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Publication Date

2020-08-01

DOI

10.1016/j.cct.2020.106074

Peer reviewed

HHS Public Access

Author manuscript

Contemp Clin Trials. Author manuscript; available in PMC 2021 August 01.

Published in final edited form as:

Contemp Clin Trials. 2020 August ; 95: 106074. doi:10.1016/j.cct.2020.106074.

Enhancing Prolonged Exposure Therapy for PTSD among Veterans with Oxytocin: Design of a Multisite Randomized Controlled Trial

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Abstract

Posttraumatic stress disorder (PTSD) is the most highly prevalent mental health disorder among U.S. military Veterans. Prolonged Exposure (PE) therapy is one of the most widely used evidence-based treatments for PTSD, but there is substantial room for improvement in outcomes and retention rates. Accumulating data suggest that oxytocin offers a promising pharmacological approach towards achieving this goal. Therefore, the primary objective of this two-site Phase II study is to examine the ability of oxytocin (vs. placebo) administration combined with PE therapy to (1) reduce PTSD symptom severity, (2) accelerate the rate of PTSD symptom improvement, and (3) improve PE adherence and retention rates. To accomplish these objectives, we will employ a randomized, double-blind, placebo-controlled trial and use standardized, repeated dependent measures of change at five time points (baseline, mid-treatment, end of treatment, and 3 and 6 month follow-up). Intranasal oxytocin (40 IU) will be administered directly prior to each PE therapy session. Findings from this study will provide critical new information regarding the efficacy of oxytocin to augment psychosocial treatment for PTSD, as well as information regarding the physiological mechanisms underlying PTSD and positive treatment response.

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Conflict of Interest: The authors have no financial conflicts of interest to declare.

Keywords

prolonged exposure therapy; Veteran; PTSD; oxytocin; psychophysiology

1. Introduction

1.1. Research Objectives and Hypotheses

Posttraumatic stress disorder (PTSD) is a chronic, debilitating condition and the most common mental health disorder among treatment-seeking Veterans[1,2]. The high rates of impairment, disability, and healthcare utilization among Veterans with PTSD result in substantial economic burden for the individual, their family, and our nation[3].

Prolonged Exposure (PE) therapy one of the most effective treatments for PTSD[4,5]. However, approximately 30% of patients drop out before treatment completion[4,6–10] and a significant proportion of patients continue to experience unremitting PTSD symptoms[2,11]. Compared to civilians, Veterans demonstrate the highest dropout rates and the lowest treatment response to PE[7,9,10,12]. Although early dropout is not the only cause of PE nonresponse, Veterans might continue to experience clinically significant symptoms and continue to meet diagnostic criteria for PTSD following an incomplete “dose” of PE treatment[2].

Pharmacological augmentation strategies may help optimize PE treatment engagement and outcomes among Veterans with PTSD. While many medications have been investigated for treating PTSD, both alone and in combination with PE and other behavioral interventions, only selective serotonin reuptake inhibitors (SSRIs) have received FDA approval. However, findings show that only 20–30% of patients experience PTSD remission with SSRI treatment[13]. 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[14,15]. Evidence-based psychotherapy for PTSD is critical to maximize treatment outcomes[16], but relatively few studies to date have examined a combined medication plus psychotherapy approach to PTSD treatment[17–21]. The oxytocin system is another promising target for pharmacological development to treat PTSD[22].

Prevailing hypotheses suggest that oxytocin may help mitigate barriers to engaging in behavioral treatments that specifically target avoidance, which would thereby allow patients who might otherwise be unable to tolerate PE to engage effectively, obtain an adequate treatment dose, and experience long-term PTSD remission[23–25]. For example, data indicate that oxytocin administration exerts anxiolytic and anti-stress properties in animal models[26,27], and oxytocin has anxiolytic and prosocial effects in individuals with PTSD[28–30]. Oxytocin reduces neurobiological reactivity to social stress among healthy individuals and those with PTSD using laboratory paradigms[31] and can also mitigate dysregulation of neural circuitry in corticolimbic brain regions associated with PTSD[32–37]. 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[24,38,39]. Notably, in a randomized, placebo-controlled pilot study, we 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, as well as accelerated reduction in PTSD symptoms during treatment[39].

The primary objective of the current project is to evaluate whether oxytocin administration 30 minutes before each session of PE (1) reduces PTSD severity and (2) enhances retention and adherence rates among Veterans with PTSD. Secondary objectives are to evaluate whether oxytocin in combination with PE improves associated areas of functioning. We will also include within-session physiological measurements because emerging literature suggests that objective physiological monitoring during PE therapy can yield valuable supplemental assessment of treatment effects[40–43]. Although one study found that in a controlled laboratory setting, a single dose of oxytocin was not effective in reducing physiological reactivity during one-session exposure therapy for PTSD[44], a heightened physiological response to trauma cues is a hallmark symptom of PTSD[45]. Furthermore, another recent study indicates that, when compared to placebo, yohimbine treatment in combination with PE resulted in increased physiological arousal during treatment and lower heart rate reactivity one week following treatment completion[46]. In another study, members of our team demonstrated that among Veterans with PTSD (N=35), heart rate and skin conductance significantly decreased during the course of PE. Findings also indicated that Veterans with greater physiological reactivity at baseline experienced greater reductions in PTSD symptom severity during treatment[40].

2. Materials and Methods

2.1. Research Design

This is a 10-week, randomized, double-blind, placebo-controlled trial examining the efficacy of combining intranasal oxytocin (40 IU) with Prolonged Exposure (PE) therapy in the treatment of PTSD among Veterans. Dosing will occur 30 minutes prior to each weekly PE therapy session. A repeated measures design with two intervention arms will be used: (1) PE + oxytocin compared to (2) PE + placebo. Participants will complete follow-up visits at 3 months and 6 months following completion of the treatment phase (Figure 1). This study also will examine longitudinal changes in within-session psychophysiological assessments. The study will be conducted at two sites and will last for approximately five years.

2.2. Participants

Participants will be 188 U.S. military Veterans. Inclusion criteria are: (1) male or female; any race or ethnicity; age ≥ 18 years, (2) English fluency and intellectual functioning sufficient to provide informed consent and complete assessments (as assessed by a criterion of ≥ 26 on the Mini-Mental Status Exam [MMSE][47]), (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, since initiation or change of psychotropic medications during the study may interfere with interpretation of results. Primary exclusion criteria include: (1) meeting DSM-5 criteria for psychotic, bipolar or current moderate or severe substance use disorders (given the marked overlap of alcohol and drug use among Veterans with PTSD, mild substance use disorders

are allowable; participants who meet diagnostic criteria for moderate or severe substance use disorder will be referred for clinical treatment), (2) participants who present a serious suicide or homicide risk or are likely to require hospitalization during the study, and (3) pregnancy or breastfeeding for women.

2.3 Procedures

This study was reviewed and approved by the Institutional Review Board (IRB) of the Medical University of South Carolina (MUSC) and University of California-San Francisco, as well as the Research & Development committees at both the Charleston and San Francisco VAs. Following phone screening for preliminary eligibility, participants complete an in-person informed consent and baseline assessment. In a private room, participants are given a full description of the study procedures and asked to read and sign an IRB- and R&D-approved informed consent form before any study procedures are conducted. During the baseline visit, participants will complete a pregnancy test (for women; women are eligible for enrollment regardless of birth control utilization or form), a history and physical (H&P) exam, and a battery of standardized self-report and interview measures (Table 1). Ineligible Veterans will be referred for clinical treatment. Participants who meet full eligibility criteria will be invited to enter the treatment phase of the study.

2.3.1 Study Medication, Dosage, and Administration.—

Participants are randomized in a 1:1 manner to the oxytocin or placebo condition. All participants and study staff including investigators, research assistants, assessors, clinicians, and supervisors will be blind to drug condition. In order to ensure that the treatment groups are balanced with respect to PTSD symptom severity, a stratified randomization process will be used (described below). Participants receive the same medication at each session. A 40 IU dose of intranasal oxytocin or matching placebo (saline) will be self-administered under observation 30 minutes prior to the start of each weekly PE therapy session. The dose and timing of medication administration is based on past research in our group and others, including the positive pilot study that informed the current project[39,48–51]. A 40 IU dose has demonstrated safety and efficacy, is within the normal dosing range, and one of the most common concentrations utilized in human research[25,52,53]. In order to ensure consistency of study medication across study sites, oxytocin (Novartis) and matching placebo will be supplied directly to either study site by the compounding pharmacy (Volksapothke, Zum Roten Ochsen, Switzerland). A research pharmacist not involved with patient contact will maintain the blind. Research staff will instruct participants on the correct method of oxytocin administration and will observe participants self-administer study medication. Randomization will be stratified by sex and PTSD symptom severity and carried out by study biostatistician in order to preserve the double-blind design. Sex is an important consideration in clinical oxytocin research because sex differences have been observed in behavioral and neurobiological effects of acute oxytocin administration in various populations[54,55].

2.3.2 Psychosocial Intervention: Prolonged Exposure Therapy (PE)—

All participants receive 10 weekly 90 minute PE therapy sessions delivered by trained clinicians consistent with the published manual[56]. Based on Pavlovian learning theory, the central

therapeutic component of PE involves repeatedly presenting a conditioned stimulus (i.e., a trauma reminder) during (1) imaginal and (2) in-vivo (in the environment) exposure in the absence of the unconditioned stimulus (i.e., the traumatic event). All PE therapy sessions will be video recorded for fidelity monitoring and for patients to listen to between the therapy sessions as homework. Within and between sessions, participants will report pre, peak, and post subjective units of distress (SUDS) on a scale of 0 (no distress) to 100 (extreme distress).

2.3.3 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. Weekly clinical supervision will include all study therapists at both sites, and will be conducted by a doctoral-level VA clinician. Therapists will complete one to two pilot study cases in which all PE sessions will be recorded and rated for therapist adherence and competency. Supervision will focus on adherence to treatment and clinical concerns about particular participants. The supervisor will provide feedback to reduce therapist departure from the treatment protocol and to assist therapists in identifying issues to be addressed in subsequent sessions. To assure that PE is delivered in a manner consistent with manual guidelines, therapy sessions will be recorded and randomly selected sessions (25% of therapy sessions) will be evaluated using the Yale Adherence and Competence Scale[57]. Interrater reliability on adherence and competence measures and intraclass correlation coefficients will be calculated.

2.4 Outcome Measures

Primary outcomes include (1) clinician-rated PTSD diagnosis and symptom severity as measured by the Clinician Administered PTSD Scale (CAPS-5[58]) and (2) self-reported PTSD symptom severity as measured by the PTSD Checklist (PCL-5[59]).

2.4.1 Clinician-Administered PTSD Scale (CAPS-5).—The CAPS-5[58] is a structured diagnostic interview with excellent psychometric properties and diagnostic efficiency. The CAPS-5 will be administered by independent evaluators blind to treatment condition in person or via tele-health at baseline, session 5, session 10, and at follow-up. Included in CAPS-5 administration will be the Life Events Checklist for DSM-5 (LEC-5[60]), which assesses lifetime exposure to potentially traumatic events.

2.4.2 PTSD Checklist.—The PCL-5[59] is a 20-item self-report measure based on the DSM-5, which has excellent psychometric characteristics for screening and as a secondary indicator of PTSD symptom severity. The PCL-5 will be administered at baseline, weekly during the treatment phase, and at follow-up.

2.4.3 Additional Outcomes.—A third aim of this project is to assess the effect of treatment (oxytocin versus placebo) on treatment retention and engagement. 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. Homework sessions are assigned as one per type each day (i.e., 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. Additional assessment measures (see Table 1) have strong psychometric properties and were selected to include common data elements established by the PhenX Measurements for Mental Health Research Projects.

2.3. Data Analytic Plan

2.3.1. General—A bivariate 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 associations with study outcomes. Sex will be examined as a covariate, and estimates will be examined across sex. The primary analysis will focus on end-of-treatment (i.e., the final three weeks of the treatment phase) outcomes using an intent-to-treat analysis. Participants who decline to continue in treatment prior to session 10 will be invited to complete all remaining study assessments.

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 baseline PTSD symptom severity, groups will be stratified based on a screening PCL-5 score of 47 (based on our team's prior and ongoing trials among Veterans with PTSD[61,62]).

2.3.2. 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) and an increased rate of early reduction in self-reported PTSD symptoms during the treatment phase. Prior work has shown that PE therapy alone is efficacious in the reduction of both clinician administered (CAPS reductions of 35–55%)[39,63,64] and participant rated PTSD symptom scores (reductions of 29–44%)[39,63,65,66]. 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 ± SD: Baseline 39.0 ± 6.3 vs. end of treatment 13.0 ± 14.7) and a 61% decrease in PCL-5 scores (mean ± SD: Baseline 52.2 ± 12.0 vs. end of treatment 20.5 ± 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 Δ=7.8, SD=14.7) and Cohen's d=0.58 (PCL-5 Δ=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[67,68]. Assuming no more than 10% of model variance is due to site differences (ρ=.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 188 total participants (n=94 per treatment arm). If imbalance in these characteristics is curtailed, statistical power may exceed 80%.

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: Δ=13.7, SD=19.8, Cohen's *d*=0.69) and clinician administered PTSD symptoms (CAPS-5:, Δ=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.

2.3.3. Clinical outcomes—We hypothesize that the PE + oxytocin group, as compared to the PE + placebo group, will demonstrate (1) significantly greater reduction in PTSD symptoms as measured by the CAPS-5 and PCL-5 from baseline to end of treatment, (2) significantly faster rate of improvement in PTSD symptoms as measured by the PCL-5, and (3) a significantly greater number of sessions attended and homework assignments completed. To test hypotheses 1, generalized linear mixed effects models will be developed. 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 baseline analysis as well as for known confounders. Possible moderating effects of study site on treatment assignment will be investigated through model interactions. Appropriate analysis methods will be employed to accommodate missing data. Mixed-effects models yield valid inferences via maximum likelihood, assuming ignorable attrition (i.e., attrition is accounted for by covariates or the dependent variable measured prior to dropout). However, we will employ a sensitivity strategy to examine and compare treatment efficacy parameter estimates between primary methods noted above and those obtained using methods of multiple imputation. Multiple imputation will be implemented using 10 imputation sets and the expectation-maximization algorithm.

In order to assess the differential rate of early decline in PTSD symptoms between groups (Hypothesis 2), models utilizing treatment measured time points from baseline to the mid-treatment time point (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 (for PCL-5 only) will be included in the model (removed when insignificant). 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. Hypothesis 2 results will be estimated independently for the CAPS-5 and the PCL-5.

In order to assess differences in the number of sessions attended (Hypothesis 3), general linear mixed effects models employing a binomial regression framework with a logit link

function will be used to assess differences in the number of attended treatment sessions as a function of drug condition. 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. Secondarily, 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.

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 within-session (during imaginal exposures, specifically) physiological reactivity (e.g., heart rate and skin conductance). 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. To assess early or incremental benefit on remission of symptoms, time to PTSD remission will be assessed using a Cox Proportional Hazards regression model. 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. Inter-beat interval and skin conductance 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 physiological 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 examine treatment group differences on outcomes commonly associated with PTSD symptom severity such as depression, aggression, and sleep using survey instruments (Table 1). 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.

Discussion

This objective of this paper is to present the design and methodology for a two-site, Phase II randomized, controlled trial examining the efficacy of intranasal oxytocin to enhance PE therapy outcomes among Veterans with PTSD. PTSD is a prevalent, chronic, and debilitating condition for which few medications are approved, and military Veterans incur heighted risk for trauma exposure, PTSD, and negative sequelae compared to civilian populations. Despite strong evidence supporting the efficacy of PE in Veteran and civilian populations, a substantial number of patients with PTSD do not complete treatment and many continue to struggle with PTSD symptoms following treatment completion, suggesting that there is ample room to improve treatment outcomes. To our knowledge, this study is the first

adequately powered trial to examine the efficacy of intranasal oxytocin treatment in combination with PE among patients with PTSD. The primary goal of this project is to examine whether a 40 IU dose of intranasal oxytocin, as compared to placebo, improves PTSD remission rates, reduces PTSD symptom severity and associated problems, and improves associated areas of functioning during 10 weeks of PE therapy.

One strength of the current study design is that we will employ a multisite, multimodal, and interdisciplinary approach to examine the efficacy of combining intranasal oxytocin with PE. Another critical strength of this project is that it leverages a gold standard behavioral intervention with strong empirical support. PE is disseminated nationwide in VA treatment clinics and among the most commonly used treatments for PTSD in VA healthcare settings. In addition, oxytocin is a generic, widely available, low cost medication. Positive findings from the current study could be rapidly transferred to treatment settings at an affordable cost. Finally, the project is designed and powered to examine mechanisms underlying both positive and null treatment outcomes.

Several alternative study designs were contemplated. Consistent with our aim to examine the ability of oxytocin to enhance PE therapy, we considered administering oxytocin daily as opposed to administering a weekly dose prior to each therapy session. Following extensive discussion, our team determined that the most well-controlled, scientifically justified, and clinically useful design is to employ a weekly dosing strategy for the following reasons: (1) the beneficial effects of acute oxytocin administration are well-documented in the literature, (2) oxytocin has a brief half-life and there is no existing literature to guide a safe and effective timing strategy to mitigate PTSD symptoms between therapy sessions, (3) the theoretical rationale for administering oxytocin prior to PTSD therapy sessions is robust[23–25], (4) there is no validated method or biomarker to confirm self-administration, and (5) there is no literature demonstrating the safety, feasibility, or acceptability of daily oxytocin dosing in PTSD populations over a lengthy treatment phase. While one study has utilized a twice daily dosing strategy to assess the ability of oxytocin to prevent PTSD onset, this study only dosed subjects for 7 days[69]. Similarly, while several studies among patients with autism and substance use disorders have utilized a daily dosing strategy, most of these studies lasted for 7 days or less[70–72]. We also considered including a PE only group within our study design. However, while administration of drug to both groups has the potential to influence outcomes, including a group with no drug administration would partially unblind drug condition assignment. Thus, our team decided that at this stage of investigation, the most scientifically meritorious and fiscally responsible approach was to employ the most rigorously controlled design. If positive findings suggest that future investigation of oxytocin is warranted in this population, a more complex three-group design might prove necessary. Additionally, we considered the possibility that oxytocin's anxiolytic effects may limit arousal during in-session imaginal exposures. However, the extant literature documents the central importance of between-session, as compared to within session, habituation in PE[73]. Finally, because oxytocin has demonstrated acute effects on functioning of the hypothalamic-pituitary-adrenal axis, we considered comparing salivary cortisol reactivity to the PE treatment sessions between drug conditions. However, cortisol reactivity is saliently influenced by diurnal and hormonal variations as well as numerous lifestyle factors (e.g.,

smoking, caffeine intake, meal times, stress). Thus, it did not seem feasible to standardize sample collection or obtain reliable sample outcomes in the proposed study.

Regardless of the direction of treatment outcomes, the study is designed to ensure that findings will provide critical new information regarding the synergistic effects of combining a novel pharmacotherapy (oxytocin) with PE for PTSD among Veterans. In addition to examining safety outcomes such as adverse events on a weekly basis, this study also examines within-session physiological mechanisms that might underscore treatment outcomes, changes in within-session SUDs, and moderators of treatment outcome such as sex, which is a known correlate of oxytocin treatment outcomes in various populations[54,55]. The findings from this study will inform future research on oxytocin in the treatment of PTSD and related psychiatric conditions, will help integrate physiological mechanisms in PTSD treatment development studies, and will be used to improve the translation of oxytocin into treatment settings for patients with PTSD.

Acknowledgments

Funding: This research is supported by funding from the Veterans Affairs Clinical Science Research & Development (CX001962) and the National Institute on Alcohol Abuse and Alcoholism (K23AA023845).

Role of the funding source: The funding sources have no involvement in the study design, the collection, analysis and interpretation of data, the writing of this manuscript, or the decision to submit this manuscript for publication.

Abbreviations:

PTSD	posttraumatic stress disorder
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
FDA	Food and Drug Administration
PE	Prolonged Exposure
GLMM	Generalized Linear Mixed Effects Models
IU	International Units
IRB	Institutional Review Board
MUSC	Medical University of South Carolina
CAPS	Clinician Administered PTSD Scale
LEC	Life Events Checklist
PCL-5	PTSD Checklist
TLFB	Timeline Follow Back
VAMC	U.S. Department of Veterans Affairs Medical Center
VAS	Visual Analogue Scale

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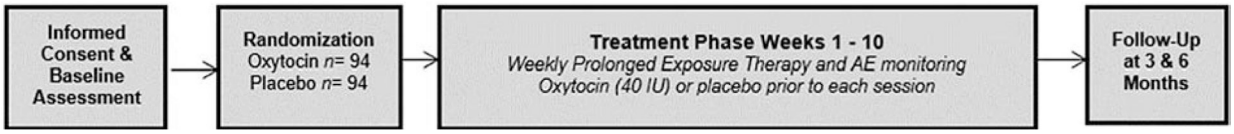

Figure 1.
Overview of study design.

Table 1.

Assessment Instruments and Timeline

Instrument	Purpose	BSL	Weekly	Week5	Week10	3MF/U	6MF/U
Demographics Form	Characterize sample	X					
Mini-Mental Status Exam [MMSE][47]	Screen for cognitive impairment	X					
MINI International Neuropsychiatric Interview (MINI)[74]	Assess DSM-5 psychiatric disorders	X					
Adverse Events	Assess adverse events		X	X	X	X	X
Concomitant Medications Form	Assess concomitant medications	X	X	X	X	X	X
Pregnancy Testing	Assess pregnancy for women	X	X	X	X		
Clinician Administered PTSD Scale (CAPS-5)[58]	**Primary Outcome: PTSD**	X		X	X	X	X
Life Events Checklist for DSM-5 (LEC-5)[60]	Assess lifetime trauma exposure	X					
PTSD Checklist (PCL-5)[59]	**Primary Outcome: PTSD**	X	X	X	X	X	X
Treatment Services Review	Monitor service utilization		X	X	X	X	X
Treatment Adherence	**Primary Outcome: Homework compliance**		X	X	X		
Patient Health Questionnaire (PHQ-9)[75]	Assess depression symptoms	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale (C-SSRS)[76]	Assess suicidality	X		X	X	X	X
Insomnia Severity Index (ISI)[77]	Assess sleep functioning	X		X	X	X	X
Aggression Questionnaire (AQ)[78]	Assess aggression/hostility	X		X	X	X	X
Social Support Survey[79]	Assess social support	X		X	X	X	X
Visual Analogue Scale[80](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[81]	Primary Outcome: Therapeutic Alliance			X	X		
Charleston Psychiatric Outpatient Satisfaction Scale[82]	Assess patient treatment satisfaction				X	X	X
Utility ofTechniques Inventory (UTI)[83]	Assess treatment adherence		X	X	X		
Penetration ofthe Blind Assessment	Assess participant/clinician blinding				X		
Alcohol Use Disorders Identification Test (AUDIT)[78]	Assess alcohol problems	X					
Drug Abuse Screening Test (DAST-10)[79]	Assess drug use	X					
Timeline Follow Back (TLFB)[80]	Alcohol, tobacco and drug use (amount and frequency)	X					
Military Service Demographics	Assess military service information	X					
Military Sexual Assessment (MST)	Assess military assault and harassment	X					
Adverse Childhood Experiences (ACE) Questionnaire[81]	Assess childhood trauma	X					

Instrument	Purpose	BSL	Weekly	Week5	Week10	3MF/U	6MF/U
Combat Exposure Scale (CES)[82]	Assess wartime stressors	X					
Revised Conflict Tactics Scale (CT S-2)[83]	Assess intimate partner violence	X					
Dyadic Adjustment Scale (DAS-7)[84]	Relationship functioning	X					
Experiences in Close Relationship Scale (ECR-S)[85]	Assess adult attachment	X					
State-Trait Anxiety Inventory (ST AI)[86]	Assess anxiety	X			X		
Fagerstrom Test ofNicotine Dependence (FTND)[87]	Assess nicotine use	X					

BSL=Baseline. F/U = Follow-Up. BP=Orthostatic Blood Pressure. BMI= Body mass index.