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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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CONTRACTING ORGANIZATION: Seattle Inst. for Biomedical & Clinical Research
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Prazosin for Prophylaxis of Chronic Post-Traumatic Headaches in OEF/OIF/OND Service Members and Veterans with Mild TBI

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12. DISTRIBUTION / AVAILABILITY STATEMENT

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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
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	10	19b. TELEPHONE NUMBER *(include area code)*

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1. INTRODUCTION:

The purpose of this 5-month randomized controlled trial (RCT) is to evaluate the centrally acting alpha-1 adrenoreceptor (AR) antagonist drug prazosin as a prophylactic treatment for persistent posttraumatic headaches (PTHAs). If effective as a prophylactic agent, its use would reduce the need for abortive and/or analgesic drugs, many of which have unacceptable cognitive side effects, addictive potential, and a tendency to increase the risk for developing superimposed medication over-use headaches. Because of its beneficial effect on improving symptoms of PTSD and decreasing alcohol abuse, prazosin may provide multi-factorial treatment for commonly co-morbid conditions in Service Members and Veterans.

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?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

The objectives of this proposed 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, depressive symptoms, alcohol consumption, global cognitive function, health-related quality of life, and clinical status.

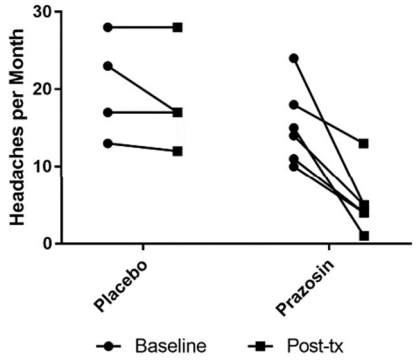
Subtask 1: Study Preparation	**Percent Completed**
Coordinate with Sites for CRADA submission	100%
Finalize consent form and human subjects protocol	100% – Main & HIPAA and HIPAA prescreening waiver of consent completed. 100% Site specific addendum completed.
Coordinate with Sites for Madigan IRB protocol 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 4.1, 5.0 and 6.0 submitted to RHC-P IRB on 01 Aug 2018, pending review. Modification r/t VA protocol Modification 7.0 will be submitted after other approvals received.
Coordinate with Sites for annual IRB report for continuing review	100% Submitted on 06 Sep 2018
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% Final staff training to include VA staff will occur after pending modification is approved.
Miletones 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 7-60	Ongoing
Respond to potential participant request for information; mail out informational materials and consent forms	Ongoing
Subtask 2b. Perform Study Procedures	Ongoing
Milestone Achieved: 160 participants completing all study procedures	85 subjects have been consented. 35 subjects completed study procedures. Due to COVID 19, all on-site clinical study visits at both VA Puget Sound and Madigan AMC were halted in March 2020. Using remote visit technology, all participants already enrolled completed the protocol by September 2020. Both sites reopened for limited on-site visits in October 2020, and recruitment has resumed with 8 Veterans and Service Members.
Task 3. Data Management and Statistical Analysis	Ongoing
Task 4. Reporting and Presentation/Manuscript Preparation	Preliminary results were presented (remotely due to COVID) at the annual scientific meeting of the American Headache Society, June, 2020.

What was accomplished under these goals?

Although recruitment for this clinical trial started slowly with extensive delays from multiple IRB reviews and the novel problems of a post mTBI headache trial in our two-site (VA and DoD) setting, we have made substantial progress and are now randomizing approximately two Service Members/Veterans per month. There are now 36 participants who have completed the 5 month study.

Preliminary results from the first 10 participant completers (4 placebo, 6 prazosin) show a substantial and already statistically significantly greater headache reduction in the prazosin condition. An interim analysis will be performed in November 2020 on data from the 36 completers following data cleaning.



2-way ANOVA: Prazosin superior to placebo, p=0.025

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

Madigan Site PI, Associate Investigator Dr. Eileen Poupore and Clinical Psychologist, Dr. Jamie Wasilewski continue 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?

The RCT design and preliminary results will be presented in the VA national external blog "VAntage Point." Results were presented as a poster at the American Headache Society meeting, June, 2020. (Dr. Cindy Mayer, first author)

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 and by mastering the VA VINCI system to screen for potential participants at the VA Puget Sound

4. IMPACT: Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

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

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 consistent with limited reopening of research October, 2020.

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.

NA

Significant changes in use of biohazards and/or select agents

NA

6. PRODUCTS:

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

- **Journal publications.**

Nothing to Report

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

Nothing to Report

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

Mayer, C., Peskind, E. Savage, P., Raskind, M., Randomized Headache Prophylaxis in Veterans and Active Duty Soldiers. Presented at: 62nd Annual Scientific Meeting of the American Headache Society, June 4-7, 2020. (virtual meeting due to COVID 19)

Website(s) or other Internet site(s)

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

Technologies or techniques

Nothing to report.

Inventions, patent applications, and/or licenses

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS:

What individuals have worked on the project?

Name	Role	PM	Contribution
Murray Raskind	PI	2.4 PM	PI
Elaine Peskind	Co-Investigator	1.2 PM	Scientific expertise
Aaron Edwards	Madigan Site PI	1.2 PM	Scientific expertise
Cynthia Mayer	Co-Investigator	1.8 PM	Scientific expertise / clinician
Laura Crews	Research Coordinator	12.0 PM	Madigan coordinator
Daniel Murray	Research Assistant	10.0 PM	IRB/study assistance
Kimberly Harms	Senior Coordinator	7.5 PM	Project coordinator
Ameryth Hargrove	Research Assistant	9.0 PM	Study support
Soleil Groh	Research Assistant	12.0 PM	Recruitment/outreach
James O'Connell	Social Worker	2.0 PM	Clinical rater
Shelby Grody	Research Assistant	12.0 PM	Data entry / support
Rebekah Rein	Program Coordinator	2.6 PM	IRB coordination
Wesley Chinn	Data Analyst	8.0 PM	Data management

What other organizations were involved as partners?

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

Quad Chart: Please see attached.

Prazosin for Prophylaxis of Chronic Post-Traumatic Headaches in OEF/OIF/OND Service Members and Veterans with Mild TBI

W81XWH-15-2-0060

PI: Murray Raskind, MD **Org:** Seattle Institute for Biomedical & Clinical Research **Award Amount:** 3,942,900

Study Aims

- To determine the effect of prazosin compared to placebo on post-traumatic HA frequency, severity, duration, use of abortive/analgesic medications, and HA-related disability.
- To determine the effect of prazosin on comorbid sleep disturbance, PTSD symptoms, depressive symptoms, alcohol consumption, global cognitive function, health-related quality of life, and global clinical status (secondary outcome measures).

Approach

The proposed study is a prospective double-blind placebo-controlled RCT to evaluate the efficacy and safety of prazosin for prophylactic treatment of frequent persistent HAs following blast and/or impact mTBI in a convenience sample of SMs and Veterans who served in Iraq and/or Afghanistan. The total trial length is 22 weeks. Participants will be randomized 1:1 to prazosin or placebo. Recruitment and study procedures will be performed at Madigan/JBLM and VA Puget Sound.

R. L. Ruff and colleagues prescribed open label prazosin for nine weeks to 63 OEF/OIF Veterans who had experienced blast concussion mTBI(s) and had postconcussive headaches.[1]

	Baseline	Week 9
Headache Frequency (# / 4 weeks)	13.3 + 0.7	4.7 + 0.7 (p<0.001)
Headache Pain Intensity (0-10 scale)	7.4 + 0.2	4.0 + 0.2 (p<0.001)

The current study seeks to confirm this important observational study in a placebo controlled randomized trial of prazosin.

1. Ruff RL1, Riechers RG 2nd, Wang XF, Piero T, Ruff SS. For veterans with mild traumatic brain injury, improved posttraumatic stress disorder severity and sleep correlated with symptomatic improvement. J Rehabil Res Dev. 2012;49(9):1305-20.

Timeline and Cost

Activities	Year 1	Year 2	Year 3	Year 4	Year 5	NCE
Regulatory Approvals						
Preparatory Tasks						
Subject Recruitment						
Enter + Clean Study Data						
Data Analysis						
Write and submit results						
Estimated Budget ($K)	$659	$659	$659	$659	$659	$648

Updated: 9/30/20

Goals/Milestones

☑ ☑ **Regulatory Approvals and Preparatory Tasks**
Completed / In progress
☑ ☐ **Recruitment and Retention Efforts**
- ☑ ☑ **Recruit and Randomize 30 Subjects**
- ☑ ☐ **Recruit and Randomize 100 Subjects**
- ☐ ☐ **Recruit and Randomize 175 Subjects**
- ☐ ☐ **Recruit and Randomize 200 Subjects**

☑ ☐ **Enter and clean study data**
☑ ☐ **Analyses and Evaluation**
☐ ☐ **Publish Results** – Not yet initiated
Comments/Challenges/Issues/Concerns – None at this time.

Budget Expenditure to date (*recalculated for NCE period)
Projected Expenditure:$3,295,000* Actual Expenditure:$3,259,800