs) for PTSD [31] with SERT and paroxetine approved by the Food and Drug Administration (FDA) for use in PTSD. SSRIs have a relatively favorable side effect profile, and fewer adverse events, as compared to other antidepressants, making them standard, first-line treatments for PTSD (e.g., [10]). Several large, multi-site RCTs have demonstrated efficacy of SERT across all three symptom clusters of PTSD (re-experiencing, avoidance/numbing, hyperarousal) with response rates of about 30% remitting with 12 weeks of treatment [10]. In addition, SSRIs provide a broad spectrum of efficacy for common comorbid conditions (i.e., depression, general anxiety). While SSRIs are generally safe, they do carry some side effects (e.g., sexual dysfunction, head ache etc.). Despite an overall efficacy, effect sizes in studies with combat-related PTSD suggest reductions in efficacy with some negative trials noted (e.g., [32]). Even in the trials with demonstrated effectiveness, as many as 50% of participants show little or no response to the initial SSRI trial despite adequate dose and duration [33]. Thus, variability in response is common and treatment refinements specifically targeting combat veterans and mechanisms may further enhance outcomes.

**Why compare?** While both PE and SSRI are first line treatments for PTSD, they have not been compared to each other, and relevant data are not available to inform treatment about when to provide which intervention to whom and when to combine the treatments. As a result, treatment is most often guided by convenience and clinic practice, resulting in many returnees with PTSD being placed on medication or started in therapy without knowledge of which is more effective overall, and without close examination of alternate treatment choices for a given individual. Further, with the previously described dissemination of PE, this comparison is more relevant than ever to clinical care as more returnees have the option to receive state of the art psychotherapy and/or medication for PTSD. All conditions in the current study are intended to closely parallel the treatments as they are provided in VHA medical centers and Military Treatment Facilities (MTFs). Medication management for PTSD often involves more than medication reconciliation and assessment of primary symptoms and side effects. Therefore, in order to standardize this component and provide an element of supportive therapy for comparison with PE, medication management will be manualized (including psychoeducation for PTSD, supportive discussion and brief problem solving). Comparing these primary interventions as they would optimally be provided in clinical care with outcomes focused on symptoms as well as possible treatment mechanisms involved will provide crucial information to providers to direct how patients receive these first line treatments.

While differences in effect size from randomized trials of each treatment separately support the efficacy of each treatment for PTSD and suggest that SSRI may have a lower overall effect size [d (compared to placebo) = 0.8, [34]] than PE (compared to average waitlist controlled d = 1.5, [23]), differences between methods used in medication and psychotherapy trials suggest that direct comparison of effect size from previous trials might not be informative. For instance, placebo control groups used in medication trials are not equivalent to waitlist or supportive psychotherapy conditions. Further, medication trials often have more restrictive inclusion and exclusion criteria than many of the primary trials of prolonged exposure therapy, including differences in levels of key comorbidities (i.e., depression and alcohol abuse). It is very likely these methodological differences influence effect size. Thus, direct comparison of these treatments delivered in the same protocol is urgently needed to address this question.

**Why neurobiological predictors, correlates of change, and mechanisms of response?** To achieve best clinical outcomes and to utilize available treatment most effectively, it is critical to identify effective predictors of response to treatment in general and to a specific treatment (SERT vs. PE) in particular. If valid biomarkers (HPA, brain, genetics) can differentially predict treatment response to PE or SSRI, these biomarkers can be used to guide patients to a particular treatment, which would improve the likelihood of success, thereby saving time and resources. Using specific neurobiological predictors, treatment techniques (psychotherapeutic and medication) can also be more efficiently delivered. Increased efficiency may assist in acceptability of the

treatment and aid in access as treated cases may respond in fewer sessions, lower dose, or shorter duration allowing more patients treated per provider and potentially reducing drop out as patient burden is reduced. **Thus identifying predictors of response to specific treatment has direct implications for questions of treatment efficacy and efficiency.** Understanding the neurobiological mechanisms behind effective treatment for PTSD can guide further treatment development, the development of effective combined treatments, and the modification of the existing protocols. With regard to psychotherapy, understanding the mechanisms behind effective treatment can enable optimization of the treatment such that critical elements are retained, while elements that can tolerate modification are changed. Knowledge of predictors and mechanisms can improve the match of the individual patient to specific therapy, and as a result improve efficiency, effectiveness and dissemination. With regard to existing pharmacotherapy, predictors and mechanisms can inform whether medication is used alone, started first, started simultaneous with therapy, or started after partial response to therapy. **Thus, understanding mechanisms involved will improve development of new and optimization of existing therapies and lead to improved treatment efficiency.** Finally, few studies to date have examined neurobiological changes with PTSD treatment and none have simultaneously examined multiple factors. Indeed, our research group has the combination of unique expertise in key areas necessary for the successful, simultaneous, state of the art examination of outcomes, genetics and genomics, brain mechanisms, and HPA axis function.

**Neurobiological predictors/correlates/mechanisms.** Neurobiological mechanisms potentially involved in PTSD are complex. Based on previous research and preliminary studies conducted by our research team, we will focus on four neurobiological factors: genetics and genomics, brain mechanisms, and HPA axis function.

Genetics and Genomics. The response of patients with mood and anxiety disorders to treatment can be highly variable, and there are few known specific predictors of response to SSRIs or therapy in PTSD. Accumulating evidence suggests that genetic factors may be involved in the etiology of PTSD (i.e. vulnerability) (for review see [35-37]) and gene association studies have identified several specific genetic polymorphisms associated with PTSD, including variants in the *FKBP5* [38], *RSG2* [39], and *SLC6A4* [40, 41] (serotonin transporter) genes. No studies of genetic association with SSRI responses have yet been reported in PTSD. With regard to depression, genetic factors related to treatment responses to SSRI have been examined. The largest pharmacogenetic study of SSRI treatment response to date (STAR*D) was performed in 1,914 patients with non-psychotic depression and identified several variants in the *HTR2A* (serotonin 2A receptor) [42], *GRIK4* (glutamate receptor subunit) [43], *KCNK2* (potassium channel) [44], and *OPRM1* (mu opioid receptor) [45] genes that were associated with treatment response. Findings have also implicated *SLC6A4* [46] and *FKBP5*[47] in treatment response. Additional genes were implicated in adverse side effects (*GRIK2, GRIA, CREB1*) [48]. If such predictors of response and side effects were found in PTSD, they could: 1) be immediately practically useful in optimal treatment selection for PTSD patients, 2) help to elucidate the pathophysiology of PTSD and therapeutic mechanisms, and 3) help to identify new treatment strategies and drug targets. Understanding the genetics of treatment response in PTSD will ultimately require larger numbers than the current study will provide (i.e. ~300 PTSD patients treated with SERT and 300 with PE including those who receive the combination treatment). However, our proposed study is the largest treatment response study in PTSD in combat veterans to date to collect these data, and will provide an **outstanding opportunity to develop an initial "discovery" dataset**, which can be replicated in validation cohorts. While the current cohort is not sufficiently powered for genome-wide association study (GWAS), the incremental costs associated with collection of deoxyribonucleic acid (DNA) and genome-wide genotyping are relatively small compared to the costs of obtaining the psychiatric treatment phenotype. The benefit of having these GWAS data on our initial discovery dataset (with high quality phenotypic and genotypic measures) archived and available for immediate delivery to partners with subsequent replication cohorts will be highly valuable to the field of PTSD treatment research.

In addition to prediction of response by genetic variations, changes in brain gene expression may also accompany or mediate successful treatment response. While brain gene expression levels are not readily accessible to measurement in living subjects, easily accessible peripheral blood gene expression changes can provide useful biomarkers of the therapeutic mechanisms of PTSD treatments. The relationships of peripheral

blood gene expression to that in the brain is supported by preliminary, yet encouraging, data[49]. Very few studies to date have examined peripheral blood ribonucleic acid (RNA) expression patterns associated with psychiatric disorders. However, there have been a few encouraging preliminary studies, albeit with very small N's, including a study of trauma survivors where changes in leukocyte messenger RNA (mRNA) predicted development of PTSD. Segman et al. [50] used a whole genome Affymetrix oligonucleotide chip (HU95A, which probes 12,000 nominal transcripts) to examine peri-traumatic peripheral blood cell gene expression, and found specific profiles that predicted 4-month PTSD outcomes, both categorically (in cluster analysis with diagnostic outcome) and associated with symptoms scores, including altered expression profiles of immune system (cytokines and receptors), neural (e.g. serotonin and gamma amino butyric acid (GABA) receptors) and endocrine system genes (nuclear hormone receptors and *FKBP5*, SNPs recently associated with risk for PTSD)[38]. Follow-up expression profiles also classified PTSD, suggesting the pathophysiology of PTSD may be characterized by stable differences in gene expression patterns. Subsequent work in peripheral blood gene expression has implicated gene expression changes in myelination and growth factor signaling in depression using bioinformatic approaches ("convergent functional genomics") [51] and inflammatory and signal transduction molecules in bipolar disorder [52], suggesting additional potential pathways to investigate in PTSD. The current proposal involves a treatment study of 447 patients, thus our study will be by far the largest psychiatric treatment cohort to date in which gene expression will been studied. Furthermore, we will also have access to genotype information for the same individuals, which will allow us to examine specific effects of polymorphisms within specific genes on the expression levels of their transcripts.

Brain Function. Several groups, including ours, have proposed a brain-based model of PTSD [53-55] that implicates amygdala-ventromedial prefrontal cortex (vmPFC) dysfunction. This model hypothesizes that PTSD involves amygdala hyperresponsivity to perceived threat and inadequate medial prefrontal and hippocampal regulation of the amygdala. Hyperresponsivity in the amygdala is thought to mediate hyperarousal symptoms and to contribute to persistence of the traumatic memory. Diminished top-down control by medial prefrontal regions is thought to contribute to deficits in contextualization, fear memory extinction, and the inability to suppress attention and inhibit responses to trauma-related stimuli. Hippocampal dysfunction is thought to underlie explicit memory deficits and problems distinguishing safe from threatening contexts. This model is supported by animal research on fear extinction and recall (see [56] and [57] for reviews). The anatomical specificity of dysfunction in PTSD was recently supported by a quantitative meta-analysis of independent fMRI studies (PTSD, n=15) in relation to social phobia/anxiety (n=8) and specific phobia (n=7) which show that amygdala hyper-reactivity is shared by all 3 anxiety disorders but that only PTSD was associated with hypo-activity of vmPFC [58].

More recently, neuroimaging studies have been used to examine predictors and correlates of successful treatment in psychiatric disorders like major depressive and anxiety disorders. Consistent with prefrontal dysfunction hypothesis in depression, pretreatment activity in the vmPFC has been associated with treatment outcome. [59]. Patients with the *highest* vmPFC activity (either at rest or evoked by an emotionally negative state) at pre treatment exhibited the fewest and least severe symptoms after treatment in some [60, 61] but not all [62] studies. The extent of vmPFC modulation by venlafaxine was related to extent of improvement in depressive symptoms [63], and amygdala-vmPFC activation has been associated with improvement in depressive symptoms following paroxetine treatment [64]. Collectively, these studies suggest that SSRI treatment can normalize amygdala-vmPFC function and while Mayberg and colleagues have theorized that SSRIs therapeutic actions involve vmPFC and amygdala, this has not been tested in PTSD [65]. A few structural and functional neuroimaging studies have begun to examine mechanisms of change during pharmacological and psychological treatment in

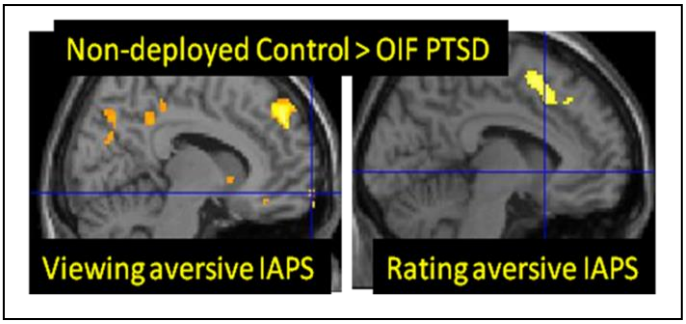



**Fig. 1: Decreased dorsal mPFC During Viewing and dorsal ACC During Emotion Regulation**

PTSD. A number of small single photon emission computed tomography (SPECT) treatment studies linked citalopram [66] and eye movement desensitization and reprocessing (EMDR) [67] treatments with perfusion changes in a number of brain regions in association with symptom improvement in PTSD. A small (n = 8) fMRI study of exposure therapy in PTSD reported greater bilateral activation during an emotion induction task in the rostral anterior cingulated cortex (rACC) post treatment [68] that correlated with reductions in PTSD severity. Bryant and colleagues [69] also reported that PTSD patients who responded to CBT had larger rACC prior to treatment, and that poor response was associated with greater bilateral amygdala and ventral anterior cingulated cortex (ACC) activation [70]. Given that amygdala and vmPFC dysfunction are observed in PTSD at baseline, these may serve as a potential markers for SSRI treatment response in PTSD. However, few studies have been published on the effects of treatment on amygdala-vmPFC function in PTSD or whether these neuromarkers can be used to predict treatment response. No studies have compared effects of SSRI to PE. While existing studies provide an initial support for the idea that specific changes associated with treatment response in PTSD can be identified, research involving larger samples, appropriate clinical controls, and well designed, PTSD relevant probes in established neuroimaging paradigms, are urgently needed to address this issue. Our previously published work as well as ongoing pilot neuroimaging work on predictors of treatment response in PTSD, ***strongly support the proposed mechanistic model, the choice of specific markers and the feasibility of successful completion of the proposed projects***. Ongoing pilot fMRI studies at the VAAAHS have examined neural correlates of aversive emotional processing (viewing aversive International Affective Picture System (IAPS) pictures) and emotional regulation among healthy OEF/OIF/OND Veterans, OEF/OIF/OND Veterans with PTSD, and non-deployed controls (Liberzon and colleagues, unpublished). We found decreased dorsal mPFC activity ([6,48,40], Z=4.01, p<.001) in PTSD when viewing aversive IAPS, and decreased activity in dorsal ACC/ supplemental motor area ([10,14,50] Z=3.14, p<.005) during emotional regulation task (rating their emotional responses; see Figure 1). In a separate sample, OEF/OIF/OND veterans with PTSD, (Co-I Phan's 'Neurofunctional Markers of SSRI Response in PTSD' VA Merit grant) also had exaggerated amygdala reactivity to threat (angry/fearful) faces while performing the proposed Emotional Face Assessment Task (EFAT). In a different study PTSD patients showed greater bilateral amygdala responses to threat faces (Left: [-28, 0, -26], $t$=3.3, $p$<0.05; Right: [32, -2, 24]; $t$=2.7, $p$<0.05), and the signal difference between groups (PTSD > controls) was confirmed by extracted Blood Oxygen Level Dependent (BOLD) signal response (β weights) from both left and right amygdala (Figure 2; Left: β±SEM: PTSD: 0.21±0.06 vs. HC: -0.02±0.05, $t$=3.2, $p$<0.05; Cohen's $d$=1.71; Right: ±SEM: PTSD: 0.16±0.05 vs. HC: 0.02±0.02, $t$=2.7, $p$<0.05; Cohen's $d$=1.45).

HPA axis. HPA axis abnormalities have been reported in PTSD; however these have not yet been linked to PTSD symptom development or improvement (For a review see [71]). Though inconsistencies exist, review of the literature suggests that patients with PTSD have enhanced HPA axis negative feedback [72]. These abnormalities may reflect a stable trait vulnerability, a component of pathophysiology, or represent a homeostatic response. Among other indices of HPA function, cortisol response to awakening (RTA) is of particular interest due to its stability [73], ease of collection, and association with perceived stress [74] and psychiatric symptoms. A recent study of police officers found current PTSD symptom severity was strongly associated with attenuated cortisol RTA [75]. The data regarding HPA reactivity is

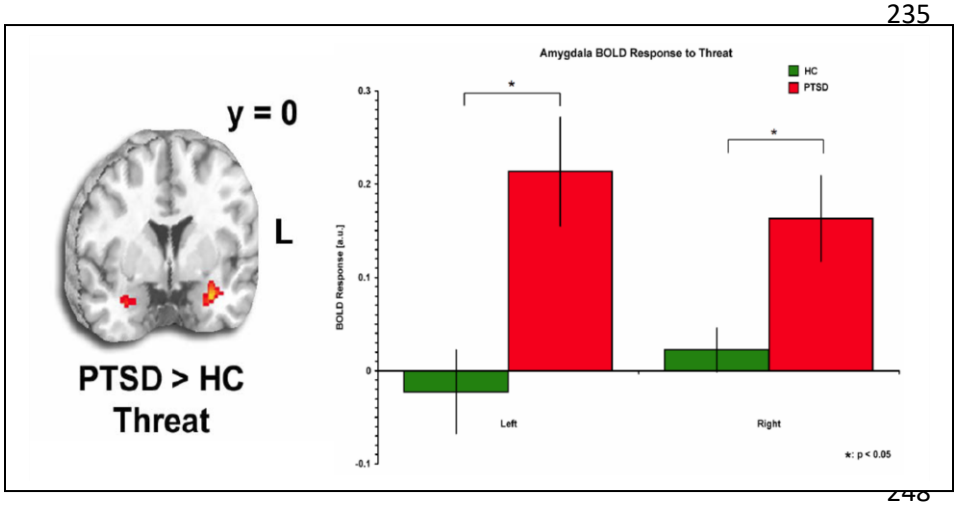
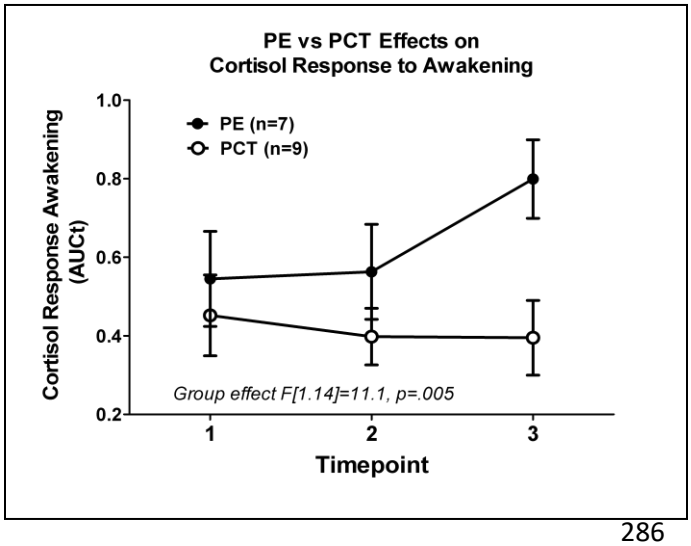



**Fig. 2: Exaggerated AMYG Reactivity to Threat Faces**

also complex, but overall it suggests that HPA (Adrenocorticotropic hormone (ACTH)/cortisol release) is most sensitive to novelty, threat in the absence of social support, and decreased sense of control over negative outcomes [76-78]. Preliminary data from an ongoing study conducted by the PI suggest that HPA reactivity to traumatic cues prior to treatment predicts response to PTSD treatment. Cortisol RTA area under the curve (AUC) is negatively correlated with PTSD symptoms at intake, consistent with previous studies of PTSD in police officers [75]. Interestingly, PE but not a supportive intervention lead to normalization of cortisol awakening response such that the PE group has a higher RTA AUC than the controls, $F$ (1,14) = 11.1, $p$ = 005; see Figure 3. Our collaborator's laboratory findings are also consistent with a normalization of cortisol response with PE such that responders to PE showed reductions in cortisol response during in session exposures [79]. PE changes may be related to specific reappraisals, emotional desensitization and physiological extinction used in PE. Indeed, PE may be effective because it addresses phenomena that are "salient" to the HPA axis, by reducing novelty ("desensitizing" to memory of the trauma), increasing sense of self- competence and control over negative outcomes (i.e., "I can handle bad things that happen"), and enhancing the experience of social support (i.e., "other people think I am a good person"). Thus, we will examine RTA cortisol over treatment in order to examine changes in HPA axis function that may differ based on treatment type and response.

Specifically, we will randomly assign (N = 441) OEF/OIF/OND veterans or Active Duty Service members with chronic PTSD (at least 3 months post target trauma) to receive: 1) PE/PLB, 2) SERT plus enhanced medication management, or 3) PE/SERT. All inclusion and exclusion criteria are minimized and include only those factors that contraindicate one or both of the primary randomized treatments for PTSD or prevent the veteran from benefiting from the current program. Participants complete six major assessments (Intake Wk, Wk 6, Wk 12, Wk 24, Wk 36, Wk 52). Each major assessment will include examination of PTSD and comorbid symptoms. Data collected will include detailed information on treatment acceptability, satisfaction, adherence, and early treatment departure. Salivary cortisol will be collected in RTA at each major assessment point (except Intake Week) and Week 0. Blood draws will be taken at Week 0 (or within 7 days prior to) and Wk 24 for genetic and genomic assessment. Up to 210 returnees who are eligible and consent will complete the fMRI paradigm scans at Intake Wk and Wk 24. Study blind will be broken after the Wk 24 assessment. Participants will be followed for one year from treatment initiation.

**Fig. 3. Cortisol responses to awakening**




## Hypotheses

Based on previous trials of each intervention separately as presented in the background, we hypothesize:

1) All three treatments will demonstrate significant reductions in PTSD, general anxiety, and depression, and increases in function. PE/SERT will result in larger reductions than PE/PLB and SERT. PE/PLB will result in larger reductions than SERT. In addition, we hypothesize:
   a. More remission in PE/SERT and PE/PLB than SERT.
   b. More treatment drop in SERT/PE than either SERT or PE/PLB.
2) Specific genetic variants (SNPs) will be associated with treatment response to SERT and PE/PLB. Candidate genes include: *HTR2A, GRIK4, KCNK2, OPRM1, SLC6A4* and *FKBP5* associated with SSRI response, as well as genes implicated in PTSD pathophysiology.
3) Treatment will be associated with changes in leukocyte gene expression (mRNA) profiles.
   a. SERT will lead to specific changes in mRNA expression related to primary pharmacological effects.

b. Treatment response in both PE/PLB and SERT will be associated with specific changes in leukocyte mRNA expression related to therapeutic change or biomarkers, which may partially overlap the main effects of SERT.

4) Changes in amygdala-vmPFC function over treatment will be associated with treatment response such that:

a. Pre-post treatment change in amygdala-insula reactivity to threat and vmPFC engagement during emotion regulation will *differentiate treatment responders from non-responders*. Specifically, significant change will be observed in treatment responders to SERT (i.e., reduction in amgydala reactivity) and to PE (i.e., enhancement of vMPFC response) but not in non-responders.

b. Pre treatment amygdala reactivity to threat faces will predict extent of SERT response (pre-post change), such that *higher* amygdala reactivity will be associated with a greater reduction in PTSD symptoms. Pre treatment vmPFC response during emotion regulation will predict extent of PE response (pre-post change), such that *lower* vmPFC response will be associated with a greater reduction in PTSD symptoms.

5) Positive treatment response will be associated with increased cortisol RTA across treatment.

**Technical Objectives**

**Objective 1. Examine the relative efficacy of PE/PLB, SERT, and PE/SERT in OEF/OIF/OND returnees with PTSD.** Focus will include PTSD symptoms and related psychopathology (e.g., depression, alcohol/substance abuse, general anxiety) as well as general functioning (e.g., violence, employment, pain, etc.). Further, treatments provided will reflect optimal standard of practice in the VA and MTFs in order to provide information directly relevant to clinical care providers in these settings. Detailed information on acceptability, adherence, and compliance for all treatment will be examined.

**Objective 2. Identify SNPs associated with treatment response to SERT and PE.** Our candidate genes include: *HTR2A, GRIK4, KCNK2, OPRM1, SLC6A4* and *FKBP5*, as well as genes implicated in PTSD pathophysiology. We will also conduct a GWAS analysis to develop initial "discovery" dataset for future unbiased search of predictors of treatment response

**Objective 3. Identify gene expression alterations associated with treatment response.** We will conduct a gene expression (mRNA microarray) study of peripheral blood collected at Week 0 (or within 7 days prior to) and Wk 24 comparing SERT and/or PE.

**Objective 4. Characterize the effects of SERT and PE treatment on amygdala, insula, and vmPFC function in OIF/OEF PTSD patients and identify brain-based predictors of treatment response to PE/PLB, SERT and PE/SERT treatment.** If amygdala is *hyperactive* when processing signals of threat, while the vmPFC is *hypoactive* when processing negative affect in PTSD patients, then effective regulation (via cognitive reappraisal) engaging vmPFC, amygdala and/or vmPFC function at pre treatment could predict those who respond to treatment. We will examine baseline and pre to post changes in amygdala, insula and mPFC function and the connectivity between these regions using threat detection/emotional activation and effective regulation paradigms, and relate these findings to treatment response in SERT, PE/PLB and PE/SERT.

**Objective 5. Examine alterations in HPA axis function over treatment and their relationship to treatment response both as predictors and mechanisms of change.** RTA cortisol will be used to examine HPA axis function. As mentioned previously, this measure has been related to PTSD symptom severity and preliminary data have demonstrated it is related to change with treatment in PE.

**Project Milestones.** (a) Timetable. The first 6 months will include evaluator and therapist training and regulatory preparation and approval processes (local IRBs, Office for Research Protections (ORPs), etc.). Recruitment and study treatment will then begin (month 7) and continue through month 48 (42 months at 2-3 pts per month per site). Data cleaning and preliminary analyses will be conducted throughout the study. There will be 3 months to complete treatment on the last enrollees and the last 9 months will be devoted to follow up assessments, primary data analyses, and manuscript preparation.

**Military Significance**

Combat exposure is a common part of today's military service. While most veterans who experience combat do not go on to experience mental health problems, research demonstrates that a significant minority of OEF/OIF/OND returnees report symptoms consistent with PTSD and related impairment [3, 7]. The primary aim of this proposal is to compare the relative efficacy of PE, SERT and PE/SERT. These treatments are frequently provided, evidence based, first line treatments in VHA and MTFs for PTSD. While it has been demonstrated that each treatment works better than standard comparators in the same modality (placebo, waitlist, supportive therapy) in clinical trials, to date no direct comparative trial has been conducted to inform which treatment may be most effective for which OEF/OIF/OND returnees with PTSD. Further, many of these trials included very few, or no veterans. With studies suggesting effects sizes are reduced in veterans and availability of state of the art medication and therapy, knowing how these treatment options compare in the OEF/OIF/OND population is more relevant than ever. In clinical practice in the VHA and MTFs, many PTSD patients are started on an SSRI prior to consideration of psychotherapy. As a result if and when they are offered psychotherapy, many returnees end up on a combined intervention that has not yet been empirically examined. Thus, examination of this combination treatment is critical. The current proposal aims to demonstrate the comparative efficacy of these treatments in the OEF/OIF/OND population as well as identifying psychological and neurobiological predictors and mechanisms of treatment change in this population. Knowing how PTSD treatment/s work and how to predict response to each of these treatments will give mental health providers critical information to improve efficacy, to use in treatment planning, and to assist in improving treatment efficiency. In the end, improved treatments will allow more troops to efficiently return to duty and reduce PTSD related disability.

**Public Purpose**

Our proposed study will examine the comparative efficacy of PE/PLB, SERT, and PE/SERT and provide an in depth examination of predictors of response and mechanisms of change in PTSD treatment. Understanding the relative benefits of these interventions and their mechanisms is equally critical for military and other populations suffering with PTSD. When completed, this carefully designed project that prospectively addresses inconsistencies and knowledge gaps in available studies, promises to provide concrete, evidence based direction for clinical decisions. Specifically, this study will inform the clinical questions, "How do I decide between medication and psychotherapy?" and" Should I combine them?" With continued dissemination of PE and other evidence based interventions for PTSD and the availability of effective medications, providers need to know who to send to which treatment and what issues to discuss with patients in order to help them make informed decisions. This design is intended to address these questions in a sample that will represent the "real world" of PTSD patients, given "real world" treatments, in an optimized and formalized fashion that

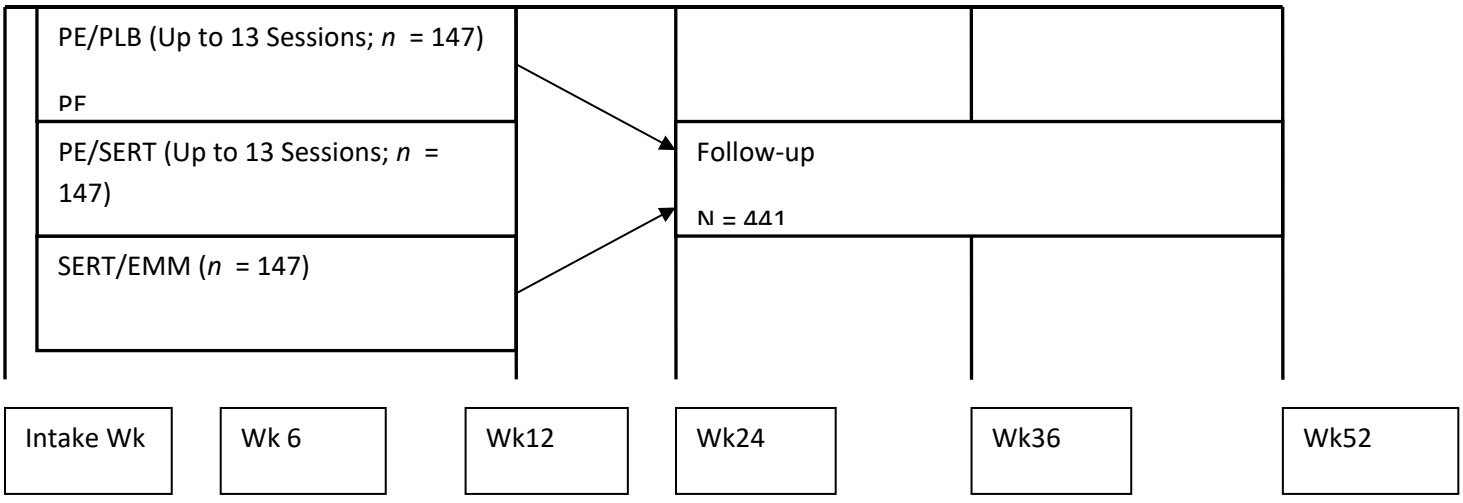



Figure 4. Overall Design and Assessments.

allows comparison across treatment cells. In addition, examination of predictors, mechanisms and outcomes in a single sample provides efficiency and depth of data that will enrich our understating of PTSD treatment on the whole.

## Methods

**Overview.** 441 OEF/OIF/OND combat veterans with chronic PTSD (CAPS > = 50) of at least three months duration who meet minimal inclusion and exclusion criteria (see below) will be randomly assigned to receive up to 13 sessions of PE/PLB, SERT plus enhanced medication management, or PE/SERT. They will be assessed at 6 major assessment time points: Intake Wk, Wk 6, Wk 12, Wk 24, Wk 36 and Wk 52. Assessments will include psychological and symptom assessment with neurobiological assessment occurring at all major assessments (except Intake Week) and Week 0. In addition, 35 Combat Control Veterans will also be recruited for intake only (see below for details). While PTSD is one primary mental health condition in OEF/OIF/OND returnees, high rates of depression [3], and alcohol and substance abuse [80] often co-occur with PTSD [81]. In order to ensure we are examining outcomes in a multifaceted and informative manner, we will include assessments of primary comorbid conditions as well as general health and functioning to provide the most comprehensive and informative data to inform clinical practice with this complicated population. Neurobiological assessment will include salivary cortisol collection in RTA at each major assessment (except Intake Week) and Week 0, blood draw for genetic and genomic analysis, and fMRI assessment at Intake Wk and Wk 24. Imaging will be an optional component due to the additional patient burden and travel required (see below). Imaging will include response to two emotion activation and regulation tasks (EFAT and Emotional Reappraisal Task). In addition, bi-weekly self-report assessment of symptoms (PTSD, depression, and anxiety) will be completed. While our primary aim will focus on symptom change, we will also examine differential drop out/early response and treatment adherence.

**Participants, Recruitment, and Sites.** The study population includes military personnel and veterans who served in OEF/OIF/OND with significant PTSD symptoms of at least 3 months duration. We plan to recruit 441 participants over 42 months of recruitment at 4 study sites: VAAAHS/UM Medical School, VASDHS/UCSD, Charleston VAMC/ MUSC, and MGH. Participants will be recruited and inclusion/exclusion criteria will be assessed during intake evaluation at each site. The only addition to standard clinical intake is that all Veterans who appear to meet eligibility criteria will provide a urine screen (ONLY after fully reviewing the study consent and Form 10-3203) for a drug and pregnancy screen. The urine will be provided based on Mental Health Service Standard clinic protocols for urine toxicology and pregnancy screens in the patient facility. Those Veterans who have a positive pregnancy screen will not be eligible for the study due to the contraindication of SSRI in pregnancy (see exclusion #6). Those Veterans who screen positive for drug use will be required to discuss this with a clinical study staff member prior to intake in order to ensure that PTSD treatment is warranted given the frequency and quantity of drug use (as noted in the inclusion/exclusion criteria #3). All tests will be posted to CPRS in the interest of continuity of patient care. Among other measures, the intake will include: 1) the MINI [82], a brief diagnostic evaluation with excellent psychometrics and agreement with the Structured Clinical Interview for DSM-IV(SCID) and Composite International Diagnostic Interview (CIDI), 2) the CAPS [83], and 3) a brief medical and psychiatric history. In addition, at the VAAAHS/UM site only, we will recruit an additional 35 OEF/OIF/OND veterans who have been exposed to combat but have not developed PTSD (Combat Control/CC group). The CC group will undergo the same fMRI scanning protocol at baseline in order to have brain function data for comparison with the OEF/OIF/OND combat Veterans with PTSD. The following recruitment methods will be utilized for both the treatment and non-treatment groups of Veterans:

- IRB approved flyers will be posted in approved community locations (i.e., VAAAHS and university announcement areas, Veteran organizations, restaurants, grocery stores, etc.) where OEF/OIF/OND Veterans are likely to congregate
- IRB approved letter and flyer will be mailed to a list of OEF/OIF/OND Veterans registered with the VAAAHS, as well as OEF/OIF/OND Veterans who are included on the case management tracking system and post-deployment health reassessment (PDHRA) roster. The letter will include general information

regarding this research study, which will be applicable for both treatment eligible participants and combat controls (CC).

- Posting study flyers on IRB approved websites such as Facebook, Twitter, Reddit and Craigslist. Flyers will have URL-shortened links and QR codes that direct those interested to our approved VAAAHS study webpage for more information about participation.
- Promotional swag (i.e., mugs, post-it notes) with the study logo and contact information are also used as a recruitment tool and only given out to providers who may come into contact with potential participants
- IRB approved public service announcements

Potential participants (participants with and without PTSD) who express an interest in the study will initially complete the phone screen. If they qualify at that point, they will be invited for a meeting at the VA.

Feasibility of recruitment.

1) Ann Arbor: for 2009, the VAAAHS PTSD Clinic completed 139 evaluations of OEF/OIF/OND veterans. The average age was 29 (*SD* = 8), and only 13% were service connected for PTSD. Fifty percent were married and 15% divorced or separated. 88% were Caucasian, 7% African American, and 5% other. Sixty-one percent met criteria for current major depressive episode and 25% met criteria for alcohol abuse. Of 139 subject, 122 (88%) would meet the minimal inclusion and exclusion criteria for this study. Given these numbers and assuming a 50% recruitment rate we expect up to 5 veterans consented per month. Thus, recruitment goals should easily be met.

2) San Diego: The OEF/OIF/OND PTSD clinic at the VASDHS completes approximately 30 evaluations each month with over 70% of those meeting criteria for PTSD. The clinic has over 600 patients in active treatment at any given time. Given the minimal inclusion and exclusion criteria, a majority of these veterans will be eligible for the study. Given other studies currently being carried out in the clinic and a 50% rate of willingness to participate in research, we expect up to 4 veterans consented per month at this site.

3) Charleston: The PTSD clinic team (PCT) at Charleston VAMC receives approximately 7 OEF/OIF/OND Veterans referrals each week, of these 83% meet criteria for PTSD. Based on current characteristics, approximately 20% will meet exclusion criteria. In recent polls of all PCT referred patients, 40%-50% agree to be evaluated for participation in at least one study. In addition to VAMC patient flow, the Charleston PCT maintains clinical services for 3 Community-Based Outpatient Clinics (CBOCs). One in particular, the Savannah CBOC, currently serves as a PTSD research recruitment site for a DOD study expected to be completed June 2010, and processes equal number of potential referrals, conservatively bringing the total predicted recruitment figure for Charleston to 2-3 Veterans per week.

4) Boston: Since its inception in 2009 the Home Base Program at the MGH has received 5 consults per week for OEF/OIF/OND veterans, reservists and active duty service members. Of these, 1-2/week met inclusion criteria. Given the minimal exclusion criteria, a majority of these veterans will be eligible for the study. Assuming a 50% recruitment rate, we expect 2-4 veterans consented per month at this site.

Screening data including drop at all possible points will be collected in order to meet requirements of Consolidated Standards of Reporting Clinical Trials (CONSORT) guideline [84]. MICHR Velos data system will include collection of screen failures in compliance with these requirements to ensure uniformity across sites.

**Inclusion/Exclusion Criteria.** All inclusion and exclusion criteria are minimized and include only those factors that contraindicate primary treatment for PTSD, that prevent the veteran from benefiting from the current program, or that may interfere with the mechanisms under study. Inclusion criteria are OEF/OIF/OND veterans with combat related PTSD with significant impairment (CAPS $\geq$ 50) of at least 3 months duration. Active duty service members who obtain care at one of the identified sites are eligible to participate in this study. Exclusion criteria are: 1) current, imminent risk of suicide (as indicated on C-SSRS), 2) active psychosis, 3) alcohol or substance dependence in the past 8 weeks, 4) unable to attend regular appointments, 5) prior intolerance or failure of adequate trial of PE or SERT (defined as at least 2 months of SERT at least 100mg/day), 6) medical illness likely to result in hospitalization or for which treatments are contraindicated (based on lab results, medical history and physical exam), 7) serious cognitive impairment (as evidenced by cognitive impairment felt likely to interfere with the ability to participate meaningfully in the study), and 8) concurrent

antidepressants or antipsychotics. Potential participants who are currently on ineffective antidepressants but want to enter the study can work with their prescribing physicians to discontinue antidepressants if clinically appropriate prior to study randomization. They must be a minimum of 2 weeks off of all antidepressants prior to randomization. Stable doses of benzodiazepines, prazosin, and sleep agents (e.g., trazodone; eszopiclone; zolpidem) will be allowed as long as the dose has been stable for at least 2 weeks.

Of note, participants with traumatic brain injury (TBI) will not be excluded from the study. Only those people who evidence significant cognitive impairment at intake (as evidenced by confusion, inability to track discussion or answer questions, or other clear and significant indicators of cognitive impairment) will be excluded. This inclusion is warranted based on the rates of TBI in the returnee population and the need for our sample to represent the returnee population. In addition, preliminary results from an ongoing PTSD treatment trial conducted by the study PI as well as data from another PTSD program (Chard and Rothbaum, personal communications) indicate that those participants with probable mild traumatic brain injury (mTBI) have excellent response to PTSD treatment. TBI status will be tracked and examined to determine its impact on outcomes. Specific deidentified demographic information (age, gender, race, education level, religious identification, relationship status) and reasons for exclusion will be retained for those who are not eligible in order to comply with clinical trials reporting requirements (CONSORT Guidelines). This information will be destroyed upon publication.

To prevent delays in study start and to ensure that the study sample is representative of OEF/OIF/OND returnees with PTSD, participation in the fMRI portion that requires travel to Ann Arbor (see below) will not be mandatory to enter the study. We aim to recruit 210 participants (local or willing to travel to Ann Arbor) for the fMRI component (70 per condition). Additionally, fMRI specific exclusion criteria include: 1) left-handedness 2) ferrous containing metals within the body (e.g., aneurysm clips, shrapnel/retained particles), and 3) inability to tolerate small, enclosed spaces (e.g. claustrophobia) 4) Patient girth exceeds allowable fMRI machine dimensions. Eligible veterans will be offered the study and those who agree to participate will review consent documents with study staff (see consent below).

To be included as a subject in the Combat Control (CC) group, the following CC Inclusion criteria must be met: a) Absence of any history of PTSD symptoms (CAPS < 20), related to any type of trauma; b) Exposure to Criterion A Combat Trauma with Combat Exposure Scale (CES) score ≥ 17 (e.g., at least moderate exposure) during OEF/OIF/OND involvement. Otherwise, the same inclusion/exclusion criteria apply for the CC group as that used for the PTSD patient group noted above. If a Veteran or Active Duty Service Member is interested in participating in the CC procedures, they will not be required to register with the VAAAHS or have their consent form scanned into CPRS.

**Procedures.** The study will utilize the MICHR Clinical Trials group to provide study oversight, data management, clinical trial compliance monitoring, data management, randomization, regulatory support, and protocol standardization. Use of this resource will ensure the highest level of standardization and data quality we can obtain for a multi-site trial. Participants will be block randomized by site with central distribution of randomized condition from the MICHR study staff to the study coordinator for PE status and to the study pharmacist at the facility for pill status. This will ensure that blind is maintained. Randomization will be based on a computer generated table of random numbers. MICHR will be responsible for providing these randomizations at the time of consent. Once eligibility is determined as part of the standard intake in the clinic, those returnees who meet inclusion and exclusion criteria and are interested will review study consent documents (see Consent below). No study procedures will be conducted prior to obtaining consent. All study treatments and procedures will be completed at the VA Ann Arbor Healthcare System and patients who are in the treatment group will have their progress documented in his/her medical records in the form of session notes and notes to document completion of study procedures and patient status. Finally, those who are eligible for the fMRI study will review additional optional consent if desired. Consented participants will complete the following procedures as appropriate. Major study assessments will occur at Intake Week, Weeks 6, 12, 24, 36, and Wk 52. These assessments will include interview and self reports of symptoms and function (see Table 1). In addition, neurobiological assessment (salivary cortisol RTA) will occur at all major assessments (except Intake Week)

and Week 0. Blood draws for genetics and genomics will occur at Week 0 (or within 7 days prior to) and Wk 24. Participants will receive $50 for each major assessment visit completed at Intake Week, Wk 6, 12 and 24. . Participants will receive $75 for a completed Week 36 major assessment visit and finally $100 for a completed Week 52 major assessment visit All fMRI component participants will receive $100 for each fMRI study scan completed. In addition, participants traveling to Ann Arbor to complete the fMRI study will receive $700 per day and travel expenses, including hotel, flight, ground transportation, and GSA set per diem ($42/per day). The study will require one day for travel to Ann Arbor. We will scan on Day 2 and return travel home day 2 whenever possible. For any participants who are active duty, payments will be discussed in order to ensure they do not receive payments when on-duty. Combat control participants will receive $50 for completion of the interview procedures and $100 for completion of the fMRI scan. All intakes and interview measures will be completed by the independent evaluator (IE) blinded to treatment assignment and trained in both the MINI and CAPS. Interviews will be audiotaped for use in recalibration and interrater reliability assessment. All IEs will complete bi-monthly recalibration assessment reviews for CAPS and yearly MINI recalibration assessment reviews. In addition to the assessments listed below, the evaluator will collect comprehensive information regarding past and current treatment (medication and psychotherapy). All self-report measures will be accessible on-line for those veterans who choose to complete them through the secure Velos server using their secure password and research identification. This will allow flexibility for the participants and will also be available for participants who do not follow through on study protocol so that information on their status as well as reasons for drop from study treatment can be collected. No patient health information (PHI) except for dates of assessment visits and dates of side effects and adverse events will be collected through Velos (see data management).

**Consent Procedures.** All patients will complete intake assessment in the PTSD Clinic at each respective enrollment site prior to study entry. Patients who appear to meet criteria for entry into the study will be informed of the study and if interested will review study consent, HIPAA Authorization (VA and University of Michigan), and Form 10-3203 with study staff who the Principal Investigator (PI) has identified as being qualified on the Delegation of Authority Log. During review of consent, study staff will detail study procedures and ensure that patients understand the study procedures and what is part of standard treatment for PTSD prior to signing consent. Patients will receive in the consent document emergency contact information for use in case of acute exacerbation of symptoms. Patients will be informed that they can withdraw from the study at any time and receive alternate care outside of the study in outpatient psychiatry. The consent process will take place at the identified site where the participant completed their intake. Participants will be afforded as much time as they need to make a decision regarding their desire to participate in the study. Additionally, study staff will provide contact information and will be available to discuss any questions or concerns potential participants may have. If the patient decides he/she would like to participate more than four weeks after their intake assessment in the clinic, inclusion and exclusion will be reviewed again prior to consent. No study procedures will be conducted prior to obtaining consent. The fMRI portion of the study will be discussed after completing consent for the main study. The study staff member will review the participant's interest and the additional exclusionary criteria for the fMRI. The consent will then be reviewed and the participant signature will be obtained if they understand and agree. This will occur at all sites for all patients consented until the recruitment goal for the fMRI procedures (n = 210) is reached. All subjects will complete consent prior to any scheduling of travel and the consent will be reviewed again prior to the scan.

Patient Randomization. Study subjects will be block randomized by site with central distribution of randomized condition from the MICHR study staff to the study coordinator for PE status and to the study pharmacist at the facility for pill status. This will ensure that blind is maintained. Randomization will be based on a computer generated table of random numbers. The Study Coordinator will provide the required information that determines randomization to MICHR via the MICHR Randomization Subject Look-up Tool (website). The Tool would provide the Study Coordinator the patient's PE status as well as the randomization code for the pharmacy. The pharmacist would review the list of patient randomization treatment assignments received from MICHR and prepare the study drug as appropriate for the randomization code (i.e. sertraline or placebo).

**Blinding and Unblinding. Randomization can be broken if the treating provider or Site PI finds it is necessary to ensure subject safety. The blind will only be broken by the Site or Study PI except if the patient is in acute danger. If patient is in acute danger as assessed by the treating provider or Site PI, the Site pharmacist can break the blind. Documentation (as noted below) will then be completed after the blind is broken.** In situations where the patient is not in acute danger the following procedure should be followed to unblind the patient. The treating provider will contact the Site or Study Principal Investigator to request patient treatment unblinding and document his/her request on a Request for Patient Treatment Unblinding Form. If the Site or Study Principal Investigator agrees that the patient's treatment can be unblinded, she will sign the Request for Patient Treatment Unblinding Form. This form will then be submitted to the treating provider's pharmacy. The Site pharmacist will communicate the patient's treatment assignment to the treating provider or Site PI and document date of communication and treatment on the Request for Patient Treatment Unblinding Form. The completed form will be filed in the site patient file.

Interview measures.

a) The Mini International Neuropsychiatric Interview (MINI) [82] is a short, structured diagnostic interview that assesses current major DSM-IV axis I diagnoses and takes approximately 15 to 30 minutes to complete with diagnostic agreement with Structured Clinical Interview for DSM-III-R, patient version (SCID-P) and good inter-rater and test retest reliability (Sheehan, et al., 1998).

b) Clinician Administered PTSD Scale (CAPS) [83] is an interview measure of PTSD severity and the primary outcome measure for the study. Current PTSD will be assessed in relation to the OEF/OIF/OND war-zone trauma that is currently most upsetting. The CAPS has excellent psychometrics. Completion requires about 45 minutes. Four additional items will assess proposed modifications to diagnostic structure that may be implemented during the study period.

c) Brief Traumatic Brain Injury Screen (BTBIS) [85] will be used to assess for possible TBI. As per measure protocol, all positive items will be queried at interview to ensure accuracy and validity. The BTBIS will be completed at Intake Week, Week 24 and Week 52.

d) Columbia-Suicide Severity Rating Scale (C-SSRS) [87] is a standardized 8 point clinician-administered suicidal rating system designed to track suicidal adverse events across a treatment trial and covering the wide spectrum of suicidality.

e) Clinical Global Impressions Severity Scale (CGI-S) is a 1-item scale asking the evaluator to assess the patient's overall level of illness severity. The evaluator integrates all aspects of the patient's condition when using this scale [88].

f) Clinical Global Impressions Improvement Scale (CGI-I) is a 1-item scale asking the investigator to assess the patient's overall improvement compared to the patients' condition at study entry. The evaluator integrates all aspects of the patient's condition when using this scale [88].

g) Study Update Form (SUF) will be used to collect information about treatment and changes since the previous assessment. Versions of this form have been used in multiple clinical trials conducted by Drs. Rothbaum, Foa, and Rauch (included in the appendices).

h) Utility of Techniques Inventory (UTI) is a measure of the frequency and perceived utility of each of the key techniques that are part of PE administered in each session. This measure was developed at the Center for the Treatment and Study of Anxiety under the direction of Dr. Edna Foa and has been used in all PE treatment outcomes studies conducted through her research group as well as studies conducted by the PI.

i) Adherence Questionnaire (AQ), a 2-item questionnaire is used to determine what proportion of the time between visits the participant took their study medication as recommended, and to establish the reason(s) for deviating from the recommended dose (e.g., forgot, side effects, thought not needed, etc.).

j) Demographic Questionnaire (DQ), a 17-item questionnaire to collect demographic (gender, age, marital status) and military background information (period of service, service connection rating, military experiences).

k) Combat Trauma Interview (CTI), an interview measure assessing response to traumatic events during deployment. Completed in session during PE therapy (Session 1). A brief version of the CTI will also be completed at MM visit to assess alcohol and drug use.

Self report measures.

a) Combat Experiences Scale (CES) [89] is a seven-item measure of combat exposure severity and inquires about the frequency of various combat experiences including receipt of or witnessing someone hit by enemy fire, conducting combat patrols etc. Total scores range from 0 to 41. The CES has demonstrated good reliability.

b) Revised Patient Health Questionnaire (PHQ-15) [90] will be used to asses physical health status with additional post-concussive symptoms added as reported by Hoge and colleagues [91]. Our study will use the revised scale with a range of 0 to 28 with high severity indicated by a score of 15 or higher. Five additional questions, which were not part of the PHQ-15, were asked regarding important post concussive symptoms that concerning memory, balance, concentration, ringing in the ears, and irritability.

c) PTSD Checklist – Symptom (PCL-S) is a 17-item self-report assessment of PTSD severity using a 5-point scale, from 1 (not at all) to 5 (very often). It has good reliability and validity [92]. The PCL will be administered at each major assessment and every other week of study through Wk 24.

d) Depression Anxiety Stress Scale (DASS-21) [93] assesses depression, general anxiety, and stress symptomatology. The DASS short version is a 21-item scale with 3 subscales (depression, anxiety, and stress). The subscales show low intercorrelations between factors and high item loading within factors [93]. Internal consistency of subscales (.87 to .94) and concurrent validity is excellent [93].

e) Deployment Risk and Resilience Inventory (DRRI) is a set of 14 self-report inventories developed by the National Center for PTSD [94] to assess aspects of military deployment-related stress reactions (2 pre-deployment factors, 10 deployment and war zone factors, and 2 post-deployment factors).The DRRI has good reliability and validity.

f) Substance Abuse Outcomes Module (SAOM) [95] measures alcohol and drug use in the past month [95]. Alcohol use questions concern the number of days of alcohol use, the average consumption per drinking day, the maximum consumption, and the number of binge days (days that more than five drinks were consumed). The SAOM also examines substance use for various recreational drugs (e.g., marijuana, cocaine or crack, prescribed stimulants, heroin, anabolic steroids, and tobacco).

g) Posttraumatic Cognitions Inventory (PTCI) [96] is a 36-item assessment of negative thoughts about the self, negative thoughts about the world, and self-blame. It has good psychometrics and has been related to change in PTSD symptoms with treatment [20].

h) Social Function Scale (SFS) is an investigator created assessment of behaviorally based functioning including assessment of interactions with the legal system (DUIs, arrests, etc.), getting in fights, loss of job, loss of relationships, and other indicators of problematic social function.

i) Inventory of Functional Impairment (IFI; Brian Marx, Personal Communication) is a new 87-item self-report measure of functional impairment across the domains of relationships, work, parenting, education, and general daily functioning over the past 30 days. In a development study with veterans, the scale demonstrated internal consistency (subscale Cronbach's alphas between .76 and .91) and correlated highly with other established measures of functional impairment but covers specific areas that are related to our population.

j) The Brief Pain Inventory (BPI) [97] is a 9-item measure developed for use with cancer pain but since has been used in other pain settings. It has demonstrated reliability and validity for the assessment of pain.

k) Anxiety Sensitivity Index (ASI) [98] is a 16-item measure of beliefs about anxiety symptoms. The measure has excellent reliability and validity and has been found related to the development and effective treatment of anxiety disorders [99, 100].

l) Neurobehavioral Symptom Inventory (NSI) [101] is a 22-item self report of common symptoms of postconcussive syndrome will be used to assess severity of symptoms over the course of the study. The NSI will be completed at all major assessments.

m) The Client Satisfaction Questionnaire (CSQ-8) [102] will be completed as a self-report measure at Week 24 to examine acceptability and feasibility of PE/PLB, PE/SERT, and SERT. This measure has demonstrated good reliability and validity [102, 103].

n) Treatment preference will be assessed with one questions asking patient prior to their knowledge of treatment assignment, whether they prefer to receive PE, SERT or PE/SERT. This will be sealed in an envelope and not opened until after blind has been broken. After blind is broken the Follow-up form will be used to assess whether patients have decided to continue in treatment after being made aware of their treatment condition (medication or placebo).

o) The Inventory of Complicated Grief (ICG) is a well validated 19-item patient administered scale assessing the impact on the patient of loss and associated complicated grief symptoms. The scale will be completed only if the participant selects yes to a significant lifetime loss on the cover sheet.

p) Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996) is a 21 item self report measure of depression severity. Using a scale from 0-3 individuals' rate how they have been feeling in the past week. BDI-II has excellent reliability and validity.

q) Trauma Related Guilt Inventory (TRGI) is a 32-item self-report questionnaire designed to measure cognitive and emotional aspects of guilt associated with the experience of a traumatic event.

r) Frequency, Intensity, and Burden of Side Effects Rating (FIBSER) is a self report provides 3 global ratings each on a Likert-type scale rated 0-6. One rates frequency, another intensity, and the third estimates the overall burden or degree of interference in day-to-day activities and function due to the side effects attributable specifically to the antidepressant treatment. The FIBSER will be used to guide evaluation of side effects, and to determine whether or not the dose of medication should be increased.

**Table 1. Assessment Schedule, Source, and Domain**

| Measure | Domain | Source | Intake Week | @ Med. Manage (Wk. 0,1,2,4,6, 8,10,12,16 20,24) | PE (Wk.0-12) | Wk 6 | Wk 12 | Wk 24 | Wk 36 | Wk 52 |
|---|---|---|---|---|---|---|---|---|---|---|
| **MINI** | Diagnoses | IE | X* | | | | | X | X | X |
| **CAPS** | PTS Severity | IE | X* | | | X | X | X | X | X |
| **CGI-S** | Overall Function | IE, MM | X | X** | | X | X | X | X | X |
| **CGI-I** | Overall Function | IE, MM | | X** | | X | X | X | X | X |
| **BTBIS** | Screen TBI Status | IE | X | | | | | X | | X |
| **C-SSRS** | Suicidality | IE, MM | X (Baseline version) | X ** (FU version) | | X | X | X | X | X |
| **AQ** | Medication Adherence | MM | | X | | | | | | |
| **FIBSER** | Side Effects Monitoring | Patient | | X | | | | | | |
| **UTI** | Therapy Adherence | Therapist | | | X | | | | | |
| **DQ** | Demographics and Treatment | IE | X | | | | | | | |

| Measure | Domain | Source | Intake Week | @ Med. Manage (Wk. 0,1,2,4,6, 8,10,12,16 20,24) | PE (Wk.0-12) | Wk 6 | Wk 12 | Wk 24 | Wk 36 | Wk 52 |
|---|---|---|---|---|---|---|---|---|---|---|
| **CES** | Combat Exposure | Patient | X | | | | | | | |
| **DRRI** | Deployment Experiences | Patient | X | | | | | | | |
| **PCL-S** | PTS Severity | Patient | X | X*** | X*** | X | X | X | X | X |
| **DASS-21** | Depression, Anxiety and Stress Severity | Patient | X | | | X | X | X | X | X |
| **PHQ-15 (Rev.)** | General Distress | Patient | X | | | X | X | X | X | X |
| **PTCI** | PTSD Cognitions | Patient | X | | | X | X | X | X | X |
| **NSI** | PCS Symptoms | Patient | X | | | X | X | X | X | X |
| **SAOM** | Alcohol/Sub Use | Patient | X | | | X | X | X | X | X |
| **BPI** | Pain | Patient | X | | | X | X | X | X | X |
| **ASI** | Anxiety Sensitivity | Patient | X | | | X | X | X | X | X |
| **CSQ** | Client Satisfaction | Patient | | | | | | X | | |
| **IFI** | General Function | Patient | X | | | | X | X | | |
| **ICG** | Comp. Grief | Patient | X | | | | | X | | |
| **BDI-II** | Depression | Patient | X | X*** | X*** | X | X | X | X | X |
| **TRGI** | Guilt | Patient | X | | | X | X | X | X | X |
| **SFS** | Function | Patient | X | | | X | X | X | X | X |
| **SUF** | Psychosocial status | IE | | | | X | X | X | X | X |
| **CTI** | Response to events during deployment | MM, Therapist | | X (abbreviated version at Week 0 only) | X (at Session 1) | | | | | |
| **Treatment Preference** | Treatment preference and decision to continue/discontinue treatment | Patient | X | | | | | X-FU Form | | |

*Measures repeated for Wk 0 only if delay from intake of 4 weeks or more.

** Measure is completed for MM use only, not entered into Velos

***Measures will only be given at either the Medication Management or PE session (whichever is first)

The CC group will have the same assessments described above at the Intake session. They will not have repeat assessments and will not undergo any interventions described below.

Interventions. Participants will complete up to 13 weekly sessions of the randomly assigned treatment with 12 additional weeks of continuation on stable medication and completion of missed sessions up to 13 for PE. In all

conditions, participants will complete the PCL every other week. Those participants who obtain a PCL score below 28 for two consecutive assessments will be considered completers for PE or enhanced medication management visits. PE sessions will end at this point. For those who do not meet this remission criterion, PE will continue for up to 13 sessions total. For those in medication management who meet the remission criterion, pharmacotherapy visits will continue at the manualized schedule without the additional supportive contact and intervention. Participants will be removed from the study treatment due to imminent risk of suicide (as indicated on the C-SSRS), significant medical risk, patient refusal to continue, or clinician determination that the participant's best interests will be harmed by study continuation. For those removed, appropriate clinical care will be provided either through referral or care outside of the study. Whether study assessment will be continued will be determined in the best interests of the patient.

Clinical Video Telehealth (CVT)

Participants in this research study, who are receiving their regular VA health services outside of the Ann Arbor VA facility, may receive their treatment (medication and/or therapy) visits at Community Based Outpatient Clinics (CBOCs) within the VA Ann Arbor Healthcare System through Clinical Video Telehealth (CVT). In addition, participants may be asked to complete research assessment visits through CVT at CBOCs within the VA Ann Arbor Healthcare System. The treatment visits will be video recorded. The research assessment visits will be audio recorded.

a) PE (see manual [104]) includes breathing retraining; psychoeducation; prolonged, repeated exposure to trauma memories (imaginal exposure); processing of trauma related material that emerges during exposure; and repeated in vivo exposure to trauma related avoided situations (in vivo exposure). The Principal Investigator (PI), Dr. Rothbaum, and Dr. Foa created an addendum to this manual specifically for use with OEF/OIF/OND in 90 minute sessions in accord with VA practice (see Addendum in Appendices). Each of the up to 13 individual sessions will last roughly 90 minutes. Participants will complete practice (in vivo exposure and listening to tapes of imaginal exposures) between sessions.

Dr. Peter Tuerk will serve as supervisor of therapy for the study. Dr. Tuerk is currently a clinical consultant supervisor and one of 12 national workshop trainers for the VA PE Roll Out, he works closely with the developers of PE to ensure treatment fidelity in other federally funded trials, and he has a number of scientific publications specifically concerning OEF/OIF/OND-related PTSD and PE. The VA National PE Roll Out will provide all therapist training with consultation provided by Roll Out approved consultants on the study team to ensure PE is provided to VA standard. This program includes a 4-day didactic training created by VA training specialists and Dr's Edna Foa and Elizabeth Hembree, and it includes a minimum of 2 training cases with session by session consultation with a proficient PE provider. Study therapists will complete both didactic training and training cases to ensure compliance with PE manual elements. All study sessions will be videotaped for fidelity assessment and supervision purposes. Throughout the active treatment phase of the study, weekly group supervision will occur, including viewing session videotapes. Twenty percent of session tapes will be rated for fidelity to ensure that prescribed and proscribed interventions coincide with the assigned groups (i.e., no directions for exposure in the medication management group). All symptomatic and interested veterans receiving PE/PLB will be offered SERT immediately after blind is broken at Wk 24.

b) Medication management will be manualized to include review of status, main and side effect monitoring as well as additional psychoeducation about PTSD and present centered supportive content (see Pharmacotherapy Manual and PCT Manual). Each visit will be between 10-45 minutes. The first 3 weeks will include weekly contact. Visits will decrease to every other week for Wks 4, 6, 8, 10, and 12. Active treatment phase will then be complete and medication will remain stable unless changes are indicated for safety until Wk 24. Visits will occur at Wk 16, 20, and 24. After the Wk 24 assessment is complete, the blind will be broken and all symptomatic and interested veterans receiving medication management will be offered additional treatment as warranted (PE or alternate medication). Data collection on any treatment changes and follow up will continue until the end of the study. Pharmacotherapists will complete a 3 hour training and monthly supervision calls to ensure standardization of pill administration and "enhanced" intervention across sites.

Sessions will be videotaped. Twenty percent of session tapes will be rated for fidelity to ensure that prescribed and proscribed interventions coincide with the assigned groups (i.e., no directions for exposure in the medication management group). For those randomized to PE/SERT, every effort will be made to schedule the two visits in the most convenient way for the patient. Pharmacotherapists will also be available by phone or pager for between session consultation should side effects occur or symptomatic worsening develop. All symptomatic and interested veterans receiving medication management will be offered clinical care as appropriate (PE or alternate medication) immediately after blind is broken.

SERT is FDA approved for use in oral administration for the treatment of PTSD. The recommended minimal dosing of SERT is mg per day in single dosing, with safety and effectiveness also shown for doses up to 200 mg per day. A bulk supply of over-encapsulated SERT 25 mg and 50 mg will be prepared by the site pharmacist. SERT 25 mg active capsules will be prepared by placing one-half of a 50 mg generic SERT tablet into the bottom half of a gelatin capsule, size #0. The surrounding dead space will be filled with microcrystalline cellulose NF. SERT 50 mg active capsules will be prepared in a similar fashion using intact generic SERT 50 mg tablets. Each bulk supply of active SERT 25 and 50 mg capsules will be prepared using a single lot of generic SERT. Bulk SERT 25 mg and 50 mg active capsule supplies will be labeled as to the dose, date of manufacture, lot number and expiration (beyond use) date. Expiration date for the SERT 25 and 50 mg active capsules will be 12-months from date of manufacture, the lot-specific expiration date of the generic sertraline tablets used or the lot-specific expiration date of the microcrystalline cellulose filler, whichever occurs first. SERT is usually well tolerated. The most common side effects associated with SERT are nausea, headaches, sweating, change in appetite, dizziness, insomnia, tremor, sexual dysfunction, and nervousness. As with other antidepressants, there is a black box warning regarding the risk of increased suicidality, particularly in the initial weeks of treatment and in individuals under age 25. Suicidality will be closely monitored with C-SSRS at each contact. Baseline interview will be completed at Intake Week and the follow-up since last visit interview will be completed at each pharmacotherapy contact. The provider will follow up the VA Safety Plan for Reducing Suicide Risk for those who are positive for items 1 or 2 on past month or since last visit versions of the C-SSRS. If the Veteran already has a Safety Plan, it will be reviewed at each additional visit where significant risk of self-harm is reported (items 3, 4, or 5 are endorsed). The need for study treatment termination will be determined on a case-by-case basis in coordination with the care team, site PI, and study PI. However, no prohibition against necessary treatment will be in place if needed. Abrupt discontinuation of SERT can also be associated with withdrawal symptoms, such as depressed mood, irritability, moodiness, dizziness, pins and needles feelings, anxiety, confusion, headache, sluggishness, nightmares, vertigo, vomiting, tremor, and insomnia. Thus, a gradual reduction in dosage rather than abrupt discontinuation will be highly recommended for any individuals wishing to stop study medication. Patients will also be asked to contact the investigator before discontinuing the study medication to discuss their concerns and to devise an appropriate plan. Placebo medication will be used in this study because there is a need to establish the relative effect of PE without SERT pharmacotherapy compared to combination treatment. All participants in this study receive at least one intervention with previous demonstrated efficacy for PTSD (PE and/or SERT).

Placebo capsules (PLB) will be used in this study because there is a need to establish the relative effect of PE without SERT pharmacotherapy compared to combination treatment. The PLB is composed of microcrystalline cellulose and poses no additional risk. PLB capsules will be prepared using size #0 gelatin capsules, filled entirely with microcrystalline cellulose. A bulk supply of PLB capsules will be prepared using a single lot of microcrystalline cellulose and will be labeled with contents (PLACEBO capsules), date of manufacture, lot number and expiration date. PLB capsule expiration dating will be 12-months from date of manufacture or the lot-specific expiration date of the microcrystalline cellulose filler, whichever occurs first. Medication Managers are blind to pill condition. All participants in this study receive at least one intervention with previously demonstrated efficacy for PTSD (PE and/or SERT). Dosage and titration will follow the same schedule and monitoring as SERT. Individual subject study prescriptions for SERT 25 mg, SERT 50 mg or PLB capsules will be processed by the site Research Pharmacist or designee upon receipt of a valid, study-specific paper or electronic order from an authorized study prescriber. Study medication will be provided in plastic amber prescription vials labeled with a standard VA outpatient prescription label clearly identifying it as study

medication. Monitoring of adverse events and adjustments to dosage will also follow the same procedures a SERT (as providers are blinded).

*1. Acute Treatment with Blinded SERT or PLB (weeks 0 to 12).* During the 13 weeks of acute treatment, all participants will receive blinded SERT or placebo, titrated flexibly as follows based on tolerability and symptomatic response. Patients will initiate double-blind SERT at baseline (week 0) with 25 mg/day followed by a dose increase to 50 mg/day at week one. If patients are unable to initially tolerate 50 mg/day they will be permitted to remain at 25 mg/day during week 1, but the dose must be titrated to 50 mg/day by week 8. If unable to tolerate SERT 50 mg/day at week 8, patient will be discontinued from the protocol and transferred to clinical care. If no slowing of dose titration is required, at week 4 the blinded SERT dose will be raised to 100 mg/day. Upward dose titration may be slowed and the dose decreased if necessary due to side effects but the clinician will attempt to titrate all symptomatic patients to at least 100 mg/day, and up to 200 mg/day if tolerated by week 8. All symptomatic patients will be titrated to their maximally tolerated dose (≤ 200 mg/day SERT), with the last dose increase at week 10. Any participant who meets discontinuation of study treatment criteria (as noted above) will be discontinued from the pharmacotherapy protocol and transferred to clinical management.

**Flexible Medication Dosing Guideline.** The target dose goal is 200 mg/day by week 8. Patients will initiate double-blind sertraline at week 0 with 25 mg/day followed by a dose increase to 50 mg/day at week one. If patients are unable to initially tolerate 50 mg/day they will be permitted to remain at 25 mg/day during week 1, but **the dose must be titrated to 50 mg/day by week 8.** If no slowing of dose titration is required, at week 4 the blinded sertraline dose will be raised to 100 mg/day. Thus, for a patient with no significant side effects or slowing of titration dosing will be 25 mg at week 0, 50 mg at week 1 and 100 mg at week 4, 150mg at week 6 and 200mg at week 8 (as summarized in Table format below). However, upward dose titration may be slowed and the dose decreased to the prior level if necessary due to side effects. The clinician will attempt to titrate all symptomatic patients to at least 100 mg/day, and **all <u>symptomatic</u> patients should be titrated to their maximally tolerated dose (<u>≤</u> 200 mg/day sertraline**: see guidelines for doing increases) by week 8 if tolerated, but with the last possible dose increase at week 10.

<u>Summary Table of Flexible Blinded SERT/PLB Dosing Guidelines by Week</u>

| | |
|---|---|
| Week 0 | 25mg/d |
| Week 1 | 50mg/d |
| Week 4 | 100mg/d |
| Week 6 | 150mg/d |
| Week 8 | 200mg/d |
| Week 10 | last possible dose increase |

Use of the CGI-S and Side Effect Monitoring Scales are Summarized below but discussed in more detail at Visit 1 (see page 20).

<u>Use of CGI-Severity and Side Effect Monitoring to Guide Dosing Decisions:</u>

- **Specifically, if the CGI severity rating is greater than 2 (borderline ill), and the side effect burden is low, the dose is increased per schedule.**

Use of the FIBSER as a Starting Point for Side Effect Guidelines for Dosing: The FIBSER will be used as a guide in side effect assessment and dosing decisions at every visit.

- **A FIBSER score of 5 or more should trigger extra attention to side effect monitoring and review**
- **A score of >7 on the FIBSER will signal no increase in dose, although specific side effects should be reviewed in detail before a final determination and a dose increase may occur with justification for**

**increasing the dose.** If the dose is not increased because of side effects, the pharmacotherapist should continue to evaluate for possible increase at each subsequent visit.

If medication dose is held or decreased beyond these outlined adjustments, the reason for doing so must be clearly documented on the deviation record. All such deviations must be approved by the overall study pharmacotherapy supervisor (Dr. Simon).

*2. Continuation Pharmacotherapy (weeks 12 to 24).* All study participants who do not meet study discontinuation criteria as a result of lack of efficacy or tolerability will be continued on blinded medication during the 12 week follow-up phase. If discontinuation criteria are met during this follow up period, discontinuation procedures will be initiated. No dose change will occur during the follow up phase. Follow up pharmacotherapy visits to monitor compliance, safety and symptomatic status will occur at weeks 16, 20 and 24, with pharmacotherapists available for consultation as needed should side effects or symptomatic worsening develop between visits.

*3. Capsule Adherence Monitoring.* At each session, the physician or study coordinator will collect, count, and record unused capsules. In addition, the physician will review the AQ, a 2-item questionnaire used to determine what proportion of the time between visits the participant took their study medication as recommended, and to establish the reason(s) for deviating from the recommended dose (e.g., forgot, side effects, thought not needed, etc.). The study physician will record the use of both study medications and concomitant medications on a study tracking form.

*4. Concomitant Medications.* Concomitant antidepressants and antipsychotics will be prohibited in the study. The use of benzodiazepines, prazosin and hypnotics (such as Ambien), which are amongst the most common psychoactive medications utilized by this population, will be allowed as long as the participant has been stable on the medication and dose for at least 2 weeks. Participants assigned to PE will be instructed not to take their medication before, during, or for one hour after any exposure exercises. Potential participants who are currently on ineffective antidepressants but want to enter the study can work with their prescribing physicians to discontinue antidepressants if clinically appropriate prior to study randomization, but must be a minimum of 2 weeks off of all antidepressants prior to randomization. Participants will not begin any additional psychotropic medication during the course of the study or make changes to any other medication unless specifically approved by the study PI in consultation with the pharmacotherapist. All pharmacotherapists will remind study participants at each visit to discuss any medications prescribed by non-study physicians with the study doctor prior to initiating them.

*5. Safety Assessments.* Potential discomforts associated with the treatment interventions are not specific to the experimental design: the design formalizes assessment and monitoring of symptoms during the treatment process. Patients will be queried at each treatment visit regarding the presence of adverse effects associated with administration of the study medication. All adverse events from the time patient signs consent through Week 24 assessment or treatment termination (whichever occurs first) will be documented. Furthermore, all SAEs occurring from the time the patient signs consent through the Week 52 assessment must be reported. SAEs that occur after Week 24 will be ascertained by the Study Update Form (SUF) and additional documentation completed as required. Review of medical history and laboratory tests will be performed at admission.

**Test Article Dispensing and Accountability**

All of the following is pulled from the VAAAHS Pharmacy Investigation Drug Handling Policy (119-04) and applied to our test article (SERT/PLB).

a. SERT/PLB is approved as a test article and identified in the VA Drug File as a study medication. Two separate, study-specific Drug File entries will be made: SERT25/PLB STUDY DRUG and SERT50/PLB STUDY DRUG. The SERT25/PLACEBO entry will only be used during the first week of titration (week 0). The SERT50/PLACEBO entry will be used for the remainder of the titration period and for maintenance therapy to minimize the number of capsules necessary to achieve a target dose of 200 mg. Study subjects who do not tolerate the dose increase at week 1 (50 mg) will be down-titrated to SERT25/PLB.

b. All SERT/PLB, supplies and other pharmaceuticals required by PROGRESS will be stored in a secure area of the pharmacy and separated from regular drug stock intended for general patient use. SERT/PLB will be dispensed and administered in accordance with procedures indicated below. In compliance with VA policy, pharmaceuticals are not to be dispensed from clinic areas or physician offices.

c. The investigator (or authorized study staff noted on the delegation of authority log) will obtain consent on VA Form 10-1086 and any other consent agreement required per protocol. Before SERT/PLB may be dispensed, the research pharmacist or designee must confirm that consent has been obtained through receipt of a completed and signed informed consent form. Copies of signed informed consents for all study participants must be maintained in the pharmacy protocol files.

d. Those administering SERT/PLB must have information readily available to them regarding SERT/PLB and be able to demonstrate an understanding of the therapeutic effect, dispensing, side effects, toxicity, precautions, and other relevant information to allow for the administration of the drug without increased risks to the patient.

e. The protocol with all amendments, pertinent information about the drug, drug accountability logs, copies of signed informed consent forms, relevant correspondence and other study documents will be maintained by the research pharmacist or designee.

f. The Research Pharmacist or designee is responsible for the receipt, storage, security, labeling, dispensing and disposition SERT/PLB. SERT/PLB will be:

(a) Secured in the pharmacy.
(b) Stored separately from the non-investigational drugs.
(c) Be clearly identified.

Pharmacy Service will maintain a file of SERT/PLB. These files will include approvals by the IRB, any sponsor-related correspondence (specific to SERT/PLB) to the site investigator and all correspondence from the FDA (and other involved authorities) specific to SERT/PLB. Pharmacy Service will ensure that the Research Consent Form (VA Form 10-1086), dated and signed by both the patient and the individual conducting the consent process, is received for each patient prior to dispensing.

(1) Records involving SERT/PLB are subject to several standards for retention. The longest standard will be used.

(2) Pharmacy will maintain a log of all transactions involving receipt, storage, security, dispensing, and disposition of unused stocks of SERT/PLB.

g. Prescribing Procedure.

(1) The approved study staff reviewing consent will fully inform the patient receiving SERT/PLB of all inconveniences or hazards to be reasonably expected, the existence of alternative forms of therapy (if any), and the effects upon the patient's health and person that may result.

(2) The investigator, or properly delegated study staff, will obtain consent of the patient on VA Form 10-1086, and any specific informed consent form that might be required by the protocol. A copy of this form and any other forms required by the protocol will be forwarded to the research pharmacist and/or scanned into the Computerized Patient Record System (CPRS).

(3) The investigator, or properly delegated study staff, will document in the patient's medical record that informed consent has been obtained.

(4) An authorized study prescriber will order the SERT/PLB using a written or electronic order form specific to the PROGRESS study.

h. Dispensing Procedure.

(1) PROGRESS study medication will only be dispensed upon receipt of a completed written or electronic order signed by an authorized PROGRESS study prescriber. The site Research Pharmacist or designee will dispense the study medication to the study coordinator, medication manager or study subject. If the patient does not show for the visit, the study article is returned to the Research Pharmacist or designee.

(2) The prescription label, in addition to the information required on other prescription labels, must clearly identify the contents as a study medication

(3) The research pharmacist or designee will not dispense SERT/PLB until a copy of the current version of the protocol, a signed VA Form 10-1086, and other relevant materials have been received from the investigator.

i. Storage Procedure.

(1) An investigational drug log (automated or written) authorized by the facility or clinical investigation sponsor must be maintained and contain the following information:

(a) Name of the drug, dosage form, and strength.
(b) Manufacturer or other source.
(c) Date of receipt of the drug (if applicable)
(d) Quantity received (if applicable)
(e) Expiration, retest, or repass date.
(f) Control, lot number, or other identification number.
(g) Name of site investigator.
(h) Protocol name or number.
(i) Name of subject or other subject identifier for individuals receiving the medication.
(j) Quantity dispensed.
(k) Balance of drug currently available (when amenable to protocol design).
(l) Patient identifier (not the patient's name).
(m) Recorder's initials.
(n) Date the protocol was approved.
(o) A final entry is made when drug therapy for the entire study (at the site) has ended. This entry documents the date of termination of the use of the drug, the quantity remaining, the action taken to dispose of the balance on hand and the agent or individual responsible for drug destruction or return.

(2) All entries will be checked and initialed by a pharmacist.

Neurobiological measures.

a) Genetic Variables. We will examine genetic predictors of treatment response by analyzing DNA markers as potential predictors of treatment response. Genomic DNA will be obtained from blood specimens, which will be collected at Week 0 (or 7 days prior to), frozen, and shipped to repository at VAAAHS. Genomic DNA will be purified in our repository using a automated membrane method (Autogen), quantified (Picogreen) and stored at -80 in our VAAAHS LIMS based archival system with bar-coded labels. Genotyping will be performed i.) in our VA laboratory using standard PCR / RFLP methods (5-HTTLPR), and in our University of Michigan DNA Sequencing Core using ii.) Illumina Infinium "iSelect" custom SNP panel (candidate genes) beadarray, and iii.) 1M-Omni (1 million-genome-wide) beadarrays. Our ***custom SNP panel array*** includes ~5000 SNPs in 170 candidate genes in a custom Illumina (iSelect) beadarray that we have already developed (and currently using for case-control genetic association studies of PTSD in traumatized civilian cohorts, total n ~4500 subjects). It includes dense coverage of selected candidate genes (e.g. *FKBP5, SLC6A4, GRIK4, TPH2, HTR2A*) previously associated with PTSD, depression, etc., and as well haplotype-tagging SNPs (htSNPs) from CEU and YRI (European and African ancestry) populations in HapMap in candidate genes in neurotransmitter and stress responsive systems, and redundant coverage of previously reported SNPs; ~400 psychiatric GWAS "hits"; and 200 ancestry informative markers. The ***Illumina 1M Omni chip*** provides coverage of >1,000,000 tag SNPs (marker spacing ~2.5 kb) derived from HapMap data (release 23) provides coverage across many populations, and targets the majority of known common SNP variation, and ~60,000 copy number variation (CNV) markers. Infinium beadchips will be hybridized with ~400 ng of genomic DNA (quantified by Picogreen at >60 ng/ul), plated onto 96-well PCR plates) using standard Illumina protocols at our Core facility, and scanned on the Illumina BeadArray 500GX using Illumina BeadScan acquisition system, and Illumina BeadStudio software (with standard QC procedures) to generate an output genotype call file for statistical analysis.

b) Gene Expression Variables. To investigate treatment-related changes in peripheral gene expression that may reflect brain gene expression, peripheral blood leukocyte mRNA expression profiles will be tested as potential predictors. Week 0 (or within 7 days prior to), or as correlates (change Week 0 (or within 7 days prior to) to Wk 24) of response. Blood samples will be obtained from patients at each site at Week 0 (or 7 days prior to) and again at post treatment (Wk 24). Blood will be drawn in morning (overnight fast), collected into RNA blood collection tubes ("Tempus", Ambion Inc.), which stabilizes RNA at room temperature for 3 days, allowing minimal processing at phlebotomy sites. Blood will be shipped to the central repository at VAAAHS

via overnight courier, archived in LIMS, and stored at –20C. Whole blood contains multiple leukocyte cell species; the majority globin mRNA can interfere with measurement of leukocyte mRNA and will be removed ("GLOBINClear, Ambion). RNA yield and purity (260 nm:280 nm) will be determined using NanoDrop, and integrity of total RNA using Agilent Bioanalyzer 2100. Anti-sense RNA will be synthesized and hybridized to Illumina ***Human HT-12 Expression Whole Genome*** beadchips, this medium-throughput (12 samples / chip) system provides genome-wide transcriptional coverage of >48,000 transcripts of well-characterized genes, gene candidates, and splice variants. Samples will be scanned on the Illumina BeadArray 500GX Reader, following Illumina protocols. Illumina BeadStudio software with a standard background normalization and controls will generate an output file for statistical analysis; transcripts with detectable quantitative expression will be identified by comparing distribution of expression values to embedded on-chip controls. Abundance values of all detectable transcripts will be z-scored within individuals. Positive results in gene expression beadchips will be validated using quantitative RT-PCR (using TaqMan primer-probes and Stratagene Mx2000 RT-PCR system.)

c) fMRI scan will occur at Intake Week and Wk 24. Each scanning session will include two tasks – 1) an emotional faces task (matching emotional faces to target); and 2) an emotion regulation task (effortful reappraisal of aversive pictures). All scanning will be done at the VAAAHS fMRI Center, on a 3.0 Tesla Phillips scanner (Excite release, Neuro-optimized gradients). T1-weighted images (T1 overlay) are prescribed approximately parallel to the AC-PC line with the following or similar parameters (GRE, TR = 250msec, TE = 5.7msec, FA = 90º, FOV = 22cm, 40 sl/vol, sl thk = 3mm, matrix = 192 x 256). For the functional volumes, we use a reverse spiral acquisition sequence with the following or similar parameters (GRE, TR = 2000msec, TE = 30msec, FA = 90 º, FOV = 22cm, 40 sl/vol, sl thk = 3mm, matrix dia. 71 - equivalent to 64 x 64), in the same prescription as the T1-overlay. A high resolution 3D structural scan are acquired to provide more precise anatomical localization with the following or similar parameters (3D IR SPGRE, TR = 9msec, TE = 1.8msec, FA = 15 º, FOV = 25/26cm, sl thk = 1.2mm, matrix 192 x 256 x 124). Participants are positioned in the scanner and head movement is minimized through instructions and snug but comfortable foam packing of the head inside the coil. Stimuli are presented by a BrainLogics (PST, Inc., Pittsburgh, PA) digital magnetic resonance projector, which provides high resolution video (1024 x 768) by back projection. The goggles contain miniature video screens to view the stimuli, and will measure eye movement using reflected light (Nordic Neurolab System). Responses are recorded by an radio frequency (RF) shielded button transducer, integrated with the E-Prime package (PST, Inc., Pittsburgh, PA). We measure heart rate, respiration, pupil dilation and gaze direction as general markers of physiological arousal. With structural data acquisition, participants spend about 90 minutes in the bore of the magnet.

1. *Emotional Face Processing Tasks.* The Emotional Face Assessment Task (EFAT) is a variant of the Emotional Face Processing Task [105]. It has been previously shown to reliably and robustly engage the amygdala and has been used in other pharmacological fMRI studies [106, 107]. In brief (Fig.5), participants view a trio of faces and are instructed to match one of the two faces (bottom) that expressed the same emotion as the target face (top). The identity of all three faces is always different, and an equal number of male and female faces are presented. This task allows us to isolate amygdala reactivity specifically to threat (Angry and Fearful faces) relative to non-threat (Happy and Neutral faces). The face photographs are selected from the stimulus set of Gur and colleagues [108], or another similarly validated, standardized face photograph image stimulus set. Angry, fearful, happy and neutral target faces are presented in separate blocks. Three blocks of each target expression are presented, and no target stimuli are repeated. Face matching tasks are interspersed with a 'baseline' task, of matching simple geometric shapes (circles, rectangles or triangles). The paradigm consists of approximately 24 experimental 20 sec blocks: twelve blocks of matching emotional faces,

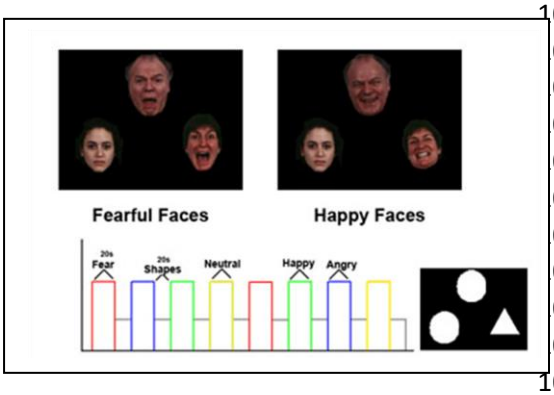



**Fig. 5: EFAT - Stimuli & Block Design**

interleaved with twelve blocks of matching shapes, counterbalanced across 2 runs. Each task block contains four sequential matching trials/faces, 5 sec each. Participants respond to tasks by pressing the left or right response buttons with their dominant hand. These responses also provide a measure of participants' response accuracy and reaction time. In addition to the EFAT, subjects will also passively faces presented in individual and/or blocked trials, as well as view faces along other control stimuli (e.g., indoor/outdoor) and instructed to focus your attention on different parts of the pictures as you respond to different questions, such as "Is this scene indoors or outdoors?" and "Is the person a man or a woman?". Together, these face processing tasks will take approximately 30 minutes.

2. *Emotional Reappraisal Task (ERT)*. This task employs two main conditions: Maintain and Reappraise. On Maintain blocks, participants are instructed to passively view pictures and simply experience the emotional state elicited by the pictures. On the Reappraisal blocks, participants are instructed to decrease the intensity of their negative emotional responses by engaging in the cognitive strategy of reappraisal. For each picture viewed, participants are asked to reinterpret the content of the picture so that it elicits a less negative emotional response, and to rate their subjective emotional responses to each picture a scale of 1-5 by button press (see Figure 6). The stimulus set will consist of approximately 80 highly aversive and arousing and 80 emotionally neutral pictures from the IAPS [109] and blank gray-scale images (fixation cross). The pictures elicit negative affect and generally depict complex scenes of dead animals, people crying, burns etc. Pictures have been chosen as 'aversive' and arousing based upon normative ratings from the IAPS. They have been extensively validated (e.g. [110]) to evoke negative emotions and activations in the amygdala and limbic regions. Our laboratory has used these pictures in neuroimaging studies of PTSD subjects for many years. An hour prior to pre treatment scanning, participants will receive instruction and practice the reappraisal task using pictures not shown in scans. For training in reappraisal, two well validated examples are provided to facilitate understanding: 1) transforming the depicted scenario into less negative or more positive terms (e.g., women crying outside of a church is interpreted as expressing tears of joy at a wedding), and 2) rationalizing or objectifying the content of the pictures (e.g., a woman with facial bruises could be translated as an actor wearing makeup rather than a victim of domestic abuse). We provide these examples for illustrative purposes, and explain that no single type of reinterpretation is applicable to every picture. This task will last approximately 15 minutes.

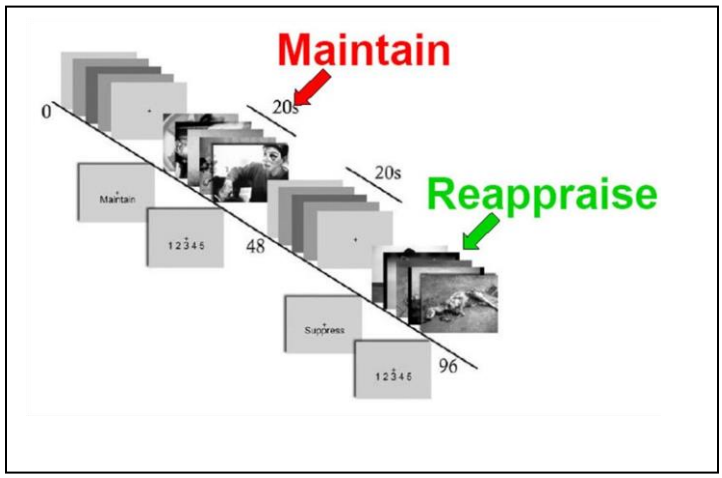



**Fig. 6. ERT - Stimuli & Block Design**

3. *Visual-Motor Task (VMT):* Each subject will perform a well-validated task to selectively and reliably activate primary motor and visual cortex (M1 and V1, respectively). In brief, the activation task consists of visual stimulation using a flashing checkerboard pattern at 10 Hz ("on" blocks), and interspersed by periods of rest ("off" blocks) where subjects view a blank screen/fixation crosshair; subjects are instructed to press their right (e.g., dominant) index finger on the button press rhythmically during "on" blocks and remain motionless during "off" blocks. This is a long trial on-off design of about 20 sec for activation and 20 sec rest periods, this sequence consisted of about 8 on and 8 off epochs over 2 runs for a total task time of approximately 5 minutes seconds for each imaging sequence.

4. *Resting State Task (RST):* In this task, subjects are instructed to simply "rest, try to empty your mind, and relax" while maintain their head still and looking at a blank screen for about 8 minutes.

d) Cortisol RTA is a measure of HPA axis homeostasis, will be assessed with collection of salivary cortisol at each major assessment (except Intake Week) and Week 0. Subjects will receive instructions and 3 Salivettes for collection of saliva samples at awakening, 30 minutes and 45 minutes after awakening. Saliva will be collected by cotton swabs ("Salivettes') placed in the patient's mouth for 30 seconds for each collection.

Patients will be instructed to refrain from eating, drinking, brushing their teeth, or smoking for at least one hour before sampling. They will bring the samples to the laboratory that day. Assays will be performed in Dr. Liberzon's laboratory at the Ann Arbor VA (Room 108 Blg 22). Cortisol will be assayed using the Diagnostic Products Corporation (DPC) Coat-a-Count cortisol radioimmunoassay (RIA) kit. This 125I RIA method is rapid and simple to perform, and has an intra- assay and inter-variability of <5%, and is a standard protocol in the Liberzon lab. Cortisol RTA will be calculated as AUC produced by the three samples with reference to the awakening sample.

All sites will collect several biological specimens (as noted above for Cortisol RTA and genetic and genomics) from patients that will be sent to VAAAHS for analysis. These will include:

**A. Saliva specimens** Saliva will be collected in bar coded salivettes (tubes containing small cotton swabs which are chewed by patients) for measurement of salivary cortisol for each major assessment (except at Intake Week) and at Week 0. Patient instructions (see Sample Collection Form) include that the cotton swabs (salivettes) is placed in the patient's mouth for 30 seconds for each collection. Patients will be instructed to refrain from eating, drinking, brushing their teeth, or smoking for at least one hour before sampling. Saliva specimens will be collected at home by the patient for each major assessment (except Intake Week) and Week 0 at awakening, 30 and 45 minutes after awakening. The major assessments will be at Intake Week, Wks 6, 12, 24, 36 and 52. Patients should bring the samples to the site on the day of the major assessment (except Intake Week) and at Week 0.
No processing of the saliva samples is required at remote sites. Saliva specimens, with bar-coded labels, will be turned in to study staff at each site upon collection, and temporarily stored at each site in freezers until they are shipped to VAAAHS. Each site will maintain an electronic collection tracking "log" containing tracking information including subject ID number, follow-up, and date of specimen collection and date of storage, and other meta-data as necessary (e.g. missing tubes, mistakes, etc.). This information will be stored in the patient tracking database on the secure server at each site. Periodically, saliva specimens will be shipped to our laboratory in VA Ann Arbor for assay and analyses. The bar-code labeled specimen tubes will be shipped frozen on dry ice by United Parcel Service (UPS) or FedEx, with a detailed manifest, including the above tracking information, but no PHI. Saliva is not classified as a biohazard, and thus standard dry-ice shipping methods will be utilized. Samples should be shipped Monday-Thursday (Next Day Delivery), as long as WEEKDAY DELIVERY TO LAB is assured. Upon arrival at the VA Ann Arbor laboratory, the manifest will be logged and specimens inspected, and each will be logged into our laboratory information management system (LIMS) using barcode, and specimen tubes transferred to freezers until time of assay (see assay section) at which time they will be centrifuged and saliva used up.

**B. Blood for DNA and RNA:** Blood samples will be obtained from patients at each site at Week 0 (or 7 days prior to) and again at post treatment (Wk 24). Blood will be drawn in morning (after overnight fast), collected in two separate collection tubes: 3 ml blood for RNA collected in a RNA collection tube (tempus) and 10ml blood for DNA and cortisol collected in a purple capped EDTA collection tube (vacutainer). The collection tubes will have bar-coded labels, containing subject ID and follow-up time-point, and each site will also maintain a "tracking log" containing data such as subject ID and time-point, and other relevant meta-data (time and date of collection, technician, date of shipping, etc.) but no PHI. At each site, the RNA tubes will be shaken vigorously or vortex for 10seconds. For DNA and cortisol, each site will spin the tube in a centrifuge, aspirate the plasma into a fresh, appropriately labeled tube for cortisol. They will then save the RBC pellet in the original collection tube for DNA. For RNA: Store the RNA tempus tubes at room temperature until used. For DNA and cortisol: The plasma and RBC pellet samples will be stored in a box on-site in a freezer until being shipped. Blood will be shipped to the central repository at VAAAHS via overnight courier at room temperature. Blood is classified as a biohazard, and therefore appropriate DOT approved shipping methods will be used for biohazard, including containment and absorbent materials, etc. Shipping will be done Mon – Thursday, and email notification will be made to the lab at time of shipping, including tracking numbers and ETA, etc. Upon arrival in the VA Ann Arbor laboratory, the manifest and contents will be inspected, and each bar-coded tube will be archived in LIMS, and stored at –20C until the time of DNA and RNA preparation and subsequent analyses.

Tracking:
Each site will maintain an electronic collection tracking log containing tracking information including subject ID number, follow-up, and date of specimen collection and date of storage, and other meta-data as necessary (e.g. missing tubes, mistakes, etc.). This information will be stored in the patient tracking database on the secure server at each site.
Packaging and Shipping:
For RNA: The RNA collection tubes will be shipped OVERNIGHT to our laboratory in VA Ann Arbor at room temperature by UPS.
For DNA and cortisol: Periodically, the samples will be shipped to our laboratory in VA Ann Arbor for assay and analyses. The tubes will be shipped frozen on dry ice by a commercial shipping company, with a detailed manifest, including the above tracking information, since blood is classified as a biohazard, appropriate DOT approved shipping methods must be used (i.e. containment and absorbent materials etc).

All samples will be shipped Monday-Thursday (Next Day Delivery), as long as WEEKDAY DELIVERY TO LAB is assured.

Update the electronic collection tracking "log" with the date shipped.

Upon arrival at the VA Ann Arbor laboratory, the manifest will be logged and specimens inspected, and each will be logged into our laboratory information management system (LIMS) using barcode. The plasma for cortisol and RBC pellet for DNA and RNA tempus tubes will be transferred to freezers until time of assay.

**Risks**

Risks listed below may not apply to all patients if a patient is not involved with a specific procedure (i.e., not in the fMRI portion of the study or a combat Veteran without PTSD who is not getting treatment). Specific risks for the specific patient groups are covered in each relevant consent form for the patient at entry to the study.
Risks may include discomfort over touching the cotton when obtaining the saliva measure; discomfort, bruising, infection at the site and formation of a blood clot at blood draws; and fainting at blood draws. Participants who screen positive for pregnancy or drug use may be embarrassed that other VA treatment providers know the results of the urine screen. In addition, some participants may experience increased distress or anxiety during interviews and self-report measures. If confidentiality is lost for the assessment audiotapes and/or session videotapes you may be embarrassed. We do not foresee any social, legal, or economic risks beyond those related to standard care for PTSD barring breach of confidentiality in which case participants may be embarrassed that others know of their mental health and/or genetic status, and for active duty or military reserve members this may impact their military career. Participant confidentiality will be protected by storing consent forms, audiotapes, and other information with protected health information (PHI) in a separate and locked location from study data at each site. Study data will include only research ID. While paper case report forms (CRFs) for the study will be held at each site in locked filing cabinets in secure study space, all study data will be entered by research ID into Velos where it will be held and securely stored. Data Transfer Agreements will be obtained as necessary and submitted for review to the institutional review boards (IRBs) and Human Research Protections Office (HRPO). In addition, de-identified data may be sent to the other participating research sites (the VA San Diego Healthcare System, VA Charleston Healthcare System, and Massachusetts General Hospital) for the purposes of data analysis and dissemination. All study staff with access to data will complete all VA privacy and data security training procedures or comparable NIH privacy and security training procedures (if not a VA site). All study staff will complete VA or NIH training in Good Clinical Practice.

For those patients receiving sertraline (SERT), the most common side effects associated are nausea, headaches, sweating, change in appetite, dizziness, insomnia, tremor, sexual dysfunction, and nervousness. Other side effects (occurring in 2% to 5% of people) included: vomiting, anxiety, nervousness, or agitation, rash, parestheia (a sensation of tingling, pricking, or numbness of a person's skin with no apparent long-term physical

effect), and abnormal vision. These side effects tend to decrease with continued treatment. As with other antidepressants, the US Federal Drug Administration requires that all providers who use this medication let patients know about a possible increased risk of suicidality, particularly in the initial weeks of treatment and in individuals under age 25. Risk of self harm and all side effects will be closely monitored. Medication managers will titrate medication as indicated in the protocol to minimize and/or reduce side effects.

Abrupt discontinuation of sertraline can also be associated with withdrawal symptoms, such as depressed mood, irritability, moodiness, dizziness, pins and needles feelings, anxiety, confusion, headache, sluggishness, nightmares, vertigo, vomiting, tremor, and insomnia. Patients are asked to contact their study medication provider and/or the investigator before discontinuing the study medication.

For those patients who receive PE, increased distress may occur during therapy procedures. However, these increases tend to decrease with continued treatment. Patients will be monitored for all side effects. All patients will receive at least one active treatment (PE or SERT). As such, placebo does not involve additional risk.

All staff conducting interviews and study procedures have experience with PTSD populations. They will work with the patient to reduce distress at the time of any exacerbations and will end procedures if in the best interest of the patient. Patients will be made aware that they can request to end a procedure at any time and can choose not to respond to interview or self report items if they choose. Blood will be drawn by trained personnel in a resting position in order to minimize potential discomfort.

The Primary Investigator (PI) and other study staff and clinical care providers will be available should the patient require additional assistance due to distress or side effects.

Magnetic Resonance Imaging:
There is little risk to participating in the fMRI research study tasks other than boredom or mild subjective anxiety. The image set used in the emotional regulation task contains images that you may find disturbing or psychologically troubling. If at any time during the task you feel these images are too disturbing to you, you can discontinue the task. Additionally, the investigator or his investigative team (all mental health providers, psychiatrists/psychologists) will be available during and after all behavioral tasks in order to evaluate and recommend treatment if necessary for any anxiety or panic that may occur.

Magnetic resonance imaging (MRI) is non-invasive, widely used and safe. There is a minor risk of discomfort or anxiety from being in the confined space of the MRI scanner. Study team will provide pads and blankets to make patients as comfortable as possible. Patients may become anxious due to the loud noise (below) and images (see above) that are involved in this study. Patients are able to communicate with the MRI technologist/operator and research staff via an intercom and may self-trigger an alarm at any time to stop the scanner and alert the research staff. Patients will be constantly monitored for any side effects and will be treated appropriately by physicians and nurses available. Patients are reminded that they may choose to terminate this procedure at any time. If the patient is not able to tolerate the procedure, the scan will be stopped immediately. A mental health professional, associated with the study will be available to evaluate and discuss this experience and the patients' reactions with them immediately, or if they prefer, at a later time.

The MRI scanner makes loud, vibrating noises. Patients will wear foam earplugs to reduce the loud noises made by the scanner and prevent any hearing damage. Some studies, like this one, have the potential to cause "peripheral nerve stimulation" (PNS). PNS is a light touching sensation on the skin surface, lasting only for a few seconds. It may cause mild discomfort, but is not harmful to patients. The fMRI machine is operated within the Food and Drug Administration (FDA) guidelines so the potential for causing Peripheral Nerve Stimulation is low. Sometimes, participants report a temporary, slight dizziness, light-headedness, or nausea during or

immediately after the scanning session. If patients feel dizzy or light-headed, study staff will have them get up slowly from the scanner.

Because the strong electromagnetic fields can move metal objects and cause heating, there is a risk that loose objects (jewelry, keys) outside your body could be accelerated by the magnetic field and strike patients, causing you injury. There is also a risk that the magnetic fields could disturb a metal fragment in patients' bodies, interfere with an implanted device, such as a pacemaker or neurostimulator, or cause metal (including foil-backed medication patches) on or in patients 'bodies to heat up, causing them harm. Study staff keep the environment around the MRI scanner completely free of loose metal objects that could be moved by the magnetic field, and we will make sure that patients have no metal on their bodies that could be affected by the MRI scanner. We will also ask patients questions and have them complete an MRI screening form to make sure that they have no metal inside their bodies that would cause them harm during the MRI scan.

There is the potential that a magnetic resonance image may reveal an abnormality that is already in a patient's body, such as a cyst or tumor. The investigators on this project are not trained to find abnormalities on an fMRI scan. We do not expect to report back to patients about any of the results from your fMRI scans. However, if we believe that we have found a medical problem or something abnormal in a patient's fMRI scan, we will contact the patient and will help him/her get medical follow-up for the problem. Many such abnormalities are not clinically significant, but the patient may need or want to investigate them further. Such a finding might require additional studies, and maybe even treatment, which would not be paid for by the investigators, the sponsor, or the University of Michigan. The type of scans we will use are not very sensitive to many abnormalities. The scanning procedures used for this study will not be read by a specialist trained to make medical diagnoses from the scan. That is, even if there is an abnormality in a patient's body, it is likely that it would not be discovered by the people who inspect the images. Therefore, it is likely that any abnormality that a patient may currently have will not be revealed by the images obtained in this experiment. If a patient has any current health concerns, he/she should consult his/her doctor. Discussion of this will occur during informed consent to ensure patient understands that these research scans should not be used for clinical purposes.

Pregnant women will not be allowed to participate in the fMRI portion of this study. Urine pregnancy tests will be performed. If this pregnancy test is positive, you will be removed from the fMRI portion of the study.

**Data Management and Analyses**

**Data Management.** All PHI will be managed within each site. This will include contact information and protected electronic crosswalk files connecting returnee names to research ID numbers. All research data will be identified by research ID only. All data with the exception of fMRI data will be remotely entered into Velos. The Velos eResearch servers are physically located in the University of Michigan Medical School Information Systems (MSIS) data center. Physical security is provided in a professionally managed and equipped data center with tightly controlled access. Remote data access employs SSL encryption and role-based access mechanisms. Role-based access to the application, the database, and the underlying systems infrastructure rigorously comply with industry best practices and meet HIPAA security and privacy requirements, governed by HIPAA's "minimum necessary" principle. The application provides audit trails on user access to and modification of data. Data Clarification Forms will be issued and tracked, with updates made to the database as data is verified by the site. In addition, standard reports will be provided to monitor site performance, assess progress of the trial, and for safety reporting purposes. Upon completion of the study and after resolution of any outstanding data issues, the database will be locked. Study project data can then be securely transferred via password protected compressed files or via the B2B secure file transfer process supported by the University of Michigan's Medical Center Information Technology group.

Copies of coded fMRI data will not be stored in the Velos database at MICHR, but will be transferred for purpose of analysis to the Psychiatry Affective Neuroimaging Laboratory at the Rachel Upjohn Building at the University of Michigan. Copies of fMRI data files will reside on a firewall and password-protected secure

server within the Psychiatry Affective Neuroimaging Laboratory with limited access (SSH only) to the internet. In addition, de-identified data may be sent to the other participating research sites (the VA San Diego Healthcare System, VA Charleston Healthcare System, and Massachusetts General Hospital) for the purposes of data analysis and dissemination. The information collected from the study is stored in a secure area and will not be made a part of the subject's medical record. Subject's name or other personal identifier will not appear on any of the research materials. All data is coded by research ID only. Only trained personnel with password access will access data for purposes of processing and analysis.

**Power Analysis.** Our hypotheses are that all three interventions will be effective in reducing PTSD related symptoms, with PE/SERT being most effective, followed by PE/PLB, and then by SERT. The study is powered to detect outcome differences between the **PE/PLB** compared with **SERT** to directly assess the effect of PE relative to sertraline, and **PE/SERT** compared with **PE/PLB** to assess the augmentation effect of SERT to PE. We hypothesize that the effect sizes between the two comparisons to be similar; i.e., PE effect relative to sertraline will be similar to the augmentation effect of sertraline to PE. CAPS scores will serve as the primary outcome for the study. Accepted standards for estimating clinically significant and reliable difference/change are based on the reliability of the measure [111]. Given estimates for test-retest reliability for the CAPS [112], a conservative estimate of clinically reliable PE effect is 11.4 points. With a standard deviation for the CAPS from Dr. Rauch's current OEF/OIF/OND treatment trial of N = 24, the clinically meaningful and detectable standardized effect size (cohen's *d*) is 0.48. To detect this effect size as a between-group difference at 24 weeks after treatment initiation with 90% power using a 0.025 significance level test (adjusted for the pairs of comparison) based on a mixed-effects model, adjusting for baseline values of the outcome variable with an assumed correlation of 0.5 between the repeated measures and an average of 10 participants per therapist with 0.03 within-therapist correlation, each group requires 103 participants. With an estimated 30% drop by 24 months follow-up (primary measurement time) based on Dr. Rauch's previous treatment trial, each group requires 147 participants (N = 441). Because we expect even the least effective group (SERT) to show an effect size as large as the assumed clinically meaningful effect size of 11.4 points, the proposed sample size will give more than 90% power to detect pre to post treatment effect across all three intervention groups.

**Primary Symptom Outcomes.** As relevant in analyses below, treatment responder is defined as a 50% or more reduction in CAPS from Intake Week to Wk 24. All measures of change will utilize residualized gain scores [113] to account for repeated assessments. The primary endpoint will be Week 24 with parallel analyses conducted for week 12 to examine early response.

Baseline Analysis and Covariate Adjustment. Because randomization does not guarantee comparability across groups, the three groups will be compared to ensure reasonable similarity in the distributions of their baseline (or intake) characteristics. We will examine and compare the distribution of various baseline variables including demographic variables such as age, gender and race and intake CAPS scores using analysis of variance for continuous variables and chi-square test for categorical variables. Variables showing differences across the groups at a 0.15 significance level will be included in the primary analysis as potential covariates.

*Our primary hypothesis is that PE/PLB, compared with SERT, will result in larger reductions of PTSD, general anxiety, and depression, larger increases in function and more remission, increases in cortisol in RTA, and similarly for PE/SERT compared with PE/PLB.* Primary outcome will be the change from baseline in CAPS scores at Wk 24. Means and mean changes from baseline for each group as well as the mean difference between pairs of each group will be reported, along with their 95% confidence intervals. The primary outcomes will be compared using a linear mixed-effects model with the combined data from all three groups. A mixed-effects model is needed to address the potential within-therapist correlation, where we will include the therapists as random effects. For SERT group patients, the pharmacotherapist providing the EMM will be considered as the cluster. The model will include two indicators for PE/PLB group and PE/SERT group. The parameter estimate of the PE/PLB indicator will estimate the effect of PE/PLB to SERT at Wk 24, and contrasting the parameter estimates of the two indicators of PE/SERT and PE/PLB will allow us to estimate and test for the effect of PE/SERT to PE/PLB. Though the patients are randomized into three groups, we will obtain covariate adjusted estimate of the between group differences, in which the covariates will include baseline CAPS scores, OEF/OIF/OND status, marital status, substance or alcohol abuse, and other baseline variables assessed to be

potential confounders in the baseline analysis. Similar analyses will be done using other secondary outcome variables of interest such as depression, general anxiety, alcohol and substance use, general assessment of function, and collection of behaviorally based function measures. Rates of remission across the three groups will be compared using generalized linear mixed-effect model with logit link and two indicators for the two PE intervention groups to adjust for within-therapist correlation.

Non-adherence. While our primary aim will focus on symptom change, we will also examine differential drop out/early response and treatment adherence. *Our explorative hypothesis is that PE/SERT, compared with either SERT or PE/PLB, will have more treatment drop.* These comparisons will be made using treatment drop as the response variable and using generalized linear mixed-effect model with logit link and two indicators for the three treatment groups. The primary analysis will be done by intent-to-treat with participants retained in their randomized groups regardless of their treatment adherence status. We will, however, also do additional as-treated analyses for which we will define the groups by the actual intervention each participant is randomized to, but the outcomes will be censored at the time when participants switched or stopped the treatment to which they were assigned. For participants in the PE/PLB or PE/SERT group, data will be censored at the time when both therapy and medication (SERT or placebo) prematurely stopped. We note that in this study, if some patients in SERT group stop or switch medication early due to side-effects or intolerance, as-treated analysis may give a better outcome estimate for SERT group, thus likely to give an under-estimate of the PE effect compared with the intent-to-treat analysis.

Missing Data. The extent of missing outcome values at each measurement times will be assessed by the three study groups. Although we do not expect missing baseline values of more than 2 or 3%, we will assess the amount of missing data in baseline covariates as well. If the extent of missing data are greater than 5% (we conservatively assumed 30% to drop out of the assigned treatment, but we will make every effort to collect their follow-up data), we will do sensitivity analysis of the effect where we will impute the missing data using a multivariate sequential regression approach. The method can impute for nearly all types of data (binary, categorical, count, and continuous) and imputes missing values for each individual conditional on all the values observed for that individual, and thus exploits correlational structure among covariates that include all other variables observed or imputed. We will then analyze the multiply imputed data to obtain outcome differences between PE/PLB and SERT and between PE/SERT and PE/PLB, and examine for any substantive differences in the conclusions based on the imputed data analysis versus the original data analysis.

Longitudinal Outcome Comparison. We will compare outcomes over the 12-month follow-up time in order to have a good understanding of the pace of recovery and to compare retention trends after intervention. We will plot cross-sectional means of various outcome measures at each measurement time as well as outcomes over time for each individual to assess individual trends. We will use repeated measures mixed-effect model to assess and compare outcome trends over time within each group as well as across the three groups. The graphical exploration will guide the appropriate models describing the trajectory of outcomes, especially how the time and the correlation within participants will be modeled. This analysis will allow us to assess when the outcome differences occur and whether the differences remain over time using various ways to model time. In particular, if the graphical exploration shows clinically meaningfully different trends over time across the three groups, we will model the trends separately for the three groups. Similar analyses will be done using other secondary outcome variables.

Genetic Association with treatment response. ***DNA cleaning and Quality Control*** *process described in the Neurobiological Measures Supplement in appendix*. We will investigate DNA markers as potential predictors of treatment response ("pharmacogenetic" analyses) in subjects treated with SERT alone or together with PE (n=294), and subjects treated with PE/PLB or PE/SERT (n=294). Since n=147 receive both treatments, analyses of SERT will include "presence of PE" as a covariate, and vice versa. We will examine i) Replications of specific genetic variants previously implicated in SSRI responses in depression, ii) Larger numbers of SNPs in candidate genes, and iii) Preliminary genome-wide association data. Quantitative Trait association analyses, which will provide greater power, will be performed with the decrease in PTSD symptoms as a continuous variable in linear regression models. *Association Analyses* will be conducted in PLINK, unadjusted and adjusted for potential confounders including age, number of deployments and lifetime combat exposure (CES),

education, and co-morbidity, presence of the other treatment modality, as well as ancestry "scores" calculated by principal components of SNP data. A hierarchical series of analyses will examine gene association with SERT and PE/PLB response.

***i) Replications.*** We will first examine replications of ~25 specific gene variants previously reported in SSRI treatment for MDD (e.g. 5-HTTLPR and SNPs in *HTR2A, GRIK4, KCNK2, OPRM1, SLC6A4, FKBP5*, genotyped in our custom array). While N of 294 is small in this initial discovery sample, assuming 50% SERT response rate, it should allow for 80% power for detection of gene effects with an odds ratio of approximately 1.5-1.6 at Bonferonni adjusted p<.002 (25 comparisons) at alpha .05 and MAF .10-.25. We will also employ more sensitive multiple comparison correction methods (e.g. spectral decomposition ([114]), false discovery rate (FDR, [115]). Trend level effects are informative for future replication /meta-analyses. ***ii.) Candidate gene array.*** We will also examine candidate gene association in additional ~4500 SNPs included in our custom Illumina array. ***iii.) GWAS.*** We will perform preliminary genome-wide analyses, in our discovery cohort using Illumina 1M-Omni platform and archive these discovery data for future replication. Genotypes will be imputed using MACH[116] software, widely used for genotype imputation for GWAS, and association analyses performed as above using PLINK. We do not expect our initial discovery datasets of ~300 to be adequately powered to detect GWAS significance, but our data analyses and genotype / phenotype data will be archived according to GWAS database guidelines, and will then be available for qualified DOD/VA research groups (after obtaining appropriate HRPO and IRB permissions) conducting replication /meta-analyses. ***Neuroimaging Genetics*** analyses briefly described in *Neurobiological Measures Supplement in appendix.*

Gene Expression Analyses. Statistical strategies will be employed to identify patterns of gene expression associated with treatment responses, including a) pre-treatment gene expression that predict treatment response to SERT and PE/PLB, and b) changes in gene expression patterns from pre-post treatment that are associated with PTSD symptom response. We will examine the relationship of changes in gene expression in specific hypothesized categories of genes, including inflammatory, neuroendocrine, signal transduction, growth factor system genes, as well as overall changes in gene expression in patients treated with SERT (potentially direct pharmacological actions on leukocytes) and changes specific to decrease in PTSD symptoms following treatment with SERT and/or PE. We will use unsupervised hierarchical cluster analyses (i.e. blind to treatment or response status) to categorize patients before and after SERT treatment to examine pharmacological overall effects of SERT on hypothesized and whole genome gene expression. We will then examine patients who respond to either SERT or PE (separately and together) in categorical responder analyses, and also in linear regression models of continuous measures of response (CAPS) to identify specific patterns of gene expression changes that predict treatment responses to either SERT or PE. Validation studies in quantitative RT-PCR will examine changes in specific mRNA species identified in microarray data.

Neuroimaging Data Analysis. *fMR Data Preprocessing (including magnetic susceptibility issues), and fMRI Data Analysis* are *described in Neurobiological Measures Supplement.* To characterize the effects of SERT, PE/SERT and PE/PLB on amygdala, insula, and prefrontal function (e.g., vmPFC), we will extract BOLD signal for each condition and calculate percent signal change (PSC), as an index of amygdala, insula, and prefrontal cortex (PFC) activation. For example, from the data of the EFAT and ERT tasks describe above, will employ basic analyses of brain activation using *t*-tests and ANOVAs to examine ERT (Reappraise > Maintain) and EFAT (match Fear/Angry > Neutral) activations. In the EFAT, we will use the Neutral Faces condition as baseline, and calculate PSC in terms of Fear/Angry vs. Neutral Faces. Similarly, in the ERT, we will use the Maintain condition as baseline, and calculate PSC in terms of Reappraise vs. Maintain Task. We will examine differences in fMRI BOLD signal during ERT and EFAT between PTSD and CC groups at baseline/pre-treatment (Intake Week) and in the PTSD group at the Intake Week and Wk 24 with PE/PLB, SERT, and PE/SERT. We will perform pre and post treatment comparisons within each group, comparing activation within the amygdala, ACC, dMPFC, dLPFC, insula, vPFC, and examine relationships between pre-post change in activation in these regions and CAPS pre-post change in PTSD severity using Pearson/Spearman correlational analyses. We will explore additional findings from the other face tasks, the VMT and RST of brain function data collected.

a) We will first test if amygdala or PFC activation at baseline (pre-treatment) can be used as a *predictor of treatment response* with a logistic regression analysis, as described by Hosmer and Lemeshow [117]. In this model, the dependent variable is the dichotomous treatment response variable (responder or non-responder), and the independent or predictor variable is the pre-treatment amygdala/vmPFC BOLD signal change to Fearful Faces and Reappraise Task. We will also include age, gender, age of onset, duration of illness, and pre-treatment CAPS scores as additional potential predictor variables in the model. The model produces the coefficient (β) of each predictor variable, and this coefficient is tested for significance with a Wald test using a Z statistic, which is then squared yielding a Wald statistic with a chi-square distribution. The α level will be set at $p < 0.05$, two-tailed.

b) Next, we will examine treatment change and predictors of treatment response – exploratory whole-brain voxel-by-voxel analysis: In addition to the directed amygdala, insula and PFC ROI analysis, we will employ a voxel-wise analysis of BOLD signal change across the entire brain to explore other brain effects and generate novel hypotheses for subsequent studies. With the availability of a relatively large sample size in this study, we will have adequate power to formally test other relevant linear sub-group analyses (responders vs. non-responders), main effect of time (pre vs. post), main effect of symptom change (pre vs. post CAPS score reduction), and group x time interactions. Significance will be set at $p < 0.05$, corrected for multiple comparisons based on the False Discovery Rate [118].

*c) Finally, we will examine correlations between treatment response and functional MRI data*: We hypothesize that changes in amygdala-vmPFC function over treatment will predict treatment response. Positive responses will be defined as 50% or more reduction in CAPS. We will use t-test to compare pre-post treatment change in amygdala-insula reactivity to social threat in responders to SERT versus non-responders to SERT (reduction in amgydala reactivity is expected in responders), and vmPFC engagement during emotion regulation between responders to PE/PLB and non-responders to PE/PLB (enhancement of vMPFC response is expected in responders) but not in non-responders. We also use correlation analyses to assess if *higher pre-treatment amygdala reactivity to threat faces* is associated with a greater reduction in PTSD symptoms in response to SERT, and *lower pre-treatment vmPFC response during emotion regulation* is associated with greater reduction in PTSD symptom in response to PE.