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TITLE:	Prazosin for Prophylaxis of Chronic Post-Traumatic Headaches in OEF/OIF/OND Service Members and Veterans with Mild TBI
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13. SUPPLEMENTARY NOTES

14. ABSTRACT

(from original proposal) Headaches following combat-related mild traumatic brain injury (mTBI) are common, can be refractory to standard therapies, and may persist and worsen to become a debilitating chronic pain syndrome. The purpose of the proposed study is to evaluate the centrally acting alpha-1 adrenoreceptor antagonist drug prazosin as a prophylactic treatment for chronic posttraumatic headache. The impetus for this study comes from a large open-label case series in Iraq and Afghanistan Veterans with mTBI and posttraumatic headaches and data from a placebo-controlled trial evaluating use of prazosin for PTSD in Iraq and Afghanistan active-duty Service Members that found beneficial effect of prazosin for decreasing the frequency and severity of headaches, in addition to decreasing PTSD-related symptoms and improving the quality of sleep. The objectives of this study will be accomplished by conducting a randomized placebo-controlled double blind trial of prazosin vs placebo in 160 Iraq/Afghanistan active-duty Service Members and Veterans with persistent PTHAs.

15. SUBJECT TERMS

Headache, mTBI, prazosin, pain, clinical trial, placebo-controlled

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
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Table of Contents

1. INTRODUCTION:

Headaches following combat-related mild traumatic brain injury (mTBI) are common, can be refractory to standard therapies, and may persist and worsen to become a debilitating chronic pain syndrome. The purpose of the proposed study is to evaluate the centrally acting alpha-1 adrenoreceptor antagonist drug prazosin as a prophylactic treatment for chronic posttraumatic headache. The impetus for this study comes from a large open-label case series in Iraq and Afghanistan Veterans with mTBI and posttraumatic headaches and data from a placebo-controlled trial evaluating use of prazosin for PTSD in Iraq and Afghanistan active-duty Service Members that found beneficial effect of prazosin for decreasing the frequency and severity of headaches, in addition to decreasing PTSD-related symptoms and improving the quality of sleep. The objectives of this study will be accomplished by conducting a randomized placebo-controlled double blind trial of prazosin vs placebo in active-duty Service Members and Veterans with persistent PTHAs. This RCT builds upon strong open label study data from a case series (n=62) performed by Robert Ruff, MD (then VA National Director of Neurology) published in 2012.

2. KEYWORDS:

Headache, Posttraumatic headache, Headache Disorders, combat trauma, mild traumatic brain injury (mTBI), Adrenergic alpha-1 Receptor Antagonists, prazosin, concussion

3. ACCOMPLISHMENTS:

What were the major goals of the project?

The objectives of this study are to evaluate the efficacy and safety of the alpha-1 AR antagonist drug prazosin as a prophylactic medical treatment for persistent posttraumatic headaches (PTHAs). These objectives will be accomplished by conducting a randomized placebo-controlled double blind trial of prazosin vs placebo in Iraq/Afghanistan Service Members and Veterans with frequent persistent PTHAs.

Specific Aim 1: To determine the effect of prazosin compared to placebo on HA frequency, HA severity and duration, use of abortive/analgesic medications, and HA-related disability.

Specific Aim 2: To determine the effect of prazosin on sleep disturbance, PTSD symptoms, depression symptoms.

Subtask 1: Study Preparation	**Percent Completed**
Coordinate with Sites for CRADA submission	100%
Finalize consent form and human subjects protocol	100% – Main & HIPAA and HIPAA prescreening waiver of consent completed. 100% Site specific addendum completed.
Coordinate with Sites for Madigan IRB protocol submission	100%
Coordinate with Sites for Military 2nd level IRB review (ORP/HRPO)	100%

Submit amendments, adverse events and protocol deviations	100% Change of PI Amendment submitted and approved by RHC-P and ORP/HRPO IRBs. Modification related to VA Protocol 7.0 and 8.0. Certificate of Confidentiality extension approved by DHHS.
Coordinate with Sites for annual IRB report for continuing review	100% Approved 01/19/2021. Drafting in process for 2022 review.
Milestone Achieved: Local IRB approval at Madigan/JBLM	100%
Milestone Achieved: CIRO, ORP/HRPO approval	100%
Subtask 1B. Study Preparation	
Prepare recruitment and informational materials	100%
Identify potential referring clinicians	100%
Set up phone contact line	100%
Train study staff on exam procedures, rating scales, data recording	100%
Milestones Achieved: Recruitment materials and venues finalized; phone contact line and database established; research staff trained	100% – recruitment materials approved, venue, and phone contact line finalized.
Task 2. Recruit Study Participants and Perform Study Procedures	Ongoing
Subtask 2a. Recruit Study Participants on a Rolling Basis from Months 7-96	Ongoing
Respond to potential participant request for information; mail out informational materials and consent forms	Ongoing
Subtask 2b. Perform Study Procedures	Ongoing
Milestone Achieved: 1000 participants completing all study procedures..	146 participants consented, following screening, 81 were randomized with 65 completers.
Task 3. Data Management and Statistical Analysis	Ongoing
Task 4. Reporting and Presentation/Manuscript Preparation	Preliminary positive results presented at June 2020 annual meeting of the American Headache Society, at the September, 2021 Defense Intrepid Network Research Symposium, and at the September 2021 national VA HSR&D TBI webinar.

What was accomplished under these goals?

An intent-to-treat analysis of the first 48 study participants randomized since study inception (32 prazosin and 16 to placebo) has been completed, with planned submission to the journal Headache. For the primary outcome measure (change from baseline in 4-week headache frequency), the reduction in headache frequency for the prazosin group at week 12 of treatment was 11.9 ± 1.0 days compared to a reduction of 6.7 ± 1.5 days for the placebo group. The overall differences in headache frequency trajectory by treatment group were significant (p=. 010). An additional measure of efficacy, the number of participants achieving at least a 50% reduction in headache frequency, revealed that at week 12 of treatment, 70 ± 8% of those in the prazosin arm had a =50% reduction in headache frequency compared to 29 ± 12% in the placebo arm. This was statistically significant (p=0.0035). An additional secondary outcome measure, change in headache-related disability and quality of life, was assessed using the Headache Impact Test-6 (HIT-6), a well-validated self-report instrument. At baseline, both the prazosin and placebo groups had mean HIT-6 scores within the "severe impact" range (mean ± SE prazosin 61.0±1.5 vs. placebo 63.6±2.1). With treatment, participants in the prazosin group showed a significantly greater reduction over time in HIT-6 scores compared to the placebo group, p=0.020. For the final 4-week maintenance dose period (week 12), mean scores were reduced to the "some impact" range in the prazosin group (55.0 ± 1.5), whereas mean scores remained in the "severe impact" range in the placebo group (64.2 ± 2.1), with a difference of 6.6 points between groups (95% CI [2.2, 11.0], p=0.0035.

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

The Madigan Site PI continues to be actively involved in the clinical research process. This project has continued to demonstrate a significant collaborative effort between VA and DoD team members and the VA Coordinating Center. This RCT is the central professional development component for the VA Career Development Award of Dr. Cynthia Mayer, Neurologist.

How were the results disseminated to communities of interest?

Results presented at June 2020 American Headache Society annual meeting (poster), National VA Center for Research and Information Dissemination (CIDER) TBI Series Webinar September 2, 2021 (240 attendees), Platform Presentation at September 16, 2021 Defense Intrepid Network Symposium (judged "first runner up") presentation at the symposium.

Invited virtual presentation to the VA National Mental Illness Research, Education, and Clinical Centers (MIRECC) "Prazosin for Posttraumatic Headaches – Randomized Controlled Trial in Veterans and Active-Duty Service Members." by C. Mayer, M. Raskind

Abstract/Poster (not outcome data, baseline data)
Li, Y.I., Rau, H.K., Engle, C. K., Gunn, H., Raskind, M., & Mayer, C. L.: Characterizing actigraphy-measured sleep disturbances in Veterans and service members with chronic post-traumatic headaches following mild traumatic brain injury. SLEEP conference, June 2022

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

We have substantially expanded our referral network by developing close working relationship with Madigan AMC Neurology Service. We continue to receive a steady stream of referrals from providers with whom we have developed relationships. We plan to achieve the target of 100 completers prior to September 2023

4. IMPACT:

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

The preliminary demonstration of prazosin's efficacy for PTH provides a novel treatment for often intractable PTH following mTBI in both psychiatric and neurologic practices in VA and DoD.

What was the impact on other disciplines?

An effective pharmacologic treatment for PTH also facilitates psychologist and rehabilitation therapists to better assist PTH patients.

What was the impact on technology transfer?

Because prazosin is an inexpensive generic medication long off patent, technology transfer is not a meaningful issue

What was the impact on society beyond science and technology?

Because PTH is the most common long term problem following traumatic brain injury in civilians (motor vehicle accidents, contact sports injury), a trial of prazosin for civilian PTH is warranted.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change:

Nothing to report.

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

The major problem has been the adverse impact of the COVID 19 pandemic causing shutdown of all clinical research at both sites. Our team has developed innovative approaches to remote assessment that have enabled recruitment resumption. Evolving COVID-19 policies continue to provide challenges to the study team; however, strong relationships have enabled continued recruitment, enrollment, and successful study completion by participants

Changes that had a significant impact on expenditures:

In August 2022, the project was granted a further NCE through September 2023. The remaining funds will be utilized for study subject fees and pharmacy costs at Madigan Army Medical Center.

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:

N/A

Significant changes in use of biohazards and/or select agents

N/A

6. PRODUCTS:

Publications, conference papers, and presentations:

- **Journal publications:**

Mayer C., Savage P., Hargrove A., Engel C., Shofer J., Williams T., Poupore E., Holmes H., Peskind E., Raskind M., Prazosin for Prophylaxis of Posttraumatic Headaches in Active Duty Service Members and Veterans (in preparation for submission to "Headache").

- **Books or other non-periodical, one-time publications:**

Nothing to Report

- **Other publications, conference papers, and presentations**:

See page 7, "How were results disseminated to Communities of Interest

- **Website(s) or other Internet site(s) technologies or techniques**:

VA external blog "VAntage Point" at https://www.blogs.va.gov/VAntage/

Inventions, patent applications, and/or licenses:

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS:

Name	Role	PM	Contribution
Murray Raskind	PI	2.4 CM	PI
Elaine Peskind	Co-Investigator	1.2 CM	Scientific expertise
Paul Savage	Madigan Site PI	1.2 CM	Scientific expertise
Cynthia Mayer	Co-Investigator	1.8 CM	Scientific expertise / clinician
Daniel Murray	Research Assistant	1.4 CM	Study assistance
Ameryth Hargrove	Research Coordinator	2.8 CM	Study coordination
James O'Connell	Social Worker	1.0 CM	Clinical rater
Shelby Grody	Research Assistant	2.8 CM	Data entry / study support
Rebekah Rein	Program Coordinator	2.0 CM	IRB coordination

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

See attached updated previous/current/pending support for Dr. Raskind, Dr. Peskind, Dr. Mayer, and Dr. Savage.

What other organizations were involved as partners?

This study is an important example of a successful research collaboration between Department of Defense and Department of Veterans Affairs. Madigan Army Medical Center (Madigan) and Henry M. Jackson Foundation (HMJF) are partners in this collaboration. Dr. Savage is the site PI for the subaward to HMJF, which manages the project at Madigan

8. SPECIAL REPORTINGREQUIREMENTS:

Quad Chart: Please see attached.