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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 design 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 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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TABLE OF CONTENTS

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 PTS symptoms. 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 severe PTS nightmares in the setting of PTS. We will be using a flexible dose design of doxazosin 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 have been 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: Complete

The experienced full-time research coordinator and full-time research assistant continue on the team. Five fully trained, part-time volunteers continue to assist in making recruitment calls. We are in the process of finding one more part time research assistant to assist with study procedures, data entry and cleaning in the upcoming quarter.

Major Task 3 (Months 6-42): Randomized Controlled Trial: In Progress
Implementation of the randomized controlled trial continues, and study staff are actively recruiting and enrolling subjects in the clinical trial. Thirty-two subjects have completed all study procedures. This is a notable increase since our nineteen completers reported at our 2021 annual report. Two subjects are actively enrolled on study drug and are scheduled to complete the study at the end of June and mid-July. One subject is completing baseline sleep assessments and is scheduled to begin study drug on 6/21/2022. There are several promising recruits completing various stages of the eligibility process. Recruitment of participants through advertising and telephone pre-screening of interested participants is ongoing. The research study staff continue to pre-screen medical records of participants attending clinics at the SFVAMC to identify potentially eligible participants for study recruitment. Study staff continue to virtually present the study to clinical staff at the SFVAMC to educate staff about the study and referral procedures. Our website is up to date with study information to enhance online recruitment advertisement and outreach. Additionally, the study continues to successfully recruit nationally using UCSF PRP social media recruitment service and the specialized patient recruitment service Trialfacts.

Major Task 4 (Months 4-48): Data Analysis and Dissemination of Findings: Pending
Data continues to be entered into the study database as collected. Preliminary analyses regarding factors affecting recruitment and eligibility rates are being examined to guide recruitment processes. The research team monitors data quality on an ongoing basis to ensure readiness for analysis upon completion of enrollment.

What was accomplished under these goals?

1) Major Activities: We have continued to actively recruit veterans through emailing, advertising, and telephone pre-screening of interested participants. Thirty-two subjects have completed all study procedures, which has increased from nineteen reported at the last annual report time. We aim to continue aggressively recruiting and enrolling remote participants in the upcoming year. Additionally, we continue to implement a variety of national recruitment strategies. Our successful online advertising and recruitment efforts continue through Reddit, Facebook, Qualtrics, UCSF PRP, and Trialfacts. We are primarily targeting groups on these web-based platforms associated with Veterans as well as those who identify as having experienced a trauma. Also of note, we requested and were approved for a NCE through June 2023.
2) Specific Objectives: Our specific objectives were consistent with our major activities. We aim to continue implementing the randomized controlled trial and increase enrollment numbers through various avenues including: Trialfacts marketing campaign, aggressive advertising via various internet-based platforms (Reddit, Facebook, Craigslist, UCSF PRP), telephone pre-screening, outreach at community-based outpatient clinics nationally, pre-screening medical records of SFVAMC clinic attendees, presenting to VA clinical staff, and reaching out to broader list of Bay Area veterans through the Defense Manpower Data Center (DMDC).
3) Significant Results/Key Outcomes: No results to date.
4) Other Achievements: The mobile sleep diary application is approved and available in the Apple App Store and Google Play store. Participants continue to successfully utilize the app for sleep diary reporting and endorse positive user experience. Research staff continue to find the app to be extremely efficient in following subject sleep diary reporting.

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

Dr. Richards attended and presented at the 2021 ISTSS Annual Meeting.

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?

Our main priority is to continue aggressive, national recruitment and enrollment using the resources described above. With our experienced, full-time and part-time staff we are confident in our ability to meet enrollment goals in the coming year.

4. **IMPACT:**

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

Nothing to Report: pending completion of enrollment and data analysis

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

Major IRB-approved updates since the 2021 annual report:

1. Requesting use of DocuSign for the informed consent process. Staff will follow the standards of procedure for DocuSign provided by the VA. To fully make use of the application, we will include both the consent form, the HIPAA form, the Equipment Loan Form, and forms required to compensate participants in the DocuSign envelope that we send to participants. If it is not feasible for a participant to use DocuSign due to technological burdens or other issues, we will complete consent procedures using physical consent documents.
    a. Justification: DocuSign will heavily reduce burden on participants for the consent process since it will allow them to review and sign consent documents without having to mail documents back and forth between their homes and the VA. It also guarantees to study staff that we will receive signed consent forms in an expeditious manner.
2. Adding ResearchMatch as a recruitment method.
    a. Justification: I am requesting IRB approval to contact potential study volunteers through ResearchMatch.org. ResearchMatch.org is a national electronic, web-based recruitment tool that was created through the Clinical & Translational Science Awards Consortium in 2009 and is maintained at Vanderbilt University as an IRB-approved data repository. UCSF is part of the ResearchMatch network, so UCSF researchers are allowed to use this registry with IRB approval. ResearchMatch will send an announcement for this study to its registry participants that appear to be a good match for my study. The announcement is attached to this submission for your review.
3. Adding UCSF PRP Social Media Recruitment
    a. Justification: Online advertising will be used to recruit potential participants. Advertisements will be targeted based on study eligibility criteria (e.g. age, sex, interest in study-related topics). Advertisements will consist of a combination of ad text and images (see attached document “Online Recruitment Ad text and images”) that will be used in combination and may appear as banners, posts, text, or URLs links for users to click on if they are interested in the study. By

clicking on an advertisement, the user will be directed to our study screener. Until recruitment for the study is complete, we will be assessing the advertisements on a regular basis. Some ads will be used and some may not.

Actual or anticipated problems or delays and actions or plans to resolve them

The specialize patient recruitment service, Trialfacts, was initially less successful than we had anticipated. However, they implemented new recruitment strategies after our team worked with them to reevaluate our campaign. Their revised strategies included: their advertising specialist adjusted ad targeting, aimed at a lookalike audience based on previous PTSD passed referrals from previous successful studies they have worked on; their advertising specialist also adjusted targeting based on PTSD study landing page visitors from previous PTSD studies they have worked on; and, they targeted the areas listed on the VA's "criticality list" with the aim of finding more Veterans eligible and interested in participating.

These changes to the campaign strategy have proved fruitful in finding several eligible Veteran participants. Of note, by targeting the VA's "criticality list" areas we have been able to reach rural Veterans with typically less access to care. In combination with our remote enrollment practices and our contract with Quest Diagnostics we have been able to smoothly bring them in to the study. Our team is optimistic that we have found a successful campaign strategy through Trialfacts and will continue to bring in eligible participants.

Additionally, our recruitment strategy through UCSF's PRP social media recruitment also required adjustment. This service primarily targets Facebook users and Facebook updated the interest keywords pertinent to our target audience that we are allowed to use. We noticed there was an issue due to a sudden, sharp decline in responses to our Qualtrics screener linked with our ads. We connected with our contact at UCSF, and she explained the back-end algorithm changed to no longer allow us to target users associated with keywords such as "Veterans" and "PTSD association". We met with our contact and revised our targeted keywords and screener responses have returned to baseline as a result.

Our team is confident in our recruitment and enrollment strategies at this point. We aim to continue implementing these strategies over the next year to meet enrollment goals.

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.

Significant changes in use or care of human subjects

Nothing to Report.

Significant changes in use or care of vertebrate animals

Nothing to Report.

Significant changes in use of biohazards and/or select agents

Nothing to Report.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications.

Richards, A, Inslicht SS, Ruoff LM, Goldstein L, Metzler TJ, Chapman CM, Hubachek SQ, Neylan TC. An open-label pilot study of doxazosin extended release in PTSD: Results and recommendations for future research on doxazosin. FOCUS. 2018 Jan; 16:1, 67-73.
Status of publication: Published
Acknowledgment of federal support: Yes

Books or other non-periodical, one-time publications.

Nothing to Report.

Other publications, conference papers and presentations.

Nothing to Report.

- **Website(s) or other Internet site(s)**

www.richardslab.ucsf.edu

- **Technologies or techniques**

Nothing to Report.

- **Inventions, patent applications, and/or licenses**

Nothing to Report.

- **Other Products**

Mobile Sleep Diary Application, available in the Apple App Store and Google Play store.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

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:	Emily Staggs
Project Role:	Research Coordinator
Researcher Identifier:	N/A
Nearest Person Month Worked:	12
Contribution to Project:	Ms. Staggs 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:	Corinne Sigmund
Project Role:	Research Assistant
Researcher Identifier:	N/A
Nearest Person Month Worked:	11
Contribution to Project:	Ms. Sigmund 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.

Name:	Abigail Colyer
Project Role:	Clinical Interviewer
Researcher Identifier:	N/A
Nearest Person Month Worked:	1
Contribution to Project:	Ms. Colyer is responsible for administering pre and post treatment clinical interview assessments.

Name:	Olga Mayzel
Project Role:	Data Manager
Researcher Identifier:	N/A
Nearest Person Month Worked:	1
Contribution to Project:	Ms. Mayzel is responsible for the creation and management of the study's database.

Name:	Leslie Ruoff (Yack)
Project Role:	Senior Sleep Technician
Researcher Identifier:	N/A
Nearest Person Month Worked:	2
Contribution to Project:	Ms. Ruoff is responsible for the management of sleep EEG and actigraphy devices and data.

Name:	Anna West
Project Role:	Clinical Interviewer Supervisor
Researcher Identifier:	N/A
Nearest Person Month Worked:	1
Contribution to Project:	Dr. West is responsible for the oversight of all clinical interviewers.

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.