IRB #3166: An electrophysiological predictor of SSRI response in Veterans with PTSD

Funding Agency: VA Clinical Sciences R&D

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Abstract

OBJECTIVES: The primary aim of the proposed project is to investigate the usefulness of the Loudness Dependence of Auditory Evoked Potentials (LDAEP) for predicting those individuals who will most likely show a favorable or adverse response to SSRIs. A secondary aim is to determine LDAEP cut-off values that would enable a clinician to make an individualized SSRI treatment decision based on a patient's LDAEP score. A tertiary aim is to evaluate LDAEP as an objective outcome measure of SSRI response. An exploratory aim will test whether the relationships between LDAEP and SSRI response differ for men and women and whether men and women have different optimal LDAEP cut off scores.

RESEARCH DESIGN: A sample of 94 trauma-exposed Veterans (50% male; 50% female) will participate in a 12-week sertraline trial preceded by a 2-week single-blinded placebo lead-in phase. Embedded in this study are four assessment sessions: pre-placebo, pre-sertraline, and one and three months after initiating sertraline.

METHODOLOGY: The procedures conducted during each assessment session will be mostly the same. Participants will: a) engage in the ERP procedure that will yield the LDAEP score, b) complete a battery of symptom outcome measures including measures of PTSD and depressive symptom severity [with Clinician Administered PTSD scale (CAPS) and HAMD scores c) complete self-report assessments of current medication use, medication adherence, and side effects, and d) provide a blood sample for measurement of SSRI level and platelet measurement of serotonin reuptake. Additional adherence data will be collected via pill counts.

FINDINGS/PROGRESS TO DATE: Recruitment for this study began in June 2019. Of the 70 participants that have been enrolled to date, sixteen have been randomized.

CLINICAL RELATIONSHIPS: Findings from this study may contribute to development of a precision-medicine approach when choosing an initial psychopharmacological intervention for Veterans with PTSD or MDD. Development of a biological screening method that can be used to identify those individuals who are most likely to be clinically responsive to an SSRI and those who are more likely to benefit from a different intervention could save the medication provider and patient weeks of waiting to see whether or not the patient will be responsive to an SSRI. It may also aid in avoiding adverse reactions to SSRIs. The proposed methodology is noninvasive and the test can be administered in about 40 minutes. The costs, expertise and time necessary to implement this test in usual care would conceivably be comparable to that of an electrocardiogram (EKG).

IMPACT/SIGNIFICANCE: N/A

List of Abbreviations

5HT	Serotonin
AAHRPP	Association for the Accreditation of Human Research Protection Programs
Ag/AgCl	Silver/Silver Chloride
AUC	Area under curve
AUDIT	Alcohol Use Disorders Identification Test
BUSM	Boston University School of Medicine
CAPS-5	Clinician Administered PTSD Scale for DSM-5
CAVHAS	Central Arkansas VA Healthcare System
CDA-II	Career Development Award-II
CIMIT	Center for Integration of Medicine and Innovative Technology
CSR&D	Clinical Sciences Research and Development
CSS-RS	Columbia Suicide Severity Rating Scale
DFAQ-CU	Daily Sessions, Frequency, Age of Onset, and Quantity of Cannabis Use Inventory
DASS-21	Depression, Anxiety, and Stress Scale-21
DNA	Deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual for Mental Disorders, 5th edition
EDTA	Ethylenediaminetetraacetic acid
EEG	Electroencephalogram
EKG	Electrocardiogram
EOG	Electrooculogram
ERP	Event-related potential
FDA	Food and Drug Administration
FTND	Fagerström Test for Nicotine Dependence
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GSI	Global Severity Index
HAM-D	Hamilton Depression Scale
HPLC	High-performance liquid chromatography
IRB	Institutional Review Board
LDAEP	Loudness dependence of auditory evoked potentials
LEC-5	Life Events Checklist-5
LIMS	Laboratory Information System
MAVERIC	Massachusetts Veterans Epidemiological Research and Information Center
MDD	Major Depressive Disorder
M&IE	Meals & incidental expenses
MEMS caps	Medication event monitoring system caps
N1	N1 component of an ERP represents a negative (“N”) response that occurs approximately 100 (“1”) msec following onset of a stimulus
N1/P2	Ratio of N1 component of an ERP / P2 component of an ERP
NCPTSD	National Center for PTSD
NCPTSD-WHSD	National Center for PTSD, Women’s Health Sciences Division
NIMH	National Institute of Mental Health
P2	P2 component of an ERP represents a positive (“P”) response that occurs approximately 200 (“2”) msec following onset of a stimulus

P300	P300 component of an ERP represents a positive (“P”) response that occurs approximately 300 msec following onset of a stimulus
PAL	Pharmacogenomics Analysis Laboratory
PCL-5	PTSD Checklist for DSM-5
PI	Principal Investigator
PTSD	Posttraumatic Stress Disorder
QIDS-SR	Quick Inventory of Depressive Symptomatology-Self Report
RCT	Randomized controlled trial
RNA	Ribonucleic acid
SCID-5	Structured Clinical Interview for DSM-5 Disorders
SCL-90-R	Symptom Checklist-90-Revised
SNRI	Serotonin-norepinephrine reuptake inhibitor
SPL	Sound pressure level
SSRI	Selective serotonin reuptake inhibitor
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
STIM	Neuroscan auditory stimulus software
TAU	Treatment as usual
TB	Terabyte
TLFB	Timeline Followback Method for Drugs, Cigarettes, and Marijuana
VA	Department of Veterans Affairs
VABHS	VA Boston Healthcare System
VHA	Veterans Health Administration

Contents

Protocol Title: An electrophysiological predictor of SSRI response in Veterans with PTSD (IRB# 3166)

- This study is expanding to include two study recruitment and participation sites: VA Boston and Ralph H Johnson VA Medical Center. Each site will be overseen by their local IRB and a single IRB waiver will be sought.

1.0 Introduction

(a) Background.

LDAEP and serotonergic transmission

The P2 component of an ERP represents a positive ("P") electrophysiological response that occurs approximately 200 ("2") msec following onset of a stimulus. It is thought to reflect the sensitivity of a gating mechanism that regulates sensory input to the cortex.[20] Using a 4-tone, stimulus-intensity-modulation (i.e., augmenting-reducing) paradigm, the slope of the change in P2 response amplitude across a series of increasing sound intensity levels (74, 84, 94, and 104 dB) is calculated and represents the LDAEP.[38] A reduction in the amplitude of the P2 component at higher tone intensity levels produces a shallow LDAEP. This ERP response pattern of decreased intensity dependence, or "reducing", may reflect a protectively tuned sensory system that protects the organism from sensory overload. In contrast, the opposite pattern of an increasing LDAEP (i.e., "augmenting" or increased intensity dependence) is thought to reflect a cortex tuned to "seek out" increases in stimulus intensity.[39-41] LDAEP is calculated by different research groups in one of two ways: using P2 alone or by computing the ratio of the ERP N1 and P2 (N1/P2) components. As findings from studies using these methods largely parallel each other, we propose to evaluate both scoring methods as predictors of SSRI response but will refer to them both simply as "LDAEP." LDAEP has excellent test-retest reliability (r's > .76 for test-retest intervals of 1 week to 1 year)[39-41] in the absence of intervention.

There is substantial evidence from human studies and rodent models demonstrating that aberrantly strong or weak intensity dependence reflect inverse abnormalities in central serotonergic (5-HT) transmission,[27] which are also thought to play a key role in the pathophysiology of anxiety and depression.[42, 43] Specifically, increased LDAEP appears to reflect low 5-HT neurotransmission in the primary auditory cortex, whereas decreased LDAEP appears to reflect high 5-HT neurotransmission in this brain region. Direct support for this position comes from animal studies,[44, 45] while human studies provide indirect support,[27, 42, 43]

Abstinent users of 'ecstasy' (methylenedioxy-methamphetamine), a drug with neurotoxic effects on central serotonergic terminals, show increased LDAEP compared to normal controls.[46, 47] At 18-month follow-up, prior ecstasy use remained associated with increased LDAEP.[48] Changes in ecstasy use at follow-up were not related to changes in the LDAEP, suggesting that the increased intensity dependence evidenced by ecstasy

users represented a pre-existing trait or an irreversible change in 5-HT function induced by ecstasy use.

Abnormalities in LDAEP have been found in several neuropsychiatric disorders. Increased LDAEP has been observed in bipolar affective disorder,[49] histrionic personality disorder,[50] fibromyalgia [51] and migraine conditions.[52] Decreased LDAEP has been reported in unipolar depression [49] and generalized anxiety disorder [53] In PTSD, some studies have found increased LDAEP,[19, 20, 54] while others found decreased LDAEP.[55, 56]

It is possible that the heterogeneity in LDAEP across PTSD studies represents biological, and potentially genetically based, variations in PTSD endophenotypes. The notion that different subpopulations of clinical patients specified by a DSM diagnosis will show distinct biological abnormalities (e.g., specific alterations in 5-HT regulation that influence LDAEP) has been discussed in a study that found LDAEP abnormalities limited to a subgroup of patients in a study of depression.[57] The authors suggested that such clinical subtypes reflect unique genetic underpinnings, although it is also possible that environmentally induced or epigenetic changes in underlying biological processes play a role.

LDAEP as a measure of an underlying mechanism predicting SSRI response
Compelling evidence for an inverse relationship between 5-HT neurotransmission and LDAEP comes from several studies demonstrating a link between increased pre-treatment LDAEP and a favorable response to SSRIs in depressed individuals.[10-18] Notably, this association was demonstrated despite mixed findings regarding whether LDAEP differed between groups of individuals with and without depression.[10] Although there is growing evidence for the potential usefulness of LDAEP as a predictor of SSRI response, it is important to note several limitations of the work to date. First, the research has been limited to studies of depression and has not included populations with primary diagnoses of PTSD or anxiety disorders. Second, most of these studies have contrasted the top half of their sample (i.e., stronger LDAEP) with the bottom half.[18] Consequently, the mid-point used to form the high and low groups is study specific and the results cannot be translated into clinically useful cutoff scores for predicting potential SSRI benefit in individual patients. Third, with few exceptions,[13] most of this research has focused on LDAEP as a predictor of SSRI response and has not examined whether LDAEP normalizes as a function of successful SSRI treatment. Such information may increase our understanding the mechanism(s) underlying clinical response. Finally, no studies have examined gender differences in the association between LDAEP and SSRI response. Because women are more likely to respond to SSRIs than men,[58] and there are gender differences in other electrophysiological predictors of SSRI response,[59, 60] the proposed study will explore whether men and women have different optimal cut-off LDAEP scores that best predict SSRI response.

LDAEP may be selectively related to the unique mechanisms of action of SSRIs, as LDAEP has been found to have an inverse relationship with SNRI treatment outcome, i.e., reduced LDAEP predicts a more positive outcome in response to SNRIs.[12, 15, 37] The

different findings for increased versus reduced LDAEP underscore the position of Linka and colleagues regarding the clinical heterogeneity of depression, i.e., that subgroups of depressed patients may have different underlying pathophysiological processes that require different treatments (e.g., SSRIs vs. SNRIs).[57] As suggested by Linka et al.,[37] reduced LDAEP could be used as an indicator for the use of an SNRI rather than an SSRI. In addition, a recent case report suggests that low LDAEP is an indicator of who should *not* be given an SSRI; a patient diagnosed with major depressive disorder who showed a reduced LDAEP experienced significant side effects in response to SSRI treatment, but not in response to tianeptine, a selective serotonin re-uptake enhancer.[61]

(b) Significance. Explain the potential importance of the proposed work and identify any unique ideas or potential contributions that might result from this study.

The costs associated with PTSD and trauma-related distress are substantial; posttraumatic stress disorder (PTSD) impacts work productivity, relationship functioning, and physical health, with estimated annual costs to VA in disability payments of $4.28 billion.[28] Ineffective treatments substantially contribute to the perpetuation of chronic PTSD symptoms and functional impairment in Veterans and, as a consequence, the enormous public health burden associated with PTSD.[29-32]

Selective serotonin reuptake inhibitors (SSRIs) such as sertraline, citalopram, fluoxetine, and paroxetine are the most commonly prescribed medications for PTSD, as well as clinical depression, which is often co-morbid with PTSD.[33-35] Among VA healthcare users, approximately 60% of Veterans with PTSD are prescribed SSRIs[24], however, many patients are unresponsive.[2, 3, 36] Typical response rates are 50-55% and remission rates are only 30-35%. Currently, there is no way to determine who will benefit from an SSRI. Determining whether SSRI treatment will be efficacious for a given individual is accomplished by 'trial-and-error'. Typically, patients go through a several-week process of slowly increasing the SSRI dose to reach the hypothesized therapeutic level, only to discover that the SSRI is not effective or causes significant side effects. Consequently, an individual who was initially hesitant to take a psychotropic medication may not be willing to try a second medication or may drop out of treatment entirely.

Development of a method for predicting who is or is not likely to benefit from SSRI treatment could greatly facilitate the therapeutic process and thereby enhance quality of life and expedite a return to productivity. Ultimately, a very large number of individuals with a range of psychiatric diagnoses could potentially benefit from the proposed screening method. The impact on the healthcare system of more efficient and effective targeting of SSRIs would be substantial.

The goal of the proposed work is to develop a physiological screening method that can be used to predict who is likely to be clinically responsive to an SSRI. The proposed study will investigate whether a brief pre-treatment auditory event-related potentials (ERPs) procedure offers a means for predicting treatment response to an SSRI. Specifically, the slope of P2 and N1/P2 amplitudes, in response to a series of

increasingly loud tones (i.e., LDAEP), appears to be strongly influenced by brain serotonin level. LDAEP holds considerable promise as a potential indicator of the brain's responsiveness to SSRIs. In addition, although the goal of this proposal is to identify who will and will not respond to an SSRI, there is also evidence to suggest that the LDAEP profile for SSRI non-responders may predict a positive response to a serotonin-noradrenalin reuptake inhibitor (SNRI).[12, 15, 37] Therefore, the ultimate goal of this program of research is not solely to identify people for whom an SSRI will or will not work. Rather, it is a necessary first step toward a rigorous multi-site study aimed at testing whether pre-treatment LDAEP can be used to guide selections within a range of potential treatments.

Precision medicine is an approach to healthcare in which individual differences are considered when developing treatment plans. Of note, the proposed innovative LDAEP methodology is noninvasive and can be administered in about 40 minutes. The cost, expertise and time necessary to implement this test in usual care could be comparable to that of obtaining an electrocardiogram (EKG). Incorporation of pre-treatment predictors of treatment success, such as LDAEP, into psychiatry would be akin to the use of technological advances (e.g., pharmacogenomics and imaging) that routinely inform treatment decisions in oncology. An LDAEP cut-off score that can reliably predict who is most or least likely to benefit from an SSRI would save prescribers and patients weeks of waiting to see whether the patient will be SSRI responsive. It may also aid in avoiding adverse reactions to SSRIs such as irritability, sleep disturbance, or akathisia.

(c) Relevance to Veterans Health.

This study will contribute to the development of a precision-medicine approach to prescribing pharmaceuticals to Veterans with PTSD and MDD. LDAEP is a measure that shows great scientific promise as a pretreatment indicator of: a) clinical response to SSRI treatment, and b) SSRI-related adverse outcomes. Because most of the extant work on LDAEP has contrasted the top half of respective samples (i.e., higher LDAEP) with the bottom half,[18] the results cannot be translated into clinical cutoff scores that could be used to suggest whether a given patient is likely to benefit from an SSRI. Therefore, Aim 2 is a critical step toward using LDAEP as a pretreatment assessment measure that could be implemented in clinical care settings. Furthermore, although there is growing evidence for the potential utility of LDAEP as a predictor of SSRI response in depressed individuals, the proposed work is the first, as far as we are aware, that has not focused exclusively on depression and instead focuses on trauma-exposed individuals with PTSD or MDD, diagnoses that causes significant functional impairment to a large number of Veterans.

SUMMARY, CURRENT STATUS OF THE FIELD, AND PROPOSED RESEARCH

A significant proportion of patients prescribed SSRIs receive minimal or no benefit[2, 3, 62] and currently there is no rapid or uncomplicated way to determine who will or will not likely benefit from this class of medications. LDAEP appears to be strongly influenced

by serotonin level and holds considerable promise as an indicator of clinical responsiveness to SSRIs. Although studies focused on examining group differences in LDAEP between patients with and without PTSD or depression have yielded mixed results,[10, 19, 20, 54, 55] studies assessing LDAEP as a predictor of SSRI response in individuals with MDD have found compelling support for the usefulness of this measure.[10-18] Studies in PTSD have yet to be undertaken. The proposed study is an innovative and logical next step towards translating laboratory findings into clinical practice. The study will provide the foundation for a future multi-site RCT that would test the clinical utility of pretreatment LDAEP in guiding providers in the choice of medications with the highest likelihood of success and lowest risk of adverse outcomes.

The primary aim of the proposed work is to determine the strength of the relationship between LDAEP and clinical response to SSRI treatment. A secondary goal is to determine LDAEP cut-off value(s) that would enable clinicians to make SSRI treatment decisions for patients based on this technology. If the proposed biological screening method is able to provide a prognostic indicator of positive vs. negative treatment response to SSRIs, providers will have a relatively quick, non-invasive, and simple tool at their disposal to facilitate treatment selection. A third goal is to assess the usefulness of changes in LDAEP as an objective measure of treatment response to SSRIs. We also propose an exploratory aim to examine gender differences in the association between LDAEP and treatment response. Although we expect women and men to show similar relationships between LDAEP and clinical response to sertraline, optimal cut-off scores for LDAEP may differ for men and women.

2.0 Objectives

(a) Statement of the Problem.

Selective serotonin reuptake inhibitors (SSRIs) are prescribed to approximately 60% of Veterans with PTSD treated within the Veterans Health Administration (VHA).[23, 24] However, many patients are not responsive to SSRIs.[2, 3] Currently, there is no way to determine whether a particular patient will benefit from an SSRI; treatment is primarily accomplished through ‘trial and error’ over several weeks or months. The overarching aim of this project is to investigate the pre-treatment usefulness of a simple electrophysiological test [i.e., loudness dependence of auditory evoked potentials (LDAEP)] for predicting the likelihood of a favorable response to an SSRI.

(b) Hypotheses or Key Question.

The Specific Aims of the proposed study are:

Aim 1. To determine the strength of the relationship between LDAEP and clinical response to SSRI treatment.

Hypothesis 1: Higher pre-sertraline LDAEP will be associated with a positive response to sertraline, operationalized as a significantly greater reduction of PTSD or depressive symptoms measured at 1-month and 3-months following sertraline initiation.

Aim 2. To determine LDAEP cut-off values that would enable clinicians to make individualized SSRI treatment recommendations.

Aim 3. To assess the usefulness of change in LDAEP as an objective measure of SSRI response.

Hypothesis 2: Normalization of LDAEP from the pre-sertraline baseline to follow-up assessments will be associated with significantly greater reduction of PTSD or depressive symptoms at the respective assessment time points.

Exploratory Aim 4. To determine whether the relationship between LDAEP and clinical response to sertraline differs between men and women.

Exploratory Hypothesis 4: Although we expect women and men to show similar relationships between LDAEP and clinical response to sertraline, optimal cut-off scores for LDAEP may differ for men and women.

(c) Specific Objectives.

Immediate objectives:
Aim 1. To determine the strength of the relationship between LDAEP and clinical response to SSRI treatment.

Aim 2. To determine LDAEP cut-off values that would enable clinicians to make individualized SSRI treatment recommendations.

Aim 3. To assess the usefulness of change in LDAEP as an objective measure of SSRI response.

Exploratory Aim 4. To determine whether the relationship between LDAEP and clinical response to sertraline differs between men and women.

Long-term objectives:
Study findings will inform a precision-medicine approach to choosing initial interventions for Veterans with PTSD and/or MDD. Future directions for intermediary goals include: a) simplifying the technology so that LDAEP assessments can be easily implemented in a clinic setting by personnel without formal electrophysiological training; and b) conducting a multi-site randomized clinical trial to test whether pre-treatment LDAEP can guide participants toward different treatments that might be most effective [e.g., SSRI vs. serotonin-norepinephrine reuptake inhibition (SNRI)].

3.0 Study Procedures

3.1 Study Design

Project Management Plan and Timeline

A highly experienced and productive multidisciplinary team has been assembled with expertise in psychopathology, psychopharmacology, electrophysiology, primary care research, clinical trials, and statistical analysis. Many team members have previously collaborated. The study will begin with an infrastructure preparation stage, data will be collected for approximately 3.25 years, starting 3 months after funding begins. The final 6 months of funding will be dedicated to completing study analyses and preparing reports of findings for dissemination.

	Year 1				Year 2				Year 3				Year 4				Year 5				Year 6			
Activity	Q 1	Q 2	Q 3	Q 4	Q 1	Q 2	Q 3	Q 4	Q 1	Q 2	Q 3	Q 4	Q 1	Q 2	Q 3	Q 4	Q 1	Q 2	Q 3	Q 4	Q 1	Q 2	Q 3	Q 4
*Recruit, hire and train research staff	X												X	X										
**Finalize study materials and purchase materials	X												X											
**Develop data management system	X												X											
Recruit and run study participants		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Send genetic samples and serum SSRI assays to lab for analysis																							X	
Data entry and management		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Data analysis, manuscript submissions, & final report preparation																								X

* Y1Q1 reflects recruiting, hiring, and training research staff at VA Boston – Jamaica Plain Campus. Later quarters reflect recruiting, hiring, and training research staff at Ralph H Johnson (RHJ) VAMC PTC clinic, in Charleston, SC

**Y4Q1 reflects project modifications approved to add Ralph H Johnson (RHJ) VAMC PTC clinic, in Charleston, SC as a second study site.

To reach our goal of 94 eligible participants across both sites, we will enroll 2-3 participants/month who meet the study's inclusion/exclusion criteria. To meet our goal of 2-3 eligible participants per month, we will aim to conduct in-person screens on 3-4 individuals each month per site. Study participation will start after the informed consent process is completed during a remote or in-person consenting session and end immediately after the 3-month assessment for individuals who chose to continue on sertraline and transfer the oversight of their prescription to their primary care or psychiatry provider. For those who choose to stop taking sertraline after the study end, their participation will end approximately 3-5 weeks after the 3-month assessment (i.e., two weeks after having stopped sertraline completely).

RESEARCH DESIGN AND METHODS

Overview of Study Design

For individuals who meet study eligibility criteria during two in-person screening sessions, this study will be conducted within the context of a 14-week study that incorporates a 2-week, placebo lead-in phase followed by a 12-week sertraline trial. Throughout this trial, participants will complete self-report assessments and meet with the study psychiatrist about every two weeks. Diagnostic interviews will be administered at screening and at the point they wish to discontinue the study medication (typically week 14; 3 months after starting sertraline). Additional diagnostic interviews may be administered if the screening visit occurred more than 1 month prior to start of the placebo lead in (see below). The LDAEP task will be administered week 0 (pre-placebo) and at the point they wish to discontinue the study medication (typically week 14; week 14; 3 months after starting sertraline). Individuals who show a meaningful symptomatic reduction during the placebo lead-in phase [50% improvement on the PCL-5 and QIDS-SR] will be continued on placebo for the duration of the study and excluded from the primary analyses.

After the 2-week placebo lead-in phase, during which placebo pills of the same size, color and taste as the active drug will be administered, placebo-non responders will receive sertraline 25 mg daily for 2 weeks. Thereafter, sertraline will be increased flexibly by 25 to 50 mg per day (at a rate no higher than 50 mg per week) to achieve a total daily dose of 50 to 200 mg, based on clinical response and tolerability, with a maximum dose of 200 mg/d.[3] Subjects unable to tolerate higher doses may be dropped back to the previous dose and remain at that dose for the remainder of the study. (For individuals who are placebo responders initially, but worsen significantly (e.g., have a 25% increase on the PCL and/or QIDS from pre-sertraline assessment sustained for two visits, participants will be started on sertraline and follow the same dosing schedule

as participants who started sertraline at the pre-sertraline assessment. Sertraline taper plan will still begin at 3-month assessment or when clinically indicated.)

To monitor clinical response and tolerability, there will be brief clinic visits every two weeks (i.e., psychiatrist check-in visits) to check in with the psychiatrist and complete the PCL-5, QIDS-SR, Columbia Suicidality Severity Rating Scale (CSS-RS) (via interview with the psychiatrist), and a measure of side effects. At each of these psychiatrist check-in visits, self-reported medication adherence will be assessed, pill counts will take place and the presence of side effects will be queried. The adverse events tracking form will be used as needed to document and evaluate outcomes if an adverse event occurs. The FIBSER will be administered if side effects are reported. Medication side effects will be determined via a clinical interview, and the FIBSER will be used to assess global experience of side effects, as well as the frequency, intensity, and impairment attributed to each reported side effect. During weeks when a longer study assessment visit is scheduled (week 0, week 2, week 6, and week 14) or a longer battery of questionnaires will be administered, the procedures conducted within psychiatrist check-in visit will be embedded within this longer assessment session.

At the end of study treatment (i.e., 3 months post-sertraline [week 14] assessment visit), the default would be for participants to taper off of sertraline. At this point, there will be a taper period from sertraline in which participants will decrease their sertraline dose by 50mg/week for the number of weeks necessary (based on dose). During this taper period, whenever it is clinically indicated, participants will have regular contact with the study psychiatrist. Remote telephone or video psychiatrist check-in visits will occur regularly and as clinically indicated until 2 weeks after the participant is no longer taking any active drug. Should a participant experience intolerable side effects, or through discussion with the study team decide to discontinue sertraline for any reason, the participant and study team will work together to develop an appropriate taper regime as would be conducted in usual clinical care.

The following procedures will be conducted during this study at timepoints detailed below. Participants will: a) engage in the ERP procedure that will yield the LDAEP score, b) complete the proposed symptom outcome measures [i.e., CAPS-5, Hamilton Depression Scale (HAM-D) and a battery of self-report measures including the PCL-5 and measures to assess negative affect, depression, anxiety, and global distress], c) complete self-report assessments of current medication use, medication adherence, and side effects, d) provide a blood sample for measurement of SSRI level and platelet and plasma measurement of serotonin reuptake progesterone and its neuroactive metabolites (including allopregnanolone, pregnanolone, and 5α-DHP), estradiol, adrenocorticotropic hormone (ACTH), and norepinephrine, e) pill counts will take place, and f) the CSS-RS will be administered via interview with a clinical assessor as

frequently as clinically relevant. In addition, psychiatrist check-in visits are included for the purposes of monitoring clinical response and tolerability and tracking possible side effects using the FIBSER; if a serious adverse event occurs, than the adverse events tracking form will also be used to and evaluate and document outcomes.

Procedures to ensure adequate clinical follow-up at end of the study

The default option for this study is for participants to taper off sertraline after the week 14 visit (as discussed above). However, because sertraline is an FDA-approved medication, some participants may wish to continue taking sertraline rather than taper off of the medication. In order for participants to have this option available to them, they will need to have a provider (primary care provider or psychiatrist/psychiatric nurse) who is willing to continue prescribing the study medication. For Veterans, this provider can be a VA or non-VA clinician. For non-Veteran participants, this provider must be a non-VA clinician. For participants who do not wish to use VA or are not eligible for VA healthcare and who do not have a primary care provider when enrolling in the study, research staff will research community resources and provide contact phone numbers to participants to assist them establishing care with non-VA providers.

Procedures to coordinate care with existing providers: For participants who have VA or non-VA providers at the start of the study, we will obtain a ROI for permission to contact their providers. As noted in the ICF, we do not want to enter a participant into the study if participating in the study would interfere with their other care, or if in the opinion of the participant's provider, being in the study would present a risk to the patient. Therefore, we will let the participant know this and that entry into the study is contingent on contacting the provider about the appropriateness of including the participant in the study. We will inform the participant that we will share the following information with their current relevant care provider: information about the design of the study, inclusion and exclusion criteria, the participant's psychiatric and medical diagnoses as well as illness severity, as assessed in the screening evaluation, and any history of safety issues such as risk to self or others. If the participant doesn't sign a release of release of information (ROI) to contact the provider, the participant will not be entered into the active study.

Procedures to facilitate referrals: For those without providers at the start of the study, we will ask for this ROI if/when they are connected with a potential after-study provider. We will begin working with participants at the pre-placebo (week 0) study visit to help connect them with providers who could potentially help manage their psychiatric symptoms at the end of the study and continue sertraline should the participant wish to continue sertraline after the study. We will continue to work with participants on connecting with a provider throughout the study. Depending on the participant's eligibility and preference, the provider will either be a VA clinician (only if eligible) or a non-VA clinician.

We will let the participants without a current provider know that they will have to sign an ROI to contact a potential provider and will provide the following information to the provider: information about the design of the study, inclusion and exclusion criteria, the participant's psychiatric and medical diagnoses as well as illness severity, as assessed in the screening evaluation, and any history of safety issues such as risk to self or others. We will let the participant know that: a) if the participant doesn't sign the release of release of information (ROI) to contact the provider, or b) if the prospective provider is not willing to see the participant after the study or continue sertraline seamlessly based on the participant's wishes (at least initially), we will taper the participant from the study drug after the week 14 visit, or when clinically appropriate.

To further facilitate successful aftercare for participants enrolled in the study, we will begin to reach out to the participant's provider to confirm an appointment with the participant at least four weeks before the week 14 visit (or later if a provider willing and able to schedule the participant soon after the Week 14 visit is located prior to the week 14 visit). Participants will be informed that if for any reason a previously identified and willing provider is not able to commit to seeing the participant within four weeks of the week 14 visit, we will taper the sertraline.

Discussions between study psychiatrist and participant regarding post-study aftercare: For all study participants, the study psychiatrist and the participant will discuss post-study treatment options during the psychiatrist check-in visit embedded at the end of the week 14 visit (i.e., the 3 months post-sertraline assessment visit). Psychoeducation will be provided about common pharmacological and evidenced based psychotherapies.

For those participants with whom we have obtained an agreement from the participant's (VA or non-VA) provider to work with study staff to coordinate seamless transition, this discussion will include the possibility of ***not*** tapering off sertraline during the context of the study and instead working with the study team and their VA provider to develop a plan to transition care to the provider.

For those who still have not obtained a provider by the end of the study, we will provide a list of common VA and non-VA referral options to the participant and, if eligible, place consults into the medical record for appropriate VA referrals for aftercare. These participants will taper off sertraline in the context of this study (as described above).

For those participants with whom we obtained an agreement from the participant's VA or non-VA provider to work with study staff to coordinate a seamless transition, this discussion will include the possibility of ***not*** tapering off sertraline in the context of the study and instead working with the study team and their VA or non-VA provider to develop a plan to transition care to the provider--e.g., providing a one-month supply of sertraline to the participant to cover the participant's needs until the follow-up appointment with the VA or non-VA provider.

For participants who elect to taper off sertraline in the context of this study (or are not given this option due to lack of provider agreement), we will continue the discussion of treatment options during the psychiatrist check-in phone call(s)/visits during the taper period and post-taper psychiatrist check-in visit. We will also continue to work to facilitate appropriate referrals during this time.

For all participants, we will also provide emergency phone numbers and emergent care options should the participant need emergency care before connecting to their follow-up provider or should they not wish to be connected to a follow-up provider.

Veteran and non-Veteran participants who experience medication side-effects, and subsequently discontinue the SSRI, will be monitored by study physicians until (1) the physician determines either side-effects have abated or (2) care is transferred to a primary care physician at the study physician's discretion. At that time, the participant will have completed the study and will not be scheduled for additional study appointments. While enrolled in the study, additional appointments will be scheduled at the study physician's discretion to monitor vitals, conduct an EKG, and/or analyze clinical labs to reduce risk and provide appropriate medical care.

Medication and dose rationale

Because the goal of this study is to identify pre-treatment predictors of SSRI response that ultimately could be used in routine clinical care, we designed the study with ecological validity in mind. Specifically, we chose sertraline as the study medication because it is: a) the most commonly prescribed SSRI in the US,[23, 29] b) one of only two FDA-approved drugs for treating PTSD, and c) one of the two most effective SSRIs for major depression, a common comorbidity with PTSD.[67] Dosing will follow clinical practice guidelines, i.e., doses will be chosen based on clinical response and tolerability.

Placebo response

There is a considerable response to placebo (30%) in studies comparing antidepressants to placebo.[68] Because the goal of this study is not to establish the efficacy of sertraline, we believe that adding a placebo control group is not necessary or feasible as it would necessitate an extremely large sample size. Such a study would need to be powered to detect a medication group X LDAEP interaction (i.e., LDAEP would be expected to predict response in the SSRI group and not the placebo group). A high rate of placebo response will inflate variance in the sample. Thus, we plan to employ several strategies described in the literature to minimize placebo response. Specifically, as suggested by Fava et al.,[69] we plan to use standardized clinical measures that are sensitive to change, enter data in duplicate (using macros to highlight inconsistencies) to ensure minimal data entry errors, use independent assessors unaware of LDAEP level, and administer both self-report and clinician rated scales as

some research suggests that self-report measures may be less sensitive to placebo effects. In addition, we will employ a *2*-week, placebo lead-in period to help screen out patients who are responsive to placebo. We also plan to use change in self-report and LDAEP from pre-placebo assessment to pre-sertraline assessment as potential covariates in analyses as an additional control for error variance due to placebo response that is below threshold for exclusion from the active drug group.

Resuming In-Person Subject Interactions

The main aim of the project is to determine the strength of the relationship between the LDAEP, measured with EEG, and clinical response to SSRI treatment. This study requires an in-person physical to determine eligibility for the study, the collection of blood and urine samples, as well as EEG testing during 2 study assessments. As a result, the study necessitates 3 appointments during which some procedures are done in-person to determine ongoing eligibility, monitor health of participants being prescribed study medication, and assess LDAEP. All additional data collection during these partly in-session visits, as well as all data collected during the other study sessions can be conducted remotely.

Space

In-person interactions will take place in the research space in VA Boston—Jamaica Plain Campus. The office in which in-person assessments are conducted is used solely for research purposes.

Number of In-Person Interactions

There will be 3 sessions during which some of the procedures will take place in person and some procedures will take place remotely: Screening Session-2, pre-placebo session (week 0) and 3 month session (week 14).

Covid-related Procedures

Any Covid-related procedures will be done as required by hospital policy.

Scheduling

The lab space will operate at the capacity dictated by the research reopening committee. We will regularly communicate with other research teams to coordinate use of the research study rooms.

Cleaning

All research study areas will be sanitized at the beginning of the day before the research participant arrives and sanitized again after each participant visit. The research study staff member holding the participant visit is responsible for cleaning the office in which they place their research participant, as well as any study materials (e.g., EEG caps) which come into contact with staff or participants. Sanitizing methods will include the use of germicidal cleaning wipes and/ or spray.

Remote Contact

Remote sessions will be conducted via phone or video chat platforms. The preferred tool for communication with participants will be WebEx, with VVC, Doximity, and phone calls utilized as secondary options, as needed. Participants will receive study materials for remote sessions through the mail and/or via secure email with Azure RMS encryption. In the event that VA study staff requires a participant to share a document with PHI, VA study staff will initiate contact with the participant using Azure RMS, and the participant will respond to that email to ensure that the information communicated remains encrypted. All research materials may be sent to, and received from, participants using secure email with Azure RMS encryption.

Pill Distribution

To minimize contact between participants and VA staff, placebo and sertraline pills will be mailed directly to participants; rather than having participants and study staff directly interact with pharmacy.

Payment Procedures

Participants will have several options by which to receive payment. As available, participants may be paid with cash or electronic direct deposit. To minimize contact between participants and VA staff, we plan to either process payments immediately for sessions conducted remotely or give the participant the option to delay these payments until their next in-person appointment when they can be paid in cash. For appointments conducted in-person, participants will have the option to either have their payment processed via direct deposit or receive their appointment compensation in cash. Participants will also be given the choice to sign up for electronic payments for all study appointments: participants can enroll in either direct deposit to their bank or credit union account, or to a Direct Express Debit Mastercard card from the VA.

If participants who have completed any compensated sessions are found ineligible or are otherwise uninterested in continuing with the study prior to their first in-person visit (i.e., unable to provide a wet signature on the EFT direct deposit sign-up form on-site, as occurs in regular study procedures), study staff will attempt to contact them via phone and email. Staff will leave the participant voicemail messages at each call, and send a hard-copy form to the participant with return packaging and brief instructions on filling out the form. After five unanswered calls with no response to any contact from the participant, study staff will disengage any further attempts and the incident will be logged as a note-to-file.

Screening sessions

In order to assess study inclusion/exclusion criteria, we will first use a phone screen (see Appendix). Those who potentially meet study inclusion criteria will be invited to schedule a remote or in-person consenting session:

1. Following the phone screen, eligible individuals will be given the option to complete the informed consenting process remotely (via WebEx) or in-person at the Jamaica Plain VA. Potential participants who choose to complete the informed consent remotely will be mailed and/or emailed the ICF and HIPAA, and if a non-Veteran then also the Notice of Privacy Practices and form to create a medical record. For participants who chose mailing as their preferred way to mail back forms, a prepaid envelope will also be included in this mailing to allow participants to mail back the informed consent documents (ICDs) to study staff. Participants will be given the option of signing all informed consent documents electronically via DocuSign as well, once the study team has been approved for DocuSign use. If participants chose to use DocuSign during the consenting appointment, they will be emailed the DocuSign materials and sign the ICDs electronically.
2. Potential participants who choose to complete the consenting appointment remotely will then schedule a 30-minute consenting call with a study team member at least 3-5 business days after ICDs are mailed, or email receipt of ICDs have been confirmed, to ensure participants have received the informed consent documents.
3. Potential participants who choose to complete the consenting appointment in person will then schedule an in-person appointment with the study team.
4. For participants who choose to complete the informed consent process remotely: During this consenting call, study staff will review the documents. Participants who choose the mailing option will then sign the forms and hold the signed forms to the camera, allowing study staff to take a screenshot of the signed document; study staff will only take a screenshot of PHI when logged into a device behind the VA firewall (i.e., while logged into a VA computer or while using CAG/VPN remote access). These screenshots will be saved on the IRB-approved secured shared drive where PHI is stored electronically. Participants will then use the prepaid envelopes provided to them to mail the signed documents back to the study team. If participants choose to sign consent forms with DocuSign, screenshots will not be taken and paper versions of the ICDs will not need to be mailed back to the study team.
5. Participants who choose to complete the consenting appointment in person will review the documents with study staff and sign the forms. Participants will receive one copy of all documents to keep for their own records.
6. Any participants who are not currently enrolled in VA will also have a medical record created for them as soon as study staff receive the signed document to create a medical record (via mail, DocuSign, or in person).
7. The study team will then schedule the first remote screening appointment for 3-5 business days later (or as soon as possible for participants completing in-person

consenting or using DocuSign), to allow for the receipt of the ICDs and to mail or electronically send (via emailed PDFs or link to Qualtrics survey) participants self-report measures to be completed as part of the screening process.

8. All self-reports (via hard copy, PDF, or Qualtrics link) will be identified with participant ID and session number; no PII is recorded on these surveys. Any electronic communication will be conducted via encrypted email, including emailing Qualtrics links.

LEC-5 Administration

9. To minimize participant burden and ensure that participants complete the LEC-5 Extended Version Self-Report measure prior to their screening 1 appointment, participants will be offered multiple ways of completing the measure. After study staff receive the ICDs, participants may be administered the LEC verbally by study staff, complete the LEC via Qualtrics link, or chose to complete the LEC using Azure RMS secure email, and instructed to complete the form and send it back using Azure RMS at least 48 hours prior to screening session 1.

10. Participants who complete the consenting process in-person will complete the LEC during their appointment. Participants will also be given the option to complete other session 1 or session 2 study activities [such as completing self-report measures, clinical interviews (with assessor on the phone) and lab work] during this appointment to lessen participant burden during their remote session 1 appointment.

After completing the remote or in-person consenting session and receiving the ICDs, participants will complete Screening Session-1 (typically remote, but possibly in person for participants doing in-person informed consent):

1. Participants will confirm receipt of paper and/or digital forms of self-report measures (either PDF versions via encrypted email or via Qualtrics link). Participants who are not eligible after remote Screening Session-1 will use prepaid enveloped provided to them to mail the packet of completed self-report measures (listed below in Table 2) to study staff. Those participants who are eligible after the remote Screening Session-1 will schedule an in-person Screening Session-2 and bring the packet of self-report measures to the Session-2 appointment. Participants that chose to use Qualtrics as a method to complete self-report measures, will not need to mail any forms back to the study team.

During the typically remote Screening Session-1, the study PI, project director, or study assessor will administer the LEC-5 (if not received prior to Screening Session 1 or previously administered), CAPS-5, Structured Clinical Interview for DSM-5 Disorders (SCID-5), Hamilton Depression Rating Scale (HAM-D) and the CSS-RS. Participants

who remain eligible following Screening Session-1 will be scheduled for the in-person Screening Session-2:

1. Study staff will confirm receipt of completed self-report measures; participants may mail the measures back to the study team with the prepaid envelope provided to them by the study, email the measures using Azure RMS, submit the measures using Qualtrics, or bring the completed paper forms with them during the in-person component of Session 2. Participants who fail to complete or send the self-report measures will complete them in Screening Session-2.
2. Participants' hearing threshold for 780 Hz tones will be estimated using a 5-dB descending and ascending staircase method. In addition, the subject will be asked to provide blood (CBC, Chem 7, Calcium, B12, Liver Profile, TSH, folate, T4, ferritin, PT, PTT, and lipid profile for those on statins) and urine samples (urinalysis/toxicology/cotinine/saliva alcohol test strip /alcohol GGT and pregnancy test for females). All of these lab tests will be repeated at week 14 (end of sertraline trial) or at the request of the study psychiatrist, and the toxicology, saliva alcohol test strip, alcohol GGT, pregnancy and cotinine testing will be repeated at each in person study visit.
3. During this session, medical eligibility will be determined via chart review, review of clinical laboratories as well as through data collected during this session through a physical examination, a neurological evaluation, an EKG, and vital signs.

For participants who have a positive toxicology screen during the screening session for illegal substances, but (1) meet all other study eligibility criteria, (2) commit to discontinuing illegal substances, and (3) express interest in continuing to participate in the study, subsequent visits may be scheduled to conduct additional urine drug screens. Enrollment in the study would be contingent on completing a negative drug screen. Of note, having a positive cannabinoids screen does not render a participant ineligible unless the participant also meets criteria for a substance use disorder with symptoms present within the past three months.

For participants who have a positive toxicology screen for illegal substances after beginning the medication portion of the study (i.e., week 0, we will work towards terminating study participation by beginning the medication taper procedures typically enacted at the end of the study (see below).

If liver function tests (LFTs) at screening are between ULN and 2x ULN, the study physician will make a decision about patient eligibility based on other lab tests, medical history, or any indicated further evaluation. Furthermore, LFT elevations > 3.5x normal will require study discontinuation. If the participant is deemed eligible, follow up liver function tests will be conducted with the frequency determined by the study physician.

Post-screening Study Appointments

The 2 assessment sessions that may include both in-person and remote data collection, designed to minimize the amount of time participants will be required to spend engaging

in direct contact with study staff. Participants will be provided with a packet of self-report measures and prepaid envelope and instructed to complete the measures within 48 hours of the in-person appointment and mail them or send them via Azure RMS to study staff. Participants may also opt into receiving the self-report measures via Qualtrics link and may complete them electronically. In addition to the schedule outlined below, the CSSRS will be administered as many times as clinically relevant. Study staff will follow the most updated VA guidance on research safety guidelines to offer participants the option to complete any component of the assessment session in-person.

Week 0 (Pre-Placebo): This session will include both in-person and remote data collection.

In-Person: LDAEP, P300, Labs (blood draw and urine), collect vitals
Remote or in-person: Self-report measures (see Table 2), Clinician administered assessments (CSSRS), brief check in with psychiatrist focused on medication instructions.If screening session 1 was more than 1 month before this session, the CAPS and HAM-D will be re-administered or at the discretion of the PI.

Week 2 (Pre-Sertraline): This session will be conducted remotely.

Remote. Self-report measures (see Table 2), Clinician administered assessments (CSSRS), pill count, brief check in with psychiatrist focused on medication instructions, response, and side effects (FIBSER administered as necessary)

Week 4 (Brief Psychiatry Check-in): This session will be conducted remotely.

Remote. Self-report measures (see Table 2), Clinician administered assessment (CSSRS), pill count, brief check in with psychiatrist focused on medication instructions, response, and side effects (FIBSER administered as necessary)

Week 6 (1-month Post-Sertraline): This session will be conducted remotely

Remote. Self-report measures (see Table 2), Clinician administered assessments (CSSRS), pill count, brief check in with psychiatrist focused on medication instructions, response, and side effects (FIBSER administered as necessary)

Week 8 (Brief Psychiatry Check-in): This session will be conducted remotely.

Remote. Self-report measures (see Table 2), Clinician administered assessment (CSSRS), pill count, brief check in with psychiatrist focused on medication instructions, response, and side effects (FIBSER administered as necessary)

Week 10 (Brief Psychiatry Check-in): This session will be conducted remotely.

Remote. Self-report measures (see Table 2), Clinician administered assessment (CSSRS), pill count, brief check in with psychiatrist focused on medication instructions, response, and side effects (FIBSER administered as necessary)

Week 12 (Brief Psychiatry Check-in): This session will be conducted remotely.

Remote. Self-report measures (see Table 2), Clinician administered assessment (CSSRS), pill count, brief check in with psychiatrist focused on medication instructions, response, and side effects (FIBSER administered as necessary)

Week 14** (3-months Post-Sertraline): This session will include both in-person and remote data collection.

In-Person. LDAEP, P300, Labs (blood draw and urine), medical screening laps, collect vitals, DNA and RNA

Remote or in-person. Self-report measures (see Table 2), Clinician administered assessments (CAPS, HAM-D, CSSRS), pill count, brief check in with psychiatrist focused on medication taper (if tapering) or transfer of care, response, and side effects (FIBSER administered as necessary)

***note: this session will occur whenever participant choose to end participation in study regardless of where they are at in the study.*

Taper/post-taper psychiatry visits (Brief Psychiatry Check-in): These session(s) will be conducted remotely for participants who are tapering sertraline in context of the study to ensure a safe discontinuation of sertraline and may be completed at any time that is clinically indicated.

Remote. Self-report measures (see Table 2), Clinician administered assessment (CSSRS), pill count, brief check in with psychiatrist focused

Design considerations, alternatives, pitfalls, and decisions

We have carefully considered four key design issues: a) the prominent placebo effect, b) studying prediction of response to only one SSRI, c) including participants who are not SSRI-naïve, and d) whether to evaluate potential genomic predictors of SSRI response.

1) Given the high rates of clinical change in response to placebo,[62] we carefully considered how a placebo response might affect study findings. As discussed above, we believe that adding a separate placebo control group is neither feasible nor necessary. Even with the safeguards previously outlined, which will mitigate the presence of placebo responders in the active SSRI treatment group, some SSRI responders will likely have improved on placebo or another medication as much as on sertraline. The primary threat from a placebo response is additional error variance in our predictor models and decreased sensitivity of LDAEP in predicting SSRI response. Please see Placebo Response section on p. 7 for more detailed discussion of this issue.

2) SSRIs are a family of medications and sertraline is only one of this family. As discussed above in the Medication and Dose Rationale subsection (p. 6), we chose sertraline as the study medication because it is the most commonly prescribed SSRI in the US[23, 29] and is one of only two FDA-approved drugs for treating PTSD. An inherent limitation of our study design is that our results may not generalize to other SSRIs due to possible heterogeneity of pharmacological profile across SSRIs that could influence therapeutic responses and adverse reactions. However, randomizing participants to any of several SSRIs would dramatically increase the overall sample size, decrease feasibility and increase costs of the proposed research. Thus, we believe that

developing our predictive models based on the most widely used SSRI is the best first step at this initial stage.

3) As discussed above, participants do not have to be SSRI-naïve to participate in the proposed study; they only need to have not taken an SSRI during the past 3 months and not failed a previous trial with sertraline. This decision was made to enhance generalizability of the study findings. Excluding anyone with a past history of SSRI use would likely result in a sample with less symptom severity and chronicity than is typically found in outpatient mental health settings.

4) Much excitement and attention has been directed towards identifying genomic predictors of SSRI response. However, at best, the findings have been equivocal and there are no best practices regarding reliable genetic predictors of SSRI response.[91, 92] Contributing to the mixed findings are studies that do not include a sufficient number of participants to yield reliable results. Because our sample size would be very small for a genetic study and there are currently VA-funded large-scale data collections aimed at clarifying genomic predictors of SSRI response (e.g., VA funded PRIME study PI: Oslin, Co-Is Schichman and Stone are on the executive committee), we decided to bank physical DNA and RNA biological samples in the VA Boston R&D-approved database called the Biological Predictors of PTSD and Treatment Data and Specimen Repository (R&D #1592602) for future use in combination with other studies of SSRI response. This plan was initiated in response to reviewer critiques from earlier submissions of our funded CSR&D MERIT grant and was part of the funded grant proposal.

This plan of banking genetic samples for future use in combination with other studies aligns with several VA Boston IRB-approved studies including TRACTs, the studies conducted by Mark Miller and his group, and the Million Veterans Project. To advance the science of the genomics of psychopharmacological response, huge datasets are required. The proposed study could provide very useful data in combination with similar studies of SSRI effectiveness in identifying genomic predictors of SSRI response.

There are data to suggest the promise of this line of research. For example, recent studies have provided support for associations between serotonin receptor gene polymorphisms and anti-depressant response.[49,50] _ENREF_52[51,52] _ENREF_54 Although there are 7 serotonin receptor gene candidate SNPS, meta-analyses reveal the most compelling support for two HTR2A SNPs as predictors of anti-depressant response: rs7997012 and rs6313, with particularly compelling support for HTR2A SNP:rs7997012.[50 52]

We anticipate that the banked genetic samples from this study may be used to measure genome wide SNPs that predict SSRI response, genome wide DNA methylation

changes in response to SSRIs, and to examine the effects of SSRI on changes in gene expression through measurement of RNA.

However, because the study of genomics of psychopharmacological response is in its relative infancy and the technological advances are increasing rapidly, we are unsure of the exact measures which will be considered state of the art at the time of analysis.

In sum, the overarching rationale for banking genetics samples is to contribute to the movement of contributing data from small studies in the service of consortium research groups compiling “big data” sets that include a sufficient number of participants to adequately investigate questions related to the genomics of psychopharmacology response. This will be accomplished by adding our samples and electronic data to the Biological Predictors of PTSD and Treatment Data and Specimen Repository (R&D #1592602) for future use in combination with other studies of SSRI response.”

Biological Predictors of PTSD and Treatment Data and Specimen Repository (R&D #1592602) Data collected from participants in this study will be entered into a database for the purposes of this study. The study database will include birthday and last 4 digits of a subject’s social security number to track multiple study enrollment. In addition, data from this study, including the scored electrophysiological data, results of blood labs, score results of interviews and questionnaires, and information pertaining to DNA and genes, will be entered into the VA Boston R&D-approved database Biological Predictors of PTSD and Treatment Data and Specimen Repository (R&D #1592602). Any future studies that make use of data in the Biological Predictors of PTSD and Treatment Data and Specimen Repository will be reviewed by the Institutional Review Board (IRB) at VA Boston Healthcare System.

Risk to Human Subjects

(a) Human Subjects Involvement and Characteristics

All study participants (aged 18-75) have a history of trauma exposure, as defined by criteria A for PTSD in the DSM-5, and will meet criteria for a diagnosis of PTSD, Subthreshold PTSD, or MDD as defined by DSM-5 PTSD Criteria (n=94; 50% male, 50% female). Because research suggests that women are more likely to respond to SSRIs than men, it is important to compare the pattern of results between men and women.

Inclusion criteria: a) has a history of trauma exposure as defined by criterion A of PTSD in the DSM-5, b) meets diagnostic criteria for PTSD, subthreshold PTSD, or MDD as defined by DSM-5, c) study psychiatrist’s judgment that SSRIs are an acceptable treatment option for the participant’s presenting concerns, and d) interest in starting a trial of an SSRI.

Exclusion criteria: a) current or past history of bipolar I disorder, schizophrenic or other psychotic disorders, b) current organic brain disorder including severe traumatic brain injury, factitious disorder, or malingering, c) pregnancy, d) major neurological problems, e), current moderate or severe substance use disorder with symptoms present within the past three months , f) active risk to self or others, g) evidence of clinically significant hepatic or renal disease or any other acute or unstable medical condition that might interfere with safe conduct of the study, h) intolerance or hypersensitivity to sertraline, i) failed past trial of sertraline (confirmed by medical record review), j) drugs that directly affect the serotonin system (e.g., SNRIs, antipsychotics) within 3 months of the study k) use of an SSRI within 3 months of the study. Use of other psychotropic medications must have been stable for 3 months prior to enrollment and remain stable throughout participation, l) hearing impairment for 780 Hz tones, m) current enrollment in trauma-focused psychotherapy, and n) for those participants who currently have a VA psychiatrist or primary care provider who is willing to prescribe mediations, they must be willing to sign a release of information (ROI) for study staff to communicate with their providers and the provider believes that including the participant in the study is potentially appropriate. As discussed above, we will inform the participant that we will share the following information with their current relevant care provider: information about the design of the study, inclusion and exclusion criteria, the participant's psychiatric and medical diagnoses as well as illness severity, as assessed in the screening evaluation, and any history of safety issues such as risk to self or others. If the participant doesn't sign a release of release of information (ROI) to contact the provider, the participant will not be entered into the active study.

(b) Sources of Materials.

All of the data for this project will be collected specifically for research purposes. Hard copy files will be kept in locked file cabinets within locked offices at VA Boston. This includes the hard copies of diagnostic interviews completed for both sites that are conducted by assessors located at VA Boston. Electronic data (e.g., audio files for diagnostic interviews, electrophysiological data, and Qualtrics data) for both sites will be kept in a secure folder on a secured server, with access restricted to staff for this specific research study. Study staff across both sites who are listed on both the Ralph H. Johnson VAHCS and the VABHS IRB protocols will have access to this secured folder. Identity masking participant numbers assigned to each participant will be the only means by which collected information is labeled. Each participant will have his/her own assigned number. The only list that will link the names of the participants with their participant numbers will be kept in a secure, password-protected computer account on a separate drive from the data and accessible only to the research team.

Seven sources of data will be included in this project: (a) the initial telephone screen, (b) questionnaires, (c) diagnostic interviews, (d) medical record review, (e) event-related potentials (ERPs), and (f) biological samples. Data will not be removed from the VA at any time.

(a) Telephone screen: Each participant will be interviewed separately to determine study eligibility. A file linking participant names and numbers described above will be stored on a secure, password-protected computer account on a separate drive from the larger data set, which will not include names or contact information, and accessible only to the research team.
(b) Questionnaires: Self-report questionnaires will be administered. These measures will be administered to obtain information regarding trauma history, psychological symptoms, medication use, adherence, and side effects. All information from these questionnaires will be identified with participant numbers only.
(c) Diagnostic interviews: Structured diagnostic interviews will be completed by assessment core, overseen by co-LSIs in the Behavioral Health Sciences Division of the National Center for PTSD, and independently trained and supervised clinicians to determine PTSD and depression symptoms, as well as assess for inclusion/exclusion criteria and suicidal ideation, intent, plan, and behaviors. All information from these interviews will be identified with participant number only. Data from these interviews will be entered into the database that also contains the questionnaire data and, thus, will be stored in the same secure folder as the questionnaire data. Additionally, these interviews will be audio recorded in order to determine diagnostic reliability. The audio recordings will be identified with participant numbers only and stored on a secure folder on a secured server, with access restricted to staff for this specific research study. These data will be stored on a server that is separate from the self-report, diagnostic interview, and electrophysiological data.
(d) Medical record review: In addition to self-report, previous medication trials and other current medication use will be assessed through review of the VA electronic medical records. All information will be entered into the database that also contains the questionnaire data and, thus, will be stored in the same folder as the questionnaire data.
(e) ERPs: Electroencephalogram (EEG) activity will be recorded during a four-tone, stimulus-intensity modulation procedure on the neuroscan laboratory computer. These data will be used to score the LDAEP and P300. Raw data will be identified with participant numbers only and moved to the same secure folder as the self-report and diagnostic interview data. The VA-issued thumb drive used to move these data will be protected with VA approved FIPS 140-2 compliant technology.
(f) Biological samples: Blood samples (whole blood, serum, plasma, RNA and DNA) will be stored in the MAVERIC biorepository located at VA Boston. These samples will be labeled with a sample number. A list linking the participant number and the biological sample numbers will be stored in the same folder as the questionnaire, diagnostic interview, and electrophysiological data. Once data collection is complete, the DNA quantification and RNA extraction will be conducted by the Pharmacogenomics Analysis Laboratory at Central Arkansas Veterans Healthcare System. Measurement of analytes from SSRIs in human serum by

Mass Spectrometry and whole-blood measurement of 5-HT in platelets by HPLC-fluorescence will be conducted in the Research Service Laboratory at Central Arkansas Veterans Healthcare System. Measurement of progesterone and its neuroactive metabolites will be conducted by Dr. Graziano Pinna's laboratory at University of Illinois at Chicago. Measurement of NE will be conducted by Dr. George Anderson's laboratory at Yale University and measurement of ACTH and estradiol and progesterone (for menstrual phase verification) will be conducted by Dr. Richard Hauger's laboratory at UCSD/SDSU.

Dr. Matthew Kimble at Middlebury College and Dr. Scott Orr at Harvard Medical School will assist with data processing of brain activity. Other non-VA investigators (to be named) may be added as investigators to this study protocol to conduct analysis of blood measures and/or to contribute to this study. Data will be securely transmitted off-site using VA approved methods and will be verified as to having no PHI by the privacy officer before being shared. We will use FIPS 140-2 validated encryption. The FISMA compliance of the server that will store VA information will be certified before information is sent.

Once study team members are no longer a part of the research team, their access to data and research materials will be terminated.

(c) Potential Risks.

Because this study involves the physician-monitored administration of sertraline, therapeutic risks for this study include risk for the possible side effects of sertraline, including: nausea, dizziness, drowsiness, dry mouth, loss of appetite, increased sweating, diarrhea, upset stomach, or trouble sleeping. There are also several unlikely, but more significant, potential side effects including: easy bruising/bleeding, decreased interest in sex, decrease in sexual ability (ejaculation delay), muscle cramps/weakness, shaking (tremor), and unusual weight loss. Finally, rare but serious side effects include: black/bloody stools, vomit that looks like coffee grounds, eye pain/swelling/redness, widened pupils, vision changes (such as seeing rainbows around lights at night, blurred vision), and painful or prolonged erections. This medication may increase serotonin and rarely causes a very serious condition called serotonin syndrome/toxicity. A very serious allergic reaction to this drug is rare; symptoms include: rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, and trouble breathing. Additional relatively rare risks of sertraline include the risk (especially in people younger than 25) of worsening depression, other mental/mood symptoms, or suicidal thoughts/attempts. If the event of a death of a study participant, we will use the VA IRB SAE form to alert the IRB immediately.

Although we are using a standard approach to clinical trials, which represents enhanced clinical care in that participants discuss medication levels, side effects, and symptoms with a psychiatrist every two weeks, we recognize that many participants will not ultimately benefit from sertraline, as is also the case in routine clinical care. This is another potential risk of physician-monitored administration of sertraline.

Potential physical research risks of the study not related to sertraline include: bruising from the blood draw and some discomfort from the application of the electrodes, which involve mild abrasion and the use of alcohol to cleanse the surface of the participants' skin, and the use of saline solution on the participants' scalp. The PI and staff members have received extensive training on the electrophysiological procedures, which serves to minimize discomfort from the application of the electrodes. Any future staff on this project will receive similar training. The risk from the laboratory equipment is negligible. A participant may find some of the loud tones distressing. In addition, there may also be some discomfort during the administration of the EKG. When conducting the EKG, participants will be required to remove their shirt, and may be asked to shave areas where the EKG stickers will be placed. Participants can be provided with a medical covering upon request, and female research technicians will be administering the EKG unless otherwise requested. Study staff have been trained in conducting the EKG, and the risk from the laboratory equipment is negligible. A participant may find removing their shirt to be distressing, and accommodations (e.g., female staff administering the EKG) will be offered.

Potential psychological research risks include breach of confidentiality; coercion to participate; possible emotional distress when completing trauma and psychological symptom measures; and inconvenience of study procedures.

- We will take all possible steps to protect the confidentiality of all study data including the DNA specimens and results. However, despite these protections there is always a possibility that information could be disclosed in an unexpected or uncontrolled fashion. This could conceivably result in discriminatory action against participants by insurers, employers, or other groups. There may be unanticipated risks from the future use of genetic information by groups or individuals that we are unaware of today.
- The risk of discomfort from reporting on their trauma history and mental health symptoms is mild-moderate in both severity and likelihood.

All study procedures will be fully explained during the informed consent process such that participants can make an informed decision regarding their participation in the study.

Adequacy of Protection from Risks

(a) Recruitment and Informed Consent.

Participants will be recruited through: primary and specialty mental health care clinics; VINCI patient lists; consult lists; flyers posted at local hospitals, clinics, college campuses, and public bulletin boards; and advertisements placed on websites (e.g., Craigslist), and free newspapers (e.g., Boston Metro with a circulation of 238,000 daily readers). Interested potential participants will phone study investigators and will undergo a phone screen. During this phone call, the study and its procedures will be described and a short screen for eligibility will be administered. If the initial eligibility requirements are met, participants will be scheduled for an in-person appointment, during which the informed consent process and assessments of inclusion/exclusion criteria will be completed. These assessments will include clinical interviews, a physical examination, and standard laboratory work. Prior to completing any study procedures, the participant will undergo the informed consent process. First, the participant will be presented with a written explanation of the study and the associated risks and benefits to review on his/her own. A member of the study team will verbally explain the purpose of the study and the risks and benefits associated with participation. The participant will be given an opportunity and encouraged to ask questions. The participant will be asked questions to ensure comprehension of the study procedures along with risks and benefits and informed that he or she may discontinue participation at any time without personal consequences. The participant will review and sign the consent form if he or she agrees to participate. Each participant will receive a copy of his/her signed consent form for his/her records.

(b) Protection Against Risk.

Although there are a range of potential side effects associated with sertraline, most are mild to moderate in severity; the more severe side effects and medical consequences are very rare. In addition, this medication has the potential benefit of improving psychiatric distress.

Risks for side effects, allergic reactions, and medical consequences will be mitigated by: a) careful assessment of previous medication trials and current medication use by a trained psychiatrist during screening (including medical record review), b) exclusion criteria aimed at screening out individuals who are at increased risk for the more serious side effects or who are taking medications that are contraindicated, c) the provision of both verbal and written education regarding signs to look for regarding side effects, allergic reactions, or serious medical consequences, d) the provision of both verbal and written education regarding medication and other drug interactions and contraindications, e) in-person psychiatrist appointments on an every-other-week basis during which symptoms, suicidality, and side effects will be monitored to inform potential real-time changes in dosing, f) 24-hour psychiatry coverage for questions regarding side effects, allergic reactions, or physical reactions to study medication, g) a psychiatrist-monitored SSRI taper period after the completion of the sertraline trial, or as clinically

indicated, followed by a post-taper psychiatrist safety visit two-weeks later, h) additional clinical laboratories conducted at 3-months post-sertraline (week 14) or at the point they wish to stop taking the study medication and end participation, and i) vital signs data collected during each in person appointment during the medication trial component of the study.

Should Veteran and non-Veteran participants experience medication side-effects, and subsequently discontinue the SSRI, they will be monitored by study physicians until (1) the physician determines either side-effects have abated or (2) care is transferred to a primary care physician at the study physician's discretion. At that time, the participant will have completed the study and will not be scheduled for additional study appointments. While enrolled in the study, additional appointments will be scheduled at the study physician's discretion to monitor vitals, conduct an EKG, and/or analyze clinical labs to reduce risk and provide appropriate medical care.

To address the possible risk of sertraline not leading to significant symptom improvement for some participants, we will discuss this possibility during the informed consent process. We will remind the participant that they are free to withdraw from the study at any time with no adverse consequences, including no adverse consequences on their ability to seek VA care or participate in other research studies. We will also have an independent data safety monitoring board to ensure ethical treatment of participants.

To protect against risk of suicidal thoughts and behaviors, the Columbia Suicide Severity (CSS) rating scale will be administered at the screening visit and participants who endorse active suicidal ideation, plan and/or intent will not be enrolled in the study. In addition, homicidal ideation/intent will also be assessed at screening and participants who endorse active homicidal ideation, plan and/or intent will not be enrolled in the study. These participants will meet with the study PI (a clinical psychologist) to evaluate the patient's safety and she will determine if the participant needs to be evaluated by a clinician in the urgent care clinic for possible hospitalization. She will also work with these participants to ensure they are connected with needed services. For participants who are enrolled in the study, the CSS will be administered at each assessment visit by a masters or Ph.D. level clinical psychologist and every two weeks at each brief, psychiatry check-in visit by the study psychiatrist. Participants who endorse active suicidal/homicidal ideation, plan and/or intent will meet with the study PI or Dr. Rasmusson (Co-investigator/psychiatrist) at the VA Boston site and Drs. Hamner or Wang (site PIs) at the Ralph H. Johnson site to evaluate risk and to develop a safety plan. Participants will also be told to call the study PI or study psychiatrist if suicidal/homicidal ideation, plan, or intent occur or increase between sessions.

If the suicidal/homicidal ideation necessitates clinical intervention to ensure the safety of the participant (i.e., if not passive and with either intent or plan or if the participant is unwilling to contact study personnel or access other help should the ideation become more persistent or evolve to development of intent or plan), the participant will be referred to an appropriate level of clinical care and deemed ineligible or discontinued from the study. The study doctor will follow the participant until such time as such care is reestablished elsewhere and arrangements for taper of study drug will be made if at all possible.

If a participant is thought be at imminent risk to self or others (i.e., has active ideation with near-term intent and plan or a lack of certainty about the trajectory of the ideation or a lack of willingness and means to access help should the ideation evolve in intent or planning), he/she will be referred immediately to the psychiatric emergency room for further evaluation—against the participant's will if necessary.

For assessments that are conducted remotely by the VA Boston assessment core, there is a manual that outlines the action steps to take in the event of psychiatric risk for all of the studies they conduct assessments for across the country. These steps will be the same for participants assessed at both study sites and include:

1. Assessing for additional risk/protective factors and engaging in help reducing risk,
2. Reaching out to the assessment core supervisor (i.e., Dr. Bovin) who is available during all assessments.
3. The assessor and supervisor will then consult on the needed next steps which may include providing the veteran with the VA National Suicide Prevention Hotline number and determining if he/she needs a warm handoff to the VA National Suicide Prevention Hotline. The potential need for a wellness check will also be considered. Of note, the assessors have the home addresses, local police phone number, and local VA phone number for the participant they are assessing in case it is needed for a wellness check.
4. If there is a safety issue, the assessor and assessment supervisor will alert the PIs at the relevant site and the PIs will help ensure the participant is getting adequate follow-up assessment and intervention.

In addition, if the participant's symptoms have worsened by more than 50% as measured by the PCL or QIDS or if the participant has become a safety risk or is otherwise newly at risk of suffering a significant functional set-back (e.g. loss of job, school failure, threat to family structure), the participant will be evaluated by the PI or study psychiatrist to determine if study termination and referral should be arranged.

To ensure confidentiality, questionnaire and interview data will be stored in locked filing cabinets within locked offices. Each participant will have his or her own participant

number. All additional identifying information will be removed, with the exception of the last 4 digits of participants' social security numbers and their birthday; these identifiers will be retained to allow the study team track participants who enroll in multiple studies being stored in the data repository (R&D #1592602). Electronic data will be stored on a secure private, password-protected drive that can only be accessed by members of the study team and labeled only with the participant number. One list of names and participant numbers will be kept on a private, password-protected computer account on a separate drive from the de-identified data and accessible only to the study team.

We expect that issues related to coercion will be very low. First, participants who do not wish to participate in the study or who wish to drop out of the study after enrollment will not experience any negative consequences. Second, a potential human subjects concern is whether the financial compensation offered is too high and therefore coercive to participants. We believe the rate of compensation for the current study is fair due to the length of the study and the biological measurements. Participants will be compensated up to $570 for the optional in-person consenting session, two screening appointments plus the four assessment appointments and 5 brief psychiatry screening visits over a 3.5-month timespan. Participants will not be compensated for visits related to administering and monitoring psychopharmacology dosing.

We will seek to protect participants from the emotional distress that might be aroused by the clinical interview and self-report assessments in the following ways: (a) assessment interviews will be conducted by a Ph.D.-level clinical psychologist or advanced doctoral-level graduate students with extensive clinical experience, and (b) only a highly trained research assistant will conduct the LDAEP procedure and a Ph.D.-level licensed clinical psychologist will always be available during assessment sessions should the participant need psychological assistance. Some participants may feel uncomfortable about being recorded during their diagnostic interviews (necessary for reliability checks). The purpose of the recording will be explained, confidentiality will be respected, and both informed consent and authorization for the recording will be obtained as per requirements put forth by the HIPAA. Participants will be informed that digital recordings will be marked only by subject identification codes, stored on a secured server that is password protected, and only available to study personnel. Because recording will be a mandatory component of the project, if participants are unwilling to be recorded, they can end their participation in the study without penalty.

Risks involved in the LDAEP (e.g., potential rash from electrodes) and blood draw (e.g., bruising) will be minimized by using highly trained staff. The study team has received extensive training on the electrophysiological procedures, which will minimize discomfort from the application of the electrodes. Future staff will receive similar training. Blood will be drawn by either a VA phlebotomist through the VA Boston clinical laboratory or study staff trained and research credentialled by VA Boston to draw blood

(e.g., study physician). Universal precautions are used in the laboratory. Study medication and placebo will be stored and distributed by VA Boston Pharmacy service.

Finally, we will protect participants from potential inconvenience of study procedures by reminding them that they are free to withdraw from the study at any point.

Potential Benefit of the Proposed Research to the Subject and Others.

There are no known direct benefits for the subject or others from being in this research study.

Importance of the Knowledge to be Gained.

Findings from this study may contribute to a precision-medicine approach when choosing initial psychopharmacological interventions. Development of a biological screening method that can be used to predict those individuals who are most likely to be clinically responsive to an SSRI could save the medication provider and patient weeks of waiting to see whether or not the patient will be responsive to an SSRI. It may also aid in avoiding adverse reactions to SSRIs. We believe the risks to participants are reasonable given the importance of knowledge that could result from this study.

3.2 Recruitment Methods

To reach our study goal of 94 study completers, we anticipate enrolling approximately 300 study participants for the in-person screening session.

Participants will be recruited through: primary care and specialty mental health clinics, the National Center for PTSD participant database, VINCI patient lists, consult lists, flyers posted at local hospitals, clinics, college campuses, and public bulletin boards, and announcements of research placed on websites (e.g., Craigslist) and free newspapers (e.g., Boston Metro -- circulation of 238,000 daily readers).

We will also purchase the services of TrialFacts, a specialized patient recruitment agency, to increase study enrollment. TrialFacts will customize a social media plan to recruit eligible participants by creating promotional materials to be approved by IRB, utilizing a mobile friendly platform to recruit participants, implementing highly targeted online advertising campaigns, providing comprehensive pre-screening services, and establishing a phone screening appointment system in which potential participants interested in our study will be able to connect with study staff. Based on our previous experiences, we anticipate no difficulty meeting the recruitment goal.
TrialFacts social media plan includes the use of special IRB-preapproved scripts to be used in videos on Snapchat, Facebook or Instagram. These videos will have their comment sections turned off and will include a link to the landing page for the study, the same one that Facebook takes the referral to, where the referral can read further about the study and go on to complete a questionnaire about their interest if they would like to.

To create these videos TrialFacts uses a platform called Billo which has vetted and professional content creators. Billo enables TrialFacts to connect with the content creators to have their own user generated content videos created. They first raise a task on the platform, where they submit the scripts and requirements, then creators who are interested in making the videos let them know. TrialFacts then screens the creators and selects one to create the two videos for us. They look for friendly, professional creators who match the targets we are looking to reach. Once they create the video, TrialFacts then screens it and approves it or sends it back if they feel it needs to be remade. They then send the videos to us to send to the IRB for final approval before campaigning. TrialFacts ad specialist posts the campaign on their own TrialFacts Snapchat,Facebook, or Instagram account and they control the campaign from there (as they would on Facebook). It is a very similar process to how they use Facebook, they just have the videos made by content creators.

We will also purchase the services of CliniContact, a specialized recruitment service that helps researchers accelerate participant recruitment and enrollment through novel data-driven digital engagement approaches. This service includes a CliniContact landing page and a streamlined screening process. Customer support, site and database management and maintenance, storing and maintaining data in a HIPAA compliant secure database, customization, and real-time recruitment analytics is included in the services offered by CliniContact. Custom-designed social media advertisements, optimization of advertising deployment, and advertisement monitoring and adjustments will be part of the social and online media campaign creation and deployment and management services offered by CliniContact. CliniContact uses data aggregated from social media, online services, and health websites to recruit the particular demographics needed for the study and they provide a cloud-based recruitment management system to streamline the process. CliniContact uses a digital engagement strategy to recruit potential participants (through Health information websites, Instagram, Google, Facebook, etc) as well as through network outreach/engagement, connecting with employers (specifically companies that publicly employ/ support veterans, such as Patriot Family Homes, Latch, Tabs, etc) and relationship building with referral networks (such as support groups or senior centers).

CliniContact has a HIPPA compliant, Cloud-Based Management System that ensures security and privacy. All data is securely stored in this database to maintain confidentiality. Their Secure Socket Layer (SSL) software, which encrypts all inputted information, keeps the information private and safe. CliniContact complies with the U.S. and E.U. Privacy Shield, expounded upon by the U.S. Department of Commerce. Further, CliniContact complies with the Safe Harbor Privacy Principles of notice, choice, onward transfer, security, data integrity, access, and enforcement. Any data that CliniContact collects will belong to the CliniContact database until it is passed along to the VA for phone screening. VA will not send PII or PHI to CliniContact. VHA study staff will be given a login to the HIPAA compliant, Cloud-Based Management System and access the participant information. In the event that the cloud-based system is not working, CliniContact will use secure email with Azure RMS encryption to send the study team any documents containing PHI.

Approximately 140,000 male and 17,000 female Veterans (aged 18-75) reside in MA. For FY 2017, 6,448 male and 685 female Veterans with a documented PTSD diagnosis attended at least one appointment at VA Boston. Of these VA Boston users with a PTSD diagnosis, 55% of male Veterans and 59% of female Veterans were prescribed an SSRI. These high rates of SSRI use highlight the clinical significance of this application.

Flyers, Online Advertisements, and Newsletters. We anticipate reaching several thousand Veterans through flyers posted at Boston area VA hospitals, vet centers, and in public places around the Boston area. We also plan to attend outreach events hosted by VA Boston, with several events specifically targeted to women Veterans. Additional advertisements will be placed on websites (e.g., Craigslist) and free newspapers, including the Women Veterans Newsletter, a newsletter focused on the specific needs of female veterans in MA that is distributed to 15,600 female Veterans.

Recruitment efforts at VA Boston. In addition, targeted efforts will be made to reach users of VA Boston. The PI or a member of the study team will reach out to leadership in primary care behavioral health clinics and specialty mental health clinics, including the Women's Trauma Recovery Team (WTRT), the PTSD Clinical Teams (PCTs), General Mental Health Clinic, and the Center for Returning Veterans to provide information about this study and inquire about the possibility of attending a team meeting. If leadership agrees, we will attend clinic team meetings to briefly describe the goals, methods, and eligibility criteria for the study and leave study recruitment materials with members of the team to distribute to Veterans who may be interested in contacting study staff to learn more about the study. Providers will be given recruitment materials for potential distribution to Veterans for informational purposes only. Providers will also be given copies of the Permission-to-Contact-for-Research forms to allow participants the option to request a member of the research team contact them directly with more information, thus alleviating some burden on potential participants to initiate contact; we will not ask providers to actively ask Veterans to participate in this study or to conduct screening evaluations for this study. In addition to use of the Permission-to-Contact-for-Research forms, Veterans may also provide verbal consent to allow providers to send an encrypted email to the study team, requesting that a member of the study team directly contact the Veteran; this email would include the Veteran's name and contact information. All permission to contact requests sent through encrypted email will be saved on a secure shared drive for documentation purposes. Similarly, we will reach out to leadership in the Psychiatry Service to ask to attend grand rounds to briefly describe the goals, methods, and eligibility criteria for the study and leave study recruitment materials and the Permission-to-Contact-for-Research forms with staff to provide to Veterans who may be interested in learning more about the

study. Flyers will be included in the periodic mailings to all patients who receive primary care through VA Boston and we will contact participants who previously participated in research through the National Center for PTSD participant database.

VINCI will be used to provide Electronic Medical Record (EMR)-driven recruitment support by providing patient data stored in the VA EMR. This service will generate patient lists by searching for patients with relevant diagnoses, in reasonable proximity to the Jamaica Plain VAMC, who meet eligibility criteria for age, medications, and other key parameters. The use of VINCI in this manner will streamline recruitment efforts by ensuring that prospective participants meet eligibility criteria prior to screening. For patients who appear likely to be eligible, we will use UPS to send a letter and previously IRB-approved study brochure asking them to contact study staff if they would like to hear more about this research opportunity. In order to provide double confirmation of the integrity of the mailing process, two independent team members will verify the accuracy of outgoing correspondence.

We also will generate consult reports for any patient for whom a consult was placed within the past week at the time the report was generated. The consult reports to be generated will be for: 1) PSYCHIATRY JP OUTPT, 2) PSYCHIATRY BR OUTPT, and 3) WOMEN'S TRAUMA RECOVERY TEAM, 4) MENTAL HEALTH CONSULT JP OUTPT, 5) MENTAL HEALTH OUTPT (BR), 6) MH POST TRAUMATIC STRESS DISORDER (JP) OUTPT;,7) MH POST TRAUMATIC STRESS DISORDER (BR) OUTPT, 8) CENTER FOR RETURNING VETERANS (MH) OUTPT, 9) GMH CASE MANAGEMENT TEAM eCONSULT (JP) OUTPT, 10) GMH CASE MANAGEMENT TEAM eCONSULT (BR) OUTPT. We received a HIPAA waiver to review the medical records of Veterans on these consult lists, for the purpose of recruitment, in order to minimize participant burden and contact only those individuals who meet preliminary inclusion criteria. For patients who appear likely to be eligible, we will either a) use UPS to send a letter and previously IRB-approved study brochure asking them to contact study staff if they would like to hear more about this research opportunity or b) use USPS to send them a letter and the previously IRB-approved study brochure. This letter will state that the study staff will contact them in a week to describe the study and discuss their potential interest in the study. There will also be a number for the participant to call if they wish to hear more about the study or would prefer for study staff not to phone them phone.

In order to provide double confirmation of the integrity of the mailing process, two independent team members will verify the accuracy of outgoing correspondence.

Recruitment efforts at Boston Medical Center (BMC). A single IRB waiver from VACO and IRB Approval from BMC were obtained for the following recruitment efforts at BMC. Targeted efforts will be made to reach users of BMC through collaboration with leadership in the Behavioral Health Integration Team housed within Boston Medical Center Department of Psychiatry, and particularly with the Behavioral Health Integration Team in primary care. In addition, we will review Clinical Data Warehouse (CDW)

reports of patients seeking SSRI treatment, and work with providers to recruit appropriate participants who may benefit from the study.

Study team members will attend Behavioral Health Integration Team meetings, review Clinical Data Warehouse (CDW) reports of patients seeking SSRI treatment, and work with providers to recruit appropriate participants who may benefit from the study. Prior to contacting patients, we will review their electronic medical records (EMR) data for exclusionary medications, medical, and psychiatric diagnoses. It would be impractical to proceed without such a review because screening patients with clearly exclusionary diagnoses would cause undue burden and unnecessary stress to the patient. It poses no more than "minimal risk" to participants because no identifiable information from the consult list will be retained for research purposes. BU EMR Data will be saved on BMC network servers using VPN and will be destroyed when recruitment for this study has been completed; this will ensure that BMC patients will not be repeatedly contacted. Records will be destroyed as soon as feasible in the following manner: Paper records will be shredded; Electronic records will be destroyed in a manner in which they cannot be retrieved.

For patients who appear likely to be eligible, we will use UPS to send an opt-out letter and IRB-approved study brochure asking them to contact study staff if they would like to hear more about this research opportunity. Should a BMC patient not respond to the initial UPS letter with the study brochure after 4 weeks from the initial mailing, they may be sent one more informational letter and brochure. In order to provide double confirmation of the integrity of the mailing process, two independent team members will verify the accuracy of outgoing correspondence. Unless the study team is contacted by a patient, the study team (1) will not send more than 2 letters, and (2) will not contact BMC patients via phone or email. Unless otherwise requested by the patient, the study team will not call or leave voice messages for the participant that include information about the nature of the research being conducted.

Participants will be paid via check for each session completed. See Table 2 below for compensation schedule.

3.3 Informed Consent Procedures

Interested potential participants will phone study investigators and will undergo a phone screen. During this phone call, the study and its procedures will be described and a short screen for eligibility will be administered. Prior to completing any study procedures, the participant will undergo the informed consent process. First, the participant will be presented with a written explanation of the study and the associated risks and benefits to review on his/her own. A member of the study team will verbally explain the purpose of the study and the risks and benefits associated with participation. The participant will be given an opportunity and encouraged to ask questions. The participant will be asked questions to ensure comprehension of the study procedures along with risks and benefits and informed that he or she may discontinue participation at any time without personal consequences. The participant will review and sign the

consent form if he or she agrees to participate. Each participant will receive a copy of his/her signed consent form for his/her records.

3.4 Inclusion/Exclusion Criteria

Participants and Inclusion/Exclusion Criteria
Eligible participants (aged 18-75) will have a history of trauma exposure, as defined by criteria A for PTSD in the DSM-5, and meet criteria for a diagnosis of PTSD or Subthreshold PTSD (Other- and Unspecified- Trauma and Stressor Related Disorder), or Major Depressive Disorder (MDD) as defined by DSM-5 PTSD Criteria[70] (N=94; 50% male, 50% female). Specifically, we plan to operationalize subthreshold PTSD as meeting 3 of the 4 symptom clusters of PTSD on the Clinician-Administered PTSD Scale for DSM5. Because research suggests that women are more likely to respond to SSRIs than men [58] and other electrophysiological predictors of SSRI response perform differently in men and women,[59, 60] it is important to compare the pattern of results between men and women. Inclusion and exclusion criteria are primarily aimed at enrolling a sample of appropriate candidates for SSRI treatment. Inclusion criteria will consist of: a) meeting diagnostic criteria for PTSD as defined by DSM-5 or Subthreshold PTSD (Other- and Unspecified- Trauma and Stressor Related Disorder), b) study psychiatrist's judgment that SSRIs are an acceptable treatment option for participants' presenting concerns, and c) interest in starting a trial of an SSRI..

Exclusion criteria will consist of: a) current or past history of bipolar I disorder, schizophrenic or other psychotic disorders, b) current organic brain disorder including severe traumatic brain injury, factitious disorder, or malingering, c) pregnancy, d) major neurological problems, e), current substance use disorder with symptoms present within the past three months, f) active risk to self or others, g) evidence of clinically significant hepatic or renal disease or any other acute or unstable medical condition that might interfere with safe conduct of the study, h) intolerance or hypersensitivity to sertraline, i) failed past trial of sertraline (confirmed by medical record review), j) use of drugs that directly affect the serotonin system (e.g., SNRIs, antipsychotics) within 3 months of the study, k) use of an SSRI within 3 months of the study. Use of other psychotropic medications must have been stable for 3 months prior to enrollment and remain stable throughout participation, l) hearing impairment for 780 Hz tones, m) current enrollment in trauma-focused psychotherapy, and n) for those participants who currently have a non-VA or VA psychiatrist or primary care provider who is willing to prescribe medications, they must be willing to sign a release of information (ROI) for study staff to communicate with their providers and the provider believes that including the participant in the study is potentially appropriate. As discussed above, we will inform the participant that we will share the following information with their current relevant care provider: information about the design of the study, inclusion and exclusion criteria, the participant's psychiatric and medical diagnoses as well as illness severity, as assessed in the screening evaluation, and any history of safety issues such as risk to self or others. If the participant doesn't sign a release of release of information (ROI) to contact the provider, the participant will not be entered into the active study.

3.5 Study Evaluations

Assessment measures (see Table 2 for Assessment Timeline and the Appendix for measures)

The following measures will be included as: a) a predictor of SSRI response; b) a secondary exploratory ERP task that may be associated with SSRI response; c) outcome measures; d) assessments of inclusion criteria or potential covariates; and e) assessments of medication use, adherence, and side effects.

Table 2. Assessment Timeline – The measures included in the table below are anchored to standard use during baseline and to past week during subsequent assessments.

Measure	Consenting session	Screening session1	Screening session 2	pre-placebo (week 0)	pre-sertraline (week 2)	1 month post-sertraline (week 6)	3-months post-sertraline (week 14)***	Additional Brief Psychiatry check-in Visits (weeks 4, 8, 10, 12, 17)
LDAEP				X			X	
P300				X	X	X	X	
Outcome measures*								
CAPS-5		X					X	
HAM-D		X					X	
PCL-5			X	X	X	X	X	X
QIDS-SR			X	X	X	X	X	X
DASS-21			X	X	X	X	X	
PANAS			X	X	X	X	X	
SCL90-R			X	X	X	X	X	
CSE-T			X	X	X	X	X	
ISMIS			X	X	X	X	X	
EASI			X	X	X	X	X	
Other measures								
LEC-5**		X						
Demographics and medical hx screen			X					
Urine toxicology, cotinine and pregnancy, alcohol GGT, saliva alcohol test strip			X	X			X	
SCID-5		X						
FTND			X	X	X	X	X	
AUDIT			X	X	X	X	X	
DFAQ-CU			X					

TLFB-cannabis			X	X	X	X	X	
TLFB- alcohol			X	X	X	X	X	
CSS-RS		X		X	X	X	X	X
PABQ			X					
Review of clinical laboratories as well as through data collected during this session through a physical examination, and a neurological evaluation			X					
Collecting vital signs			X	X			X	
EKG (may be repeated at physician's discretion)			X					
Clinical labs (clinical labs of concern may be repeated as needed)			X				X	
Assessment of medication use, adherence, and side effects (FIBSER only administered if side effects reported in interview)				X	X	X	X	X
Pill count				X	X	X	X	X
Platelet and plasma serotonin reuptake measurement				X		X	X	
Serum sertraline level				X			X	
Progesterone and metabolites, estradiol, NE, ACTH				X			X	
Hearing test			X					
DNA and RNA				X			X	

Compensation schedule* **	$10 for consenting if in-person to offset travel	$60 for session 1	$50 for session 2	$120	$40	$40	$150	$20

**** NOTE:** Self-report measures collected during screening sessions 1 and 2 (PCL-5, QIDS-SR, DASS-21, PANA, SCL90-R, CSE-T, ISMIS, EASI, Demographics and medical hx screen, PABQ, TLFB, DFAQ-CU, FTND, and AUDIT) will be mailed or electronically sent (via Qualtrics link or PDF) to participants following the consenting call, and then completed between screening sessions 1 and 2. Participants completing the consenting procedures in person may complete some components of screening sessions 1 and/or 2 if they choose (as discussed in protocol text). Participants will mail self-report measures to study staff following Session 1 or send the self-report measures electronically via Azure email or via Qualtrics; see page 13 for more details.*
***** NOTE**: The LEC-5 may be completed as a self-report measure or verbally administered by study staff at any point after the ICDs are received by study staff.*
***NOTE: Any additional visits for repeat clinical labs required will be compensated with $10 and travel costs (except for repeat labs solely due to failed drug screen).*
****NOTE: Week 14 procedures will occur when a participant ends participation in study regardless of where they are at in the study session*

a) LDAEP as a predictor of SSRI response and potential outcome measure
a.1) LDAEP: Because LDAEP will be assessed as a pretreatment predictor and potential outcome measure, LDAEP will be measured at two of the four assessment sessions. We will use the same procedures that were used in our previously funded CIMIT pilot study. Testing will occur in a sound-attenuated room connected via wires to an adjoining portion of the laboratory in which the experimental apparatus is located. Participants will be seated upright in a comfortable armchair.

Electroencephalogram (EEG) activity will be recorded from the midline frontal, central and parietal sites (Fz, Cz, and Pz; 10-20 System)[71] using Ag/AgCl electrodes embedded in a nylon cap, referenced to linked earlobes, and grounded at the forehead. Electrooculogram (EOG) activity will be recorded at the outer canthus and infraorbitally to the left eye. Impedances will be kept below 5 Kohms. Signals will be amplified with a bandpass of 0.1-150 Hz using a Neuroscan SynAmps system and sampled at the rate of 1000 Hz with a resolution of .049μV/bit (Neuroscan, Inc) from 100 msec pre- to 500 msec post-stimulus onset. Trials with excessive eye-movement artifact (EOG range ±85 μV) will be excluded. Prior to averaging waveforms, signals will be digitally filtered at 0.1-30 Hz (12 dB/oct). Peak and latency measures for P2 components will be determined using a Neuroscan automated scoring program. Selected peaks will be verified by visual inspection. All auditory stimuli will be generated by STIM software (Neuroscan, Inc) and will be presented binaurally over insert earphones.

Following the procedure employed in our previous studies,[20] stimuli will consist of 500 msec, 780 Hz tones gated with rise and fall times of 25 msec. The tones will be presented at four intensities (i.e., 74, 84, 94, and 104 dB SPL) in four blocks of 16

tones, repeated four times in a Latin-Square design for a total of 256 tone presentations. The interstimulus interval will range from 2-4 sec, with a mean interval of 3 sec. This procedure will last approximately 13 minutes. All participants will receive the following instructions:

> "In this session you will hear a series of tones. The tones will vary in loudness from soft to very loud. You do not have to respond to the tones, but you should stay alert and pay attention to the tones while remaining relaxed. We ask that you try to keep your body and especially your eyes as still as possible. Try not to blink your eyes immediately before, during, and immediately after the tones. In between the tones you will have a couple of seconds to blink before the next tone. We have placed a cross in front of you as a place to focus your eyes. Use the cross as a place to look to help keep your eyes from wandering. Do you have any questions?"

P2 peak amplitude and latency measures will be determined at the Cz site from each participant's averaged waveforms for each stimulus intensity. P2 will be defined as the most positive point between 140-230 msec post-stimulus onset relative to the 100 msec pre-stimulus baseline. Other auditory-evoked ERP component data will be scored and analyzed in addition to the P2 component: specifically, the N1 component amplitude, and the P1/N1 and N1/P2 peak-to-peak amplitudes. Although P2 intensity dependence slopes are thought to reflect stimulus intensity changes more accurately than these other component slopes,[72] examination of the full set of components may add to our understanding of P2's role (e.g., P2 may be selective for serotonin).

As discussed above, the slope of the change in P2 response amplitude across a series of increasing sound intensity levels (74, 84, 94, and 104 dB) is calculated and represents the LDAEP.[38] Log transformations will be used before creating the slopes to minimize overdependence on the lowest and highest sound intensity levels. We will also test alternative methods to determine if these methods better predict SSRI response. These include a) a more parsimonious scoring method of calculating a difference score between the first and last value; and 2) a curvilinear regression model of the four sound intensity levels.

a.2) P300. Because P300 will be assessed as a secondary pretreatment predictor and potential outcome measure in relation to LDAEP, P300 will be measured at two of the four assessment sessions. Testing will occur in the same sound-attenuated room in which LDAEP was tested. Participants will be seated upright in an armchair facing a monitor set approximately 75cm away.

Electroencephalogram (EEG) activity will be recorded in the same configuration as for LDAEP (Fz, Cz, and Pz; 10-20 System) using Ag/AgCl electrodes embedded in a nylon cap, referenced to linked earlobes, and grounded at the forehead. Electrooculogram (EOG) activity will be recorded at the outer canthus and infraorbitally to the left eye. Impedances will be kept below 5 Kohms. Signals will be amplified with a bandpass of 0.1-150 Hz using a Neuroscan SynAmps system and sampled at the rate of 1000 Hz with a resolution of .049μV/bit (Neuroscan, Inc) from 100 msec pre- to 500 msec post-

stimulus onset. Trials with excessive eye-movement artifact (EOG range ±85 μV) will be excluded. Prior to averaging waveforms, signals will be digitally filtered at 0.1-30 Hz (12 dB/oct). Peak and latency measures for P3 components will be determined using a Neuroscan automated scoring program. Selected peaks will be verified by visual inspection.

All visual stimuli will be generated by STIM software (Neuroscan, Inc) and will be presented at the center of the screen. Drawing from methods used in recent studies, target stimuli (odd numbers: 1,3,5,7) will be presented for 30 trials (20% probability) and standard stimuli (even numbers: 2,4,6, 8) will be presented for 120 trials (80% probability) for a total of 150 trials. Before each task trial, a 100ms fixation cross will be presented, followed by blank intervals ranging from 700-1000ms. Then the target or standard stimuli will be presented for 500ms, followed by a 500ms interval before the next trial. The procedure will last approximately 5 minutes. All participants will receive the following instructions:

“In this session you will see a series of numbers, one through eight, on the screen. Please only keep count of how many ODD numbers- one, three, five, seven- you see. We’ll ask you to report your count afterwards. Otherwise, you do not have to respond, but you should stay alert and pay attention for the duration of the task. We ask that you try to keep your body and especially your eyes as still as possible. Try not to blink your eyes immediately before, during, and immediately after the number is presented. We have placed a cross in front of you as a place to focus your eyes. Use the cross as a place to look to help keep your eyes from wandering. Do you have any questions?”

P3 peak amplitude and latency measures will be determined at the Cz site from each participant’s averaged waveforms. P300 amplitude will be measured as the voltage of the largest positive peak of target ERP within 250–500 ms. P300 latency will be measured as the time from stimulus onset to the maximum positive amplitude within 250–500 ms.

c) Psychiatric Symptom Outcome Variables:

PTSD symptoms will be assessed by structured diagnostic interview using the CAPS-5[73] and by self-report with the Posttraumatic Checklist (PCL-5).[74] Depression symptoms will be assessed by clinical interview using the 6-item unidimensional core Melancholia subscale of the Hamilton Depression Rating Scale (HAM-D).[75] This subscale has outperformed the gold-standard 17 item HAM-D in detecting efficacy of antidepressants. The Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR)[76] will be administered as a secondary outcome measure for depression. The Depression, Anxiety, and Stress Scale-21 (DASS-21)[77] will be used as an additional outcome measure of depression, as well as a measure of anxiety and stress symptoms.

The Symptom Check List 90-Revised (SCL-90-R)[78] will be included as a measure of general psychiatric distress. The PANAS will be included as a measure of positive and negative affect. The Trauma Coping Self-Efficacy (CSE-T) will be included as a measure of perceived ability to cope with challenges and demands from a traumatic event. A modified version of the Internalized Stigma of Mental Illness Scale (ISMIS) and three subscales of the Endorsed and Anticipated Stigma Inventory (EASI) will be included to measure different facets of self-stigma about mental illness. These measures will be administered during the initial screening assessment (anchored to standard anchors or one month if no standard anchor).

In addition, these outcome measures (anchored to the past week), along with LDAEP, will be assessed at week 0 (pre-placebo), and week 14 (3-months after starting sertraline) or at the point they wish to stop taking the study medication and end participation. The 3-month assessment was chosen because 12 weeks is commonly considered to be a necessary length of time to accurately determine the extent of possible therapeutic benefit from most SSRI medications.[79, 80]

c.1) The CAPS-5[73] is the “gold standard” clinical interview for assessing PTSD. This measure will be used to characterize the sample regarding PTSD diagnosis and as a measure of PTSD severity. Each of the 20 symptoms of PTSD included in DSM-5 is rated on a 5-point scale ranging from 0-4, with a 0 or 1 indicating that the symptom is absent or subthreshold and a score of 2-4 indicating that a symptom has reached the threshold to be included as a symptom and ranges in severity from moderate to extreme. The total range of the CAPS-5 is 0-80.

c.2) The HAM-D[75] is the most widely used clinician-administered scale for assessing severity of depression symptoms. The 6-item unidimensional core Melancholia subscale of the HAM-D will be used as our primary depression outcome variable.

In order to ensure high inter-rater reliability on clinical interviews, interviewers will be trained to criterion on the CAPS-5 and the HAM-D (95% agreement regarding diagnoses) using structured training materials. Assessments will be administered by independent assessors who are not familiar with study hypotheses and who will be blind to study design with regard to timing of placebo. Ten percent of these tapes will be re-rated by another interviewer who is blind to diagnosis. To further aid in diagnostic reliability, Dr. Michelle Bovin will lead diagnostic consensus meetings.

In addition to the clinical interviews, self-report measures of PTSD and depressive symptom severity and anxiety will be included as secondary outcome measures. Self-report scales are often found to be more robust against placebo effects than clinical interview.[69]

c.3) The PCL-5[74] is a 20-item measure that assesses DSM-5 symptoms of PTSD. Participants will rate how much they experienced each symptom on a 5-point Likert-type scale (0 = "not at all" to 4 = "extremely") during the past week (total range=0-80). The PCL-5 will be anchored to participants' worst traumatic event. In addition to the administration of these measures during the four assessment sessions, the PCL-5 will also be administered bi-weekly at each psychiatrist check-in visit.

c.4) The QIDS-SR[76] will be used to measure the severity of depressive symptoms. The QIDS provides equivalent weightings (0-3) for each symptom item, gives clearly stated anchors that estimate the frequency and severity of symptoms, and includes all items required to diagnose a major depressive episode.

c.5) DASS-21[77] is a 21-item measure that assesses the severity of a range of symptoms common to depression, anxiety, and stress. The total score can be used as a measure of general distress or depression, anxiety, and stress subscales can be scored separately.

c.6) SCL-90-R[78] measures the following nine primary psychiatric symptom dimensions: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. The Global Severity Index (GSI) is the average rating given to all 90 items and provides a measure of general psychopathology.

c.7) The PANAS (Watson et al. 1988).consists of two, 10-item mood scales that measure positive (e.g., ‘‘enthusiastic’’) and negative (e.g., ‘‘upset’’) affect separately.

c.8) CSE-T (Benight et al., 2015) is a 9-item measure using a 7-point Likert scale ranging from 1 ("not at all capable") to 7 ("totally capable") that assesses current perceived ability to cope with trauma-related stressors.

c.9) ISMIS (Ritsher, Otilingam, & Grajales, 2003) is a 29-item measure using a 4-point Likert scale ranging from 1 (“strongly disagree”) to 4 (“strongly agree”). We replaced the term “mental illness” with “PTSD” to assess internalized stigma about PTSD specifically as all the focus of this study is on treatment to address posttraumatic symptoms.

c.10) EASI (Vogt, Leone, Wang, Sayer, Pineles, & Litz, 2014) is a measure consisting of 8-item subscales using a 5-point Likert scale ranging from 1 (“strongly disagree”) to 4 (“strongly agree”). The three subscales administered in this study are Beliefs About Mental Illness, Beliefs About Mental Health Treatment, and Beliefs About Treatment Seeking, to assess internalized stigma about seeking treatment for mental health problems.

d) Diagnostic interviews and self-report measures included to assess inclusion criteria, for use as potential covariates, or as additional pre-treatment predictor variables.

d.1) The Structured Clinical Interview for DSM-5 Disorders (SCID-5)[8] is a semi-structured diagnostic interview that assesses a range of diagnoses. The following SCID modules will be assessed: Non-patient overview, core screening, enhanced screening, Module A_without specifiers, Module BC screen, Module D, module E, module F, Module G, Module I, and module K. This interview will be conducted at the in-person screening session to assess exclusion diagnoses and to characterize comorbid psychiatric diagnoses.

d.2) The CSS-RS [9] will be administered by clinical assessor or study psychiatrist to assess potential suicidality at intake, during each assessment session and psychiatrist visit.

d.3) The Life Events Checklist for DSM-5 (LEC-5) Extended Version[81,94] solicits and rates the frequency of previous traumatic event(s) in the participant's life. This will be used to assess whether a participant has experienced a traumatic event and to identify the index trauma for the CAPS-5 and PCL-5 assessments.

d.4) The Fagerström Test for Nicotine Dependence (FTND)[82] is a 6-item test that measures heaviness of cigarette smoking and will be used as a potential covariate.

d.5) The AUDIT Alcohol Consumption Questions (AUDIT-C)[83] is a 3-item alcohol screen that aids in identifying persons who are hazardous drinkers or have active alcohol use disorders. This will be used as a potential covariate.

d.6) A questionnaire assessing demographics, psychiatric, and medical history will be administered during the in-person screening session to characterize the sample and assess relevant inclusion/exclusion criteria.

d. 7) Using an audiometer (AMBCO, model 640A), participants' hearing threshold for 780 Hz tones will be estimated using a 5-dB descending and ascending staircase method. Participants will be fitted with headphones and face away from the audiometer.

Using a frequency of 1000 HZ, we will start with a tone of 50 dB. Starting with the right ear, we will present the tone by pressing the "tone" button for 1-2 seconds. If the participant responds, we will lower the hearing level in 5 dB increments and repeat until the participant no longer responds. This will be repeated for the left ear. The lowest dB to which the participants responded for each ear will be recorded. Participants who test as having moderately severe, severe, or profound hearing loss (i.e., an average threshold level greater than 55 dB across both ears) will be excluded from the study.

d. 8) The Daily Sessions, Frequency, Age of Onset, and Quantity of Cannabis Use Inventory (DFAQ-CU; Cuttler & Spradlin, 2017) will be used to assess daily sessions, frequency, age of onset, marijuana quantity, cannabis concentrate quantity, and edibles quantity.

d. 9) A modified version of the Timeline Followback Method for Drugs, Cigarettes, and Marijuana originally developed by Sobel and colleagues (1996; TLFB-cannabis) will be used to track ongoing cannabis use.

d. 10) A Timeline Follow Back developed by Linda and Mark Sobell (1992; TLFB) will be used to track ongoing alcohol use.

d.11.) The Posttraumatic Avoidance Behaviour Questionnaire (PABQ; Van Minnen & Hagenaars, 2010) will be included as a measure of trauma-related avoidance. The PABQ is a 25-item measure using a 4-point Likert scale ranging from 1 ("(almost) never") to 4 ("(almost) always") that index distinct forms of posttraumatic avoidance; scores are summed to create the subscales and total score (ranging from 25-100), with higher scores indicating more severe avoidance.

e) Assessment of medication use, adherence, and side effects via multimodal assessment

e.1) Pill counts will also be conducted at each remote psychiatry appointment.

e.2) Self-report measures of medication use, adherence, and side effects will also be completed at each assessment session and brief psychiatrist check-in. Medication side effects will be determined via a clinical interview during the psychiatrist check in. If participants report medication side effects, they will be asked to complete the 3 item FIBSER—a three item measure of frequency and intensity of side effects of antidepressant medications. Participants will be asked to answer these 3 questions regarding their global experience of side effects, as well as regarding each reported side effect.

e.3) Finally, medication adherence will be measured biochemically via serum sertraline levels and plasma and platelet serotonin (5HT) concentration.

Analytes from sertraline in human serum will be quantified using an Agilent 6460 Triple Quadrupole Liquid Chromatography Mass Spectrometry system. Peak integration will be performed using the Agilent Mass Hunter Quantitative Analysis software and the AUC of each analyte will be normalized to the AUC of the internal standard. Samples will be spun at 600 g for 10 min at room temperature. Serum will then be drawn off and stored at -20 degrees Centigrade until shipped to CAVHAS PAL on dry ice.

Whole blood platelet 5-HT concentrations will be quantified using HPLC-fluorometic methods.[84] Westgard procedures for quality control will be used. Samples will be collected in small EDTA-anticoagulated tubes and aliquots of 500 µL whole blood will be place in cryogenic tubes; an internal standard, alpha-methyl-5-HT, will be added. Samples will be stored at -20 degrees Centigrade until shipment to CAVHAS PAL on dry ice.

The data from the multimodal assessment collectively will be used to determine whether participants received an adequate dose degree of sertraline. In the event of inconsistent data among the panel of measures, a consensus group who are unaware of LDAEP scores (e.g., Dr. Rasmusson, Dr. Houranieh) will review the array of adherence measures to determine whether it is consistent with compliance. For example, having a sertraline level of zero in the context of adequate pill counts and MEMS data would be considered inconsistent with protocol adherence.

f) Assessment of alternative neurobiological mechanisms of SSRI response

1. Progesterone and its neuroactive metabolites including ALLO s will be measured using GC-MS in the laboratory of Dr. Graziano Pinna at University of Illinois at Chicago following published measures. {Pineles, 2018 #2189}

2. NE, ACTH: NE will be measured using HPLC in the laboratory of Dr. George Anderson at Yale University and ACTH will be measured using immunoassay in the laboratory of Dr. Richard Hauger at UCSD/SDSU.

3. Menstrual phase. For premenopausal women not on hormonal contraceptives, we will track menstrual cycle phase. A urine test kit will be used to determine the day of the mid-cycle luteinizing hormone (LH) surge which occurs ~24 hours before ovulation and initiation of the LP. Urine will be tested for LH surge during all study visits. Women will be instructed to use the LH surge test kit on non-visit days until LH surge is detected and they will receive reminder phone calls to improve adherence. Participants will be reminded to call when the LH surge occurs. We will also ask female participants at each visit whether they have begun menstruating and on what date. Additionally, at each session during which blood is drawn, progesterone and estradiol will be measured by Dr. Hauger's laboratory at UCSD/SDSU using solid-phase RIA (Coat-A-Count, Diagnostic Products Corporation, Los Angeles, CA), which has a sensitivity of 0.5 ng/ml. The intra-assay CV for progesterone and estrogen is <5%; the inter-assay CV varies from 5-12%.

4. For participants who consent during the informed consent process (and initial the ICF), 20 cc of blood will be drawn for genetic testing (DNA and RNA banking) during the screening session and at 3 month follow up.

Blood Sampling:

30 cc of blood will be drawn for medical testing during the screening evaluation and 30 cc of blood will be drawn two times (week 0 and week 14 [or at the point they wish to stop taking the study medication and end participation]). An additional 20 cc of blood will be drawn at week 0 and week 14 [or at the point they wish to stop taking the study medication and end participation] for banking DNA and RNA samples from participants who opt-in to this during the informed consent process. Blood samples will be processed by MAVERIC personnel. Samples will be placed on ice and spun immediately in a refrigerated centrifuge prior to aliquotting and freezing at –70°C in the MAVERIC repository.

3.6 Data Analysis

Power Analysis

Primary analyses will focus on the strength of the relationship between LDAEP and clinical improvement following SSRI treatment. For power=.80 and alpha=.05 (two-tailed), the proposed sample of N=94 study completers will allow for the detection of a moderate effect size (r=.30). Power analyses for identification of a cutoff value to differentiate probable SSRIs responders from non-responders (Aim 2) indicate that the proposed sample size will allow for detecting an area under the curve (AUC) of .65 (for power=.80 and alpha=.05).[5] The rule of thumb when developing a diagnostic test is to use a sample size that can detect an AUC of .80.[4] AUC values range from 0-1, whereby larger AUCs indicate better discrimination between responders and non-responders on a diagnostic test, i.e., the LDAEP. Having power to detect an AUC of .65 indicates that our sample size exceeds that needed to detect an AUC of .80. These calculations include adjusting for a conservative estimate that excludes 10% of participants who are placebo responders during the placebo lead-in period.[84] Because we are using intent-to-treat analyses, participants who dropout of the study will not impact power. We also calculated power for the treatment completers with an estimated 30% dropout rate from the non-placebo responder subsample (n=60). With this subsample, we will still be able to detect a slightly larger than moderate effect size (r=.36) and detect of an AUC of .68, exceeding the sample size needed to detect an AUC of .80.[2, 3]

Statistical Plan and Data Analysis

Multilevel (i.e., mixed-effects) growth modeling using the Mplus[85] software program will be conducted to examine changes in symptoms of PTSD, as well as depression, anxiety, and general distress across assessments at week 2 (pre-sertraline), week 6 (1 month after starting sertraline), and week 14 (3 months after starting sertraline). Time will be modeled using days since medication initiation. As discussed above, individuals who show meaningful symptomatic reduction during the placebo lead-in phase, 50% improvement on the PCL-5 and QIDS-SR will be excluded from the analyses. These

models will be used to test Hypothesis 1 (Aim 1), Hypothesis 2 (Aim 3), and Exploratory Hypothesis 3 (Aim 3). This approach is the gold-standard for analyzing changes due to an intervention and: a) is state-of-the-art for analyzing unbalanced data sets due to dropouts, loss to follow-up, or missing data, b) offers extreme flexibility in how time is modeled (i.e., linear or non-linear, categorical or continuous), c) can specify a variety of covariance structures, d) uses powerful estimation procedures, and e) can evaluate the impact of a variety of different types of predictors and covariates (categorical or continuous, time invariant or varying). In addition to using full information, maximum-likelihood estimation procedures, which are extremely robust to missing data,[88] the use of multilevel regression will allow one of several methods to be used to correct biases due to missing data, e.g., pattern-mixture modeling.[89] Before testing the primary study hypotheses, we will test alternative unconditional change Level-1 models (i.e., change without predictors) to determine the most reliable and powerful way to model time/change in symptoms (e.g., linear vs non-linear change, proper covariance structure). We expect a non-linear pattern of change with minimal symptom change during the placebo period that is followed by a substantial decrease in symptoms during the sertraline phase. We will evaluate multiple non-linear models including the use of power polynomials (i.e., time and time-squared), a natural-log transformation of time, and piecewise growth models that break the overall trajectory into multiple components (i.e., placebo and sertraline phases). The differences in the -2 log-likelihood value (i.e., deviance statistic) across models will be used to determine the best fitting model.

For the intent-to-treat analyses: To address the potential issue of medication noncompliance, participants who took an inadequate dose of sertraline (i.e., <80% of doses or as determined by consensus panel after reviewing the panel of adherence measures described above) will be considered as non-responders for the purposes of Aim 2. For the other analyses, their data will be considered missing for the data points after which they became medication noncompliant.

In addition to running the analyses with the intent-to-treat sample, analyses will also be conducted in the per-protocol sample of study completers who received an adequate dose of sertraline (i.e., ≥80% of doses or as determined by consensus panel after reviewing the panel of adherence measures described above).

To test Hypothesis 1 (Aim 1), LDAEP at baseline will be added as a Level 2 predictor of the change parameters to evaluate the impact of LDAEP on PTSD, depression, anxiety, and general psychiatric symptom trajectories. These analyses will be conducted for the intent-to-treat sample, excluding placebo responders, and per-protocol sample of study completers.

To address Aim 2 and answer the practical question of whether LDAEP is a useful treatment predictor, we will determine such test attributes as sensitivity, specificity, and resultant number of false positives and negatives. As a first step we will determine cutoff values for LDAEP that maximally predict positive or negative clinical outcomes. Above a certain point the clinician would decide to use SSRIs, while below a certain point the provider would not use an SSRI.

Participants will be dichotomized into two groups on the basis of positive treatment response or negative treatment response based on clinical outcome measures. Discriminant analysis will be used to identify the LDAEP cut-off value that optimally separates treatment non-responders from responders. These analyses will be run two ways. First, analyses will include all participants, i.e., including study dropouts. A sertraline non-responder will be identified as a participant who is: a) no longer taking the prescribed sertraline or took an inadequate dose of sertraline (i.e., < 80% of doses or as determined by consensus panel after reviewing the panel of adherence measures described above), or b) who is taking sertraline as prescribed, but has not made clinically significant improvement on the CAPS-5, HAMD, PCL, or QIDS-SR (i.e., 50% decrease in symptom severity). Based on these two criteria, we anticipate that approximately 50% of the sample will be defined as non-responders. A sertraline responder will be a participant who is taking the prescribed dose of sertraline and has made clinically significant improvement on clinician or self-report measures of PTSD or depression. Second, because it is possible that study dropouts may add additional error variance, we will rerun these analyses excluding study dropouts. Thus, a sertraline non-responder for this set of analyses will only include those who are taking an adequate dose of sertraline but have not made clinically significant improvement on the clinical or self-report measures of PTSD or depression.

To address Hypothesis 2 (Aim 3), we will use a similar approach as described above for Hypothesis 1, but with a slight variation. We will test a multivariate change model[90] that estimates change in both the predictor variable (i.e., LDAEP) and the outcomes (i.e., PTSD, depression, anxiety, and general psychiatric symptoms). Mplus readily estimates multivariate models and will allow us to regress the change parameters of the outcomes on the change parameters of the predictors to test the hypothesis that change in LDAEP predicts change in symptoms. These analyses will be conducted for both the intent-to-treat sample, excluding placebo responders, and per-protocol sample of study completers.

To address Exploratory Hypothesis 4 (Exploratory Aim 4), the analyses will parallel those used to address Aims 1 and 2 but will be performed separately for men and women. This aim is exploratory as it will not be fully powered, but will provide effect size estimates and data to address whether cutoffs need to be gender specific and tested in larger samples.

In the above analyses, sertraline dosage and compliance, as well as gender, age,[21] nicotine use, alcohol use, and menopausal status and hormone therapy use (for

women) will be examined as potential covariates. We will also consider change in pre-placebo assessment to pre-sertraline assessment LDAEP and clinical symptoms for use as potential covariates indexing placebo response.

3.7 Withdrawal of Subjects

We may end subjects' participation in the study early if they are unable to respond to interview questions (for example, due to substantial cognitive or psychological impairment, extreme drowsiness, or due to the immediate effects of substance use) or display aggressive or inappropriate behavior towards study staff. Subjects also could be terminated from study if you fail the drug or alcohol screens. We may also discontinue participation in this study if subjects are at immediate risk of harming themselves or others. In that event, we will follow all applicable laws and assist them in obtaining appropriate clinical care.
If participants wish to terminate the study early, we will urge them to work with the study physician to safely taper off the sertraline.

4.0 Reporting

Data and Safety Monitoring

Participation in this study presents relatively small risks to the participants. Should any serious adverse events (SAE) occur, they will be reported within 48 hours to the VABHS IRB. In the event of a death, we will use the VA IRB SAE form to alert the IRB immediately. In addition, we will summarize all adverse events (cumulative and annual) in our annual request for IRB re-approval. The PI will also regularly consider whether any adverse event affects the Risk/Benefit ratio of the study and determine whether modifications to the protocol (risks section) or consent form (risks and inconveniences sections) are required. We will assure the accuracy and integrity of the data by checking completeness of assessments prior to the end of each session and scoring electrophysiological data as it is collected. These strategies will help reduce the likelihood of incomplete or problematic data.

In addition, we will work with the CSR&D Data Monitoring Committee (DMC). This is a service CSR&D provides to ensure independent oversight of the safety and integrity of this project.

Data destruction: Audio/visual recordings on tape and/or printed photographs will be shredded.

Suspected information security and privacy incidents will be reported within one hour to the Information Security and Privacy Officers and Research Administration.

5.0 Privacy and Confidentiality

Information collected for the purpose of this research study will be kept confidential as required by law.

PHI is protected in the following way: Only the research team will have access to the information collected from you for this study. The paper data collected from this study will be kept in a locked cabinet in a locked office, while the electronic data will be coded and stored without personal identifiers. Any personally identifiable information will be kept on a separate drive of the computer with password protection or in a locked cabinet in a different locked office from the other information collected in this study.

Blood samples labeled with only the subject code will be processed and stored using the appropriate procedures in the MAVERIC biorepository located within VA Boston. The blood samples will be sent for measurement of sertraline levels and serotonin levels from the VA MAVERIC bio-repository to the CAVHS. The blood samples will be sent for measurement of stress hormones and other chemicals to VA or non-VA laboratories. These samples will be labeled only with subject code. Researchers at these laboratories will not have access to identity or any individual private, protected health information.

Clinical interviews will be audiotaped for training and reliability purposes, and to help clinicians make accurate psychiatric diagnoses. These audio files will be saved on a limited access folder on a secure VA server with only subject number as a label. Only members of the research team will have access to the audio recordings. Digital audio recordings will be deleted from the recording device.

Any personally identifiable information (i.e., Informed Consent Form) will be kept in a locked cabinet in a different locked office from the other information collected in this study.

We have obtained a Certificate of Confidentiality from the National Institutes or Health.

Records will be destroyed, when allowed, in the following manner:

- Paper records will be shredded
- Electronic records will be destroyed in a manner in which they cannot be retrieved.
- Digital images (photographs, x-rays, scans, video/audio recordings, etc) will be destroyed in a manner such that they cannot be retrieved.
- Audio/visual recordings and/or printed photographs will be shredded.

Data (not including the audio recordings) will be entered into a data repository and may be used for future studies approved by an IRB. This data repository is called the Biological Predictors of PTSD and Treatment Data and Specimen Repository. Dr. Suzanne Pineles is the Principal Investigator of this repository and it is located at VA

Boston Healthcare System. Only authorized personnel on the Biological Predictors of PTSD and Treatment Data and Specimen Repository (R&D #1592602) will have access to the data in this data repository. If participants opt in, genetic information will also be stored in this data repository.

6.0 Communication Plan

Study SOPs are generated and adhered to based on the most up to date IRB-approved procedures. Study staffed are trained by the PI and observed as they are learning the protocol. Data, ICFs, and HIPPAs are routinely checked to ensure compliance.

7.0 References

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