

V17 8/19/24

Title of Study: Enhancing Prolonged Exposure Therapy for PTSD with Oxytocin  
NCT04228289

Document Date: 8/19/2024

## SPECIFIC AIMS

Posttraumatic stress disorder (PTSD) is a chronic, debilitating condition and the most common mental health disorder among treatment-seeking Veterans<sup>1,2</sup>. The high rates of disability and healthcare utilization among Veterans with PTSD result in substantial economic burden for the individual Veteran, their family, and our nation<sup>3</sup>. Veterans with untreated PTSD are at risk of developing other mental health problems (e.g., depression, anxiety, suicidal ideation, and substance abuse), as well as social and occupational impairment. Prolonged Exposure (PE) therapy is a highly efficacious, evidence-based, cognitive-behavioral treatment for PTSD<sup>4,5</sup>. In 2007, a nationwide rollout of PE was initiated at the direction of the VA Mental Health Services in order to train VA clinicians across the country in the delivery of PE. While the nationwide rollout of PE was an important step in reducing the burden of PTSD among Veterans, there is an immediate need for empirical data to further enhance PE retention and outcomes. Although PE is one of the most effective treatments for PTSD, approximately 30% of patients dropout before treatment completion<sup>4,6-10</sup> and a significant proportion of patients who do complete PE continue to experience unremitting PTSD symptoms<sup>2,11</sup>. Furthermore, in comparison to civilians, Veterans demonstrate the highest dropout rates and the lowest treatment response to PE<sup>7</sup>. Thus, there is a critical need to develop effective strategies to optimize the delivery of PE and improve outcomes for Veterans with PTSD. **Building on promising preliminary data, the proposed study directly addresses this knowledge gap by testing the efficacy of oxytocin in combination with PE to accelerate reduction in PTSD severity and improve treatment retention and adherence.**

Accumulating research indicates that the neuropeptide oxytocin is a promising candidate to augment PE. Higher endogenous oxytocin levels are associated with improved fear extinction<sup>12</sup>, which is a central component underlying the positive effects of PE. In addition, preclinical and clinical research show that oxytocin has anxiolytic effects<sup>13,14</sup> and attenuates fear responses<sup>12,15,16</sup>. Therefore, converging evidence suggests that augmenting PE with oxytocin may simultaneously target the neurobiological and psychosocial underpinnings of PTSD, and result in improved treatment outcomes<sup>17-20</sup>. Our team conducted a proof-of-concept study to examine the combination of PE and oxytocin. In this randomized, placebo controlled, double-blind pilot study we found that individuals with PTSD who were treated with PE and intranasal oxytocin (40 IU) for 10 weeks demonstrated greater reduction in PTSD severity and depression as compared to those treated with PE and placebo. Furthermore, the combination of PE + oxytocin was safe, feasible and well tolerated.

The primary objective of the proposed two-site Phase II study is to evaluate the ability of oxytocin in combination with PE to (1) reduce PTSD severity and (2) enhance retention and adherence rates among Veterans (N=210) with current PTSD. Secondary objectives are to evaluate oxytocin in combination with PE in improving associated areas of functioning (e.g., depression, sleep, aggression). We will also include physiological measurements to investigate mechanisms of change and identify prognostic indicators of positive treatment response. In order to accomplish this we will employ an intent-to-treat, double-blind, placebo-controlled randomized controlled trial that will consist of 10 weeks of PE treatment and intranasal oxytocin (40 IU) or placebo medication delivered prior to each PE session. We will also examine standardized, repeated dependent measures of: (a) PTSD symptom severity, (b) rate of PTSD symptom reduction and time to diagnostic remission, and (c) treatment retention and adherence. The following specific aims are proposed:

- Specific Aim 1:** Examine the efficacy of PE + oxytocin vs. PE + placebo in reducing self-report and clinician-rated PTSD symptomatology.
- Specific Aim 2:** Evaluate the ability of intranasal oxytocin, as compared to placebo, to accelerate PTSD symptom reduction (i.e., slope of change) and time to diagnostic remission.
- Specific Aim 3:** Examine the efficacy of PE + oxytocin vs. PE + placebo in improving treatment retention and adherence (e.g., number of sessions attended, homework compliance).

The proposed study will address critical questions regarding the potential of oxytocin as an effective pharmacotherapy to improve PE outcomes and retention among Veterans. This study has the particular advantage of building directly on positive preliminary findings; using a double-blind, placebo-controlled randomized design; measuring functioning in related areas, such as depression, suicidality, and aggression and

employing a multidisciplinary team of experts who have successfully collaborated in the past and are uniquely qualified to implement this type of investigation. This project is directly responsive to the mission of the Veterans Health Administration Blueprint for Excellence in that it seeks to advance mental health care for Veterans. The findings from this study have the potential to significantly improve the standard of patient care, advance the science in the area of PTSD, and decrease public health expenditures among Veterans.

## BACKGROUND AND SIGNIFICANCE

**Overview.** As a result of sustained operations in Iraq and Afghanistan, a large and growing number of Veterans are suffering from posttraumatic stress disorder (PTSD). Approximately 11% of the 8 million Veterans receiving care at the Department of Veterans Affairs (VA) are diagnosed with PTSD<sup>21</sup>, resulting in enormous healthcare expenditures for our nation<sup>3</sup>. While several behavioral interventions for PTSD have demonstrated efficacy, there remains a scarcity of effective pharmacological treatments for PTSD and ample room to improve existing behavioral interventions. To address this critical need, this two-site, Phase II, randomized, placebo-controlled trial will examine the synergistic effects of combining a novel pharmacotherapy (oxytocin) with an evidence-based treatment for PTSD (i.e., Prolonged Exposure therapy). We will examine the amount and rate of reductions in PTSD severity, treatment retention and adherence, and improvement in associated areas of functioning (e.g., depression, aggression, suicidality, sleep). This project may help optimize PTSD treatment, reduce the individual, familial, and societal burden associated with PTSD, and reduce public health expenditures associated with PTSD among Veterans.

**PTSD among Veterans.** Compared to civilians, Veterans incur a four-fold heightened risk for PTSD<sup>22,23</sup>. PTSD is a highly prevalent, chronic, and debilitating psychiatric condition characterized by: (1) intrusive cognitions, memories, and nightmares; (2) avoidance of people, places or situations that are reminders of the traumatic event(s); (3) negative cognitions and mood (e.g., thoughts and feelings related to guilt and shame); and (4) alterations in arousal and reactivity (e.g., trouble sleeping, aggression, exaggerated startle response). PTSD is the most commonly diagnosed mental health condition among U.S. military and Veteran populations<sup>1</sup>, and it is associated with extensive health and economic burdens. If left untreated, Veterans with PTSD are at risk for developing other psychiatric problems (e.g., depression), suicidality, interpersonal violence, physical health problems, neuropsychological impairment, increased mortality, unemployment, and family/occupational impairment. Recent estimates suggest that the cost of treating PTSD and depression alone, solely among Iraq and Afghanistan war Veterans, has exceeded \$900 million<sup>3</sup>. Therefore, the need to optimize PTSD treatment outcomes among Veterans is paramount.

**Prolonged Exposure (PE) Therapy for PTSD.** PE is a manualized, cognitive-behavioral treatment consisting of 10 weekly, 60-90 minute individual therapy sessions<sup>24</sup>. Based on Pavlovian learning theory, the central therapeutic component of PE involves repeatedly presenting a conditioned stimulus (i.e., a trauma reminder) (1) imaginably and (2) in-vivo (in the environment) in the absence of the unconditioned stimulus (i.e., the traumatic event). Abundant evidence documents the efficacy of PE for the treatment of PTSD across diverse clinical populations including Veterans from various eras of service<sup>6,25</sup>. On average, PE demonstrates a robust improvement of 1-2 standard deviations in symptom severity<sup>4,25,26</sup>. PE is recognized by the VA and the Department of Defense as one of only four evidence-based psychotherapies with sufficient empirical evidence to be deemed effective in the treatment of PTSD<sup>27</sup>. Indeed, PE is a “gold standard,” first-line psychosocial treatment for PTSD<sup>5</sup>. VA clinicians nationwide are trained to deliver PE; thus the proposed study will leverage an evidence-based treatment that is already widely implemented in VA healthcare settings across the country. While PE consistently outperforms control and waitlist conditions in randomized clinical trials<sup>8,26</sup>, there is a critical need to improve retention and there is substantial room to improve outcomes. PE dropout rates are approximately 30%<sup>2,10,28</sup>, with the highest dropout rates observed in military and Veteran populations<sup>7</sup>. Indeed, many Veterans struggle with distress and avoidance during treatment, and fail to receive an adequate dose of PE therapy<sup>9,10,24,29</sup>. As a result, a substantial proportion of Veterans maintain clinically significant symptoms and/or continue to meet diagnostic criteria for PTSD following an incomplete “dose” of PE treatment<sup>2</sup>. Pharmacological augmentation strategies may help optimize PE treatment response, enhance treatment retention and adherence, and significantly improve long-term outcomes for Veterans with PTSD.

**Pharmacotherapies for PTSD.** The PTSD Psychopharmacology Working Group within the VA Office of Research and Development recently determined that investing in the development of novel medications to treat PTSD is an urgent public health priority for our nation<sup>30</sup>. Findings from this group note that because

substantial advancements have been made in the science examining the neurobiology of PTSD, clinical trials examining novel medications are particularly critical to advance PTSD treatments for Veterans. While many medications have been investigated, only selective serotonin reuptake inhibitors (SSRIs) have received FDA approval to treat PTSD. However, findings show that only 20-30% of patients experience PTSD remission with SSRI treatment<sup>31</sup>. SSRIs have also not demonstrated improved patient tolerability or retention in psychotherapy, and results are mixed regarding whether augmenting PE with SSRIs is superior to PE alone<sup>32</sup>. Overall, little progress has been made toward developing new pharmacotherapies for PTSD.

**Neurobiological Mechanisms Underlying Oxytocin Treatment of PTSD.** Dysregulation of the oxytocin system, which includes functional impairments in the hypothalamic-pituitary-adrenal (HPA) axis and corticolimbic brain regions such as the prefrontal cortex (PFC) and amygdala (AMY), are well-established biomarkers of PTSD pathophysiology and maintenance. Individuals with PTSD evidence lower basal oxytocin levels as compared to healthy controls<sup>33</sup>, although one recent study found that endogenous oxytocin levels did not predict PTSD development over combat exposure<sup>34</sup>. Moreover, variants in the oxytocin receptor gene have been linked to the brain's responsiveness to stress. For example, recent findings from the National Health and Resilience in Veterans Study found that one polymorphism in the oxytocin receptor gene, in combination with attachment style, contributed to risk for PTSD among Veterans<sup>35</sup>.

With regard to corticolimbic brain functioning, recent imaging studies demonstrate hypoactivation of the PFC and hyperactivation of the temporal lobe (including AMY and hippocampus) among individuals with PTSD<sup>36</sup>. Compared to healthy controls, individuals with PTSD exhibit hyperactive AMY and hypoactive medial PFC activity<sup>37</sup>, and significant uncoupling between the medial PFC and the AMY during symptom provocation and at rest<sup>38</sup>. Dysregulation of the PFC-AMY circuitry makes it difficult to modulate repetitive cognitions (e.g., intrusive trauma-related memories), and impairs working memory, executive decision making, ability to distinguish between a memory vs. reality (e.g., flashbacks), and emotional control (e.g., exaggerated startle response)<sup>39,40</sup>. Importantly, oxytocin attenuates AMY reactivity and increases resting state connectivity between corticolimbic brain regions<sup>41</sup>. A recent study by our group demonstrates that oxytocin improves working memory and mitigates hyperactive AMY responses to fearful faces among individuals with PTSD compared to trauma-exposed resilient controls<sup>19,42</sup>. Oxytocin is a promising candidate to help restore the neurobiological impairments underlying PTSD and enhance long-term outcomes.

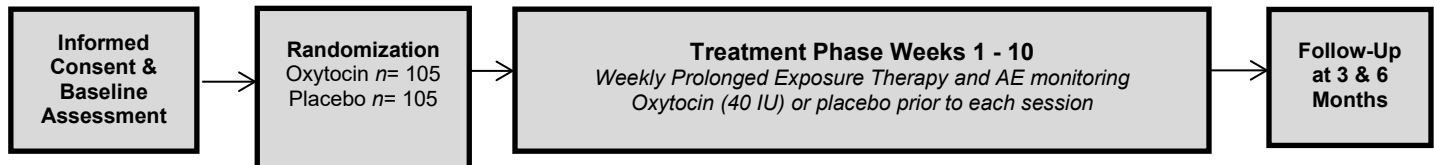
**Behavioral Mechanisms Underlying Oxytocin Treatment of PTSD.** Data indicate that central and systemic oxytocin administration exerts anxiolytic and anti-stress properties in animal models<sup>14,43</sup>, and oxytocin has anxiolytic and prosocial effects in individuals with PTSD, including increased trust, empathy, compassion, and improved social cue recognition<sup>13,44,45</sup>. Oxytocin has demonstrated the ability to reduce neurobiological reactivity to social stress among healthy individuals and those with PTSD using laboratory paradigms such as the Trier Social Stress Task<sup>46</sup>. In addition, oxytocin enhances fear extinction recall in healthy individuals, suggesting that oxytocin has potential as an adjunct therapy for extinction-based PTSD treatments such as PE<sup>15,18,47</sup>. A recent cross-sectional study among patients with PTSD found that a single dose of oxytocin had positive effects on anxiety, irritability, mood, intensity of intrusive thoughts, and desire for social interaction<sup>48</sup>. Our team recently found that pairing PE with weekly doses of oxytocin, as compared to placebo, resulted in lower self-reported PTSD and depression symptoms at end of treatment<sup>47</sup>. Dr. Miranda Olf (Consultant) and others have shown that oxytocin may synergistically mitigate some of the most salient behavioral, physiological, and social underpinnings of PTSD, thereby facilitating therapeutic alliance, adherence, and engagement, all of which are critical for positive outcomes in PTSD treatment<sup>49</sup>.

**Summary.** PTSD is a chronic, debilitating and common mental health disorder among Veterans. Prolonged Exposure (PE) therapy is an evidence-based treatment for PTSD that is widely used in VA clinics nationwide<sup>4,6,7</sup>. However, there is significant room for improvement with regard to PE retention and treatment response<sup>2,28</sup>. Oxytocin is a promising candidate pharmacotherapy to enhance PE treatment outcomes and retention in Veterans with PTSD. Oxytocin has well-documented positive effects on interpersonal behavior and cognition, as well as fear extinction and neurobiological underpinnings of PTSD in human and animal studies<sup>13,15</sup>. The proposed project will examine the efficacy of combining PE with oxytocin to enhance treatment outcomes and retention in Veterans with PTSD.

## RESEARCH DESIGN AND METHODS

**Overview.** The proposed study is a 10-week, Phase II, double-blind RCT examining the efficacy of combining Prolonged Exposure (PE) with intranasal oxytocin for the treatment of PTSD among Veterans. A repeated measures design with two intervention arms will be used: PE + oxytocin vs. PE + placebo (see Figure 3).

**Figure 3. Overview of Study Design**



**Participants.** Participants will be 210 VAMC Veterans (specifically regarding the Charleston site, n=105 Veterans must be enrolled at RHJ VAMC or eligible for care) with current PTSD. Inclusion criteria are: (1) male or female; any race or ethnicity; aged  $\geq 18$  years, (2) English fluency and intellectual functioning sufficient to provide informed consent and complete assessments (as assessed by a criterion of  $\geq 26$  on the Mini-Mental Status Exam [MMSE]<sup>50</sup>), (3) meet DSM-5 criteria for current PTSD (assessed via the CAPS-5), and (4) participants taking psychotropic medications will be required to be maintained on a stable dose for at least one month before study initiation. This is because initiation or change of psychotropic medications during the study may interfere with interpretation of results. In the event of telehealth, the MMSE will only be administered if deemed necessary. Exclusion criteria include: (1) meeting DSM-5 criteria for psychotic, bipolar or substance use disorders (those participants will be referred clinically), (2) participants who present a serious suicide or homicide risk or are likely to require hospitalization during the study, (3) participants on maintenance psychotropic medications initiated during the past month, and (4) pregnancy or breastfeeding for women. See Human Subjects section for additional exclusion criteria.

**Recruitment.** The primary recruitment sites will be the outpatient PTSD Treatment Clinics (PCT) at the Ralph H. Johnson VAMC (directed by Dr. Bethany Wangelin, Co-I) and the San Francisco VAMC (directed by Dr. William Wolfe (Co-I). Participant referrals will also be received from clinicians at affiliated VAMCs and community-based outpatient clinics (CBOC), as well as referrals from other studies operating at the Medical University of South Carolina (MUSC) and the University of California, San Francisco (UCSF). Participants will also be recruited through IRB-approved flyers in (a) VAMC Women's Health Clinics, Primary Care Clinics, Emergency Departments, and throughout the VAMC common areas and additional treatment clinics; (b) in affiliated CBOCs; (c) in MUSC and UCSF treatment clinics; and (d) via direct mailing. Finally, we will place advertisements on social networking sites (e.g., Craigslist, Facebook) and in local newspapers. Our research teams have used these methods successfully in previous RCTs among Veterans with PTSD. To maximize retention, participants will be asked to list the names and contact information of two family members or close contacts.

**Screening, Eligibility, and Informed Consent.** Initial eligibility will be conducted by the PI, Co-Is, Coordinator, or a trained Research Assistant by telephone or in person. Following phone screening for preliminary eligibility, participants will be given a full description of the study procedures and asked to read and sign an IRB- and VA R&D-approved informed consent form before any study procedures are conducted. Consent will take place in a private office or via telemedicine and will be conducted by trained staff, including the PIs, Co-Is, or Study Coordinators. Ineligible participants will be referred clinically for treatment. Individuals who meet inclusion/exclusion criteria will be invited to come into the office or will schedule a telemedicine appointment for a baseline assessment.

**VA eConsent:** In the case of VA eConsent, study staff will send the paper consent document to the study participant via email or snail mail prior to the consent and baseline appointment. Study staff will arrange to have a call with the study participant where the study participant will sign the physical consent form and/or sign electronically via DocuSign. This electronic signature would then be saved by the study staff as documentation.

**General Procedures.** All procedures will be conducted at the Ralph H. Johnson VA Medical Center (RHJVAMC) or through VA approved telemedicine interface (consent, baseline appointment, weekly assessments, prolonged exposure therapy via VVC, MUSC DoxyME, Microsoft Teams, Zoom OR WebEX). Participants will be consented via telemedicine only if and when consent via telemedicine is approved at VA. Following phone screening for preliminary eligibility and informed consent, participants will complete a baseline assessment. During the baseline visit, participants will complete a pregnancy test (for women of childbearing potential), a history and physical (H&P) exam, and a battery of standardized self-report and interview measures (Table 2). H&P exams will include a physical and neurological examination; orthostatic blood pressure and pulse measurements; and weight and body mass index calculation (BMI). In the case of telemedicine, female participants will be shipped pregnancy tests and will be asked to take the pregnancy test at home (as opposed to in the office) and confirm a negative result prior to enrollment in this study. Basic information such as blood pressure, pulse, weight and BMI will be obtained by CPRS record, self-report from the participant, or provided from a recent medical appointment (past 3 months). This information will be reviewed by trained medical staff during the H&P exam. An IRB-approved clinician and Co-I on the SFVAMC team will direct the PTSD assessment core for the proposed project via telemedicine, described below.

Provided full eligibility criteria are met, participants will enter the treatment phase, which is a 10-week, double-blind, placebo controlled RCT during which they will receive weekly PE therapy sessions in combination with intranasal oxytocin or placebo. Following completion of the week 10 therapy visit, participants will also complete 3- and 6-month follow-up visits. PTSD symptoms, treatment adherence, and functioning in associated areas (e.g., depression, aggression, sleep) will be assessed weekly. Women of childbearing potential will complete weekly pregnancy tests prior to receiving the medication. Participants' heart rate and skin conductance will be measured continuously throughout each PE session. All procedures that take place via telemedicine will be performed and completed as though they were in-person/in-office. Data will be collected and entered electronically using the MUSC or UCSF REDCap database allowing for study participants to complete assessments via survey links. A copy of all data will be stored on the VA server. Data will be securely stored using MUSC or UCSF REDCap and will not leave the VA.

**Primary Outcome Measures.** Primary outcomes include (1) clinician-rated PTSD diagnosis and symptom severity (CAPS-5<sup>51</sup>) and (2) self-reported PTSD symptom severity (PCL-5<sup>52</sup>). In order to ensure that CAPS-5 assessment is conducted in a standardized manner across sites by reliable interviewers, all clinical assessors will have completed the accredited VA Employee Education System CAPS-5 training program (VA TMS 31134). Assessors who demonstrate reliability with at least two pilot cases will then conduct assessments with participants through VAMC approved telemedicine program. Assessment supervision will occur bi-weekly or more as needed, and cases will be discussed and adjudicated as necessary in collaboration with PIs. Additional proposed assessment measures have strong psychometric properties and have been used successfully in our group's previous and ongoing research among Veterans with PTSD.

**Telemedicine.** Participants in this research study may choose to complete this study via telemedicine home-based telemedicine (HBT) care (i.e., service delivery to patients in their homes using consumer friendly, video-conferencing technology) which may likely enhance retention by directly circumventing financial and transportation barriers associated with traveling to RHJVAMC for in-person sessions. HBT sessions will be delivered via standard desk, laptop computer, tablet, or smartphone running VA approved applications. In the case of telemedicine, assessments will be administered via telemedicine by trained, IRB approved facilitators located at the SFVA or RHJVAMC. All telemedicine procedures will be completed as though they were being performed in person. Study participants who participate via telehealth will complete assessments utilizing password protected, individualized MUSC REDCap surveys.

**Table 2. Assessment Instruments and Timeline**

Instrument	Purpose	BSL	WK 1-10	WK 5	WK 10	3M F/U	6M F/U
Online/Phone Screener	Assess initial eligibility	X					
Locator Form	Comprehensive patient locator	X					
History & Physical (H&P)	Assess health and medical history	X					
Birth Control Form	Ensure participant safety	X					
Pregnancy Testing	Assess pregnancy for women	X	X	X	X		
Concomitant Medications Form	Assess concomitant medications	X	X	X	X	X	X
Demographics Form	Characterize sample	X					
Military Service Demographics	Assess military service information	X					
Mini-Mental Status Exam [MMSE] <sup>50</sup>	Screen for cognitive impairment	X					
Quick Structured Clinical Interview for DSM-5 Disorders (QuickSCID-5) <sup>55</sup>	Assess DSM-5 psychiatric disorders	X					
Life Events Checklist for DSM-5 (LEC-5) <sup>53</sup>	Assess lifetime trauma exposure	X					
<b>Clinician Administered PTSD Scale (CAPS-5)<sup>51</sup></b>	<b>Primary Outcome: PTSD</b>	X		X	X	X	X
<b>PTSD Checklist (PCL-5)<sup>52</sup></b>	<b>Primary Outcome: PTSD</b>	X	X	X	X	X	X
Patient Health Questionnaire (PHQ-9) <sup>56</sup>	Assess depression symptoms	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale (C-SSRS) <sup>57</sup>	Assess suicidality	X		X	X	X	X
Insomnia Severity Index (ISI) <sup>58</sup>	Assess sleep functioning	X		X	X	X	X
Buss Perry Aggression Questionnaire (BPAQ) <sup>59</sup>	Assess severity of aggression	X		X	X	X	X
State-Trait Anxiety Inventory (STAI) <sup>66</sup>	Assess anxiety	X			X		
Timeline Follow Back (TLFB) <sup>80</sup>	Alcohol, tobacco, and drug use	X					
Alcohol Use Disorders Identification Test (AUDIT) <sup>78</sup>	Assess alcohol use	X					
Drug Abuse Screening Test (DAST-10) <sup>79</sup>	Assess drug use	X					
Fagerstrom Test for Nicotine Dependence <sup>67</sup>	Assess nicotine use	X					
Adverse Childhood Experiences (ACE) Questionnaire <sup>81</sup>	Assess childhood trauma	X					
Combat Exposure Scale (CES) <sup>82</sup>	Assess wartime stressors	X					
(Revised) Conflict Tactics Scale (CTS2) <sup>83</sup>	Assess intimate partner violence	X					
Dyadic Adjustment Scale (DAS-7) <sup>84</sup>	Relationship functioning	X					
Experiences in Close Relationship Scale (ECR-S) <sup>85</sup>	Assess adult attachment	X					
Moral Injury Events Scale <sup>89</sup>	Assess morality	X					
Psychological Stress Associated with COVID19 <sup>88</sup>	Assess stress associated with COVID19	X					
Adverse Events Form	Assess adverse events		X	X	X	X	X
Treatment Services Review	Monitor service utilization		X	X	X	X	X
<b>Treatment Adherence</b>	<b>Primary Outcome: Homework compliance</b>		X	X	X		
Utility of Techniques Inventory (UTI) <sup>54</sup>	Assess treatment adherence		X	X	X		
Visual Analogue Scale <sup>61</sup> (VAS)	Assess subjective reactivity		X	X	X		
Physiological measures (Heart Rate, Skin Conductance)	Assess physiological reactivity		X	X	X		
Helping Alliance Questionnaire, Therapist and Client Version <sup>62</sup>	Primary Outcome: Therapeutic Alliance			X	X		
Penetration of the Blind Assessment	Assess participant/clinician blinding				X		
Charleston Psychiatric Outpatient Satisfaction Scale <sup>63</sup>	Assess patient treatment satisfaction				X	X	X

BSL = Baseline. WK = Week. F/U = Follow-Up.

### ***PTSD Diagnosis and Symptom Severity***

- Clinician Administered PTSD Scale (CAPS-5)<sup>51</sup> is a structured diagnostic interview with excellent psychometric properties and diagnostic efficiency. The CAPS-5 will be administered via telemedicine by trained study team members.
- Life Events Checklist for DSM-5 (LEC-5)<sup>53</sup> assesses lifetime exposure to trauma including two items screening for military sexual trauma and a category involving occupational exposure (e.g., military, paramedic, police, or other first responder).
- PTSD Checklist (PCL-5)<sup>52</sup> is a 20-item self-report measure based on the DSM-5, which has excellent psychometric characteristics for screening and used as a secondary indicator of PTSD symptom severity.

### ***Treatment Adherence and Retention***

- Treatment Services Review. This self-report survey will be used to monitor service utilization.
- Treatment Adherence. Homework sessions are assigned as one per type each day (one imaginal assignment and one in-vivo assignment) for the days between each treatment session (for sessions 2-10). The number and percent of completed in vivo and imaginal homework assignments will be monitored weekly and computed as indicators of treatment adherence.
- The Utility of Techniques Inventory (UTI)<sup>54</sup>. The UTI is a self-report measure that will also be used to examine treatment adherence between PE sessions consistent with the PE manual.
- Session Attendance and Study Attrition. We will record session attendance and study attrition. A treatment dropout will be defined as a participant who does not complete at least 7/10 PE sessions or who fails to attend four consecutive therapy sessions despite attempts by phone and mail to engage the participant in treatment.

### ***Associated Areas of Functioning***

- Patient Health Questionnaire (PHQ-9)<sup>56</sup> The PHQ-9 is a self-administered depression diagnostic instrument which scores each of the 9 DSM-IV criteria as "0" (not at all) to "3" (nearly every day).
- Columbia-Suicide Severity Rating Scale (C-SSRS)<sup>57</sup> The C-SSRS will be used to assess past/lifetime suicide ideation. Participants who endorse 2 or more attempts will be considered multiple attempters.
- Insomnia Severity Index (ISI)<sup>58</sup> The ISI is a 7-item self-report measure that assesses perceived severity of insomnia. The ISI has an internal consistency alpha coefficient of 0.74 and has shown convergent validity with other measures such as the Pittsburgh Sleep Quality Index ( $r = 0.67$ ), the Dysfunctional Beliefs and Attitudes about Sleep ( $r = 0.55$ ), and sleep diaries ( $r$  ranges from 0.32-0.91).
- Buss Perry Aggression Questionnaire (BPAQ)<sup>59</sup> The BPAQ assesses aggression severity via 4 subscales: Physical Aggression, Verbal Aggression, Anger, and Hostility, demonstrating strong internal consistency (alpha coefficient of 0.89) and strong test-retest reliability (alpha coefficient of 0.80).
- Mini-Mental State Examination (MMSE)<sup>60</sup> The MMSE is a widely used tool for detecting cognitive impairment, assessing severity, and monitoring cognitive changes over time.
- Quick Structured Clinical Interview for Dsm-5 Disorders (QuickSCID-5)<sup>55</sup> The QuickSCID-5 is used to assess the 17 most common psychiatric disorders in DSM-III-R, DSM-IV and DSM-5 and ICD-10.
- Alcohol Use Disorders Identification Test (AUDIT)<sup>78</sup> The AUDIT is a 10-item screening tool developed by the World Health Organization (WHO) to assess alcohol consumption, drinking behaviors, and alcohol-related problems.
- Drug Abuse Screening Test (DAST-10)<sup>79</sup> The DAST-10 is a 10-item self-report instrument that assesses drug abuse and is used for population screening, clinical case finding and treatment evaluation research.
- Timeline Follow Back (TLFB)<sup>80</sup> TLFB is a method that can be used as a clinical and research tool to obtain a variety of quantitative estimates of marijuana, cigarette, and other drug use.
- Adverse Childhood Experiences (ACE)<sup>81</sup> The ACE Assessment is a 10-question assessment that predicts health outcomes based on the frequency of answers to questions.
- Combat Exposure Scale (CES)<sup>82</sup> The CES is a 7-item self-report measure that assesses wartime stressors experienced by combatants.
- (Revised) Conflict Tactics Scale (CTS2)<sup>83</sup> The (revised) Conflict Tactics Scale is a 20-item self-report that explores conflict and violence within a relationship.
- Dyadic Adjustment Scale (DAS-7)<sup>84</sup> The DAS-7 is a self-report measure assess relationship functioning and is a psychometrically sound short form for assessing marital adjustment.

- Experiences in Close Relationship Scale (ECR-S)<sup>85</sup> ECR is 12-item self-report questionnaires on adult romantic attachment style, comprising two scales assessing attachment anxiety and avoidance.
- State-Trait Anxiety Inventory (STAI)<sup>86</sup> STAI is a commonly used measure of trait and state anxiety that can be used in clinical settings to diagnose anxiety and to distinguish it from depressive syndromes.
- Fagerstrom<sup>87</sup> The Fagerström Test for Nicotine Dependence is a standard instrument for assessing the intensity of physical addiction to nicotine.

### **Therapy Process**

- Helping Alliance Questionnaire (HAQ-II)<sup>62</sup> Therapeutic alliance has proven to be a promising variable for predicting psychotherapy treatment outcomes. The revised HAQ-II is a well-validated measure of this construct which will be completed at midpoint and end of treatment (i.e., sessions five and ten).
- Charleston Psychiatric Outpatient Satisfaction Scale (CPOSS-VA)<sup>63</sup>. The CPOSS-VA uses a 16-item Likert scale response format to assess treatment satisfaction among Veterans seeking PTSD specialty care. Data show excellent reliability and convergent validity ( $\alpha = .96$ )<sup>63</sup>. This assessment will be completed at end of treatment and 3 and 6-month follow-up visits.

### **Within-Session Reactivity**

- Subjective Reactivity. In addition to measuring Subjective Units of Distress (SUDS) as indicated by the PE manual, we will monitor subjective reactivity (e.g., anger, fear) using a modified Visual Analogue Scale (VAS) at pre- and post-session.
- Physiological Reactivity. Consistent with the procedures used in Dr. Wangelin's completed and ongoing work, skin conductance (SC) and heart rate (HR) will be recorded using an eight-channel, multi-modality encoder commonly used by Drs. Flanagan and Wangelin (ProComp Infiniti; Thought Technology, Ltd.). HR and SC will be measured continuously throughout each PE session using non-invasive fingertip blood-volume-pulse and finger-cuff sensors attached to the participant's non-dominant hand. The raw electrocardiogram will be sampled at 256 Hz and will be examined by the interbeat interval (IBI, the amount of time between heart beats). SC will be measured in microsiemens and continuously recorded at 256 Hz. Video recording will take place during the therapy sessions to observe reactivity through telehealth procedures.

## **STUDY INTERVENTIONS AND PROCEDURES**

**Study Medication, Dosage, and Administration.** A 40 IU dose of oxytocin or placebo (saline) will be self-administered intranasally 30 minutes prior to the start of each weekly PE session. The dose and timing of medication administration is based on past research in our group and others<sup>47,64,65</sup> and determined in consultation with a leading oxytocin researcher in the area of PTSD, Dr. Miranda Olff (Consultant). The study prescribers will conduct H&P exams, provide prescriptions for oxytocin, and assist with weekly assessment of adverse events. Oxytocin will be compounded, refrigerated and shipped to the VA Pharmacy. PI will consult with VA Research Pharmacy and oxytocin will be dispensed through VA pharmacy. If participant elects to telemedicine, medication will be shipped directly to the participant's home with administration and refrigerated storage instructions. Research staff will instruct participants on the correct method of administration to achieve the 40 IU dose and will observe participants' self-administration. Participants will blow their nose, exhale through their nose, then spray into one nostril while inhaling, alternating nostrils until the 40 IU dose is achieved. A 40 IU dose has demonstrated extensive safety and efficacy, is within the normal dosing range, and is one of the most common concentrations utilized in human research, including the pilot study conducted by the investigative team<sup>47,65</sup>. Side effects and adverse events will be evaluated weekly. Treatment assignment will follow a pre-arranged randomization scheme and will be carried out by personnel not involved in clinical management of participants in order to preserve the double-blind design.

**Behavioral Intervention: Prolonged Exposure (PE) Therapy.** All participants will receive 10 individual, weekly sessions of PE therapy according to the treatment manual published by Foa and colleagues<sup>24</sup>. Each session will last approximately 60-90 minutes. All PE therapy sessions will be recorded for fidelity monitoring, for patients to listen to between the therapy sessions as homework and for psychophysiological processes and monitoring. Homework engagement and between-session habituation are especially important for treatment success<sup>66</sup>. Within and between sessions, participants will report pre, peak, and post subjective units of distress during exposure.

**Therapist Training, Supervision, and Fidelity Monitoring.** Study therapists will be Masters- or Doctoral- level VA clinicians with extensive training and experience delivering PE in VA treatment clinics. IRB-approved clinical supervisors from the Charleston team (PI or Co-I) will provide weekly supervision to study therapists at both study sites. Weekly supervision will focus on adherence to treatment and clinical concerns about particular participants. Supervisors will provide feedback to reduce therapist departure from the treatment protocol and to assist therapists in identifying issues to be addressed in subsequent sessions. If it is determined that a therapist is not competent or does not adhere sufficiently to the manual, the therapist will be replaced. This decision will be made collaboratively by Drs. Flanagan and Mitchell. To assure that PE is delivered in a manner consistent with manual guidelines, therapy sessions will be discussed during weekly therapy supervision and will be evaluated using the Yale Adherence and Competence Scale<sup>67</sup>. Interrater reliability on adherence and competence measures and intraclass correlation coefficients will be calculated.

**Participant Compensation.** Participants will receive \$50 for the baseline assessment visit. Participants will receive \$25 for each weekly PE session and study assessment. Participants will also receive \$100 for each follow-up visit. Thus, participants who complete all study components may receive up to \$600 total (\$50 for the baseline assessment, \$350 for 10 weekly PE therapy visits (including additional compensation for week 5 and week 10 sessions), and \$200 for follow-up visits). The VA will either directly deposit the compensation into the participant's bank account, or if they do not have a bank account, a direct deposit Debit Mastercard will be issued. Ink signatures from participants are required for both options prior to payment submission or be signed/submitted via MyHealthEvet. Direct deposit will be available within 3-5 days of submission. Funds for the Debit Mastercard will be available within 10 business days of submission.

## STATISTICAL METHODS.

**Power and Sample Size.** This study is powered to estimate the effects of oxytocin on significant reduction in both self-reported and clinician administered PTSD symptom severity at the end of treatment (Session 10; Aim 1) and an increased rate of early reduction in self-reported PTSD symptoms (Aim 2).

**Specific Aim 1:** Prior work has shown that PE therapy alone is efficacious in the reduction of both clinician administered (CAPS reductions of 35-55%)<sup>47,68,69</sup> and participant-rated PTSD symptom scores (reductions of 29-44%)<sup>25,47,68,70</sup>. In our pilot study, the addition of oxytocin to PE resulted in a 67% decrease in CAPS-5 scores following 10 weeks of treatment (mean  $\pm$  SD: Baseline 39.0  $\pm$  6.3 vs. end of treatment 13.0  $\pm$  14.7) and a 61% decrease in PCL-5 scores (mean  $\pm$  SD: Baseline 52.2  $\pm$  12.0 vs. end of treatment 20.5  $\pm$  22.5). Assuming a conservative estimate of the effect of PE-only on both the CAPS-5 (45% reduction from baseline) and the PCL-5 (35% reduction from baseline) and a similarly robust reduction in the oxytocin augmented PE group (CAPS-5: 65% reduction from baseline and PCL-5: 60% reduction) along with conservative estimates of variance from our pilot data (end of treatment differences); we anticipate end of treatment between group effect sizes of Cohen's  $d=0.55$  (CAPS-5  $\Delta=7.8$ , SD=14.7) and Cohen's  $d=0.58$  (PCL-5  $\Delta=13.1$ , SD=22.5). To achieve 80% power with a multiplicity corrected type 1 error rate of 2.5% to assess specific aim 1, 65 participants will be randomized per treatment arm ( $n=130$ ). Additionally, analysis of multi-center trial data must account for possible center heterogeneity and unequal participant allocation across study sites<sup>71,72</sup>. Assuming no more than 10% of model variance is due to site differences ( $p=.10$ ) and the randomization balance across sites is 55%: 45% or better, 75 participants per treatment arm will be necessary to guarantee adequate power ( $n=150$  total participants). We also anticipate up to 20% attrition between study randomization and the end of treatment CAPS-5 and PCL-5 measurements, inflating the necessary randomized sample size to 210 total participants ( $n=105$  per treatment arm). If imbalance in these characteristics is curtailed, statistical power may exceed 80%.

**Specific Aim 2:** Our pilot data showed between group changes during the first 5 weeks of PE treatment favoring PE + oxytocin over PE + placebo in both self-reported (PCL:  $\Delta=13.7$ , SD=19.8, Cohen's  $d=0.69$ ) and clinician administered PTSD symptoms (CAPS-5:  $\Delta=7.6$ , SD=11.8, Cohen's  $d=0.64$ ). In order to detect the least of the two effect sizes at the session 5 visit (Cohen's  $d>0.6$ ), 56 participants will be necessary per treatment arm to achieve 80% power with a type 1 error rate of 2.5% ( $n=112$ ). To account for up to 20% attrition, possible moderate center heterogeneity and a slight imbalance across study sites, 134 total participants ( $n=67$  per treatment arm) will be necessary to maintain adequate statistical power to detect early differences in PTSD symptom changes between groups.

**Specific Aim 3:** There is little available information on the benefit of augmenting PE with oxytocin on secondary study outcomes such as treatment retention and adherence. However, using the sample size necessary to adequately address specific aims 1 and 2, and an estimated session attendance rate of 60% in the PE + placebo group, we will have sufficient power (80%) to detect a session attendance rate of 77% or better in the participants randomized to the PE + oxytocin group.

**Statistical Analysis.** A univariate approach will be used to examine differences between treatment groups on baseline clinical and demographic characteristics. Characteristics will be examined and compared between treatment groups using chi-square tests, Fisher's exact tests, or Wilcoxon rank sum tests, as appropriate. Additionally, baseline clinical and demographic characteristics will be assessed for univariate associations with study outcomes. Sex will be examined as a covariate, and estimates will be examined across sex. If other baseline characteristics are significantly associated with an outcome, the corresponding variables will be used as initial covariates in the model analyses. Secondly, possible covariates will be tested for confounding effects on treatment and when present, they will be included in the final adjusted model. For Gaussian distribution assumptions, residual normality will be assessed using QQ plots and when deviations from normality occur, appropriate transformations will be made. All randomized participants will be included in the primary analysis (intent-to-treat; ITT) and all statistical models will be implemented using SAS v. 9.4.

**Hypothesis 1:** Veterans randomized to the PE + oxytocin group will demonstrate significantly greater reduction in PTSD symptoms on the CAPS-5 and PCL-5 from baseline to end of treatment compared to Veterans randomized to the PE + placebo group. To assess the efficacy of oxytocin added to PE as compared to PE combined with placebo, generalized linear mixed effects models will be developed. The primary outcomes for specific aim 1 is the end of treatment response in both the CAPS-5 as well as the PCL adjusted for baseline scores. Both design-adjusted and full covariate adjusted models will be assessed. Design adjusted models will include study treatment assignment, study site, sex, and baseline CAPS-5/PCL-5 scores while covariate adjusted models will additionally adjust for characteristics determined to be associated with either outcome progression in the univariate analysis as well as known confounders. Possible moderating effects of study site on treatment assignment will be investigated through model interactions. We will make every effort to prevent study attrition. However, appropriate analysis methods will be employed to accommodate missing data. Mixed-effects models yield valid inferences assuming ignorable attrition (i.e., attrition is accounted for by covariates or the dependent variable measured prior to dropout). We propose a sensitivity strategy to examine and compare treatment efficacy parameter estimates between primary methods noted above and those obtained using methods of multiple imputation (MI). MI will be implemented using 10 imputation sets and the expectation-maximization (EM) algorithm. Hypothesis 1 results will be estimated independently for the CAPS-5 and the PCL-5 using  $\alpha=0.025$  as the threshold for statistical significance.

**Hypothesis 2:** Veterans randomized to the PE + oxytocin group will demonstrate a significantly faster rate of improvement in participant rated PTSD symptoms as measured by the PCL-5 compared to Veterans randomized to the PE + placebo group. The PCL-5 will be administered weekly. To assess the differential rate of early decline in PTSD symptoms between groups, models utilizing treatment measured time points from baseline to PE session 5 will be assessed using generalized linear mixed effects models. To determine differential treatment improvement over time, a treatment x time interaction and a quadratic time term will be included in the model (removed when insignificant). A significant interaction effect will indicate that the relative change in PTSD symptoms over time were greater in one group as compared to another. Following a significant interaction, assessment of pairwise comparisons at meaningful time points will be conducted to determine the earliest study visit at which the two treatment assignments deviate in PTSD symptoms. The CAPS-5 will be administered at visit 5 and the differential effect of groups will be assessed using generalized linear mixed effects models. Design adjusted models will include study treatment assignment, study site, sex, and baseline CAPS-5/PCL-5 scores while covariate adjusted models will additionally adjust for characteristics determined to be associated in Study Aim 1. Hypothesis 2 results will be estimated independently for the CAPS-5 and the PCL-5 using  $\alpha=0.025$  as the threshold for statistical significance.

**Hypothesis 3:** Veterans randomized to the PE + oxytocin group will demonstrate a significantly greater number of sessions attended and homework assignments completed compared to Veterans randomized to the PE + placebo group. Session attendance and homework completion count will be tabulated for all randomized participants and compared across treatment assignments. To assess differences in the number of sessions attended, general linear mixed effects models employing a log-linear framework (i.e., Poisson or negative

binomial regression with a log link) will be used to assess differences in the number of attended treatment sessions as a function of treatment group. Treatment assignment will be the primary independent variable of interest and any baseline variables found to be associated with study outcomes will be considered as covariates. Because it is possible that the number of attended sessions between groups could be similar at study closeout with differing profiles over time (i.e., early vs. late dropout), we will also examine longitudinal patterns in session attendance (using GLMM) as well as time to study dropout between groups (using Cox Proportional Hazards regression models). In the longitudinal models, we will assess the treatment x time interaction in an effort to detect differential patterns of attendance over time between treatment groups. The number of homework assignments completed between each session will also be compared between groups over time. Secondly, we hypothesize that a reduction in homework completion will inform failure to complete the study protocol at upcoming visits. These models will use the time varying effects of homework completion as the primary independent variable with study attrition status as the dependent variable. All analysis for hypothesis 3 will be examined using  $\alpha=0.05$  as the threshold for statistical significance.

**Secondary Data Analyses.** In addition to the primary study outcomes, we will examine the effects of treatment condition on time to PTSD remission as measured by the CAPS-5 and changes in physiological reactivity (e.g., heart rate and skin conductance). To assess early or incremental benefit on remission of symptoms, time to PTSD remission will be assessed using a Cox Proportional Hazards regression model. Although the existing literature examining the effects of PE therapy on physiological reactivity is preliminary, data suggests that heart rate and skin conductance may decrease during the course of exposure therapy for PTSD<sup>73</sup>, providing an additional objective, non-invasive measure of treatment outcome. We hypothesize that Veterans randomized to the oxytocin condition will demonstrate greater within-session reductions in heart rate and skin conductance compared to Veterans randomized to the placebo condition. Physiological data will be downsampled to 8 Hz for analysis. Interbeat interval (IBI) and SC will be assessed using generalized linear mixed effects models that will assess within session and between session changes during study treatment. We will also examine associations between IBI and SC measurements and changes in CAPS-5 and PCL-5 scores throughout treatment. Generalized linear mixed effects models will be developed to assess physiological reactivity between study groups over time. Finally, we will also examine treatment group differences on outcomes commonly associated with PTSD symptom severity such as depression, aggression, and sleep. In addition, the durability of all primary and secondary outcome models will be assessed at 3 and 6 month follow up visits using appropriate outcome specific models. Secondary analysis will be examined using  $\alpha=0.05$  as the threshold for statistical significance.

**Missing Data.** Missing data are common in PTSD trials where end of treatment symptom severity is the primary outcome of interest. The primary cause attributed to such missing data is participant attrition. Attrition can introduce bias into the parameter estimate and reduce study power, estimate precision and generalizability. In order to minimize missing data and study attrition, study simplification and enhanced communication between study coordinators and participants will be emphasized. We will make every effort to prevent attrition, e.g., phone/text/email reminders prior to visits, compensation for participation, meeting with participants in community if needed, and reinforcing adherence at each visit. However, these methods do not ensure that all data will be collected and appropriate analysis methods will be employed to accommodate missing data e.g., (multiple imputation). In keeping with the Intent to Treat principle, we will make every effort to continue assessments for the entire course of randomized treatment, even among those who fail to adhere to randomized assignment or stop participating in the study assigned intervention. Additionally, we will perform analyses to determine whether Veterans who complete treatment and those who drop out differ on key variables (e.g., PTSD symptom severity, trauma type) and whether variables on which they differ interact with treatment to affect outcome measures. Furthermore, in general, less than 10% missing data have little impact upon study power and do not introduce bias, regardless of the missing data mechanism<sup>74</sup>.

**Randomization.** Participants will be randomized in a one-to-one manner across study site using a stratified permuted block design (block sizes of 2 and 4). In order to ensure that the treatment groups are balanced with respect to PTSD symptom severity, groups will be stratified based on self-reported sex and a baseline PCL-5 score of 47 (based on our teams prior and ongoing RCTs among Veterans with PTSD<sup>75,76</sup>). To the extent that the stratification variable is predictive, stratifying on it may enhance statistical power to identify treatment effects<sup>77</sup>. Block randomization has the advantage of treatment balance at the completion of each block. Using smaller randomly assigned block sizes of 2 and 4 further minimizes the possibility of treatment allocation

imbalance. The randomization schedule will be completed by the study biostatistician and study allocation will be completed by the VA Research Pharmacist through the VA pharmacy. The randomization allocation will be audited quarterly by the research pharmacy and study biostatistician.

## **HUMAN SUBJECTS RESEARCH**

### **1. Risks to Subjects**

Drs. Flanagan (PI), Back (Co-I), and Wangelin (Co-I) are licensed clinical psychologists with VAMC clinical appointments and Dr. Brady is a VA Staff Psychiatrist with ample training and experience in conducting clinical trials research among Veterans with PTSD. Dr. Jones is a psychiatrist and primary care physician with a WOC appointment at VA. The investigative team also has extensive experience in human subjects' research. All investigators as well as the Project Therapists and Study Coordinators have all completed the University of Miami computer-based CITI Human Subjects Research Education Course. All research activity, informed consents, and continuing reviews will be reviewed by the Office of Research and Development (R&D) at the Ralph H. Johnson VAMC, San Francisco VAMC, as well as MUSC's and UCSF's IRB in compliance with 45CFR46 before the research is started. Continuing review will occur annually. Study staff will ensure that all information needed for the continuing review is consistent with R&D requirements.

### **A. Human Subjects Involvement, Characteristics, and Design**

A total of 210 participants comprised of adults at least 18 years of age or older will be recruited over a 5 year period. Only VAMC Veterans will be enrolled in this study. Specifically, for the Charleston site, participants must be RHJ VAMC Veterans (enrolled at RHJ VAMC or eligible for care and with required verification). Women and members of minority groups will be eligible for participation. Study inclusion/exclusion criteria are as follows:

#### **Inclusion criteria**

1. Male or female VAMC Veteran; any race or ethnicity; aged  $\geq 18$  years. Specifically, for the Charleston site, participants must be RHJ VAMC Veterans (enrolled at RHJ VAMC or eligible for care and with required verification).
2. Able to provide informed consent and function at an intellectual level sufficient to allow accurate completion of the assessment instruments ( $> 26$  on the Mini Mental Status Exam).
3. Meet DSM-5 diagnostic criteria for current (i.e., past 6 months) PTSD (assessed via the CAPS-5). Participants may also meet criteria for a mood disorder (except bipolar affective disorder, see Exclusion Criteria) or anxiety disorders (e.g. panic disorder, agoraphobia, social phobia, generalized anxiety disorder, or obsessive compulsive disorder). The inclusion of participants with affective and anxiety disorders is essential because of the marked frequency of the co-existence of mood and anxiety disorders among patients with PTSD.
4. Participants taking psychotropic medications will be required to be maintained on a stable dose for at least four weeks before study initiation. This is because initiation or change of psychotropic medications during the course of the trial may interfere with interpretation of results.

#### **Exclusion criteria**

1. Meeting DSM-5 criteria for a history of or current psychotic, bipolar or substance use disorders, or with current suicidal or homicidal ideation and intent. Those participants will be referred clinically.
2. Participants who present a serious suicide risk or are likely to require hospitalization during the study.
3. Participants on maintenance anxiolytic, antidepressant, or mood stabilizing medications, which have been initiated during the past 4 weeks.
4. Pregnancy or breastfeeding for women.

### **B. Sources of Materials**

Research materials obtained from participants include self-report surveys, structured clinical interviews, and physiological measurements (e.g., heart rate and skin conductance).

## C. Potential Risks

Oxytocin Safety. Oxytocin is a neuropeptide commonly administered intravenously among women during childbirth. Risks associated with oxytocin administration have been noted among women given intravenous, but not intranasal, oxytocin for its FDA-approved purpose to induce labor and facilitate lactation<sup>135,136</sup>. These risks include seizures, mental disturbances, nausea, vomiting, irregular heartbeat, high blood pressure, and unexpected bleeding or contraction of the uterus and have been observed in a small number of women<sup>99</sup>. However, preliminary studies conducted by our group and others indicate that risks of intranasal oxytocin administration at the planned dose of 40 IU is minimal and manageable through the proposed human participants protection methods. Our teams have administered intranasal oxytocin at this dose to over 900 research participants to date, including Veterans with PTSD and complex psychiatric comorbidities, without a single related adverse event reported. Participants will be informed about the potential side effects of oxytocin and will be closely monitored by the research team. Oxytocin self-administration will occur in a fully-staffed clinical environment equipped with ready access to clinicians and emergency care if necessary.

Risks of Pregnancy. Because this study involves a 50% chance of a participant receiving active medication (i.e., intranasal oxytocin) and the effects of oxytocin on pregnancy outcome are well known, pregnant and lactating females will be excluded from the trial. We will instruct female participants to use appropriate forms of contraception, and we will perform urine pregnancy tests at baseline and weekly during treatment.

Confidentiality. All possible efforts to protect participants' privacy and confidentially will be made throughout the course of the study. Consistent with VA policy, all data and results generated during the course of this study will be kept on password-protected Research Sharing Drive at the Ralph H. Johnson VAMC or the San Francisco VA Medical Center, with deidentified data stored on a VA and IRB approved data management system such as REDCap. The data will be kept on a password-protected Research Sharing Drive where study therapists and staff will have access from the RHJVAMC and/or SFVAMC. Participants will be provided with a written informed consent document which specifies the risks and confidentiality protections and limits of study procedures. All participants will review the R&D and IRB-approved informed consent document with research staff in a private room. Through this process, research staff will inform all research participants of the risks of participation, including emotional distress. In the event that a participant experiences substantial distress or reports risk of harm to oneself or others, they will be asked to complete a safety plan. Recent safety plans completed by VA providers will be reviewed and an updated safety plan will be developed. Urgent care services at the RHJVAMC, the SFVAMC, or VA clinics local to participants are available to study staff and research participants. Risks of participation will be outlined in the informed consent and reviewed during the informed consent procedure. In similar past and ongoing studies, these resources have been sufficient to manage problems or distress related to participation. Please see Data Management and Access Plan for more information on participant confidentiality.

Emotional Distress. Some participants may experience distress in response to self-report and interview measures pertaining to PTSD symptoms or associated areas of functioning such as depression and aggression. Participants may also experience physical or psychological discomfort during the medication self-administration. However, based on the research team's past experience and available literature, the risks involved in the proposed project are minimal and manageable. Nevertheless, we have a specific protocol in place to manage participant distress in the event that it arises. This protocol is discussed in more detail below.

Randomization Risk. Participants will be randomized to receive either the Investigational Drug (oxytocin) or inactive placebo. Since there is a 50:50 chance of receiving an inactive placebo, there is a risk that half of the participants will not receive any medication to treat their condition. Even though a portion of the participants will not receive any active medication, all participants will receive an evidence-based treatment (PE) to treat their condition (PTSD).

## 2. Protection against Risks

Recruitment and Informed Consent Procedures. All personnel will be trained in the responsible conduct of research. Participants will be recruited from VAMC treatment clinics, community settings, community-based outpatient clinics (CBOC), direct mailing and ads placed on Craigslist/Facebook. The screening measure contains questions directly pertaining to the study's inclusion and exclusion criteria. Participants who meet eligibility criteria will be scheduled with research staff for a baseline assessment session. In a private room, participants will be provided with a description of the nature and requirements of study participation and asked to read and sign an IRB-approved consent form prior to beginning any study procedures. Informed consent will be collected by a Study Coordinator, trained research assistant, PI, or Co-Is. The PIs and Co-Is are all PhD or MD level clinicians. All study personnel will read and attend training sessions in the study protocol conducted by the PI and in coordination with the Co-Is. These trainings will include the essential elements of ethical conduct of research so that each member of the research staff is well-equipped to provide participants with adequate information prior to their agreeing to participate in the study.

Participants will also be informed that they are not required to make a decision about whether or not they choose to participate on that day. All participants will have the opportunity to consider and discuss participation with their provider or family members prior to providing informed consent. Participants who are eligible to participate and choose to do so will be encouraged to ask any questions they might have about the study. Both the participant and research staff member will sign the form.

The informed consent document will outline 1) the sponsorship of the study; 2) the nature, purpose and procedures of the research study; 3) the voluntary nature of participation (i.e., participation is not required and can be discontinued at any time; 4) duration of the study; 5) potential risks and discomforts and potential benefits of participating; 6) that all information will be kept confidential subject to the provisions of state and federal law; 7) compensation; and 8) alternative treatments. Participants will be informed that they can discontinue participation in the study at any time and that this decision will not influence the care they receive at any VAMC or MUSC clinic.

Emotional Distress. Some participants may experience distress in response to self-report and interview measures pertaining to PTSD symptoms or associated areas of functioning such as depression and aggression. Participants may also experience physical or psychological discomfort during the medication self-administration. However, based on the research team's past experience and available literature, the risks involved in the proposed project are minimal and manageable. Nevertheless, we have a specific protocol in place to manage participant distress in the event that it arises. This protocol is discussed in more detail below. Additionally, all participants will receive an evidence-based behavioral intervention (Prolonged Exposure) that includes techniques to help reduce distress and anxiety, and improve mood (e.g., breathing retraining, sleep hygiene, cognitive restructuring). We will also inform participants during the informed consent process that they may terminate any assessments, study procedures, or therapy sessions at any point. Our past and ongoing research with Veterans suggests that the measures and methods proposed in this study can be implemented without undue psychological distress or exacerbation of symptoms. This experience includes numerous federally-funded projects among Veterans with PTSD.

In the event that a participant becomes distressed secondary to participation, they will be encouraged to contact the Principal Investigator (PI). In addition, they will have access to urgent care services at VAMC, MUSC, and UCSF treatment clinics. Any adverse effects noted by any project personnel will be immediately reported to the PIs, who will then report these adverse effects in writing to the IRB and the VA R&D Committee per protocol (see the Data and Safety Monitoring Plan at the end of this section for more details). This also includes telemedicine procedures that are performed at the SFVA. The research team includes several licensed clinical psychologists and psychiatrists who are equipped to help participants manage distress and to evaluate conditions in which participants need additional assistance. In the event that a participant becomes significantly distressed, the PI will contact the participant later that day and the following day to check-in to ensure they have received necessary resources, and to assess their safety and welfare. If called by participants, the PI will attempt to address all participant concerns and set up an alternate referral for counseling for those who desire it from outside the project. Every attempt will be made to engage participants for the entirety of the 10-session treatment phase. Participants will be considered drop-outs from treatment if they do not complete at least 7/10 PE sessions or fail to attend four consecutive therapy sessions despite attempts by phone and mail to engage the participant in treatment. A Participant Locator Form will be used at the start of each telemedicine appointment. This will provide the location of the participant and contact information for non-emergency police line, should the study team need to send help to the participant's location. All other safety procedures will be followed.

Study Physicians. Kathleen Brady, M.D., Ph.D. and Jennifer Jones, M.D. will serve as the Study Physicians on this project at the Charleston site and William Wolfe, M.D. and Thomas Neylan, M.D. will serve as Study Physicians at the San Francisco site. Drs. Brady, Jones, Wolfe, and Neylan all have extensive experience with VA, DoD, and NIH-sponsored clinical trials involving individuals with PTSD and comorbid psychiatric conditions. They have ample experience monitoring and treating individuals with PTSD in the context of clinical practice and randomized controlled trials. Study physicians will review all adverse events, unanticipated problems involving risk to participants or others, serious adverse events, and any participant deaths associated with the protocol and provide an unbiased written report of the event within 10 calendar days. In addition, the investigative team includes psychologists with ample PTSD expertise (Drs. Flanagan, Back, Wangelin) who will closely monitor study participants. If at any point a participant necessitates medical management, psychiatric consultation or psychiatric hospitalization, they will be evaluated and referral to treatment will be provided accordingly. If a participant becomes suicidal, emergency psychiatric assessment will be arranged. The participant will be closely monitored until they are no longer suicidal or an appropriate care plan is in place.

Study Prescribers. Anjinetta Johnson, P.A., who has a without compensation (WOC) appointment at the Ralph H. Johnson VAMC, will serve as the Study Prescriber at the Charleston site and Dr. Neylan (study physician) will serve as prescriber for the San Francisco site. Dr. Jones (Study Physician) will serve as a backup prescriber. Ms. Johnson has extensive experience with federally-funded clinical trials involving Veterans with PTSD. Providers also have the ability to provide study coverage via telemedicine if necessary. Ms. Johnson along with the PIs, will conduct H&P exams, review all adverse events, unanticipated problems involving risk to participants or others, serious adverse events, and any participant deaths associated with the protocol and provide an unbiased written report of the event within 10 calendar days. PI will consult with VA Research Pharmacist as needed. Oxytocin/placebo will be dispensed through the VA pharmacy, and shipped to participants as needed for telemedicine.

Military Personnel. Because some participants may be U.S. military personnel, absolute confidentiality of research records cannot be guaranteed. However, all possible efforts will be made to protect the confidentiality of participants' data, except in the event of imminent risk to self or others, or in the event of disclosure of child or elder abuse. In the event that confidentiality must be broken to protect the safety of participants or others, only the data essential to make an adequate report to authorities will be disclosed.

Safety and Monitoring Plan. A procedure for clinical deterioration has been established based upon our experience with previous and ongoing federally-funded clinical trials. Therapists (who are trained Master's or Doctoral level clinicians) will be instructed to use their best clinical judgment regarding emergencies and inform the PI as soon as possible. In addition to relying on clinical judgment on the part of the treating therapists who are experienced with this population, we will also monitor the following symptoms and behaviors weekly: PTSD, depression, and suicidality, using standardized measures (PCL, PHQ-9) in order to detect any symptom worsening requiring further evaluation. Additionally, participants will be advised to observe any signs of worsening mental health symptoms and to discuss these challenges with their therapist.

Participants will be withdrawn from the study and referred for more intensive treatment if: (1) there are increases in mental health symptoms leading to the need for a more intensive level of care (i.e., inpatient or partial hospitalization); (2) there is active suicidal or homicidal ideation and/or intent; (3) there is an inability to manage the participant psychiatrically within the inclusion/exclusion criteria of the study (i.e., need for the initiation of psychotropic medications; development of psychosis); or (4) there is an inability to complete PE therapy appointments due to incarceration or hospitalization.

There is a well-established protocol at the Charleston and San Francisco VAMCs for emergency psychiatric evaluation, crisis intervention and/or psychiatric hospitalization, including telemedicine, for suicidal, homicidal, psychotic or other acutely distressed participants. Immediately on detection of these needs, the assessor/therapist will page a psychiatrist to review the participant's situation. If appropriate, the psychiatrist will personally evaluate the participant. Alternatively, during weekdays, the participant will be escorted by a study staff member to the psychiatric walk-in clinic or emergency room. Psychiatric hospitalization is available for emergencies.

Participants will be informed during informed consent procedures of the standard limitations of confidentiality such as imminent risk of harm to self or others, or child or elder abuse. Participants will be informed that they can decide not to answer any questions and, should they become distressed or are uncomfortable with

continuing to participate, they may discontinue participation at any time without penalty. The compensation schedule will be stated verbally and in writing in the initial study description and the informed consent procedure. The participant's copy of the consent form will provide contact phone numbers and email for the PI should a participant have any questions, comments, or concerns about their participation. Participants will have the opportunity to have a copy of the consent form mailed to them at any time.

Suicide Specific Risk Identification and Response Plan. Specific precautions will be taken to prevent harm to participants. Project therapists will be trained Masters or Doctorate level clinicians and will be supervised by Drs. Flanagan (PI) and Back (Co-I). All project therapists and staff will be specifically trained to assess suicide risk, including ideation, plan, and intent as well as history of ideation or attempts, and they will be trained to develop a safety contract with participants. In initial screening procedures, participants identified by clinical interview with both suicidal ideation and acute intent will be excluded from the study but will be offered emergency psychiatric care immediately. This care is available 24 hours per day at the Charleston VAMC and MUSC as indicated above. Moreover, during the course of the study, any participant scoring a 1 or above on the PHQ-9 question 9 (administered weekly) or a 4 or 5 on the C-SSRS (administered at BSL, WK5, WK10 and at 3- and 6-month follow-up) will be specifically queried about suicidal ideation and intent. In any instance where ideation or intent is identified, the PI will be immediately notified and will contact the participant for further evaluation. If both ideation and intent are present, the aforementioned hospital intervention will be provided. Thus, all assessment points represent suicide risk identification, assessment, and intervention opportunities. Study therapists and staff will be specifically trained regarding the increased risk of suicide in Veterans with PTSD, and will receive specific instruction of suicide risk assessment during the initial training workshop.

Study Implementation and Data Security. We will take careful precautions to maintain confidentiality for all participants, using procedures we have used with similar previous studies. Consistent with VA policy, raw data generated during the course of this study will be kept on a password-protected Research Sharing Drive at the RHJVAMC and the SFVAMC. De-identified data for study analyses from both sites will be entered into a VA approved-data storage program such as REDCap. All research personnel will attend a required in-service training conducted by PI where the screening, informed consent, and assessment protocols will be described. All members of the research team will sign a confidentiality agreement that no identifying information of specific individuals will appear in any external documents (e.g., peer-reviewed publications, presentations) or in any internal reports.

All study data related to psychological outcomes (i.e., the participant responses to questionnaires) and demographics will not have any unique identifying data attached in any way. Access to study data will be controlled through the use of standard access controls such as usernames and passwords consistent with VAMC policies. All participants will be assigned a numerical study identifier to minimize the potential to link identifying information with study data. One master list of study participants will be kept separate from all other study data and will be available only to the PIs, Study Coordinators, and RAs. To protect participant confidentiality, all data will be maintained in a manner consistent with VA R&D-approved protocol. Data will be stored in locked filing cabinets within a locked office and on VA encrypted computers and data servers. Access to de-identified study data will be limited to named project investigators, the Study Coordinators, VAMC Office of Research & Development (R&D) personnel, and MUSC IRB audit personnel. Data will be maintained per an R&D and IRB-approved protocol.

The study protocol and safety plan will be printed and kept in a central location within the research space for easy access for all research staff. Standard operating procedures (SOPs) for the management of any participant or study-related emergency will be established and research staff will be trained on these protocols. All participant assessments will be scheduled during normal working hours on the VA campus or through VA approved telemedicine to ensure the presence of clinical staff and the safety of participants and research staff. All research staff have completed or will complete the University of Miami CITI training course in the responsible conduct of research. Necessary certifications in the responsible conduct of research and the protection of human research participants will be completed on an annual basis, in compliance with VAMC, MUSC, and UCSF institutional regulations.

### **3. Potential Benefits of the Proposed Research to the Participants and Others**

While there is no guarantee of specific benefit to participants in this study, the potential benefits include a thorough psychological assessment, referral to appropriate treatment services and community resources, and remuneration. Participants may also benefit from receiving access to an evidence-based behavioral treatment which may result in a reduction in aversive PTSD symptom severity, improvement in symptoms of other mental health problems (e.g., depression) and improvements in other areas of functioning (e.g., sleep, quality of life). Other study benefits include regular contact with research staff, access to assessment information pertaining to mental health and referral to treatments for associated problems such as smoking. While these benefits may be considered minimal, we believe that they outweigh the minimal risk and burden incurred by participants. Participants will also enroll in a study that has the potential to enhance treatment for other Veterans.

#### **4. Importance of Knowledge to be Gained**

There is considerable knowledge to be gained from the proposed study. Veterans incur PTSD at uniquely high rates, resulting in a tremendous health burden in the United States. The extant literature strongly indicates the need to (1) develop strategies to improve retention and outcomes in evidence-based PTSD treatments such as Prolonged Exposure, (2) develop novel, effective pharmacotherapies for PTSD, and (3) elucidate physiological mechanisms associated with PTSD and response to treatment. Preclinical and human data suggest that oxytocin has potential to influence treatment in the field of PTSD. Thus, the proposed study has the potential to advance science and patient care in this area by applying intranasal oxytocin during weekly behavioral intervention (PE) sessions designed to treat PTSD. Results from this study may improve clinical delivery of PE by enhancing treatment outcomes, adherence, and retention. The proposed study will also help elucidate the neurobiological mechanisms underlying oxytocin response and improved PE outcomes.

#### **Data and Safety Monitoring Plan**

This section is based on the recommendations in NIH's "Guidelines for Developing a Data and Safety Monitoring Plan" to assure the appropriate clinical safety monitoring of study participants. Recruitment and safety data are monitored according to the schedule established by the monitoring board. Quality control and assurance of data entered into the database is discussed above as part of Protections Against Risk. Missing data will be considered as part of the plan for statistical analysis.

Summary of the Protocol. The proposed study aims to examine the ability of intranasal oxytocin to reduce symptoms of PTSD among Veterans. The primary outcome in this study includes a reduction in PTSD symptom severity and improvements in PE adherence and retention.

Trial Management. The study will be managed from the Ralph H. Johnson VAMC.

Data Management and Analysis. A data analytic plan is outlined in the Data Analysis section. Because this study is a preliminary test of a new medication, we are interested in examining a broad range of outcome variables. The main outcome variables include the severity of PTSD symptoms, PE adherence/retention, and psychosocial functioning in areas commonly associated with PTSD. Analyses will be guided by the specific hypotheses of the study. Post-hoc exploratory analyses will be conducted with two-tailed tests and more conservative statistical procedures which guard against Type I error (e.g., Tukey tests). All primary hypotheses will be tested at level of significance  $\alpha=0.05$ . We will also estimate the effect sizes of interest and provide 95% confidence intervals for them. See the Statistical Analysis and Power section for more details.

Quality Assurance. Data quality will be monitored by random inspection of the completed forms by research staff and any irregularities or problems detected will be discussed with the PI. Project therapists will receive standardized training from the PI and Co-I who have extensive experience training individuals to use the intervention (PE) to be utilized in the proposed study. Adherence to the manual will be monitored and reviewed during weekly supervision. If therapy drift is observed the therapists will be re-trained. Booster sessions will be held annually.

Regulatory Issues. All unexpected Adverse Events (AEs) will be reported to Charleston VAMC R&D and MUSC IRB within 10 working days. AEs are reportable if the AE is unexpected AND related or possibly related AND serious or more prevalent than expected. The IRB definition of unexpected is that the AE is not identified in nature, severity or frequency in the current protocol, informed consent, investigator brochure or with other current risk information. The definition of related is that there is a reasonable possibility that the adverse event may have been caused by the drug, device or intervention. Serious AEs (SAEs) will be reported within 24-hours. Follow-

up of all unexpected and serious AEs will also be reported to these agencies. All AEs are reviewed weekly by the PI, and annually by the Data Safety Monitoring Board (DSMB) and IRB. AEs and SAEs occurring during the course of study will be collected, documented, and reported in accordance with the protocol and R&D and IRB reporting requirements. All research staff involved with AE reporting will receive training including identification, evaluation, and documentation and reporting. All research staff will identify any potential AEs during the course of the study from self-report data and administration of assessments and interviews. This information will be provided to the PI, who will be responsible for AE/SAE assessment and evaluation including a determination of seriousness and study relatedness.

Definition of AE and SAE. Adverse Events are defined as any untoward medical occurrence that may present itself during treatment or administration of an intervention, and which may or may not have a causal relationship with the treatment. Serious adverse events are defined as any medical occurrence that results in:

- 1) Death
- 2) A life threatening event
- 3) Requires or prolongs inpatient hospitalization
- 4) Persistent or significant disability/incapacity
- 5) A congenital anomaly or birth defect

OR

- 6) Requires intervention to prevent one of the above outcomes.

Important medical events that may not result in death, be life-threatening or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Documentation and Reporting. When a reportable SAE is identified, the research assistant will initiate an SAE form, and the following individuals will be notified within 24 hours of the site's initial notification of the SAE:

- 1) Study Co-Investigators.
- 2) VA R&D personnel. Committee meets monthly. Communication with R&D personnel is through email, memos, official R&D forms, and online reporting.
- 3) The MUSC Institutional Review Board (IRB).
- 4) The Data Safety Monitoring Board.

If complete information is not available when the initial 24-hour SAE report is disseminated, follow-up information will be gathered to enable a complete assessment and outcome of the event. This information may include hospital discharge records, autopsy reports, clinic records, etc. The research staff will attach copies of source documents to the SAE report for review by the PI and for forwarding to the VA personnel as appropriate.

We will report adverse events to VA R&D and to the MUSC IRB as soon as possible, but no later than 10 working days after the investigators first learns of the event. The VAMC and MUSC IRB AE reporting requirements are as follows: All deaths that occur during the study or 30 days post termination from the study are required to be reported as adverse events even if they are expected or unrelated. Other adverse events are reportable to the VA R&D and MUSC IRB if the AE is unexpected AND related or possibly related AND serious or more prevalent than expected. All three criteria must be met for an AE to be reported to the VA R&D and MUSC IRB. The R&D and IRB definition of unexpected is that the AE is not identified in nature, severity or frequency in the current protocol, informed consent, investigator brochure or with other current risk information. The definition of related is that there is a reasonable possibility that the adverse event may have been caused by the drug, device or intervention. Reportable AEs are reviewed by the VA R&D Chair and reported to the R&D Board at the next meeting.

Study Safety. The potential risks and benefits of this study and methods to minimize these risks are outlined above. Protocols for reported AEs and SAEs are outlined above. All unexpected AE and SAEs will be monitored until resolved. A detailed summary of all AEs will be prepared weekly by the research staff. At the weekly team meetings (or before if urgent), the research staff will report any premonitory symptoms of clinical deterioration. Study procedures will follow the FDA's Good Clinical Practice Guidelines ([www.fda.gov/oc/gcp](http://www.fda.gov/oc/gcp)). Any outside requests for information or any breaches in confidentiality will be reported to the PI. All requests by participant's physicians and other medical providers will be referred directly to the applicant.

DSM Plan Administration. Dr. Flanagan will be responsible for monitoring the study. The PIs and a statistician (Mr. Baker) will examine the outcomes database for missing data, unexpected distributions or responses, and outliers. A DSMB report will be filed with R&D annually, unless greater than expected problems occur. The report will include participant characteristics, retention and disposition of study participants, quality assurance issues and reports of AEs, significant/unexpected AEs and serious AEs. We will report results at the end of the trial.

DSM Board. We will create a DSMB to monitor overall participant safety, the rate and severity of adverse events, and the validity and integrity of the data. The panel includes 2 researchers with experience in treating Veterans with PTSD (Mark Hamner, M.D., Karen Hartwell, M.D.) and a statistician (Ms. Amy Wahlquist). The board may be called at any point if needed for unexpected AEs, etc. Modifications will be made in the procedures and/or the protocol if necessary based on the recommendations of the board. Confidentiality will be maintained during all phases of the study.

### **ClinicalTrials.gov Requirements**

In accordance with Public Law 110-85, the proposed trial will be registered with ClinicalTrials.gov. Applicable requirements regarding results reporting will be adhered to.

## BIBLIOGRAPHY

1. Seal KH, Bertenthal D, Miner CR, et al. Bringing the war back home: Mental health disorders among 103,788 US veterans returning from Iraq and Afghanistan seen at Department of Veterans Affairs Facilities. *Archives of Internal Medicine*. 2007;167(5):476-482.
2. Bradley R, Greene J, Russ E, et al. A multidimensional meta-analysis of psychotherapy for PTSD. *American Journal of Psychiatry*. 2005(162):214-227.
3. Kilmer B, Eibner C, Ringel JS, et al. Invisible wounds, visible savings? Using microsimulation to estimate the costs and savings associated with providing evidence-based treatment for PTSD and depression to veterans of Operation Enduring Freedom and Operation Iraqi Freedom. *Psychological Trauma: Theory, Research, Practice, and Policy*. 2011;3(2):201-211.
4. Foa EB, Hembree EA, Cahill SP, et al. Randomized trial of prolonged exposure for posttraumatic stress disorder with and without cognitive restructuring: outcome at academic and community clinics. *Journal of Consulting and Clinical Psychology*. 2005;73(5):953-964.
5. International Society for Traumatic Stress Studies. *Cognitive Behavioral Therapy for Adults*. 2nd ed. New York, NY: Guilford Press; 2009.
6. Tuerk PW, Yoder M, Grubaugh A, et al. Prolonged exposure therapy for combat-related posttraumatic stress disorder: An examination of treatment effectiveness for veterans of the wars in Afghanistan and Iraq. *Journal of Anxiety Disorders*. 2011;25(3):397-403.
7. Schnurr PP, Friedman MJ, Engel CC, et al. Cognitive behavioral therapy for posttraumatic stress disorder in women: a randomized controlled trial. *Journal of the American Medical Association*. 2007;297:820-830.
8. Resick PA, Nishith P, Weaver TL, et al. A comparison of cognitive-processing therapy with prolonged exposure and a waiting condition for the treatment of chronic posttraumatic stress disorder in female rape victims. *Journal of Consulting and Clinical Psychology*. 2002;70:867-879.
9. Kehle-Forbes SM, Meis LA, Spoont MR, et al. Treatment initiation and dropout from prolonged exposure and cognitive processing therapy in a VA outpatient clinic. *Psychological Trauma: Theory, Research, Practice, and Policy*. 2016;8(1):107-114.
10. Goetter EM, Bui E, Ojserkis RA, et al. A systematic review of dropout from psychotherapy for posttraumatic stress disorder among Iraq and Afghanistan combat veterans. *Journal of Traumatic Stress*. 2015;28(5):401-409.
11. Bisson JI, Roberts NP, Andrew M, et al. Psychological therapies for chronic post-traumatic stress disorder (PTSD) in adults. *The Cochrane Library*. 2013.
12. Eckstein M, Becker B, Scheele D, et al. Oxytocin Facilitates the Extinction of Conditioned Fear in Humans. *Biological Psychiatry*. 2014;78(3):194-202.
13. MacDonald K, MacDonald TM. The peptide that binds: a systematic review of oxytocin and its prosocial effects in humans. *Harvard Review of Psychiatry*. 2010;18(1):1-21.
14. Missig G, Ayers LW, Schulkin J, et al. Oxytocin reduces background anxiety in a fear-potentiated startle paradigm. *Neuropsychopharmacology*. 2010;35(13):2607-2616.
15. Acheson D, Feifel D, de Wilde S, et al. The effect of intranasal oxytocin treatment on conditioned fear extinction and recall in a healthy human sample. *Psychopharmacology*. 2013;229(1):199-208.
16. Frijling JL, van Zuiden M, Koch S, et al. Efficacy of oxytocin administration early after psychotrauma in preventing the development of PTSD: study protocol of a randomized controlled trial. *BMC Psychiatry*. 2014;14(1):92.
17. Olff M, Langeland W, Witteveen A, et al. A psychobiological rationale for oxytocin in the treatment of posttraumatic stress disorder. *CNS Spectrums*. 2010;15(8):522-530.
18. Koch S, van Zuiden M, Nawijn L, et al. Intranasal oxytocin as strategy for medication-enhanced psychotherapy of PTSD: salience processing and fear inhibition processes. *Psychoneuroendocrinology*. 2014;40:242-256.
19. Flanagan JC, Hand A, Jarnecke AM, et al. Effects of Oxytocin on Working Memory and Executive Control System Connectivity in Posttraumatic Stress Disorder. *Experimental and Clinical Psychopharmacology*. 2018;26(4):391-402.
20. van Zuiden M, Frijling JL, Nawijn L, et al. Intranasal oxytocin to prevent PTSD symptoms: a randomized controlled trial in emergency department patients. *Biological Psychiatry*. 2016;81(12):1030-1040.
21. Office of Rural Health. About the Office of Rural Health. 2012; [www.ruralhealth.va.gov/](http://www.ruralhealth.va.gov/).

22. Kessler RC, Petukhova M, Sampson NA, et al. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. *Int J Methods Psychiatr Res.* 2012;21:169-184.
23. Tanielian T, Haycox LH, Schell TL, et al. *Invisible Wounds of War. Summary and Recommendations for Addressing Psychological and Cognitive Injuries.* DTIC Document;2008.
24. Foa EB, Hembree EA, Rothbaum BO. *Prolonged exposure therapy for PTSD: Emotional Processing of Traumatic Experiences Therapist Guide.* Oxford University Press; 2007.
25. Eftekhari A, Ruzek JI, Crowley JJ, et al. Effectiveness of national implementation of prolonged exposure therapy in Veterans Affairs care. *JAMA Psychiatry.* 2013;70(9):949-955.
26. Powers MB, Halpern JM, Ferenschak MP, et al. A meta-analytic review of prolonged exposure for posttraumatic stress disorder. *Clinical Psychology Review.* 2010;30(6):635-641.
27. The Management of Posttraumatic Stress Disorder Work Group. *VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder.* Washington, D.C.2017.
28. Hembree EA, Foa EB, Dorfan NM, et al. Do patients drop out prematurely from exposure therapy for PTSD? *Journal of Traumatic Stress.* 2003;16(6):555-562.
29. Gutner C, Gallagher MW, Baker S. Time course of treatment dropout in cognitive-behavioral therapies for posttraumatic stress disorder. *Psychol Trauma.* 2016;8:115–121.
30. Krystal JH, Davis LL, Neylan TC, et al. It is time to address the crisis in the pharmacotherapy of posttraumatic stress disorder: A consensus statement of the PTSD Psychopharmacology Working Group. *Biological Psychiatry.* 2017;82(7):e51-e59.
31. Stein DJ, Ipser J, McAnda N. Pharmacotherapy of posttraumatic stress disorder: a review of meta-analyses and treatment guidelines. *CNS Spectrums.* 2009;14(1):25-31.
32. Hetrick SE, Purcell R, Garner B, et al. Combined pharmacotherapy and psychological therapies for post traumatic stress disorder (PTSD). *Cochrane Database Syst Rev.* 2010;7(7).
33. Frijling JL, Zuiden M, Nawijn L, et al. Salivary Oxytocin and Vasopressin Levels in Police Officers With and Without Post-Traumatic Stress Disorder. *Journal of Neuroendocrinology.* 2015;27(10):743-751.
34. Reijnen A, Geuze E, Vermetten E. Individual variation in plasma oxytocin and vasopressin levels in relation to the development of combat-related PTSD in a large military cohort. *Journal of Psychiatric Research.* 2017;94:88-95.
35. Sippel LM, Han S, Watkins LE, et al. Oxytocin receptor gene polymorphisms, attachment, and PTSD: Results from the National Health and Resilience in Veterans Study. *Journal of Psychiatric Research.* 2017;94:139-147.
36. Woodward SH, Neylan TC, Mellman TA, et al. Distinguishing current from remitted posttraumatic stress disorder. *Arch Gen Psychiatry.* 2006;63(8):940-941; author reply 941-942.
37. Pitman RK, Rasmusson AM, Koenen KC, et al. Biological studies of post-traumatic stress disorder. *Nature Reviews Neuroscience.* 2012;13(11):769-787.
38. Sripatha RK, King AP, Garfinkel SN, et al. Altered resting-state amygdala functional connectivity in men with posttraumatic stress disorder. *Journal of Psychiatry and Neuroscience.* 2012;37(4):241.
39. Simons JS, Henson RN, Gilbert SJ, et al. Separable forms of reality monitoring supported by the anterior prefrontal cortex. *Journal of Cognitive Neuroscience.* 2008;20:447-457.
40. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience.* 2001;24:167-202.
41. Domes G, Heinrichs M, Glascher J, et al. Oxytocin attenuates amygdala responses to emotional faces regardless of valence. *Biological Psychiatry.* 2007;62:1187-1190.
42. Flanagan JC, Sippel LM, Moran-Santa Maria MM, et al. Impact of Oxytocin on the Neural Correlates of Fearful Face Processing in PTSD Related to Childhood Trauma. in preparation.
43. Eskandarian S, Vafaei AA, Vaezi GH, et al. Effects of systemic administration of oxytocin on contextual fear extinction in a rat model of post-traumatic stress disorder. *Basic and Clinical Neuroscience.* 2013;4(4):315.
44. Palgi S, Klein E, Shamay-Tsoory SG. The role of oxytocin in empathy in PTSD. *Psychological Trauma: Theory, Research, Practice, and Policy.* 2017;9(1):70.
45. Schmidt U, Novak B, Stich J, et al. Anxiolytic neuropeptides in posttraumatic stress disorder (PTSD)– Evidence from patients and various animal models. *Psychoneuroendocrinology.* 2017;83.
46. Flanagan JC, Allan NP, Calhoun CD, et al. Effects of Oxytocin on Stress Reactivity and Craving among Veterans with Co-Occurring PTSD and Alcohol Use Disorder. *Experimental and Clinical Psychopharmacology.* 2019;27(1):45-54.

47. Flanagan JC, Sippel LM, Wahlquist A, et al. Augmenting Prolonged Exposure Therapy for PTSD with Intranasal Oxytocin: A Randomized, Placebo-Controlled Pilot Trial. *Journal of Psychiatric Research*. 2017;98:64-69.
48. Yatzkar U, Klein E. P. 3.026 Intranasal oxytocin in patients with post traumatic stress disorder: a single dose, pilot double blind crossover study. *European Neuropsychopharmacology*. 2010;20:S84.
49. Kosfeld M, Heinrichs M, Zak PJ, et al. Oxytocin increases trust in humans. *Nature*. 2005;435(7042):673-676.
50. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*. 1975;12:189-198.
51. Weathers FW, Blake DD, Schnurr PP. *Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)*. Interview available from the National Center for PTSD at [www.ptsd.va.gov](http://www.ptsd.va.gov). 2013.
52. Weathers FW. *The PTSD checklist for DSM-5 (PCL-5)*. Scale available from the National Center for PTSD at [www.ptsd.va.gov](http://www.ptsd.va.gov). 2013.
53. Weathers FW, Blake DD, Schnurr PP, et al. *The Life Events Checklist for DSM-5 (LEC-5)*. Instrument available from the National Center for PTSD at [www.ptsd.va.gov](http://www.ptsd.va.gov). 2013.
54. Foa EB, Hembree EA, Dancu CV. *Prolonged exposure (PE) manual – Revised version*. University of Pennsylvania; 2002.
55. First, M. B., & Williams, J. B. (2021). *Quickscid-5: Quick Structured Clinical Interview for Dsm-5 Disorders*. American Psychiatric Association Publishing.
56. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *Journal of General Internal Medicine*. 2001;16(9):606-13.
57. Posner K, Brent D, Lucas C, et al. *Columbia-Suicide Severity Rating Scale (C-SSRS)*. New York: New York State Psychiatric Institute; 2008.
58. Morin CM. *Insomnia: Psychological assessment and management*. New York: Guilford Press; 1993.
59. Buss AH, Perry M. The aggression questionnaire. *Journal of Personality and Social Psychology*. 1992;63(3):452.
60. Sherbourne CD, Stewart AL. The MOS social support survey. *Soc Sci Med*. 1991;32:705-714.
61. Childress AR, McLellan AT, O'Brien CP. Abstinent opiate abusers exhibit conditioned craving, conditioned withdrawal and reductions in both through extinction. *British Journal of Addiction*. 1986;81(5):655-660.
62. Luborsky L, Barber JP, Siqueland L, et al. The revised Helping Alliance questionnaire (HAQ-II): psychometric properties. *The Journal of Psychotherapy Practice and Research*. 1996;5(3):260-271.
63. Frueh BC, Pellegrin KL, Elhai JD, et al. Patient satisfaction among combat veterans receiving specialty PTSD treatment. *Journal of Psychiatric Practice*. 2002;8(5):326-332.
64. Flanagan JC, Baker NL, McRae AL, et al. Effects of Adverse Childhood Experiences on the Association between Intranasal Oxytocin and Social Stress Reactivity among Individuals with Cocaine Dependence. *Psychiatry Research* 2015;229(1-2):94-100.
65. Cardoso C, Ellenbogen MA, Orlando MA, et al. Intranasal oxytocin attenuates the cortisol response to physical stress: A dose–response study. *Psychoneuroendocrinology*. 2013;38(3):399-407.
66. Kazantzis N, Whittington C, Dattilio F. Meta-analysis of homework effects in cognitive and behavioral therapy: A replication and extension. *Clinical Psychology: Science and Practice*. 2010;17:144-156.
67. Carroll KM, Nich C, Sifry RL, et al. A general system for evaluating therapist adherence and competence in psychotherapy research in the addictions. *Drug and Alcohol Dependence*. 2000;57(3):225-238.
68. Hendriks L, de Kleine RA, Broekman TG, et al. Intensive prolonged exposure therapy for chronic PTSD patients following multiple trauma and multiple treatment attempts. *European Journal of Psychotraumatology*. 2018;9(1):1425574.
69. Resick PA, Nishith P, Weaver TL, et al. A comparison of cognitive-processing therapy with prolonged exposure and a waiting condition for the treatment of chronic posttraumatic stress disorder in female rape victims. *Journal of Consulting and Clinical Psychology*. 2002;70(4):867-879.
70. Rauch SA, DeFeaver E, Favorite T, et al. Prolonged exposure for PTSD in a Veterans Health Administration PTSD clinic. *Journal of Traumatic Stress*. 2009;22(1):60-64.
71. Vierron E, Giraudeau B. Sample size calculation for multicenter randomized trial: Taking the center effect into account. *Contemporary Clinical Trials*. 2007;28:451-458.
72. Ruvuna F. Unequal Center Sizes, Sample Size, and Power in Multicenter Clinical Trials. *Drug Information Journal*. 2004;38(4):387–394.

73. Wangelin BC, Tuerk PW. Taking the pulse of prolonged exposure therapy: physiological reactivity to trauma imagery as an objective measure of treatment response. *Depression and Anxiety*. 2015;32(12):927-934.
74. Little R, Rubin DB. *Statistical Analysis with Missing Data, 2nd Edition*. Hoboken, NJ: John Wiley & Sons, Inc; 2002.
75. Back SE, Killeen TK, Badour C, et al. Integrated Exposure-Based Therapy for PTSD and Co-Occurring Substance Use Disorders among Veterans: A Randomized Controlled Trial *Addictive Behaviors*. 2019;90:369-377.
76. Back SE, Flanagan JC, Jones JL, et al. Doxazosin for the treatment of co-occurring PTSD and alcohol use disorder: Design and methodology of a randomized controlled trial in military veterans. *Contemporary Clinical Trials*. 2018;73:8-15.
77. Friedman MJ. Current and future drug treatment for posttraumatic stress disorder patients. *Psychiatric Annals*. 1998;28:461-468.
78. World Health Organization. "The Alcohol Use Disorders Identification Test (AUDIT)." Instrument available from the World Health Organization for alcohol problems at [www.drugabuse.gov](http://www.drugabuse.gov). 1989.
79. Skinner HA. *The drug abuse screening test*. Addictive behaviors. 1982;7(4):363-71.
80. Sobell LC, Sobell MB, Buchan G, Cleland PA, Fedoroff I, Leo GI. *The reliability of the Timeline Followback method applied to drug, cigarette, and cannabis use*. Paper presented at the 30th Annual Meeting of the Association for Advancement of Behavior Therapy, New York, NY, November 1996.
81. Koss MP, Marks JS. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: The adverse childhood experiences (ACE) study. *American Journal of Preventative Medicine*. 1998;14(4):245-58.
82. Keane TM, Fairbank JA, Caddell JM, Zimering RT, Taylor KL, Mora CA. Clinical evaluation of a measure to assess combat exposure. *Psychological Assessment: A Journal of Consulting and Clinical Psychology*. 1989;1(1):53.
83. Straus MA, Hamby SL, Boney-McCoy S, Sugarman DB. The revised conflict tactics scales (CTS2) development and preliminary psychometric data. *Journal of Family Issues*. 1996;17(3):283-316.
84. Hunsley J, Best M, Lefebvre M, Vito D. The seven-item short form of the Dyadic Adjustment Scale: Further evidence for construct validity. *American Journal of Family Therapy*. 2001;29(4):325-35.
85. Wei M, Russell DW, Mallinckrodt B, Vogel DL. The Experiences in Close Relationship Scale (ECR)-short form: Reliability, validity, and factor structure. *Journal of Personality Assessment*. 2007;88(2):187-204.
86. Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA. *Manual for the state-trait anxiety scale*. Consulting Psychologists. 1983.
87. Pomerleau CS, Majchrzak MJ, Pomerleau OF. Nicotine dependence and the Fagerström Tolerance Questionnaire: a brief review. *Journal of Substance Abuse*. 1989.
88. National Institute of Environmental Health Sciences. (2020). COVID-19 OBSSR Research Tools. Retrieved from [https://www.nlm.nih.gov/dr2/COVID-19\\_BSSR\\_Research\\_Tools.pdf](https://www.nlm.nih.gov/dr2/COVID-19_BSSR_Research_Tools.pdf)
89. Nash, W. P., Marino Carper, T. L., Mills, M. A., Au, T., Goldsmith, A., & Litz, B. T. (2013, Jun). Psychometric evaluation of the Moral Injury Events Scale. *Military Medicine*, 178(6), 646-652. <https://doi.org/10.7205/MILMED-D-13-00017>