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Design of a randomized controlled trial examining the efficacy and biological mechanisms of web-prolonged exposure and present-centered therapy for PTSD among active-duty military personnel and veterans

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ABSTRACT

Improved accessibility of effective and efficient evidence-based treatments (EBTs) for military personnel suffering with posttraumatic stress disorder (PTSD) is an urgent need to meet the growing demand for timely care. In addition, a better understanding of the mechanism of action of behavioral therapy can inform the delivery of care to meet accessibility demands. Effective EBTs for PTSD are available, but logistical and stigma-related barriers to accessing behavioral healthcare can deter military personnel from receiving these treatments. Web-based treatments represent an innovative way to overcome these barriers. The efficacy of previously developed web-based treatments for PTSD appears promising; however, they were not developed based on treatment protocols with strong empirical support for their efficacy. No study to date has examined web-based treatment of PTSD using a well-established evidence-based treatment, nor delineated the biological mechanisms through which a web-based treatment exerts its effects. This paper describes the rationale and methods of a randomized controlled trial comparing the efficacy and potential biological mediators of 10 sessions of a web-version of Prolonged Exposure (PE), "Web-PE," delivered over 8 weeks compared to 10 sessions of in-person Present-

Abbreviations: ALLO, allopregnanolone; AUC, area under curve; AUDIT, Alcohol Use Disorders Identification Test; CAR, cortisol awakening response; CAPS-5, Clinician Administered PTSD Scale for *DSM-5*; CEQ, Credibility/Expectancy Questionnaire; CTQ, Childhood Trauma Questionnaire; DHEA/DHEAS, dehydroepiandrosterone; DoD, Department of Defense; DSI-SS, Depressive Symptoms Index – Suicidality Subscale; *DSM-5*, Diagnostic and Statistical Manual of Mentor Disorders, 5th Edition; EBTs, evidence-based treatments; EI, electron impact; GAD-7, Generalized Anxiety Disorder Screener; GC/MS, gas chromatography mass spectrometry; HPA, hypothalamic, pituitary, adrenal; HIPAA, Health Insurance Portability and Accountability Act; HFBA, heptafluorobutyric acidanhydride; HPLC, High-performance liquid chromatography; ISI, Insomnia Severity Index; LEC, Life Events Checklist; MINI, Mini International Neuropsychiatric Interview; PCL-5, PTSD Checklist for *DSM-5*; PCT, Present-Centered Therapy; PE, Prolonged Exposure; PHQ-9, Patient Health Questionnaire-9; PHQ-15, Patient Health Questionnaire-15; PTCI, Posttraumatic Cognitions Inventory; PTSD, posttraumatic stress disorder; PWPQ, Perceptions of Web-PE Questionnaire; RCT, randomized controlled trial; SIM, single ion monitoring; SNR, signal to noise ratio; STAXI-2, State-Trait Anger Inventory-2; SUDS, Subjective Units of Distress Scale; VA, Department of Veterans Affairs; VR-12, Veterans RAND 12-Item Health Survey

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Centered Therapy (PCT) delivered over 8 weeks by a therapist in 120 active duty military personnel and veterans with PTSD.

1. Introduction

Nearly 12% of U.S. military service members recently returning from deployment in support of combat operations meet criteria for posttraumatic stress disorder (PTSD) [1,2], and nearly 1 in 3 veterans being treated in Department of Veterans Affairs (VA) healthcare facilities have a diagnosis of PTSD [3]. Exposure therapies, and in particular Prolonged Exposure (PE) [4], possess the largest body of empirical evidence demonstrating their efficacy [5–8]. Despite its recognized efficacy, PE is not routinely provided to active duty military personnel seeking treatment for PTSD. Personal and cultural barriers, such as concern about stigmatization, can deter military personnel with PTSD from seeking treatment [2,9,10]. Additionally, in many clinic settings, providers are burdened with large caseloads that prevent them from seeing patients for weekly 90-minute appointments, as recommended by the PE protocol.

Web-based treatments represent an innovative way to overcome these barriers (i.e., stigma, availability, logistics, etc.). Not only do they have the potential to substantially increase access to therapy, but also the anonymity of web-treatments may be especially attractive to military personnel. The efficacy of previously developed web-treatments for PTSD appears promising [11–14]; however, these interventions were not developed from PTSD treatment protocols with proven efficacy. PE is well suited to Internet delivery because it is highly structured, systematic, and focused on concrete behaviors and symptoms. This study evaluates the efficacy of Web-PE, a self-guided, web-based version of PE that has therapist oversight and periodic therapist phone check-ins during treatment.

As effective treatments are adapted for new administration formats or new populations of patients, a better understanding of the biological processes involved in treatment change can inform how these modifications should be made. Accumulating evidence suggests that key biological mediators of change in PTSD include neuroendocrine and neurosteroid systems. Altered glucocorticoid [15–17] and neurosteroid [18,19] levels have been linked to mood and anxiety psychopathology. Further, growing evidence suggests that PTSD treatment response may be associated with changes in these biomarkers [18,20–22] and that biomarkers may predict treatment response [21]. Establishing the link between treatment response and specific neuroendocrine/neurosteroid mechanisms will allow mechanism-informed selection of the most effective treatment components (optimizing PE effectiveness), more feasible and effective treatment response studies (increasing efficiency), and better individualized treatment tailoring (personalized medicine).

The first aim of this randomized controlled trial (RCT) is to examine the efficacy of a web-based version of PE (Web-PE) compared to an active control (in-person Present-Centered Therapy; PCT; [23]) in the reduction of PTSD symptoms and associated psychopathology. The second aim is to investigate biological mechanisms associated with PTSD treatment response. We hypothesize that biomarkers will "track" with PTSD treatment response, that Web-PE will exert a greater normalizing effect on biomarkers as compared with PCT, and that baseline levels of biomarkers will predict treatment response.

2. Methods

This study integrates two separately funded studies. The clinical trial is affiliated with the South Texas Research Organizational Network Guiding Studies on Trauma and Resilience (STRONG STAR) Consortium and funded with an award from the Department of Defense. The biomarkers study received an award through the Consortium to Alleviate PTSD (CAP), which is jointly funded by the Departments of Defense and Veterans Affairs. STRONG STAR and CAP are multidisciplinary research consortia committed to developing and evaluating effective interventions for combat-related PTSD and associated conditions in active duty military personnel and recently discharged veterans. As such, the study uses existing STRONG STAR-CAP procedures and research infrastructure, including common data elements.

2.1. Participants

Participants (N = 120) are active duty military personnel stationed at Fort Hood, Texas, and veterans in the surrounding area who have deployed since September 11, 2001, who are seeking treatment for PTSD, ages 18–65. Up to 170 individuals will be consented and screened to obtain data for analysis from 120 participants (60 participants in each treatment condition). Inclusion criteria include a PTSD diagnosis, determined by a Clinical Administered PTSD Scale for *DSM-5* (CAPS-5) clinical interview and a CAPS-5 score ≥ 25, as well as exposure to a combat-related Criterion A event that was experienced during deployment. The diagnosis of PTSD may be indexed to the combat-related Criterion A event, or to another Criterion A event. In addition, participants must expect to remain in the local area for the next three months following the first assessment. Exclusion criteria include any recent manic episode or psychotic disorder (determined by the bipolar and psychosis sections of the Mini International Neuropsychiatric Interview [MINI]), current alcohol dependence (determined by the Alcohol Use Disorders Identification Test [AUDIT]), evidence of moderate or severe traumatic brain injury (determined by an inability to comprehend baseline screening questionnaires), current suicidal ideation severe enough to warrant immediate intervention (determined by the Depressive Symptoms Index – Suicidality Subscale [DSI-SS] and corroborated by a clinical risk assessment by a credentialed provider), other psychiatric disorders severe enough to warrant designation as the primary disorder, or current engagement in evidence-based treatment (EBT) for PTSD. Concomitant medications are not exclusionary; all medication changes are monitored for the duration of the trial.

2.2. Procedures

This study was reviewed and approved by the Institutional Review Boards of Brooke Army Medical Center, the Durham VA Medical Center, Emory University, Stanford University, the University of Michigan, the University of Pennsylvania, the University of Texas Health Science Center at San Antonio, and the VA Ann Arbor Healthcare System.

Following informed consent, baseline assessment includes a battery of psychological health questionnaires and interviews administered by an independent evaluator. Participants receive a kit for measuring cortisol awakening response on three consecutive mornings. Participants who are eligible based on the questionnaire and interview symptom assessment return to complete a second baseline assessment that includes script driven imagery and collection of biomarkers for neuroendocrine assay. After this, participants are randomized into a treatment arm: Web—PE or in-person PCT (see Fig. 1). Biomarkers assessment occurs at baseline, mid-treatment, and post-treatment. Clinical assessments comprised of questionnaires and interviews occur at baseline, post-treatment, and 3- and 6-month follow-ups. In addition, participants complete self-report measures assessing symptoms of PTSD, depression, and suicidal ideation at every other treatment session.