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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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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 severe PTS nightmares in the setting of full- or partial-syndromal 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: In Progress
The research coordinator became suddenly unavailable in the beginning of May 2019. A new research coordinator was hired to take over for the previous coordinator in June 2019 and trained on relevant study procedures. Two fully trained research assistants and two fully trained volunteers continue on the team. We aim to bring on another volunteer to assist in study recruitment efforts. Currently, we do not have a study nurse practitioner as our previous NP graduated from the research residency program at the SFVAMC. The responsibilities of the previous study nurse practitioner have shifted to Dr. Richards and non-clinical study staff for procedures not requiring a clinician. For the foreseeable future we believe this arrangement will be effective and efficient for carrying out the study protocol.

Major Task 3 (Months 6-42): Randomized Controlled Trial: In Progress
Implementation of the randomized controlled trial has continued, and study staff are actively recruiting and enrolling subjects in the clinical trial. Five subjects have completed all study procedures. During the unexpected transition period between the former and new coordinator (May-June 2019), study enrollment was intentionally halted until a new coordinator was hired and sufficiently trained in essential coordination tasks. Due to this unexpected lapse in study coordination, at the end of this annual reporting period no participants were actively enrolled. Although occurring after the reporting period for this annual report, three subjects are currently consented (on 6/18/2019, 6/26/19, and 7/9/19) and undergoing eligibility screening. Recruitment of veterans through mailings, advertising and telephone pre-screening of interested participants is ongoing.
The study research staff continue to pre-screen medical records of participants attending clinics at the SFVAMC to identify potentially eligible participants for study recruitment. Study staff also continue to present the study to clinical staff at SFVAMC to educate staff about the study and referral procedures. One full time research assistant is now fully trained to conduct all study procedures at the Santa Rosa VA. We aim to aggressively recruit veterans in the Santa Rosa catchment area and to begin enrolling participants at the Santa Rosa VA immediately. We aim to finalize our lab website in the next quarter, which has already received UCSF IRB approval, to increase online recruitment advertisement and outreach. Additionally, a system has been put in place with other members of our research program to refer participants to our study based on appropriate responses to intake screeners used throughout the SFVAMC.

Major Task 4 (Months 4-48): Data Analysis and Dissemination of Findings: Pending
The Data Core staff have created the study database and data are being entered into the study database as they are collected. Preliminary analyses regarding factors affecting recruitment and eligibility rates are being examined, so as 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 mailings, advertising and telephone pre-screening of interested participants. Five subjects have completed all study procedures. As stated above, there was an unplanned transition period when study recruitment was intentionally and abruptly halted due to our Research Coordinator's sudden illness and departure. A new research coordinator was hired in June 2019 and has trained on relevant

study procedures with the guidance of the PI and support of our well-trained research assistants. We have now successfully resumed recruitment, with three consented subjects completing eligibility screening.

2) With our enhanced team, we have recently increased our presentation of the study to clinical staff at SFVAMC and to educate staff about the study and referral procedures. The research study staff have continued to pre-screen medical records of participants attending clinics at the SFVAMC to identify potentially eligible participants for study recruitment. Additionally, a system has been put in place with other members of our research program to refer participants to our study based on appropriate responses to intake screeners used throughout the SFVAMC. We have a fully trained full-time research assistant to focus on increasing recruitment efforts for this study. This full-time staff member will begin recruiting and enrolling participants at the Santa Rosa VA in the next quarter. We currently have two fully trained volunteers to assist with recruitment efforts via mailings and telephone screening.
3) We received IRB approval on several modifications over the past year that altered multiple study procedures to enhance flexibility in the implementation of the protocol and enable our team to recruit from a larger catchment area (including Santa Rosa). The primary changes captured were as follows: 1) lower CAPS IV distressing dreams item eligibility cut-off score from four to three; 2) increase maximum enrollment age from 69 to 75 years old; 3) include participants with a history of psychiatric disorder with psychotic features, bipolar disorder, or obsessive-compulsive disorder who have not experienced active psychosis or mania in the past five years; 4) perform the eligibility clinical assessment via telephone, after a thorough medical chart review; 5) allow participants to complete self-report questionnaires on pen and paper offsite and mail them to research staff; 6) obtain informed consent remotely by mailing the consent forms to the participant to complete and mail back; 7) advertise for our study for recruitment purposes on our lab website; 8) perform ECGs at eligibility only if clinically indicated as per well-defined criteria; 9) lower exclusion criteria for standing systolic blood pressure from minimum 110 mmHg to 100 mmHg at eligibility; and 10) allow phone screening t to take place in-person if preferred by the prospective participant or study staff. We anticipate all these changes to help mitigate recruitment challenges encountered thus far, increase recruitment numbers and allow for a greater flexibility in scheduling participants to complete the trial.
4) Specific Objectives: Our specific objectives were consistent with our major activities. We aim to continue implementing the randomized controlled trail and increase enrollment numbers through various avenues including: aggressive advertising, telephone pre-screening, outreach at community-based outpatient clinics, pre-screening medical records of SFVAMC clinic attendees, presenting to SFVAMC clinical staff, and responding to relevant intake screeners. We are actively beginning enrollment at the Santa Rosa VA.
5) Significant Results/Key Outcomes: No results to date.
6) Other Achievements: A new full-time research coordinator has been recently hired and trained on all relevant study material. We aim to complete the launch of the sleep diary app in in the next quarter.

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

The two study staff research assistants attended a TeleForm training to gain a greater understanding of how our clinical interviewers complete the interview data collection forms for the study. This allows our team to be of better assistance when questions arise during interviews, and to help ensure we are properly completing as many potential interviews as possible.

Dr. Richards has attended a professional development training on the computer programming language MATLAB to enhance her and the team's ability to perform sophisticated EEG analysis of the data collected with the Sleep Profiler ambulatory EEG device being used in the study. Dr.

Richards has also attended the Neuroscience School for Advanced Studies program on Sleep and Circadian Rhythms in May of this year, which provided a unique opportunity for profession training by and professional networking with sleep and circadian researchers.

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 aggressively enhance recruitment and enrollment, both at the San Francisco VA and at our satellite clinic the Santa Rosa VA, using the resources described above. Our research team is now fully trained, and we have worked out various kinks in the protocol implementation process, so that participants can now be run through the protocol smoothly and effectively. We also plan to launch the electronic sleep diary application for data collection with the support of a new part-time research assistant.

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

To enhance recruitment and eliminate factors that unnecessarily encumbered protocol implementation, multiple modifications have been submitted to the USCF IRB over the past year. All changes have been approved by the UCSF IRB and have been reported during relevant DoD quarterly reports. Recruitment of participants occurred at a slower rate than projected. We submitted several modifications to broaden eligibility criteria and enhance recruitment numbers, and these are now being implemented. The primary changes captured, and their justifications are as follows:

1) Increase maximum enrollment age from 69 to 75 years old
    a. Justification: We have found that many of our over 69y/o veteran population are interested in the benefits of this treatment and would be able to fully participate. Enrolling veterans up to age 75 will ensure the study results are applicable to a larger number of veterans and will allow us to enroll a greater number of Vietnam-era veterans. We believe the medical screening procedures and other safety measures used in the study are adequate for this age group.

2) Include participants with a history of psychiatric disorder with psychotic features, bipolar disorder, or obsessive-compulsive disorder that have not experienced active psychosis or mania in the past five years
    a. Justification: This modification is crucial for reaching the representative population consistent with the research aims. We have found that many our veteran population are interested in the benefits of this treatment and would be able to fully participate. Enrolling veterans that meet the revised criteria will ensure the study results are applicable to a larger number of veterans. We believe the medical screening procedures and other safety measures used in the study are adequate for this population, and that the treatment offered is appropriate for these veterans.
3) Perform the eligibility clinical assessment via telephone, after a thorough medical chart review
    a. Justification: Allowing for conversations between the study clinicians and research participants to take place over the phone will enhance feasibility for participants and research staff and allow for recruitment at the Santa Rosa VA Clinic, a satellite clinic of the San Francisco VA Medical Center.
4) Allow participants to complete self-report questionnaires on pen and paper offsite and mail them to research staff
    a. Justification: Allowing for subjects to complete self-report questionnaires offsite will enhance feasibility for participants and research staff and allow for recruitment at the Santa Rosa VA Clinic, a satellite clinic of the San Francisco VA Medical Center.
5) Obtain informed consent remotely by mailing the consent forms to the participant to complete and mail back
    a. Justification: Allowing subjects to complete informed consent documentation gives participants additional time to review and contemplate the materials prior to signing. Allowing for informed consent to be completed offsite will also enhance feasibility for participants and research staff and allow for recruitment at the Santa Rosa VA Clinic, a satellite clinic of the San Francisco VA Medical Center.
6) Advertise for our study for recruitment purposes on our lab website
    a. Justification: A lab website was created, and we hope to use it to recruit for our study and enhance enrollment.
7) Perform ECGs at eligibility only if clinically indicated
    a. Justification: Doxazosin is widely prescribed in clinical practice for non-cardiovascular indications and an EKG is not normally performed in such situations, in that absence of a cardiac history or symptoms suggestive of cardiac disease. We have found that performing EKG's has resulted in excess burden for participants and research staff without significant impact on enrollment decisions. We have found that non-exclusionary findings on EKG have resulted in multiple steps to consult with cardiologists and primary providers with no added benefit. Our titration plan is slow and well-monitored with bi-weekly symptom assessments and weekly vital signs assessments, including orthostatic vital signs assessments. Orthostatic BP and HR assessments already go beyond standard prescribing practice for this medication in non-cardiology clinics. To therefore avoid excess burden for staff and/or participants we plan to perform a baseline EKG only if clinically indicated, as defined by a history of cardiac disease, arrhythmia, or symptoms of potential cardiac origin such as chest pain. These rules were modeled on the VA Cooperative study of prazosin for PTSD and discussion with senior co-investigators Dr. Neylan and Karen Seal, as well as our medical monitors.
8) Lower exclusion criteria for standing systolic blood pressure from minimum 110 mmHg to 100 mmHg at eligibility
    a. Justification: Because we fear we will exclude many healthy, young participants with BPs on the low end of normal, we will lower the eligibility standing systolic blood

pressure cutoff to 100 mmHg at minimum. We consulted with and received guidance and approval from the DSMB regarding this criteria revision. Baseline blood pressure assessments are not typically done in clinical practice and asymptomatic individuals with standing blood pressure on the low end of normal may be unfairly excluded as a result. Slow titration and close monitoring as previously describe ensures the safety of our participants.

9) Phone screening can take place in-person if preferred by the prospective participant or study staff.
    a. Justification: If a participant is onsite at the VA and interested in completing screening procedures, it is beneficial for both the participant and the research team to be able to complete screening procedures in-person at the time of initial contact. Our current phone screen protocol does not specifically state that this can be accomplished in person if the participant and staff are available at the time a potential participant expresses interest in eligibility screening.

We anticipate all these changes to help mitigate recruitment challenges encountered thus far, increase recruitment numbers and allow for a greater flexibility in scheduling participants to complete the trial.

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

The research coordinator became suddenly unavailable in May 2019. A new research coordinator was hired to take over for the previous coordinator in June 2019 and trained on relevant study procedures. During this transition period, recruitment was intentionally halted as role logistics and hiring were being sorted out. This overall caused recruitment totals to be lower than originally anticipated for this time period. At this time, recruitment efforts have resumed and our coordinator is well-trained on all aspects of coordination and is completing training on study procedures carried out by research assistants. Other recruitment challenges faced throughout the past year have been addressed in multiple IRB-approved modifications. These changes, and their justifications have been noted above in the *Changes in Approach and Reasons for Change* section, as well as the *Major Activities* section. We anticipate all these changes to greatly mitigate recruitment challenges encountered thus far, and to greatly increase recruitment numbers and allow for a greater flexibility in scheduling participants to complete the trial.

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

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.

Upon reviewing the 2018 Annual Report, we noted a journal publication that was mistakenly omitted. We have listed the publication below in this report.

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)**

Nothing to Report.

- **Technologies or techniques**

Nothing to Report.

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

Nothing to Report.

- **Other Products**

Nothing to Report.

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:	3
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:	11
Contribution to Project:	Mr. Levihn-Coon was responsible for all coordination aspects of the study as well as managing study progress. This included staff hiring, database and data collection materials creation, equipment purchasing, mobile sleep diary application development, regulatory correspondence, subject recruitment, and subject visit scheduling. Mr. Levihn-Coon is no longer on study staff as of June 2019.

Name:	Emily Staggs
Project Role:	Research Coordinator
Researcher Identifier:	N/A
Nearest Person Month Worked:	1
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:	Katie Huang
Project Role:	Research Assistant
Researcher Identifier:	N/A
Nearest Person Month Worked:	12
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.

Name:	Aubrey Beck
Project Role:	Research Assistant
Researcher Identifier:	N/A
Nearest Person Month Worked:	6
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. Ms. Beck is also responsible for facilitating study

	procedures conducted at the Santa Rosa VA.

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.