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Enhancing exposure therapy for PTSD with yohimbine HCL: Protocol for a double-blind, randomized controlled study implementing subjective and objective measures of treatment outcome

Bethany C. Wangelin [a,b,*], Mark B. Powers [c], Jasper A.J. Smits [c], Peter W. Tuerk [a,b]

[a] Mental Health Service Line, Ralph H. Johnson Veterans Affairs Medical Center, 109 Bee St., Charleston, SC, United States
[b] Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, 67 President St., Charleston, SC 29401, United States
[c] Department of Psychology, Southern Methodist University, 6424 Robert S. Hyer Blvd., Hyer Hall #307, Dallas, TX 75205, United States

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ABSTRACT

Prolonged exposure (PE) therapy is considered a gold standard protocol for the treatment of PTSD, and it is associated with large treatment effect sizes in combat veteran samples. However, considering high rates of PTSD in the present veteran population, ongoing research work is important toward improving treatment efficiency by decreasing time to symptom amelioration and increasing the amount of symptom amelioration. The proposed research aims to enhance exposure therapy outcomes for veterans with PTSD via combination treatment with PE and yohimbine hydrochloride (HCL), an alpha-2 adrenergic receptor antagonist. The proposed investigation entails a randomized, placebo-controlled trial investigating the effect of a single administration of yohimbine HCL (paired with the first session of imaginal exposure) on outcome of PE in 40 veterans with PTSD. An additional goal is to establish a pragmatic method of tracking psychophysiological measures over the course of therapy for incorporation into future clinical psychotherapy trials. Thus, in addition to traditional self- and clinician-reported psychological outcomes, heart rate and skin conductance reactivity will be measured during a standard trauma-specific imagery task before, during, and after PE treatment. We will further investigate whether changes in psychophysiological measures predict changes in patient- and clinician-reported outcome measures.

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1. Introduction

The Veterans Health Administration (VHA) coordinates a nationwide initiative [1,2] to disseminate prolonged exposure (PE) therapy for Posttraumatic Stress Disorder (PTSD) [3]. PE in VA settings is associated with large treatment effects [4–10], similar to outcomes for civilians [11–13]. Although improvement is close to 2 standard deviations for treatment completers [6], reported dropout rates range from 13% to 38% [10]. Also, 20%–50% of completers retain a PTSD diagnosis despite significant symptom improvement [4,6,11,14]. Thus, there is reason to investigate potential treatment refinements to increase PE retention and response.

1.1. Yohimbine-enhanced exposure therapy

Translational research suggests that pharmacological agents could enhance exposure therapy effectiveness [15–17]. Yohimbine HCL, an alpha-2 adrenergic receptor antagonist, is one such agent shown to facilitate fear extinction in animals [18,19] and, tentatively, in humans [20]. It is associated with increased norepinephrine levels in the amygdala, hippocampus, and prefrontal cortical regions—neural structures associated with fear conditioning, extinction, and emotional processing [18,21].

* Corresponding author at: Ralph H. Johnson VA Medical Center, 109 Bee St. (116), Charleston, SC 29401, United States. Tel.: +1 336 209 7720.
E-mail address: wangelin@musc.edu (B.C. Wangelin).

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Yohimbine HCL also has been shown to increase sympathetic nervous system activity [22] and to facilitate recall of traumatic memories in humans [23].

Under-engagement and active avoidance of distress during exposure are highlighted as factors expected to inhibit recovery [3,24,25] and are often encountered by clinicians implementing PE [26,27]. Research suggests that lower emotional activation during imaginal exposure can predict poorer therapy outcome [28–30]. Considering that a principal foundation of anxiety-related behavior therapy (including PE) is that corrective information must be paired with emotional activation in order for learning to occur [25,31,32], yohimbine HCL could facilitate increased engagement with the fear memory during imaginal exposure by enhancing sympathetic nervous system activation and recall of the trauma memory, thus potentially improving PE efficiency.

1.2. Psychophysiological outcome measures

The current study also will examine a method for tracking physiological reactivity across PE treatment. Psychological and physiological factors are implicated in the theoretical model for anxiety [31,33] and PTSD [25]; thus, it is important that both are considered when examining treatment effectiveness. However, PTSD outcome research typically relies on subjective symptom measures. Although validated questionnaires, standardized interviews, and indices of functional impairment are essential tools for outcome assessment (e.g., [34–36]), all rely primarily on patient self-report and are highly correlated with non-PTSD-specific measures of distress and depression (e.g., [37,38]; see [6,39]), leading some researchers to wonder if such assessments tap into general negative affect [40] or other higher-order factors [41,42]. Accordingly, objective indices – such as trauma-specific physiological reactivity – could yield a more comprehensive assessment of treatment response.

Literature is limited concerning physiological measurement, specifically in the context of active exposure therapy for PTSD. One case study [43] and two randomized controlled trials [44,45] indicated that skin conductance and heart rate during trauma imagery significantly decreased from baseline subsequent to exposure therapy. Building on this evidence, the current study will examine a simple applied psychophysiological paradigm intended for inclusion in future multi-site psychotherapy trials.

1.3. Research Aims

The current study entails a randomized, placebo-controlled trial investigating the effect of yohimbine HCL administration (in conjunction with the first imaginal exposure session) on outcome of PE in veterans with PTSD. In addition to traditional self- and clinician-reported psychological outcomes, heart rate and skin conductance will be measured during a standard trauma-specific imagery task before, during, and after treatment. We will further investigate whether changes in these psychophysiological measures predict changes in traditional subjective patient- and clinician-reported outcome measures.

Hypotheses. Overall, we expect that psychophysiological activity is an important component of engagement with the trauma memory in PE and can be measured objectively across treatment to index PTSD symptom reduction. It is predicted that participants administered yohimbine HCL prior to the first session of imaginal exposure will show, prior to the second imaginal exposure session, greater reductions in physiological reactivity during trauma imagery, compared to participants administered a placebo. Specifically, we predict greater decreases in skin conductance and heart rate during a standard trauma imagery task between PE Session 2 (prior to first imaginal exposure session) and PE Session 4 (prior to second imaginal exposure session) for patients receiving yohimbine HCL compared to those receiving placebo. Regarding clinical outcomes, we hypothesize that patients administered yohimbine HCL will show a greater slope of change (decrease) in self-reported PTSD symptoms across the course of PE treatment and that patients receiving yohimbine HCL will require fewer sessions to symptom amelioration. Finally, we will explore potential associations between pre-treatment physiological reactivity, symptom reports, and response to yohimbine-enhanced imaginal exposure (e.g., post-treatment SC and HR reactivity, post-treatment symptom severity, therapy dropout rate, and time to symptom amelioration).

2. Materials and Methods

This randomized controlled trial is funded by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Clinical Sciences Research and Development (PI: Tuerk), and is currently ongoing (ClinicalTrials.gov registry ID: NCT01031979). Procedures are approved by the local institutional review board and local VA Research and Development (R&D) committee, which will provide oversight for data safety and management planning and execution. Ample data support the safe use of yohimbine HCL in humans [20,46–48], and the safety of actively inducing stress in PTSD-diagnosed veterans [49].

2.1. Participants

Forty male combat veterans or active duty personnel of Operation Enduring Freedom/Operation Iraqi Freedom will be recruited who meet DSM-IV diagnostic criteria for PTSD. Potential study participants will be identified via patient referrals to the VA PTSD Clinical Team. The sample will be restricted to male combat veterans aged 18 to 45 years in order to minimize potential confounding factors affecting treatment response in this controlled trial. Patients meeting these initial criteria will be invited to participate and will review informed consent documents and information with an IRB-approved study coordinator. The study coordinator will explain to the patient that the study is examining the effectiveness of prolonged exposure, a gold standard treatment for PTSD, and whether yohimbine, an herbal supplement, can make therapy more effective, in that fewer therapy sessions are required because symptoms reduce more quickly. The study coordinator also will discuss the possible side effects of yohimbine such as temporarily increased