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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

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

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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:**

- **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.

- **What was accomplished under these goals?**

  At the VA Puget Sound site, we have consented and screened 25 Veteran participants, 8 have been randomized, and 4 are on active medication. 4 Veterans have completed the protocol. We continue to recruit at the Seattle VA campus and the Readjustment Counseling Service "Vet Centers." In addition, we have established research space at the VA American Lake campus and have scheduled screening visits for 2 potential Veteran subjects in the South Puget Sound region.

At the Madigan Army Medical Center site, we have consented 2 active-duty subjects and screened one who is currently on active study medication. The other subject is scheduled to be screened next week.

- **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 and at JBLM. We have extended recruitment efforts to Vet Centers in Seattle and the surrounding area. We have initiated recruitment at VA Puget Sound American Lake campus.

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**
  Nothing to Report
- **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**
  Nothing to Report
- **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	0.6 PM	Scientific expertise
Paul Savage	Madigan Site PI	1.2 PM	Scientific expertise
Cynthia Mayer	Co-Investigator	1.8 PM	Scientific expertise
Wesley Chinn	Data Manager	3.6 PM	Data management
Laura Crews	Research Coordinator	8.0 PM	Madigan site coordination
Conner Engle	Research Assistant	9.0 PM	Study assistance
Kimberly Harms	Senior Coordinator	9.0 PM	Program coordination

Kelly Huynh	Research Coordinator	9.0 PM	VA site coordination
James O'Connell	Social Worker	7.5 PM	Clinical rater
Emma Onstad-Hawes	Research Assistant	12.0 PM	Study assistance
Anita Ranta	Study Coordinator	5.5 PM	Research recruitment
Kaitlin Todd	MS Biostatistician	2.0 PM	Database support
Robert Turner, PA-C	Physician Assistant	1.5 PM	Study support
Rebecca Tzucker	Research Assistant	9.0 PM	IRB/study assistance

- **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. Prazosin Augmentation of Outpatient Treatment of Alcohol Use Disorders in Active Duty Soldiers with and without PTSD, Raskind (PI), DoD / 10/1/12-9/30/18

- **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: 10/29/18

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** – 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:$2,322,000 Actual Expenditure:$1,709,000