

AWARD NUMBER: W81XWH-15-2-0060

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

PRINCIPAL INVESTIGATOR: Murray Raskind, MD

CONTRACTING ORGANIZATION: Seattle Institute for Biomedical & Clinical Research
Seattle, WA 98108-1532

REPORT DATE: October 2017

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. **PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.**

1. REPORT DATE October 2017		2. REPORT TYPE Annual		3. DATES COVERED 30 Sep 2016 - 29 Sep 2017	
4. TITLE AND SUBTITLE Prazosin for Prophylaxis of Chronic Post-Traumatic Headaches in OEF/OIF/OND Service Members and Veterans with Mild TBI				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-15-2-0060	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Murray Raskind, MD E-Mail: murray.raskind@va.gov				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Seattle Institute for Biomedical & Clinical Research 1660 S. Columbian Way Seattle, WA 98108-1532				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
				13. SUPPLEMENTARY NOTES	
14. ABSTRACT 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 Unclassified	18. NUMBER OF PAGES 8	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT Unclassified	b. ABSTRACT Unclassified	c. THIS PAGE Unclassified			19b. TELEPHONE NUMBER (include area code)

Table of Contents

	Page
1. Introduction	4
2. Keywords	4
3. Accomplishments	4
4. Impact	5
5. Changes/Problems.....	5
6. Products	6
7. Participants & Other Collaborating Organizations.....	7
8. Special Reporting Requirements	7
9. Appendices.....	7

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 this study is to evaluate the centrally acting alpha-1 adrenoreceptor antagonist drug prazosin as a prophylactic treatment for chronic posttraumatic headache (PTHA). The impetus for this study comes from a large open-label case series in Iraq and Afghanistan Veterans with mTBI and PTHA 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 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.

2. **KEYWORDS:** headache, mTBI, prazosin, pain, clinical trial, placebo-controlled

3. **ACCOMPLISHMENTS:**

4. **What were the major goals of the project?**

To evaluate the efficacy and safety of the alpha-1 AR antagonist drug prazosin as a prophylactic medical treatment for PTHAs, 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 global clinical status.

5. **What was accomplished under these goals?**

At the VA Puget Sound site, we have pre-screened 42 charts of potentially eligible Veteran participants, consented 9 Veterans, and randomized three Veterans in the past few months. Two Veterans are active in the pre-randomization assessment period and will be randomized in the next few weeks. Two Veterans have completed the protocol. One completed Veteran and two still in-protocol Veterans have had dramatic reductions in headache frequency and intensity. Given the 2:1 prazosin to placebo randomization ratio, we are “preliminarily” encouraged. We also are

reaching out to local VA Readjustment Counseling Service “Vet Centers” (scheduled to visit Seattle Vet Center 14 December 2017) where staff report substantial numbers of Veterans in their caseloads with chronic post concussive headaches.

At the Madigan Army Medical Center site, our regulatory frustrations continue. We finally received IRB approval, but issuance of the approval letter that is needed to begin screening potential participant service members is now being held up until the CRADA between Madigan and the Henry M. Jackson Foundation is finalized – and I cannot determine exactly where the roadblock exists. But we are working hard to find out. Any and all suggestions/help appreciated.

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

Our VA expert level MSW continues to provide training in Skilled Clinical Interview for DSM 5.

- **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?**

We will continue to recruit aggressively at VA Puget Sound Seattle campus neurology and primary care clinics. We are extending recruitment efforts to Vet Centers in Seattle and the surrounding area.

4. **IMPACT:**

- **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**

At the Madigan Army Medical Center site, our regulatory frustrations continue. We finally received IRB approval, but issuance of the approval letter that is needed to begin screening potential participant service members is now being held up until the CRADA between Madigan and the Henry M. Jackson Foundation is finalized – and I cannot determine exactly where the roadblock exists. But we are working hard to find out. Any and all suggestions/help appreciated.

- **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:**

- Nothing to Report
- **Publications, conference papers, and presentations**
Dr. Raskind has been scheduled to present a webinar on prazosin as an approach to post concussive (post mTBI) headaches by VA Rehabilitation Research Service on January 4, 2018.
- **Journal publications. *List peer-r***
Nothing to Report
- **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	Role	PM	Contribution to project
Murray Raskind	PI	2.4 PM	PI
Elaine Peskind	Co-Investigator	1.2 PM	Scientific expertise
Beverly Scott	Madigan Site PI	1.2 PM	Scientific expertise
Cynthia Mayer	Co-Investigator	1.8 PM	Scientific expertise
Laura Crews	Research Coordinator	12.0 PM	Madigan site coordination
Wesley Chinn	Data Manager	6.6 PM	Data management
Dan Morelli	Research Coordinator	2.4 PM	VA site coordination
Rebecca Tzucker	Research Assistant	12.0 PM	IRB/study assistance
Hollie Holmes	Program Manager	2.0 PM	IRB/Project management
Carol Xiang	Computer Specialist	2.0 PM	Database design
Anita Ranta	Study Coordinator	3.0 PM	VA Site coordination
Emma Onstad-Hawes	Research Assistant	3.0 PM	Study assistance
Kimberly Harms	Senior Coordinator	2.0 PM	Study 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?**

Murray Raskind and Elaine Peskind Other Support change:

No further support on:

1. Alzheimer’s Disease Research Center, P50 AG005136, Grabowski, National Institutes of Health / NIA, 5/1/15-4/30/17

- **What other organizations were involved as partners?**

A subcontract to Henry Jackson Foundation provides support for personnel expenses for Laura Crews, our Research Coordinator at Madigan AMC.

8. SPECIAL REPORTING REQUIREMENTS

- **QUAD CHARTS:**

please see attached

9. APPENDICES:

none

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: 3,967,000



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
Regulatory Approvals	█	█			
Preparatory Tasks	█	█			
Subject Recruitment					
Enter + Clean Study Data					
Data Analysis					
Write and submit results					
Estimated Budget (\$K)	\$779	\$761	\$782	\$811	\$833

Updated: 9/30/17

Goals/Milestones

Regulatory Approvals and Preparatory Tasks

Completed / In progress

Recruitment and Retention Efforts – Not yet initiated

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 – Not yet initiated

Analyses and Evaluation – Not yet initiated

Publish Results – Not yet initiated

Comments/Challenges/Issues/Concerns – None at this time.

Budget Expenditure to date

Projected Expenditure:\$1,540,000

Actual Expenditure:\$969,000