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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

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

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6. AUTHOR(S)

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5d. PROJECT NUMBER

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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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

Task/Subtask	**Percent Completed**
Task 1: Study Preparation	100%
Subtask 1a: Prepare Regulatory Documents and Research Protocol	100%

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. Renewed annually through September 2023.
Milestone Achieved: Local IRB approval at Madigan/JBLM	100%
Milestone Achieved: CIRO, ORP/HRPO approval	100%
Subtask 1b: Study Preparation	100%
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	
Subtask 2a: Recruit Study Participants on a Rolling Basis	100%
Respond to potential participant request for information; mail out informational materials and consent forms	100%
Subtask 2b: Perform Study Procedures	100%

Milestone Achieved: 100 participants completing all study procedures.	100% -- 174 participants consented, following screening 96 were randomized with 96 completers.
Task 3: Data Management and Statistical Analysis	
Subtask 3a: Continuous double data entry and data cleaning	90%
Subtask 3b: Final data cleaning in preparation for data analysis	90%
Subtask 3c: Statistical analysis of data	50%
Milestones Achieved: All data entered, cleaned, and analyzed	90%
Task 4: Reporting and Presentation/Manuscript Preparation	
Task 4a: Write and submit necessary reports to the DoD	100%
Task 4b: Share findings with all investigators	90%
Task 4c: Present results at scientific meetings, write and submit manuscripts	50%, see details below
Milestone Achieved: Dissemination of study results	50%

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, and published as the lead article in the Headache: Journal of the American Headache Society. This manuscript is appended to this report as Appendix 2. Participant flow for the intent to treat analysis is shown in Figure 2. Study population demographics at Baseline, to include age at time of mild traumatic brain injury (mTBI), mechanism of injury, days from mTBI to onset, other pertinent demographics, are shown in Table 2.

For the primary outcome measure (change from baseline in 4-week headache frequency) as shown in Table 4, the reduction in headache frequency for the prazosin group for the final 4 weeks of study drug 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). Table 4 also shows 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). As shown in Table 5, 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). 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, whereas mean scores remained in the "severe impact" range in the placebo group.

As shown in Figure 2, the trial completion rate of 94% in the prazosin group and 88% in the placebo group indicate that prazosin was well tolerated in the administered dose as shown in Table 3. Table 1 presents the targeted dose titration schedule. Anticipated prazosin-related adverse events are summarized in Table 6. Adverse effects, while more common in the prazosin treatment group, were generally mild to moderate and usually resolved during the titration phase. Adverse events were not intolerable as demonstrated by the high completion rate in Figure 2.

Enrollment was completed in the 2022-2023 project year. The data from the final 48 participants will be cleaned, data entered, and statistical analysis completed by end April 2024. A manuscript describing results will be submitted for publication by end May 2024. This work will be conducted outside of the project period and will not require DoD support.

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

The Madigan Site PI was actively involved in the clinical research process and this project demonstrated a significant collaborative effort between VA and DoD team members and the VA Coordinating Center. This RCT was 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?

Publication:

Mayer CL, Savage PJ, Engle CK, Groh SS, Shofer JB, Hargrove AM, Williams TJ, Poupore EL, Hart KL, Riechers RG 2nd, Ruff RL, Peskind ER, Raskind MA. Randomized controlled pilot trial of prazosin for prophylaxis of posttraumatic headaches in active-duty service members and veterans. Headache. 2023 Jun;63(6):751-762. doi: 10.1111/head.14529. Epub 2023 Jun 14. PMID: 37313689.

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Mayer C, Raskind M, Savage P. Randomized Controlled Trial of Prazosin for Posttraumatic Headaches – Pilot Study Results. Headache Cooperative of the Pacific Annual Meeting. Ojai, CA January 27- 28, 2023

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

Raskind M, Mayer C, Savage P. Randomized Controlled Trial of Prazosin for Prophylaxis of Posttraumatic Headaches in Active-Duty Service Members and Veterans. Accepted (competitive submission) abstract/poster for Madigan Army Medical Center Research Day presentation, May 8, 2022.

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Mayer C, Raskind M. Prazosin for Prophylaxis of Posttraumatic Headaches - Pilot Randomized Controlled Trial in Veterans and Active-Duty Service Members. PTH Brown Bag presentation (virtual). Center for Neuroscience and Regenerative Medicine, Clinical Trials Unit Uniformed Services University of the Health Sciences, November 10, 2022

Raskind, M. Panel Chair, "Prazosin for Neuropsychiatric Disorders Beyond PTSD: Efficacy Signals for Alcohol Use Disorder, for Chronic Posttraumatic Headache, and for Disruptive Agitation in Alzheimer's Disease" Mayer, C presenting component 'Randomized Controlled Trial of Prazosin for Prophylaxis of Posttraumatic Headaches' American College of Neuropsychopharmacology Annual Meeting. Phoenix, AZ, December 4-7, 2022

Mayer C, Raskind M. Prazosin for Posttraumatic Headaches – Randomized Controlled Trial in Veterans and Active-Duty Service Members. Invited (virtual) presentation for National Mental Illness Research, Education, and Clinical Centers, March 16, 2022.

National VA Center for Information Dissemination and Education Resources (CIDER) Ralph G. DePalma Memorial TBI Clinical Strategies Webinar September 7, 2021 (240 attendees)

Platform Presentation Defense Intrepid Network Symposium presentation. September 16, 2021 (judged "first runner up")

Informational Video:

Raskind M, Savage P, Mayer C. Treating TBI Headaches at Dept of Defense Intrepid Spirit Centers, sponsored by the Intrepid Fallen Heroes Fund, April 5, 2022

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

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

We plan to submit a second manuscript for publication describing results for all 96 completers. There is nothing additional to report.

4. IMPACT:

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

The 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?

Nothing to report -- 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

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Significant changes to the objectives and scope of the project were not made. Significant changes to the project have been previously reported and are discussed below. These include:
- 06/2017: added DoD independent research monitor;
- 08/2018: PI change at Madigan Army Medical Center site; and,
- 06/2020 & 09/2020: notifications regarding curtailment and resumption of clinical research due to COVID-19.

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

In 2017, there were significant delays in obtaining regulatory approval and the CRADA between Madigan AMC and the Henry Jackson Foundation. Recruitment at VA Puget Sound was challenging until we established a presence in the primary care clinics. In 2018, the PI of the Madigan Army Medical Center site was changed.

From 2020, the study team encountered the adverse impact of the COVID-19 pandemic, which initially led to a shutdown of all clinical research at both sites, and which was followed by evolving COVID-19 policies. To address these challenges, our team developed innovative approaches to remote assessment that enabled recruitment to resume in a timely fashion, and strong relationships within and between the sites enabled continued recruitment, enrollment, and successful study completion.

Changes that had a significant impact on expenditures

The project received no-cost extensions for the period 09/30/2020-09/29/2023. Funds were available for the additional three years due prudent fiscal management and institutional support from VA.

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

There were no significant changes in the use or care of human subjects. The study obtained and renewed a Certificate of Confidentiality to protect human data.

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 CL, Savage PJ, Engle CK, Groh SS, Shofer JB, Hargrove AM, Williams TJ, Poupore EL, Hart KL, Riechers RG 2nd, Ruff RL, Peskind ER, Raskind MA. Randomized controlled pilot trial of prazosin for prophylaxis of posttraumatic headaches in active-duty service members and veterans. Headache. 2023 Jun;63(6):751-762. doi: 10.1111/head.14529. Epub 2023 Jun 14. PMID: 37313689. Federal support was acknowledged.

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

Nothing to report.

Other publications, conference papers and presentations.

See, “How were results disseminated to Communities of Interest”.

- **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.

- **Other Products**

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Murray Raskind, MD
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0001-9763-2423
Nearest person month worked:	2.4 CM (annual, compensated only Apr-Sept 2022)
Contribution to Project:	No changes
Name:	Elaine Peskind, MD
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0002-3667-9129
Nearest person month worked:	1.2 CM (annual, no compensation)
Contribution to Project:	No changes
Name:	Cynthia Mayer, DO
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0002-1699-1086
Nearest person month worked:	1.8 CM (annual, no compensation)
Contribution to Project:	No changes
Name:	Paul Savage, MD
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	1.2 CM (annual, no compensation)
Contribution to Project:	No changes
Name:	Rebekah Rein
Project Role:	Program Coordinator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	8.5 PM
Contribution to Project:	No changes
Name:	Daniel Murray
Project Role:	Research Assistant
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	30.5 PM
Contribution to Project:	No changes

Name:	Ameryth Hargrove
Project Role:	Research Coordinator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	30.7 PM
Contribution to Project:	No changes
Name:	James O'Connell
Project Role:	Social Worker/Clinical Rater
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	23.2 PM
Contribution to Project:	No changes
Name:	Shelby Grody
Project Role:	Research Assistant
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	29.0 PM
Contribution to Project:	No changes
Name:	Robert Turner
Project Role:	Physician's Assistant
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	9.0 PM
Contribution to Project:	No changes
Name:	Wesley Chinn
Project Role:	Data Analyst
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	29.6 PM
Contribution to Project:	No changes
Name:	Joseph Clark
Project Role:	Research Assistant
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	4.2 PM
Contribution to Project:	No changes
Name:	Andrew Shutes-David
Project Role:	Research Associate
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	4.3 PM
Contribution to Project:	No changes
Name:	Conner Engle
Project Role:	Research Assistant
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	21.7 PM
Contribution to Project:	No changes

Name:	Carolyn Fort
Project Role:	Clinical Research Coordinator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	5.0 PM
Contribution to Project:	No changes

Name:	Soleil Groh
Project Role:	Research Coordinator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	22.4 PM
Contribution to Project:	No changes

Name:	Kimberly Harms, PhD
Project Role:	Research Coordinator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	26.5 PM
Contribution to Project:	No changes

Name:	Hollie Holmes
Project Role:	Program Specialist
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	5.2 PM
Contribution to Project:	No changes

Name:	Anh Hong Huynh
Project Role:	Research Assistant
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	10.5 PM
Contribution to Project:	No changes

Name:	Daniel Morelli
Project Role:	Research Coordinator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	5.0 PM
Contribution to Project:	No changes

Name:	Emma Onstad-Hawes
Project Role:	Research Assistant
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	26.2 PM
Contribution to Project:	No changes

Name:	Anita Ranta
Project Role:	Study Coordinator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	8.6 PM
Contribution to Project:	No changes

Name:	Jon Reid
Project Role:	Research Assistant
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	1.2 PM
Contribution to Project:	No changes
Name:	Roisin Slevin
Project Role:	Research Assistant
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	3.9 PM
Contribution to Project:	No changes
Name:	Kaitlin Todd
Project Role:	Biostatistician
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	3.4 PM
Contribution to Project:	No changes
Name:	Rebecca Tzucker
Project Role:	Research Associate
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	31.4 PM
Contribution to Project:	No changes
Name:	Yun (Carol) Xiang
Project Role:	Data Manager
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	3.5 PM
Contribution to Project:	No changes
Name:	Jane Shofer
Project Role:	Biostatistician
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	7.5 PM
Contribution to Project:	No changes

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?

Organization Name: Madigan Army Medical Center (Madigan) and Henry M. Jackson Foundation (HMJF)
Location of Organization: Tacoma, WA
Partner's contribution to the project: This study is an important example of a successful research collaboration between the Department of Defense (Madigan/HMJF) and Department of Veterans Affairs (VA Puget Sound/SIBCR). Madigan and HMJF are partners in this collaboration. Dr. Savage is the site PI for the subaward to HMJF, which manages the study at Madigan**.** During 2015-2023, the subaward funded research activities at Madigan, to include use of personnel and facilities and pharmacy costs.

8. SPECIAL REPORTING REQUIREMENTS

QUAD CHARTS: An updated Quad Chart is attached.

9. APPENDICES:

Appendix 1 – Bibliography

Appendix 2 – Published Manuscript

APPENDIX 1 – BIBLIOGRAPHY

Publications

Mayer CL, Savage PJ, Engle CK, Groh SS, Shofer JB, Hargrove AM, Williams TJ, Poupore EL, Hart KL, Riechers RG 2nd, Ruff RL, Peskind ER, Raskind MA. Randomized controlled pilot trial of prazosin for prophylaxis of posttraumatic headaches in active-duty service members and veterans. Headache. 2023 Jun;63(6):751-762. doi: 10.1111/head.14529. Epub 2023 Jun 14. PMID: 37313689.

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(virtual). Center for Neuroscience and Regenerative Medicine, Clinical Trials Unit Uniformed Services University of the Health Sciences, November 10, 2022

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APPENDIX 2 – PUBLISHED MANUSCRIPT

Received: 14 September 2022 | Accepted: 21 April 2023

DOI: 10.1111/head.14529

RESEARCH SUBMISSIONS

Randomized controlled pilot trial of prazosin for prophylaxis of posttraumatic headaches in active-duty service members and veterans

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Abstract

Objective: Evaluate the efficacy and tolerability of prazosin for prophylaxis of headaches following mild traumatic brain injury in active-duty service members and military veterans.

Background: Prazosin is an alpha-1 adrenoreceptor antagonist that reduces noradrenergic signaling. An open-label trial in which prazosin reduced headache frequency in veterans following mild traumatic brain injury provided the rationale for this pilot study.

Methods: A 22-week parallel-group randomized controlled trial which included 48 military veterans and active-duty service members with mild traumatic brain injury–related headaches was performed. The study design was based on International Headache Society consensus guidelines for randomized controlled trials for chronic migraine. Following a pre-treatment baseline phase, participants with at least eight qualifying headache days per 4 weeks were randomized 2:1 to prazosin or placebo. After a 5-week titration to a maximum possible dose of 5 mg (morning) and 20 mg (evening), participants were maintained on the achieved dose for 12 weeks. Outcome measures were evaluated in 4-week blocks during the maintenance dose phase. The primary outcome measure was change in 4-week frequency of qualifying headache days. Secondary outcome measures were percent participants achieving at least 50% reduction in qualifying headache days and change in Headache Impact Test-6 scores.

Results: Intent-to-treat analysis of randomized study participants (prazosin $N=32$; placebo $N=16$) demonstrated greater benefit over time in the prazosin group for all three outcome measures. In prazosin versus placebo participants, reductions from baseline to the final rating period for 4-week headache frequency were -11.9 ± 1.0 (mean $\pm$ standard error) versus -6.7 ± 1.5, a prazosin minus placebo difference of −5.2 (−8.8, −1.6 [95% confidence interval]), $p=0.005$ and for Headache Impact Test-6 scores were -6.0 ± 1.3

Abbreviations: AR, adrenoreceptor; BP, blood pressure; CI, confidence interval; HIT-6, Headache Impact Test-6; HR, heart rate; ICHD-3, International Classification of Headache Disorders, 3rd edition; Madigan, Madigan Army Medical Center; mTBI, mild traumatic brain injury; PTH, posttraumatic headache; PTSD, posttraumatic stress disorder; RCT, randomized controlled trial; SE, standard error; TBI, traumatic brain injury; VA Puget Sound, VA Puget Sound Health Care System; VA, US Department of Veterans Affairs.

versus +0.6 ± 1.8, a difference of −6.6 (−11.0, −2.2), $p = 0.004$. The mean predicted percent of participants at 12 weeks with ≥50% reduction in headache days/4 weeks, baseline to final rating, was 70 ± 8% for prazosin (21/30) versus 29 ± 12% for placebo (4/14), odds ratio 5.8 (1.44, 23.6), $p = 0.013$. The trial completion rate of 94% in the prazosin group (30/32) and 88% in the placebo group (14/16) indicated that prazosin was generally well tolerated at the administered dose regimen. Morning drowsiness/lethargy was the only adverse effect that differed significantly between groups, affecting 69% of the prazosin group (22/32) versus 19% of the placebo group (3/16), $p = 0.002$.

Conclusions: This pilot study provides a clinically meaningful efficacy signal for prazosin prophylaxis of posttraumatic headaches. A larger randomized controlled trial is needed to confirm and extend these promising results.

KEYWORDS
mild traumatic brain injury, noradrenergic signaling, posttraumatic headache, prazosin

INTRODUCTION

Posttraumatic headache (PTH) is common following mild traumatic brain injury (mTBI) and for many patients can become chronic, causing substantial disability and distress.[1] The paucity of randomized controlled trial (RCT) data for PTH prophylaxis continues to necessitate an empiric approach based on the predominant PTH clinical phenotype.[2-4] Prazosin is an alpha-1 adrenergic receptor (AR) antagonist that lowers noradrenergic signaling both in the periphery and in the central nervous system.[5] Approved for treatment of hypertension by the US Food and Drug Administration in 1976, prazosin has been widely used "off label" for benign prostatic hypertrophy[6] and for trauma nightmares and sleep disruption in posttraumatic stress disorder (PTSD).[7] In an open-label trial evaluating prazosin for treatment of postconcussive symptoms in veterans with combat-related mTBI, Ruff et al. demonstrated a substantial reduction in PTH frequency and severity.[8] Consistent with these results, improvement or resolution of preexisting headaches was observed in the prazosin versus placebo arm in a positive RCT of prazosin for PTSD in active-duty service members.[7] Seventy-five percent of participants in that sample had experienced at least one combat-related mTBI. Taken together, these findings provide the rationale for a pilot RCT of prazosin for prophylaxis of persistent PTH in active-duty service members and veterans. For the current study, we hypothesized that prazosin would reduce PTH frequency and headache-associated disability in this population compared to placebo. The primary study goals were to assess the efficacy, safety, and tolerability of prazosin when used for prophylaxis of persistent PTH.

METHODS

This pilot study was a parallel group prospective double-blind randomized placebo-controlled trial conducted at US Department of Veterans Affairs Puget Sound Health Care System, Seattle and American Lake, Washington (VA Puget Sound) and Madigan Army Medical Center Intrepid Spirit Center, Joint Base Lewis McChord, Tacoma, Washington (Madigan) by a collaborative team of investigators. The study population included military veterans and active-duty service members. Recruitment began in January 2017, with the last participant of this pilot study having completed in October 2021. During the trial, several modifications were made to the study protocol for the purposes of facilitating recruitment and minimizing study burden to participants. These are summarized in Appendix A of the supporting information. None of the changes made before or after enrollment of the first study participant compromised the integrity of data collection, analysis, or interpretation.

Institutional review boards at VA Puget Sound, Madigan, and the US Army Medical Research and Development Command Human Resource Protection Office approved the study protocol and provided study oversight to ensure regulatory compliance and participant safety. Prior to enrollment in the study, all participants provided written informed consent. The study was covered by a Certificate of Confidentiality. Study sites fully complied with all regulations relating to data confidentiality and the Health Insurance Portability and Accountability Act.

Trial design

The study design was based on International Headache Society consensus guidelines for chronic migraine prophylaxis clinical trials.[9] These guidelines were felt to provide a robust study structure for producing results that could be compared to those of prior and future clinical trials. Although the clinical phenotypes of PTH vary, in the experience of US Department of Veterans Affairs (VA) and Army investigators, PTH in active-duty and veteran patients more often than not has features typical of migraine.[10-12] A frequency of at least eight moderate to severe headaches per 4-week period, irrespective

of phenotype, was considered to be of substantial clinical impact and was chosen as the lower limit for study inclusion.

Figure 1 summarizes the study timeline. A pre-treatment screening baseline phase (4 weeks) was followed by study drug (prazosin or placebo) dose titration (5–7 weeks) and continuation on a maintenance dose of the study drug (12 weeks). Pre-treatment screening involved an initial clinic visit at which the study consent was signed followed by completion of self-report questionnaires, documentation of medical history and medication use, physical and neurologic exams, and structured interviews that included documentation of lifetime TBI history and characterization of headaches. When preliminary eligibility was confirmed, participants were given a paper headache log to complete daily over the subsequent 4 weeks to confirm headache frequency eligibility and to establish baseline data. The headache log documented (1) daily presence or absence of headache, (2) peak headache severity, (3) total headache hours, and (4) use of any rescue treatments. Following confirmation of eligibility, participants were randomized 2:1 to study drug, which was provided as oral capsules. The 2:1 active drug to placebo randomization scheme was selected to facilitate recruitment, that is, to provide an incentive in the form of increased odds of receiving the active drug. We recognized the reduction in statistical power caused by having a smaller sample size in the placebo arm, but the beneficial effect on recruitment was felt to offset this limitation. The study drug was slowly titrated over 5 to 7 weeks. Further details of dose titration are provided in Section Study Drug. The achieved dose was continued for a 12-week maintenance dose phase. Randomized participants continued the daily headache log for the duration of the study. Results for primary and secondary outcome measures at 4-week intervals during the 12-week maintenance dose phase were compared to baseline data.

Participants

Participants were recruited at VA Puget Sound and Madigan using institutional review board–approved procedures.

Sample size

The original study design specified enrollment of 228 participants to achieve 112 participants completing the study, according to our a priori estimate of the number needed to generate a detectable efficacy signal. That estimate was based on data from prior RCTs using a similar study design that evaluated efficacy of medications for chronic migraine prophylaxis.[13,14] Those studies reported standard deviations for change from baseline at 16 weeks in number of migraine days/month on the order of 5 to 6 days for both placebo and active drug groups and a difference in change from baseline at 16 weeks in mean number of chronic migraine days/month between treatment groups of approximately 4 days (i.e., an effect size of approximately 0.67). An inclusion criterion for these studies was a minimum of 15 headache days/month, whereas the inclusion criterion for our study was a minimum of 8 headache days/month. A trial with 112 completers randomized 2:1 prazosin to placebo yields 80% power to detect an effect size of 0.57 for a difference in change from baseline, a slightly smaller effect size than that obtained in the RCTs mentioned above, based on a standard two-sample *t*-test using a two-sided 5% Type I error level. Using linear mixed effects models to analyze this outcome, the anticipated power was >80% to detect an effect size of 0.57. A starting number of 228 participants to achieve a final sample size of 112 was determined assuming a 30%

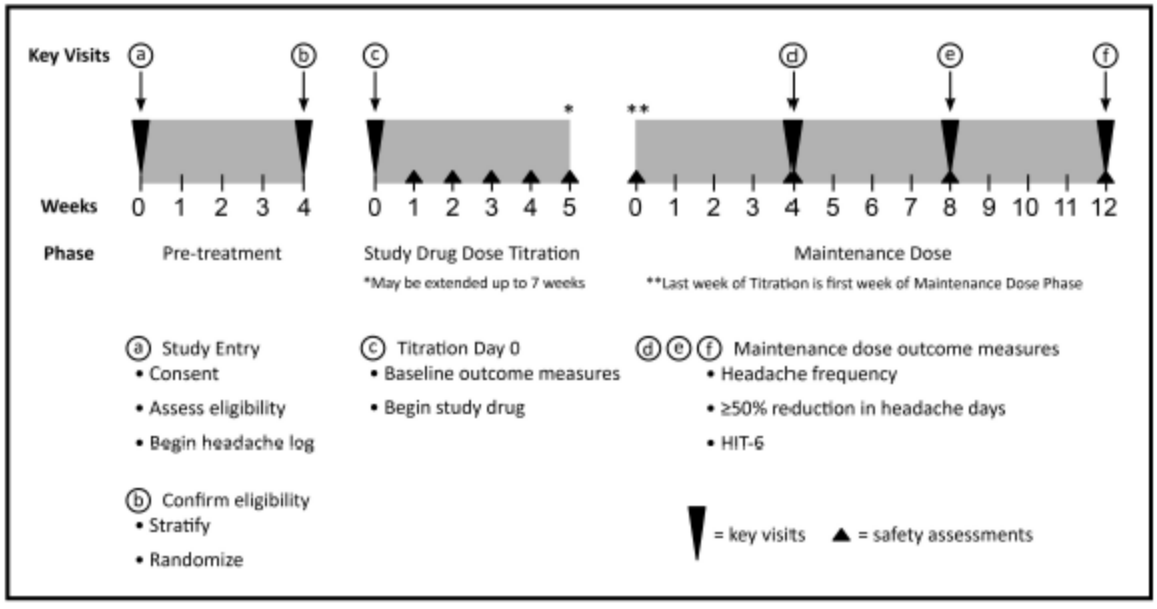

FIGURE 1 Study timeline. HIT-6, Headache Impact Test-6.

discontinuation rate during the pre-treatment headache log-keeping phase (e.g., due to an insufficient number of qualifying headaches) and a 30% discontinuation rate during the titration and maintenance dose phases (e.g., due to schedule conflicts, medication intolerance). The results reported here are for the first 48 participants who were randomized by the end of the grant funding period.

Randomization procedures and blinding

Randomization of study participants to active drug or placebo was based on a computer-generated scheme created by a staff member having no direct participant contact. Stratification blocks included birth sex (male or female), study site (VA Puget Sound or Madigan), and whether criteria for medication overuse were met. Prior to opening study enrollment, sequential identification numbers for each stratification combination were generated and randomly assigned to active drug or placebo. Each randomization result was printed on a card that was sealed in an envelope labeled with its corresponding identification number by the person who performed the computer-generated randomization. That person and the investigational pharmacists were the only ones with access to results of the randomization. The envelopes were stored in a locked cabinet within a locked office behind security doors requiring card entry. As each participant was randomized, they were assigned to one of the unique identification numbers based on sequence and stratification profile. Participants as well as staff having direct participant contact, including study coordinators, research assistants, and clinicians, were blind to treatment assignment. Each envelope containing the randomization result remained sealed until a participant's final day in the study and was opened by either the participant or study staff following completion of all other study measures. At that point, study staff became aware of a participant's randomization status, as each participant was offered the option of starting or continuing prazosin following study completion.

Inclusion criteria

Active-duty service members and military veterans aged 18 or older of any sex or gender with a history of mTBI at least 3 months prior to study enrollment and having a minimum of eight qualifying headaches per 4 weeks were eligible. Headaches must have started or substantially worsened (at least doubled in severity and/or frequency) within 90 days of mTBI of any mechanism to be considered likely posttraumatic. Qualifying headaches included those (1) lasting at least 4 h and reaching a peak intensity of moderate to severe or (2) headaches of any severity or duration for which rescue medications were taken.

Exclusion criteria

Exclusions included any lifetime history of TBI more severe than mild, by Department of Veterans Affairs/Department of Defense Clinical Practice Guidelines,[15] history of penetrating head injury, acute or unstable medical condition, psychosis, severe depression, pregnancy, current participation in another interventional study, or failure to record headache log data for at least 80% of days during the baseline pre-treatment phase. Also exclusionary were previous adverse reaction to prazosin or other alpha-1 AR antagonist and any previous use of prazosin at a dose of more than 4 mg per day. The use of any alpha-1 AR antagonist other than study drug was prohibited for 2 weeks prior to starting the study and for the duration of study enrollment.

Prior or current headache prophylaxis treatments were not exclusionary. Any current medications used for headache prophylaxis or that could potentially affect symptom severity or frequency must have been at a stable dose for at least 4 weeks prior to study enrollment and must have been intended to be continued for the duration of the trial, with adjustments allowed for safety or tolerability. Exceptions to starting such drugs were made if determined to be in the best interest of the participant. Use of OnabotulinumtoxinA was permissible if treatment response was stable during the two most recent treatment cycles. Medications used on an as-needed basis for stopping or alleviating headache pain and/or headache-related symptoms ("rescue" medications) were not exclusionary, except for butalbital, which was not permitted during the study.

Use of trazodone, prescribed stimulants, and any over-the-counter supplements containing nitrates or stimulants other than caffeine was prohibited during the study and required a 2-week wash-out period prior to study enrollment. Use of phosphodiesterase inhibitors was not permitted during dose titration but was allowed at half the usual dose during the maintenance dose phase. The cautious use of phosphodiesterase inhibitors and prohibition of nitrates were to avoid possible additive hypotensive effects when taken with prazosin. Trazodone was prohibited to avoid the unlikely possibility of additive risk for priapism. Use of opioids for treatment of headache or non–headache-related purposes was allowed during the study. Use of alcohol or of cannabis in any form was allowed unless the participant met criteria for alcohol or cannabis use disorder.

Use of non-medication prophylactic or rescue interventions (e.g., external nerve stimulation devices or biofeedback) was not excluded. For any regular activity intended to mitigate headaches or other chronic pain (e.g., meditation, yoga, support group), stable participation for at least 4 weeks prior to beginning the study was required, with the intention to continue the activity while in the study.

Study drug

Study drug (prazosin or placebo) was prescribed by a study clinician blind to the randomization designation and provided by the research pharmacist at VA Puget Sound or Madigan. The dose of study drug was titrated gradually upward using the schedule shown in Table 1 to a maximum dose of 5 mg morning and 20 mg evening, or as tolerated. This dose regimen is based on our group's clinical and research experience using prazosin for treating PTSD in active-duty service members and veterans. The gradual dose titration helps minimize known potential

TABLE 1 Study drug dose titration schedule.

	Morning dose (mg)	Evening dose (mg)
Week 1		
Days 1–2	–	1
Days 3–7	–	2
Week 2	1	4
Week 3	2	6
Week 4	5	10
Week 5	5	15
Week 6	5	20

adverse effects of prazosin. Study participants were monitored prior to each dose increase. If a participant had intolerable side effects or symptoms considered by study clinicians to be potentially unsafe, the study drug dose was decreased to the prior step and the participant monitored for an additional week at that dose, with consideration for any subsequent dose increases based on clinician judgment.

Outcome measures

The primary outcome measure was change from baseline in qualifying headache days per 4 weeks as recorded by participants in a daily headache log. Secondary outcome measures were (1) percent of participants achieving at least 50% reduction in qualifying headache days per 4 weeks (from the headache log) and (2) change from baseline in function and quality of life due to the impact of headaches, as quantified by the Headache Impact Test-6 (HIT-6).

Safety assessments

Safety assessments performed at each study visit included seated (10 min) followed by standing (2 min) blood pressure (BP) and heart rate (HR) to evaluate known potential orthostatic effects of prazosin. In addition, adverse events that were newly emergent or worsened from prior visits were queried at each study visit after the baseline pre-treatment assessment.

Statistical analysis

The intent-to-treat population consisted of all 48 randomized participants (prazosin: $N=32$; placebo: $N=16$). Generalized mixed effects regression was used to test for differences in the change in qualifying headache days per 4 weeks by treatment group. The dependent variable was the proportion of qualifying headache days over the number of days participants recorded headaches per study period. Study period, treatment group, and study period by treatment group interaction were the independent fixed effects and study participant identification was modeled as random. Errors were modeled as beta-binomial to allow for variability in each participant's number of days of recorded headaches. The study period by treatment group interaction terms allow for the estimation of the treatment group difference in the change in headache frequency from baseline. More detail on this model is provided in Appendix B of the supporting information. Similarly, linear mixed effects regression was used to test for differences in the change in HIT-6 score and BP and HR measures (the dependent variables) by treatment group. Independent fixed and random effects were defined as above. Results for all mixed effects regressions are presented as marginal mean and standard error (SE) for each treatment group and study period, mean change from baseline for each group, and differences in change by group, accompanied by SE, 95% confidence interval (CI), and p-value for the pair-wise differences. Hypothesis testing was carried out to test the significance of the treatment group by study period interaction using the likelihood ratio test (headache days) and the conditional F-test (HIT-6 score).

Generalized estimating equations were used to estimate the percent of participants who experienced at least a 50% reduction in headache frequency (the dependent variable) for each treatment group, with study period, treatment group, and study period by treatment group interaction as independent variables, and errors clustered by study participant, assuming exchangeable correlation. Results are presented as means, SEs, and odds ratios for the ≥50% improvement for prazosin versus placebo. Overall differences by treatment group were assessed by hypothesis testing for the joint significance of the treatment group main effect and the treatment group by study period interaction using the Wald test. Fisher's exact test was used to test for differences in adverse effects by treatment group. Model assumptions were assessed graphically. The criterion for statistical significance was set at 0.05. All tests were two-tailed. Analysis was carried out using R 4.0.3[16] and packages tidyverse, lme4, glmmTMB, emmeans, and geepack. The reliability of study measures is discussed in Appendix C of the supporting information. All analyses for this study are a priori. This is the primary analysis of these data. Results of this study have not been previously published. All authors have full access to all study data, which is stored on a VA secured server managed by the VA data manager.

Trial funding and oversight

The study was funded by a VA Career Development Award registered on ClinicalTrials.gov as NCT02266329 (Principal Investigator Cynthia Mayer, DO) and a Department of Defense Congressionally Directed Medical Research Program award registered on ClinicalTrials.gov as NCT02965027 (Principal Investigator Murray Raskind, MD).

RESULTS

Participant disposition and baseline characteristics

Participant disposition is presented in Figure 2. Ninety-seven potentially eligible participants completed consent at the initial study visit. Study eligibility was assessed at that time and following the first 4 weeks of

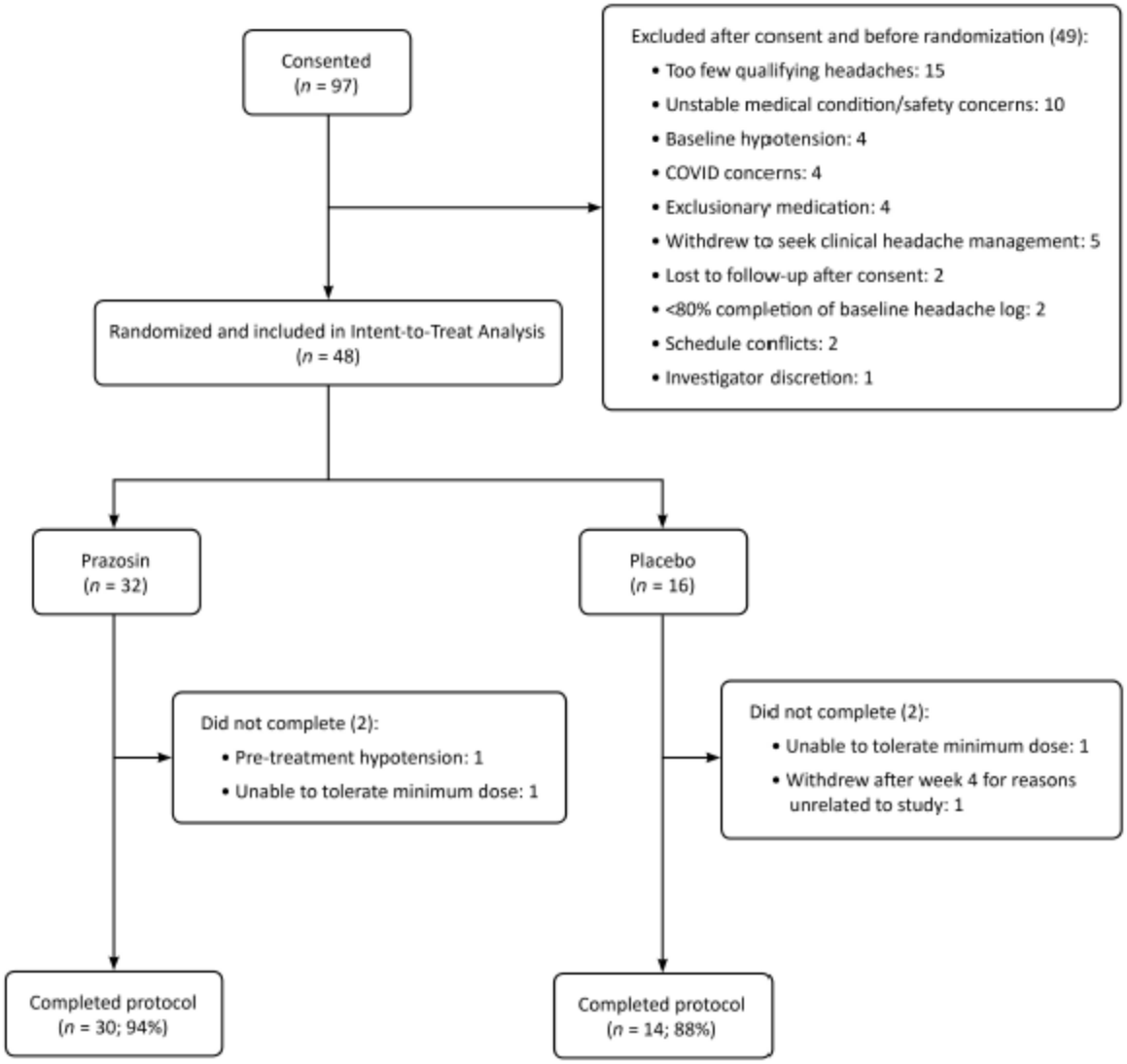

FIGURE 2 Participant disposition.

baseline headache log keeping. Among those consented, 49 were excluded or withdrew prior to randomization for the reasons summarized in Figure 2. A total of 48 participants were randomized 2:1 to prazosin ($N=32$) or placebo ($N=16$) and included in the intent-to-treat analysis. Study enrollment fell short of the target sample size of 112 for reasons that include the prolonged start-up time due to the complexity of the regulatory review and approval processes in two different government agencies and subsequently due to COVID-19–related issues.

Despite the extended trial duration, retention was excellent in both the prazosin and placebo groups. Of those randomized, three did not complete titration, including two (one each in the prazosin and placebo groups) who were unable to tolerate the minimum dose of 1 mg and one (prazosin group) who was terminated from the trial for safety concerns due to baseline hypotension confirmed prior to starting the study drug. An additional participant (placebo group) withdrew after the first 4-week maintenance dose period for personal reasons unrelated to the study.

Two of the outcome measures reported here, change in 4-week frequency of headache days and percent participants with ≥50% improvement in headache frequency, required headache log data. With a pooled mean study period length of 31.0 days (range 15–73) and a mean of 29.8 days of recorded headache log data per study period (range 6–70) among all participants, headache log data were available for a mean 96% (29.8/31.0) of study period days. Only 10% (18/180) of study periods had fewer than 90% of total possible days of recorded headache log data. Headache log completion rates were similar by treatment group. See Table S1 in the supporting information for additional details.

Demographic information and mTBI and PTH baseline characteristics are provided in Table 2. The study sample was equally distributed between active-duty service members and veterans and baseline demographic characteristics in the prazosin and placebo groups were similar. The sample was predominantly male, as is typical of samples recruited from the military and veteran populations. The specified PTH-inciting injury was more commonly impact- than blast-related. Whether or not causing persistent headaches, a history of blast exposure with concussive symptoms was common, with 50% of the prazosin group (16/32) and 38% of the placebo group (6/16) having experienced at least one lifetime blast mTBI. Comorbid PTSD was present in 66% of prazosin group participants (21/32) and in 81% of placebo group participants (13/16). The predominant PTH clinical phenotype was most commonly migraine, probable migraine, or difficult-to-characterize headaches having at least one migraine feature for 84% of those in the prazosin group (27/32) and 94% of those in the placebo group (15/16).

A headache frequency of 15 or more headache days per month and medication overuse as defined by the International Classification of Headache Disorders, 3rd edition (ICHD-3)[17] were highly prevalent in the study population at baseline. Ninety-one percent of study participants in the prazosin group (29/32) and 94% in the placebo group (15/16) had headaches on at least 15 days per month. Fifty-three percent of participants in the prazosin group (17/32) and 63% in the placebo group (10/16) met ICHD-3 criteria for medication overuse.[17] Current and prior use of prophylactic and rescue medications as well as non-pharmacologic treatments were common, as indicated in Table 2.

The study drug was generally well tolerated. Table 3 summarizes the dose of study drug achieved by treatment group. The mean achieved total daily dose of study drug was 18 (±8) mg in the prazosin group and 20 (±8) mg in the placebo group. The maximum study drug dose of 5 mg morning and 20 mg evening was reached by 52% (16/31) in the prazosin group and 75% (12/16) in the placebo group.

Outcome measures

Primary outcome measure: Change in 4-week qualifying headache frequency in intent-to-treat sample

Mean baseline qualifying headaches per 4 weeks were 18.3 (±1.6) in the prazosin group and 18.6 (±2.3) in the placebo group. With treatment, the prazosin group had a significantly greater reduction in 4-week qualifying headache frequency over time compared to the placebo group ($p = 0.010$; Figure 3; Table 4). For the final 4-week maintenance dose period (week 12), the prazosin group had a mean reduction in headache days of 11.9 ± 1.0 compared to 6.7 ± 1.5 for the placebo group, that is, 5.2 fewer headache days (95% CI [−8.8, −1.6], $p = 0.005$).

Secondary outcome measure (1): ≥50% reduction in headache frequency

The mean percentage of participants having at least a 50% reduction in frequency of qualifying headache days from baseline was significantly greater in the prazosin than placebo group at the end of both the week 8 (79 ± 8% vs. 43 ± 13%) and week 12 (70 ± 8% vs. 29 ± 12%) maintenance dose periods (Figure 4; Table S2 in supporting information), $p = 0.004$. The week 12 results indicated that more than twice as many prazosin participants had at least a 50% reduction in qualifying headache days as placebo participants.

Secondary outcome measure (2): Headache-related impact on function and quality of life as rated by the HIT-6

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 ± 1.3), whereas mean scores remained in the "severe impact" range in the placebo group (64.2 ± 1.8), with a difference of 6.6 points between groups (95% CI [−11.0, −2.2], $p = 0.004$; Table 5).

Treatment-related BP and HR effects

Seated and standing diastolic and systolic BP and HR results at baseline and at weeks 4, 8, and 12 of the maintenance dose phase are provided in Table S3 in supporting information. At baseline, there was no significant difference between the prazosin and placebo groups. Following an initial mild decline in systolic BP in the prazosin group (6.7 ± 2.2 mmHg for seated BP; 4.8 ± 2.5 mmHg for standing BP) in the first week of the maintenance dose period, BP slowly returned to near-baseline levels by week 12. There was no significant difference in change in BP or HR between the prazosin and placebo groups ($p \geq 0.248$).

Adverse events

The frequency of anticipated prazosin-related adverse events by study group is summarized in Table 6. Unanticipated adverse events not typical for prazosin use are provided in Table S4 in supporting information. Several known adverse effects of prazosin were significantly more common in the prazosin treatment group. These were generally mild to moderate in severity and usually resolved during the titration phase. No unanticipated adverse events were significantly different in frequency between treatment groups. That these

TABLE 2 Study population demographics and baseline characteristics by treatment group.

	Prazosin	Placebo
Randomized	32	16
Sex/gender*		
Male	29 (91%)	15 (94%)
Female	3 (9%)	1 (6%)
Other sex or gender identity	0	0
Veterans	16 (50%)	8 (50%)
Active-duty service members	16 (50%)	8 (50%)
Race/Hispanic ethnicity (H)		
White	19 (59%) (3 H)	10 (63%)
Black	6 (19%)	4 (25%) (1 H)
American Indian/Alaskan Native	2 (6%) (1 H)	–
Asian/Pacific Islander	2 (6%)	–
Other	3 (9%)	2 (13%) (1 H)
Body mass index, mean (± SD)	30.4 (±5.5)	30.7 (±4.4)
Age at study entry		
Mean (± SD)	43 (±12)	38 (±12)
Range	23–72	21–64
Age at time of PTH-inciting mTBI		
Mean (± SD)	29 (±8)	25 (±5)
Range	20–44	19–39
Time from mTBI to headache onset (days)		
0–7 days	14 (44%)	12 (75%)
7–30 days	7 (22%)	3 (19%)
31–60 days	2 (6%)	0
60–90 days	1 (3%)	0
Uncertain but <90 days	8 (25%)	1 (6%)
Duration of PTH, onset to study entry (years)		
Mean (± SD)	14 (±11)	13 (±13)
Range	<1–48	1–42
Mechanism of injury of PTH-inciting mTBI		
Blast	3 (9%)	2 (13%)
Impact	15 (47%)	9 (56%)
Blast + impact	7 (22%)	2 (13%)
Neck (including whiplash)	1 (3%)	0
Blast + neck	1 (3%)	0
Impact + neck	3 (9%)	2 (13%)
Blast + impact + neck	2 (6%)	1 (6%)
Any history of blast mTBI	16 (50%)	6 (38%)
Lifetime number of mTBIs		
Mean (± SD)	9.8 (±12.1)	9.3 (±10.1)
Range	1–54	1–36
PTH dominant phenotype		
Migraine[b]	19 (59%)	9 (56%)
Tension-type	3 (9%)	0
Mixed with migraine features[c]	8 (25%)	6 (38%)
Unclassifiable	0	1 (6%)
Unknown/not recorded	2 (6%)	0
Number of prophylactic and rescue medications[d]		
Mean (± SD)	6.2 (±5.3)	4.6 (±2.3)
Range	0–25	0–9
Number of non-pharmacologic prophylactic and rescue treatments[d,•]		
Mean (± SD)	1.6 (±2.1)	1.4 (±1.5)
Range	0–9	0–5
≥15 headaches per month at baseline	29 (91%)	15 (94%)
Met criteria for medication overuse at baseline	17 (53%)	10 (63%)
PTSD diagnosis at baseline, current and past	21 (66%)	13 (81%)

Abbreviations: mTBI, mild traumatic brain injury; PTH, posttraumatic headache; PTSD, posttraumatic stress disorder; SD, standard deviation.

*The gender identity of all participants was concordant with their birth sex, as determined through the medical record and collected demographic data at the time of study entry.

[b]Includes with and without aura; probable migraine.

[c]Includes tension type and/or cervicogenic along with at least one migraine feature.

[d]Current and past use for headaches and associated symptoms.

•Current and past treatments specifically for the purpose of alleviating headaches and associated symptoms, including acupuncture, chiropractic, injections other than onabotulinumtoxinA, transcutaneous electrical nerve stimulation, yoga, meditation, cannabis products, caffeine.

adverse events were not intolerable is supported by the 94% study completion rate in the prazosin group (30/32) compared to 88% in the placebo group (14/16).

DISCUSSION

This pilot RCT of prazosin for PTH in active-duty service members and veterans demonstrated a significantly greater reduction in headache frequency in the prazosin compared to placebo treatment group. Significant reductions in HIT-6 scores in the prazosin compared to placebo condition supports the clinical meaningfulness of prazosin treatment. These results provide an encouraging efficacy signal for prazosin prophylaxis of PTH. They confirm and extend previously observed reductions in headache frequency with

TABLE 3 Dose of study drug achieved (number of participants, percent of randomization group).

	1 mg	1 mg am/4 mg hs	2 mg am/6 mg hs	5 mg am/10 mg hs	5 mg am/15 mg hs	5 mg am/20 mg hs	Mean achieved dose/day, mg (SD)
Prazosin $N=31$*	1 (3%)	3 (10%)	3 (10%)	5 (16%)	3 (10%)	16 (52%)	18 (±8)
Placebo $N=16$	1 (6%)	1 (6%)	1 (6%)	0	1 (6%)	12 (75%)	20 (±8)

Abbreviation: SD, standard deviation.

*One participant randomized to prazosin was not started on study drug due to baseline hypotension.

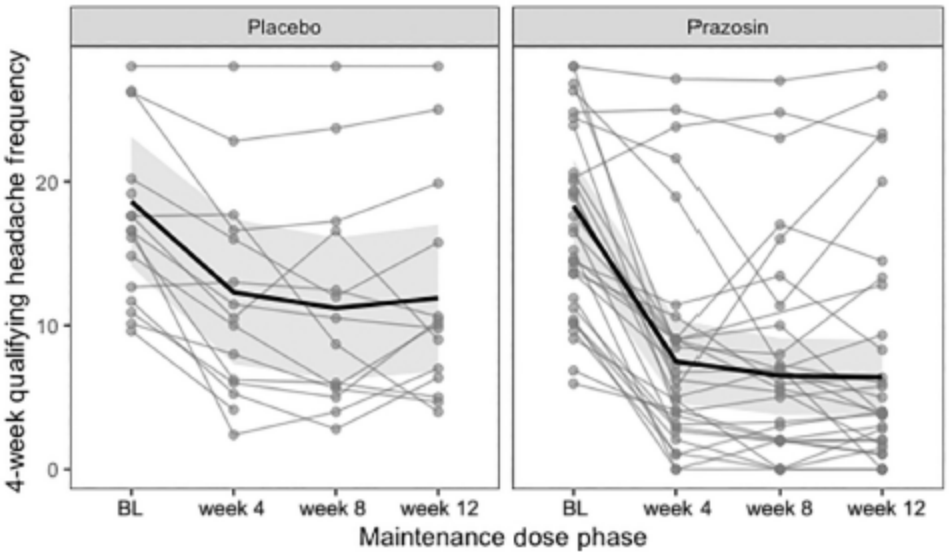

FIGURE 3 Four-week qualifying headache frequency by study period and treatment group. Mean trajectory for each group estimated from a generalized mixed effects regression of 4-week qualifying headache frequency on study period by treatment group interaction. Decline over time significantly greater in prazosin than placebo group ($p=0.010$).

TABLE 4 Change in 4-week qualifying headache frequency over time by study period and treatment group (mean ± SE, 95% CI, p-value).

	Prazosin ($N=32$)	Placebo ($N=16$)	Prazosin–placebo
Baseline	18.3 ± 1.6	18.6 ± 2.3	−0.3 ± 2.8, (−5.8, 5.2), 0.910
Week 4—Baseline	−10.8 ± 1.0, (−13.2, −8.3), <0.001	−6.3 ± 1.5, (−9.7, −2.8), <0.001	−4.5 ± 1.8, (−8.0, −1.0), 0.012
Week 8—Baseline	−11.8 ± 1.0, (−14.3, −9.4), <0.001	−7.4 ± 1.5, (−10.9, −3.9), <0.001	−4.4 ± 1.8, (−8.0, −0.9), 0.015
Week 12—Baseline	−11.9 ± 1.0, (−14.3, −9.4), <0.001	−6.7 ± 1.5, (−10.3, −3.0), <0.001	−5.2 ± 1.8, (−8.8, −1.6), 0.005

Note: Likelihood ratio test for the significance of the treatment group by study visit interaction, $p=0.010$.

Abbreviations: CI, confidence interval; SE, standard error.

prazosin treatment, including in an open-label study in military veterans[8] and in a secondary analysis of headache-related findings in a RCT evaluating prazosin for PTSD in active-duty service members.[7]

The pathophysiology of PTH and its relation to primary headache disorders are areas of active investigation, as summarized in recent reviews.[4,18,19] With respect to the findings reported here, several studies suggest involvement of adrenergic signaling in PTH pathophysiology. Increased noradrenergic activity may contribute to headache pain directly by mediating release of pronociceptive molecules and promoting afferent dural signaling. These effects were demonstrated in a rat study, in which application of norepinephrine to cultured dural fibroblasts resulted in release of pronociceptive molecules.[20] As part of the same study, facial and hind paw allodynia were demonstrated in a rat behavioral model of headache pain following dural injection of norepinephrine and of media from the cultured dural fibroblasts. In addition to promoting

release of pronociceptive molecules, noradrenergic signaling is likely involved in modulating pain perception and behavioral response pathways.[21,22]

A direct or indirect effect of noradrenergic modulation of the recently described glymphatic system[23] may also play a role. This brain-wide system of perivascular pathways, along which cerebrospinal fluid and interstitial fluid rapidly exchange, is thought to provide a route for clearance of potentially pathogenic interstitial solutes and proteins. Studies in mice suggest that adrenergic signaling is involved in controlling the volume of interstitial space.[24] Increased brain noradrenergic activity during the awake state is associated with decreased volume of interstitial space and decreased glymphatic clearance, an effect that is reversed by prazosin.[24] This observation suggests that prazosin may facilitate increased glymphatic clearance, including of pronociceptive molecules that potentially contribute to PTH pathophysiology.

Given that PTH commonly has a migraine-like clinical phenotype, it is worth noting several studies in humans that demonstrate a benefit of alpha-1 AR antagonists for migraine. An open-label case series was published in 1997 by a neurologist inspired by his personal experience of resolution of longstanding migraine after receiving terazosin for hypertension. Based on the premise that inhibition of noradrenergic signaling might explain the beneficial effect, he treated 10 of his patients (including one with posttraumatic migraine) with the alpha-1 AR antagonists terazosin or doxazosin. Including himself, 10 of 11 patients had complete resolution or decreased frequency and/or severity of their headaches.[25] In an earlier single-blind placebo-controlled study, thymoxamine, a predominately post-synaptic alpha-1 AR antagonist, aborted migraine attacks in 9 of 10 patients versus 2 of 10 in the placebo group.[26] The target for alpha-1 AR antagonism was postulated to be trigeminal innervation of the extracranial and/or dural vessels.[26]

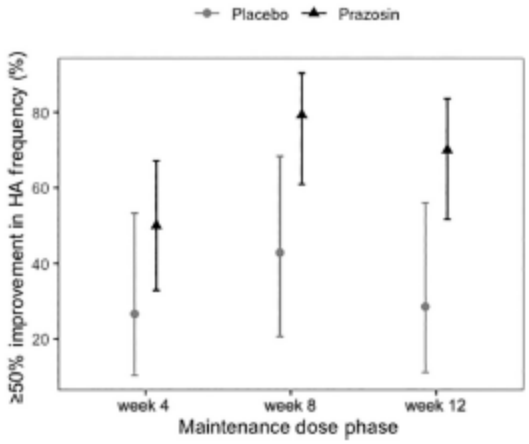

FIGURE 4 Percent participants having ≥50% improvement in qualifying headache frequency from baseline (mean, 95% confidence interval). Differences by treatment at 8 and 12 weeks were significant ($p \leq 0.021$).

The study reported here has several limitations. Despite the encouraging efficacy signal, the sample size was modest. Clinical trials at both the VA and Department of Defense often have prolonged start-up times due to the complexity of the regulatory review and approval processes. Just as a robust recruitment pipeline was achieved, the COVID-19 pandemic occurred, with a mandated research moratorium at the VA. Other factors affecting recruitment included the 6-month trial duration, which was an issue for some potential participants due to service-related obligations and for others, the desire for more immediate definitive treatment. In addition, some potential participants were already taking prazosin for PTSD, so were excluded.

A larger RCT is needed to confirm the results reported here and to detect clinical and/or biologic characteristics potentially predictive of prazosin benefit for PTH. The prazosin doses chosen for this study were high, to reduce the possibility of missing an efficacy signal by underdosing. A dose-finding study would be useful to determine whether a lower dose would retain efficacy while decreasing adverse event frequency. A potential source of bias stems from the specific nature of adverse events attributable to prazosin, which could have alerted both study participants and study staff to the possibility that a participant was randomized to active drug rather than placebo. The study sample was restricted to active-duty service members and military veterans. Women were underrepresented in the sample for a presumed combination of reasons, including the relatively low numbers of women currently or previously in military service and the overall lower incidence of TBI in women compared to men. These factors limit extrapolation of findings to the civilian PTH population. Future RCTs should include civilian participants in sufficient numbers to reach statistically robust

TABLE 5 Change in HIT-6 scores by study period and treatment group (mean ± SE, 95% CI, *p*-value).

	Prazosin ($N = 32$)	Placebo ($N = 16$)	Prazosin–placebo
Baseline	61.0 ± 1.5	63.6 ± 2.1	−2.5 ± 2.5, (−7.6, 2.5), 0.319
Week 4—Baseline	−5.6 ± 1.3, (−8.6, −2.6), <0.001	−0.1 ± 1.8, (−4.5, 4.2), >0.999	−5.4 ± 2.2, (−9.8, −1), 0.016
Week 8—Baseline	−5.8 ± 1.3, (−8.9, −2.8), <0.001	−1.3 ± 1.8, (−5.7, 3.1), 0.795	−4.6 ± 2.2, (−9.0, −0.1), 0.043
Week 12—Baseline	−6.0 ± 1.3, (−9.0, −2.9), <0.001	0.6 ± 1.8, (−3.7, 5.0), 0.950	−6.6 ± 2.2, (−11.0, −2.2), 0.004

Note: Conditional *F*-test for the significance of the treatment group by study visit interaction, $p = 0.020$.
Abbreviations: CI, confidence interval; HIT-6, Headache Impact Test-6; SE, standard error.

TABLE 6 Frequency of likely prazosin-related adverse events (number, percent, *p*).

	Prazosin *N* = 32	Placebo *N* = 16	*p*[a]
Dizziness on standing/ lightheadedness/ vertigo	22 (69%)	7 (44%)	0.124
Syncope/fall	2 (6%)	0	0.546
Palpitations	14 (44%)	3 (19%)	0.116
Nasal congestion	13 (41%)	2 (13%)	0.057
Nausea/vomiting	13 (41%)	2 (13%)	0.057
Morning drowsiness/ lethargy	22 (69%)	3 (19%)	0.002
Peripheral edema	12 (38%)	2 (13%)	0.098
Urinary incontinence	3 (9%)	0	0.541
Hypotension	1 (3%)	0	>0.999

[a]Fisher's exact test.

conclusions as to the generalizability of these preliminary results. Consideration could also be given to studying prazosin efficacy for prophylaxis of primary headache disorders, including migraine, a common PTH phenotype.

CONCLUSIONS

This pilot RCT demonstrated a clinically meaningful efficacy signal for prazosin as a novel pharmacotherapeutic agent for PTH prophylaxis. The gradual and flexible dose titration schedule likely contributed to participant tolerance of the substantial doses administered and the high rate of study completion. These results also suggest the involvement of noradrenergic signaling in the pathophysiology of PTH.

AUTHOR CONTRIBUTIONS

Study concept and design: Cindy Mayer, Murray Raskind, Kimberly Hart. *Acquisition of data*: Paul Savage, Tammy Williams, Ameryth Hargrove, Eileen Poupore, Conner Engle, Soleil Groh, Cindy Mayer, Murray Raskind. *Analysis and interpretation of data*: Jane Shofer, Cindy Mayer, Murray Raskind with help from Conner Engle, Soleil Groh, Ameryth Hargrove. *Drafting of the manuscript*: Cindy Mayer, Murray Raskind, Jane Shofer. *Revising it for intellectual content*: Cindy Mayer, Murray Raskind, Ronald Reichers, Robert Ruff. *Final approval of the completed manuscript*: All listed authors read the manuscript. Cindy Mayer, Murray Raskind, and Jane Shofer were responsible for ensuring that all reviewer comments were addressed.

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CONFLICT OF INTEREST STATEMENT

Cindy L. Mayer, Paul J. Savage, Conner K. Engle, Soleil S. Groh, Jane B. Shofer, Ameryth M. Hargrove, Tammy J. Williams, Eileen L. Poupore, Kimberly L. Hart, Ronald G. Riechers II, Robert L. Ruff, Elaine R. Peskind, and **Murray A. Raskin** declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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