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 1660 South Columbian Way SIBCR 116 MIRECC Seattle, WA 98108-1532
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OCTOBER 2021	Annual	30 Sept 2020 – 29 Sept 2021

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)

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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
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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
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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	9	19b. TELEPHONE NUMBER *(include area code)*

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 7-60	Ongoing
Respond to potential participant request for information; mail out informational materials and consent forms	Ongoing
Subtask 2b. Perform Study Procedures	Ongoing
Milestone Achieved: 60 participants completing study. To date, 48 participants have completed. Because of COVID delay and positive efficacy signal in interim analysis, 60 completers (reduced goal #) should provide adequate power.	126 participants consented, following screening, 62 were randomized with 48 completers, and 14 currently in protocol.
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, and at the September, 2021 Defense Intrepid Network Research Symposium.

What was accomplished under these goals?

A planned interim analysis was performed on data from the first 40 completers. (Randomization 2:1 prazosin to placebo yield: n=27 prazosin, n=13 placebo)

Slope of decline in headache frequency per 4-weeks significantly greater for prazosin than placebo (p=0.043) (see quad chart figure).

Percentage of participants with ≥50% reduction of headache frequency significantly greater for prazosin than placebo (Week 8: 79±8% vs. 36±15%, p=0.036; Week 12: 76±9% vs. 36±15%, p=0.036).

Reduction in Headache Impact Test (HIT-6) significantly greater for prazosin than placebo (p=0.033).

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?

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.

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:

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.

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:

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 PM	PI
Elaine Peskind	Co-Investigator	1.2 PM	Scientific expertise
Paul Savage	Madigan Site PI	1.2 PM	Scientific expertise
Cynthia Mayer	Co-Investigator	1.8 PM	Scientific expertise / clinician
Daniel Murray	Research Assistant	12.0 PM	Study assistance
Ameryth Hargrove	Research Coordinator	12.0 PM	Study coordination
Soleil Groh	Research Assistant	6.0 PM	Recruitment/outreach
James O'Connell	Social Worker	2.0 PM	Clinical rater
Shelby Grody	Research Assistant	12.0 PM	Data entry / study support
Rebekah Rein	Program Coordinator	2.6 PM	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.

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 and Henry M. Jackson Foundation are partners in this collaboration.

8. SPECIAL REPORTINGREQUIREMENTS:

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:** 3,942,869

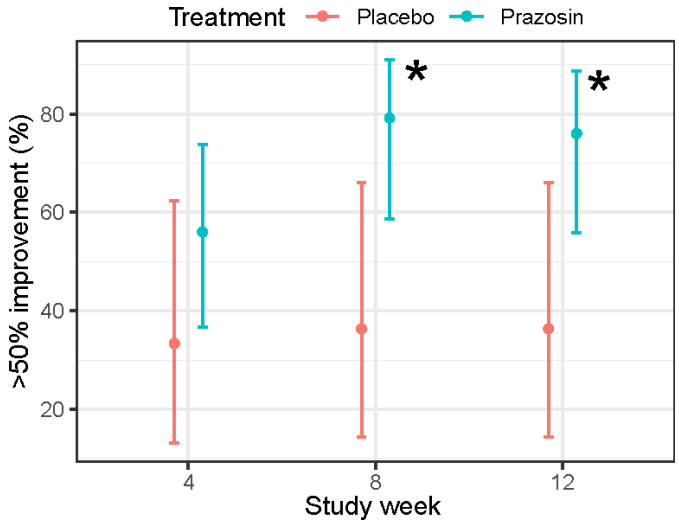
Study Aims

- 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.

Percent of participants having ≥ 50% reduction in headache frequency (Mean, 95% CIs)



* p<0.05

Timeline and Cost

Activities	Year 1	Year 2	Year 3	Year 4	Year 5	NCE1	NCE2
Regulatory Approvals	■	■	■	■	■	■	
Preparatory Tasks	■	■	■	■	■	■	
Subject Recruitment			■	■	■	■	
Enter/Clean Data			■	■	■	■	
Data Analysis					■	■	
Write/Submit results						■	
Estimated Budget ($K)	**$328**	**$603**	**$803**	**$820**	**$729**	**$431**	**$228**

Updated: 11/11/21

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 2nd NCE period)
Projected Expenditure:$3,942,869* Actual Expenditure:$3,714,914

PREVIOUS/CURRENT/PENDING SUPPORT RASKIND, MURRAY

Previous

Title: Prazosin Augmentation of Outpatient Treatment of Alcohol Use Disorders in Active Duty Soldiers with and Without PTSD
Role: Principal Investigator
Time Commitments: 2.4 calendar
Supporting Agency: Department of Defense / CDMRP, W81XWH-12-2-0094
Address: USA Medical Research Acquisition Activity; 820 Chandler St.; Fort Detrick, MD 21702-5014
Contracting/Grants Officer: Britany Hubbard, MS, Program Officer, britany.h.hubbard.ctr@mail.mil, 301-619-4289
Performance Period: 09/15/2012-09/14/2018
Level of Funding: total costs
Project Goals: This project was a 12-week randomized controlled trial (RCT) of prazosin for AUD in active duty soldiers both with and without comorbid PTSD receiving intensive outpatient AUD outpatient treatment in the Alcohol and Substance Abuse Program (ASAP) at Madigan HCS/Joint Base Lewis McChord.
Specific Aims: 1) to determine prazosin efficacy for AUD in OIF/OEF soldiers participating in outpatient AUD treatment and 2) to determine if comorbid PTSD affects prazosin efficacy for AUD. Primary outcome measures were the Timeline Followback (TLFB) and the Penn Alcohol Craving Scale (PACS) scores.
Overlap: None

Current

Title: Prazosin for Prophylaxis of Chronic Posttraumatic Headaches in OEF/OIF/OND Service Members and Veterans with Mild TBI
Role: Principal Investigator
Time Commitments: 1.2 calendar
Supporting Agency: Department of Defense / CDMRP, W81XWH-15-2-0060
Address: USA Medical Research Acquisition Activity; 820 Chandler St.; Fort Detrick, MD 21702-5014
Contracting/Grants Officer: Kathryn J Argue, Ph.D., Science Officer and GOR, kathryn.j.argue.civ@mail.mil, 301-619-4584
Performance Period: 09/30/2015-09/29/21 (NCE thru 09/29/2022 requested)
Level of Funding: total costs
Project Goals: 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. 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.
Specific Aims: 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. 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.
Overlap: None

Title: Alzheimer's Disease Cooperative Study
Role: Prazosin Project Committee Co-Principal Investigator
Time Commitments: 2.4 calendar
Supporting Agency: National Institutes of Health / NIA, U19AG010483
Address: National Institute on Aging; Building 31, Room 5C27; 31 Center Drive, MSC 2292; Bethesda, MD 20892
Contracting/Grants Officer: Kristina McLinden, Program Official, kristina.mclinden@nih.gov, 301-827-2563

Performance Period: 03/01/2016-02/28/2022 (in NCE)
Level of Funding: otal costs of subaward, to date
Project Goals: The overall aim of the ADCS is to advance research in the development of interventions that might be useful for treating, delaying, or preventing AD, particularly interventions that might not be developed by industry. The aim of the project is to evaluate the efficacy and safety of the alpha-1-adrenergic antagonist prazosin in the treatment of agitation in AD
Specific Aims: Aim 1: Test interventions to Improve cognition, slow the rate of decline, or delay/prevent the onset of AD. Aim 2: Test an intervention to ameliorate behavioral symptoms. Aim 3: Design new instruments for use in clinical trials. Aim 4: Develop novel and innovative approaches to AD clinical trial design. Aim 5: Develop novel and innovative approaches to AD clinical trial analysis. Aim 6: Expand the range of individuals studied in AD studies to include at-risk individuals and those with MCI. Aim 7: Enhance the recruitment of minority groups into AD studies.
Overlap: None

Title: Development of F-18-Labeled Radiotracers for PET Imaging of Brain Alpha1A Adrenoceptor: A Tool for Precision Medicine in PTSD
Role: Co-Investigator
Time Commitments: 2.4 calendar
Supporting Agency: Department of Defense / CDMRP, W81XWH-20-C-0116
Address: USA Medical Research Acquisition Activity; 820 Chandler St.; Fort Detrick, MD 21702-5014
Contracting/Grants Officer: Douglas Medcalf, Contract Specialist, douglas.a.medcalf.civ@mail.mil, 301-619- 2394
Performance Period: 09/25/2020-09/24/2023
Level of Funding: total costs
Project Goals: The objectives of this project are to develop an α1A adrenoceptor (α1A-AR) radioligand for positron emission tomography (PET) imaging of α1A-ARs in living human brain to use as an *in vivo* assay for identifying novel PTSD therapeutics regulating CNS noradrenergic stress response system activity via α1A-ARs.
Specific Aims: Aim 1: Develop a novel fluorine-18 labeled radiotracer for α1A-Ars. Aim 2: Assess characteristics of candidate α1A-AR radiotracers by means of in vitro and in vivo rodent studies prior to PET imaging in NHPs. Aim 3: Assess α1A-AR availability & organ/whole body dosimetry in healthy human subjects. Aim 4: Measure α1A-AR availability as a biomarker of PTSD in Veterans and measure receptor occupancy with prazosin at clinically responsive doses to facilitate future drug development
Overlap: None

Title: A Phase 2, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of AVP-786 (deudextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q]) for the treatment of neurobehavioral disinhibition including aggression, agitation, and irritability in patients with traumatic brain injury (TBI)
Role: Principal Investigator
Time Commitments: 0 calendar
Supporting Agency: Avanir Pharmaceuticals, Inc., Protocol 17-AVP-786-205 **Address:** 30 Enterprise, Suite 200 Aliso Viejo, California 92656 **Contracting/Grants Officer:** Sarah Rosenthal, srosenthal@avanir.com
Performance Period: 09/13/2021 start
Level of Funding: Based on enrollment
Project Goals: The objectives of the study are to evaluate the efficacy, safety, and tolerability of AVP-786 compared to placebo for the treatment of neurobehavioral disinhibition including aggression, agitation, and irritability in patients with TBI.
Specific Aims: N/A
Overlap: None

Pending

Title: Counteracting high altitude-related disruption of sleep and cognitive impairment through pharmacological targeting of aquaporin-4 (AQP4)
Role: Co-Investigator
Time Commitments: 0.18 calendar
Supporting Agency: Department of Defense/CDMRP, PR211182PI
Address: USA Medical Research Acquisition Activity; 820 Chandler St.; Fort Detrick, MD 21702-5014
Contracting/Grants Officer: Pending
Performance Period: 06/01/2022-05/31/2026
Level of Funding: (total costs of subaward)
Project Goals: This proposal will evaluate the mechanistic link between high altitude (HA) exposure and the development of cognitive impairment, defining the role that sleep disruption and glymphatic impairment play in these processes.
Specific Aims: Aim 1: Define the role of glymphatic impairment in HA induced cognitive and neurovascular deficits. Aim 2: Determine the role of SWD in coupling between HA exposure and decline of cognitive and neurophysiological functions.
Overlap: None