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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

PRINCIPAL INVESTIGATOR: Anne Richards, MD, MPH

CONTRACTING ORGANIZATION: Northern California Institute for Research and Education Inc.
4150 Clement St 151NC
San Francisco CA 94121-1563

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Anne Richards, MD, MPH
Email: anne.richards@ucsf.edu

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Northern California Institute for Research and Education, Inc.
4150 Clement St 151NC
San Francisco, CA 94121-1563

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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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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 research assistant continue on the team. Two part-time research assistants and three part-time volunteers continue to assist with data management and making recruitment calls.

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. Forty-six subjects have completed all study procedures. This is a notable increase since our 32 completers reported at our 2022 annual report. Three subjects are actively enrolled on study drug and are scheduled to complete the study through mid-July and August. One subject is completing baseline sleep assessments and is scheduled to begin study drug on 7/7/2023. 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. Of note, the study team is also in process of receiving approval to use BuildClinical, another specialized patient recruitment service.

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. Forty-six subjects have completed all study procedures, which has increased from 32 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, Trialfacts, and a new service BuildClinical. 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 2024.
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 her trainees presented at the annual 2023 SLEEP ASCS and 2023 SLEEP APSS meetings.

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. We will continue to ensure our data are ready for analysis once enrollment is complete.

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

No major IRB-approved updates to report since the 2022 annual report.

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

The specialize patient recruitment service, Trialfacts, was initially less successful in 2021 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 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 confident in our recruitment and enrollment strategies at this point. We aim to continue implementing our current strategies over the next year to meet enrollment goals.

Additionally, the San Francisco VA Medical Center experienced a major location move in the March 2023 due to a scheduled building retrofit. Many existing PIs, including Dr. Richards and her team, were required to move from our existing lab space to other buildings. Our study team has managed to stay organized and continued recruiting and enrolling over the last quarter, however efforts were diverted at times to manage the logistics of the move. The study team is settled into a new space and has been able to resume normal operations.

Of note, one of our full-time research assistants is transitioning out of our lab to attend a graduate school program. As a result, she transitioned from full time to part time in June 2023. The very experienced research coordinator and another experienced research assistant continue on the team.

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:	2
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:	12
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:	David Baquirin
Project Role:	Research Assistant
Researcher Identifier:	
Nearest Person Month Worked:	3
Contribution to Project:	Mr. Baquirin 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:	Aubrey Beck
Project Role:	Research Assistant
Researcher Identifier:	
Nearest Person Month Worked:	2
Contribution to Project:	Ms. Beck 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:	Nadia Malek
Project Role:	Research Assistant
Researcher Identifier:	
Nearest Person Month Worked:	2
Contribution to Project:	Ms. Malek 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:	Polina Orlova
Project Role:	Research Assistant
Researcher Identifier:	
Nearest Person Month Worked:	7
Contribution to Project:	Ms. Orlova 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:	Shane Pracar
Project Role:	Research Assistant
Researcher Identifier:	
Nearest Person Month Worked:	2
Contribution to Project:	Ms. Pracar 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:	Anthony Santistevan, PhD
Project Role:	Biostatistician
Researcher Identifier:	
Nearest Person Month Worked:	2
Contribution to Project:	Dr. Santistevan is responsible for the overall quality and fidelity of sleep EEG and other clinical trial data. He will conduct statistical analyses, in collaboration with investigators, on all study data and participate in all abstract, manuscript and other presentations of data.

Name:	Nikhilesh Natraj, PhD
Project Role:	Data Analyst
Researcher Identifier:	
Nearest Person Month Worked:	1
Contribution to Project:	Dr. Natraj is responsible for providing EEG signal analysis expertise for the analyses of sleep data for the study.

Name:	Olga Mayzel
Project Role:	Data Manager
Researcher Identifier:	
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:	
Nearest Person Month Worked:	6

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:	
Nearest Person Month Worked:	2
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.