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TITLE: A Randomized, Double-Blind, Placebo-Controlled Trial of Doxazosin for Nightmares, Sleep Disturbance, and Non-Nightmare Clinical Symptoms in Post-Traumatic Stress

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14. ABSTRACT

Posttraumatic Stress (PTS) is a condition that may develop after highly stressful life events, and affects 8-10% of adults in the U.S. civilian population and up to 30% of soldiers exposed to combat. We are conducting a randomized, double-blind, placebo-controlled trial to more definitively demonstrate doxazosin's clinical benefits for PTS nightmares, non-nightmare sleep disturbance, and overall PTS symptoms. To assess the effects of doxazosin on the main outcome of interest, PTS nightmares, eligibility will be based on the presence of PTS nightmares in the setting of full- or partial-syndromal PTS. We are using flexible-dose design of doxazosin versus placebo with a 4-week titration phase followed by a 4-week steady-dose phase. The primary scientific aims of our study are as follows: (1)To assess the effects of doxazosin, in comparison to placebo, on sleep disturbance and clinical symptoms of PTS through measures of nightmares, subjective sleep quality, and non-nightmare PTS symptoms, in adult men and women with chronic PTS; (2) To examine the effects of doxazosin on an objective measure of sleep/wake activity in adult men and women with chronic PTS; (3) To examine the effects of doxazosin, as compared to placebo, on depression symptoms, sexual health, and overall quality of life.

15. SUBJECT TERMS
Sleep disturbances, Nightmares, Post-Traumatic Stress, Doxazosin, Alpha-1 Antagonists

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1. INTRODUCTION:

We are currently performing a randomized, double-blind, placebo-controlled clinical trial to assess the effectiveness of doxazosin for the treatment of PTS nightmares, sleep disturbance, and non-nightmare PTS symptoms in adult male and female veterans with chronic full- or partial-syndromal PTS. The primary aims are to assess the effects of doxazosin, in comparison to placebo, on sleep disturbance and clinical symptoms. Eligibility is based on the presence of PTSD nightmares in the setting of full- or partial-syndromal PTS. We will be using a flexible-dose design of doxazosin versus placebo with a 4-week titration phase followed by a 4-week steady-dose phase. Clinical outcome variables are based on prior studies of prazosin and doxazosin. The primary variables (Aim 1) will be: 1) PTS nightmare severity as measured by the CAPS interview; 2) subjective sleep quality as measured by the PSQI; and 3) total PTS score, minus distressing dreams item, as measured by the CAPS interview. For Aim 2, we will compare active medication and placebo groups on objective measures of sleep measured by at-home EEG at baseline and end-of-treatment as well as wrist actigraphy at baseline, mid-treatment, and end-of-treatment. Exploratory Aims will examine the effects of doxazosin, in comparison to placebo, on measures of depression, sexual health and overall quality of life.

2. KEYWORDS:

Sleep Disturbance
Nightmares
Post-Traumatic Stress
Doxazosin
Alpha-1 Antagonist

3. ACCOMPLISHMENTS:

What were the major goals of the project?
The primary scientific aims of our study are as follows:

Primary Aim 1:
To assess the effects of doxazosin, in comparison to placebo, on sleep disturbance and clinical symptoms of PTS through measures of nightmares, subjective sleep quality, and non-nightmare PTS symptoms, in adult men and women with chronic PTS.

Primary Aim 2:
To examine the effects of doxazosin on an objective measure of sleep/wake activity in adult men and women with chronic PTS.

Primary Aim 3:
To examine the effects of doxazosin, as compared to placebo, on depression symptoms, sexual health, and overall quality of life.

We described our major tasks and target dates of achievement of these tasks as follows:

Major Task 1 (Months 1-6): Prepare Protocol and Perform Regulatory Procedures for Randomized Placebo Controlled Trial of Doxazosin: Completed

Study materials including protocol, consent form, and study documents were created and submitted to the UCSF IRB. The study underwent full committee review and was granted final UCSF IRB approval. The study was submitted to SFVAMC regulatory personnel and granted approval by the VA Clinical Research Workgroup as well as the VA Research and Development Committee. The study was submitted to HRPO and initial approval was received. A supplemental award was received by the study PI to add objective measures of sleep and sleep/wake activity. These changes were submitted to the UCSF IRB and approval was received. Final approval was received from HRPO and the study began recruitment.

Major Task 2 (Months 1-5): Coordinate Study Staff for Clinical Trial: Completed

The research coordinator and research assistant were hired and trained on relevant study procedures. The nurse practitioner was recently hired to initiate work on the study. We are currently hiring additional staff in light of receiving supplemental funds to perform sleep EEG in our participants.

Major Task 3 (Months 6-42): Randomized Controlled Trial: In Progress
Implementation of the randomized controlled trial began. The first participant was consented, screened, and enrolled to begin 7 days of pre-treatment baseline assessments. The participant is scheduled to begin study medication in mid July, 2018. Recruitment of veterans through advertising and telephone pre-screening of interested participants is ongoing.

Major Task 4 (Months 4-48): Data Analysis and Dissemination of Findings: Pending

The Data Core staff have created the study database and are prepared to monitor data collection rates, data quality, and data analysis.

What was accomplished under these goals?

1) Major Activities: HRPO granted initial project approval. Supplemental funds were awarded to the study PI to add objective measures of sleep and sleep/wake activity. Modifications to study protocol to incorporate the supplemental award were submitted to and approved by the UCSF IRB. HRPO reviewed and approved these approval documents supplied by the UCSF IRB. The research coordinator was hired and trained on relevant study procedures. We hired and trained the study research assistant as well as the nurse practitioner to initiate work on the study. We began recruiting veterans through advertising and telephone pre-screening of interested participants. Our first participant was consented, screened, and enrolled to begin pre-treatment baseline assessments. The participant is scheduled to begin study medication in mid July, 2018.

2) Specific Objectives: Our specific objectives were consistent with our major tasks. We aim to continue implementing the randomized controlled trial and begin treatment for our first participant. We also aim to increase enrollment numbers through hiring of additional

volunteers to assist with recruitment, as well as through continued outreach at other Community Based Outpatient Clinics. In addition, our goal is to hire additional personnel to work at the Santa Rosa VA to broaden our target population of veterans who may benefit from the treatment study.

3) Significant results/Key outcomes: No results to date.
4) Other achievements: A supplemental award was received to add objective measures of sleep and sleep/wake activity. The study database was created. Data collection materials were finalized and the recruitment database has been created. All study supplies and equipment were purchased and received, including Sleep Profiler devices from the supplemental award. A contract was completed with a mobile app developer to create the electronic sleep diary application for data collection. The mobile app was designed and a final app is expected to be delivered within the coming months. The first order of study medication was received. A recruitment list was acquired from the VA Corporate Database Warehouse. REDCap electronic surveys were created and tested for self-report data collection. Clinical interviewers were trained on interview procedures for the study.

What opportunities for training and professional development has the project provided?

Nothing to report.

How were the results disseminated to communities of interest?

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?

We plan to enhance recruitment through hiring of additional volunteers to screen potentially eligible veterans. We also plan to finalize and launch the electronic sleep diary application for data collection.

4. IMPACT

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

5. CHANGES/PROBLEMS

Changes in approach and reasons for change

In order to enhance recruitment, a modification was submitted to change eligibility criteria to a total CAPS score of >20 upon recommendation of Co-Is to have a more inclusive cut-off score to boost recruitment potential. Participants who are symptomatic with a score of 20 or greater on the CAPS 5 can still potentially benefit greatly from the study medication. In addition, the CAPS IV Distressing dreams item eligibility cut-off score was lowered from 4 to 3. Upon consulting with researchers in the Stress and Health Research Program, as well as study Co-PIs, the determination was made that the high threshold for inclusion based on nightmares alone created a barrier to recruitment and thereby jeopardizes the study's ability to examine all three co-primary aims of nightmares, sleep disturbance and overall PTS symptoms.

After consulting with clinical interviewers and other researchers in the Stress and Health Research Program, Study PI was advised that participants should only be excluded if the potential participant was experiencing moderate or several drug or alcohol use in the last 3 months. A diagnosis in a time frame further in the past will not interfere with a participants success in the study; thus, a modification was submitted to revise original exclusion criteria regarding alcohol or drug use disorders.

A supplemental award (Amendment/Modification No.: P00001) was received by the study PI to add objective measures of sleep and sleep/wake activity. The UCSF IRB approved changes resulted from this modification and HRPO granted final project approval to the changes. Addition of at-home EEG based measurement will significantly enhance our confidence in our findings with respect to sleep quality, and greatly improve our understanding of doxazosin's physiological effects on nightmares in PTSD. The at-home EEG has minimal risks associated with its use and participants will be compensated for their time and potential inconvenience of using the device.

Actual Problems or delays and actions to resolve them

Recruitment of participants occurred at a slower rate than projected. We submitted modifications to increase the age range for eligibility, decrease the minimum total CAPS score to 20, and lower the CAPS IV Distressing dreams item cut-off score from 4 to 3. These modifications were made to broaden eligibility criteria to potentially increase recruitment numbers. We are also hiring additional volunteers and paid research staff to increase enrollment numbers for the study.

Hiring of the nurse practitioner occurred later than projected, and was timed to coincide with the initiation of enrollment. The nurse practitioner's allotted contribution to the project is expected to remain unchanged.

Changes that had a significant impact on expenditures

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report.

6. PRODUCTS

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Name:	Anne Richards, MD, MPH
Project Role:	Principal Investigator
Researcher Identifier:	
Nearest Person Month Worked:	1
Contribution to Project:	Dr. Richards is the initiating investigator and has assumed the overall scientific and administrative responsibility for the project. She is taking the lead on study design, data quality control, data analysis, and preparation of results for dissemination.

Name:	Andrew Levihn-Coon
Project Role:	Research Coordinator
Researcher Identifier:	N/A
Nearest Person Month Worked:	12
Contribution to Project:	Mr. Levihn-Coon is responsible for all coordination aspects of the study as well as managing study progress. This includes staff hiring, database and data collection materials creation, equipment purchasing, mobile sleep diary application development, regulatory correspondence, subject recruitment, and subject visit scheduling.

Name:	Katie Huang
Project Role:	Research Assistant
Researcher Identifier:	N/A
Nearest Person Month Worked:	6
Contribution to Project:	Ms. Huang is responsible for aiding in study activities including recruitment, outreach, telephone-screening, participant visits, scheduling, subject tracking, data entry, and other study tasks as needed.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report.

What other organizations were involved as partners?

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

Not applicable.

9. APPENDICES

No appendices relevant to project status attached.