Chronic Postconcussive Headache: A Placebo-Controlled Treatment Trial of Prazosin

NCT02266329

Approved November 12, 2021

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

IRBNet# 1587677

MIRB# 00896

Department of Defense (DoD)
Office of the Congressionally Directed Medical Research Programs (CDMRP)

Principal Investigator: Murray Raskind, MD

Version 9, Revised 09/28/2021

Abstract

Background and Rationale: Headaches following 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 (AR) antagonist drug prazosin as a prophylactic treatment for chronic posttraumatic headaches (PTHAs). The impetus for this study comes from a large open-label case series in Iraq and Afghanistan Veterans with mTBI and PTHAs and data from a placebo-controlled trial evaluating use of prazosin for posttraumatic stress disorder (PTSD) in active-duty Service Members (SMs). Findings from these studies showed that in addition to decreasing PTSD-related symptoms and improving sleep quality, prazosin decreased the frequency and severity of headaches, which were common in the study populations.

Study Objectives, Specific Aims, and Hypotheses: The objective of this study is to evaluate the efficacy of prazosin as a prophylactic treatment for persistent PTHAs, which will be accomplished by conducting a randomized placebo-controlled double blind trial of prazosin vs. placebo in active-duty SMs and Veterans.

Specific Aim 1: To determine the effect of prazosin compared to placebo on headache frequency, headache severity and duration, use of abortive/analgesic medications, and headache-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.

Study Design: The study design is based on International Headache Society (IHS) guidelines for prophylactic treatment trials for migraine. The study will enroll 228 active-duty SMs and Veterans. Total trial length will be up to 24 weeks, including a 4-week headache screening period, a 1-week screening sleep monitoring period, a 5-7 week dose titration period, and a 12-week steady-dose study drug period, for which participants will be randomized 2:1 to prazosin or placebo. Headache characterization and quantitative assessment of sleep quality, PTSD symptoms, mood, alcohol/substance use, cognition, health-related quality of life, and headache-related disability assessments will be performed at baseline and at 4-week intervals during the steady-dose period. Participants will keep a daily headache log for the duration of the trial. The primary outcome measure will be change from baseline in headache frequency. Secondary outcome measures will include change in other headache measures, sleep quality, PTSD symptoms, mood, alcohol, cognition, quality of life, and headache-related disability. Data will be analyzed using standard statistical techniques.

Clinical Impact and Military Relevance: Through a carefully designed clinical trial, we hope to demonstrate the efficacy of prazosin as a treatment option for PTHA. If effective as a prophylactic agent, its use would reduce the need for abortive and/or analgesic drugs, many of which have unacceptable cognitive side effects, addictive potential, and a tendency to increase the risk for developing superimposed medication over-use headaches. Because of its beneficial effect on improving symptoms of PTSD and decreasing alcohol abuse, prazosin may provide multi-factorial treatment for commonly co-morbid conditions. Such efficacy will enhance SMs' and Veterans' work and interpersonal function, and improve their overall quality of life.

List of Abbreviations

ACE	angiotensin converting enzyme
ACRM	American Congress of Rehabilitation Medicine
AEs	Adverse Events
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AR	adrenoreceptor
ASC	Allodynia Symptom Checklist
AUDIT-C	Alcohol Use Disorders Identification Test – Consumption
BBB	Blood Brain Barrier
BMI	Body Mass Index
BP	blood pressure
BPH	benign prostatic hypertrophy
CBOC	community-based outpatient clinic
CDE	Common Data Elements
CES	Combat Experiences Scale
CIRO	Clinical Investigation Research Office
CNS	central nervous system
CoC	Certificate of Confidentiality
CRF	case report form
CSD-E	Consensus Sleep Diary E
CSF	cerebrospinal fluid
DAQ	Data Access & Quality Committee
DCI	Department of Clinical Investigation
DoD	Department of Defense
DSMB	data safety monitoring board
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
DVA	Department of Veterans Affairs
DVBIC	Defense and Veterans Brain Injury Center
EHR	Electronic Health Record
EKG	electrocardiogram
ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration
FITBIR	Federal Interagency Traumatic Brain Injury Research
GAO	Government Accountability Office
GUID	Global Unique Identifier
HA	Headache
HAM-D	Hamilton Depression Rating Scale
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIT-6	Headache Impact Test 6
HJF	Henry M. Jackson Foundation for the Advancement of Military Medicine
HR	heart rate
HRPO	Human Research Protection Office
ICC	Interclass Correlation
ICHD-2	International Classification of Headache Disorders, 2nd edition

ICHD-3 beta	International Classification of Headache Disorders, 3rd edition (beta version)
IHS	International Headache Society
IND	Investigational New Drug
IRB	Institutional Review Board
ISI	Insomnia Severity Index
ITT	Intent to Treat
JBLM	Joint Base Lewis-McChord
LC	locus coeruleus
Madigan	Madigan Army Medical Center
MIDAS	Migraine Disability Assessment
MIRECC	Mental Illness Research, Education, and Clinical Center
MoCA	Montreal Cognitive Assessment
MOH	medication over-use headache
MOS	Military Occupational Specialties
MP	Military Police
mTBI	mild traumatic brain injury
NA	noradrenergic
NE	norepinephrine
NINDS	National Institute of Neurological Disorders and Stroke
NSAID	nonsteroidal anti-inflammatory drug
NSI	Neurobehavioral Symptom Inventory
OEF	Operation Enduring Freedom
OHRP	Office of Human Research Protections
OIF	Operation Iraqi Freedom
OIG	Office of the Inspector General
OND	Operation New Dawn
ORO	Office of Research Oversight
PCL-5	PTSD Checklist for DSM-5
PHI	Protected Health Information
PHQ-9	Patient Health Questionnaire-9
PI	Principal Investigator
PRIME-MD	Primary Care Evaluation of Mental Disorders
prn	*pro re nata* - as needed
PSQI	Pittsburgh Sleep Quality Index
PTHA	posttraumatic headache
PTSD	posttraumatic stress disorder
qam	each morning
qhs	each evening at bedtime
R&DC	Research and Development Committee
RCT	randomized controlled trial
REM	rapid eye movement
Ret	retired
ROI	Release of Information
SAE	Serious Adverse Event
SCID-5	Structured Clinical Interview for DSM-5
SD	standard deviation

SE	standard error of the mean
SF-36	Short Form 36
SIBCR	Seattle Institute for Biomedical and Clinical Research
SM	Service Member
SSN	social security number
TBI	traumatic brain injury
UPSIS-12M	Utah Photophobia Symptom Impact Scale-12-Modified
US	United States of America
USAMRMC	U.S. Army Medical Research and Materiel Command
VA Puget Sound	VA Puget Sound Health Care System
VA	Veterans Affairs
VISN-20	Veterans Integrated Service Network 20
VR-12	Veterans RAND 12
VS	vital signs
WA	Washington State

Contents

Protocol Title: Chronic Postconcussive Headache: A Placebo-Controlled Treatment Trial of Prazosin

Protocol Title: Chronic Postconcussive Headache: A Placebo-Controlled Treatment Trial of Prazosin

1.0 Study Personnel

Principal Investigator:

- Cynthia Mayer, DO; Staff Physician, VA Puget Sound Health Care System. cynthia.mayer@va.gov, 206-277-6240.

VA Puget Sound Co-Investigators:

- Murray Raskind, MD (Coordinating Center PI); Co-Director, VA NW Network Mental Illness Research, Education, and Clinical Center (MIRECC) and Professor, Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine. Murray.Raskind@va.gov, 206-277-3797.
- Elaine Peskind, MD; Co-Director, VA NW Network MIRECC and Professor, Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine. elaine.peskind@va.gov, 206-277-3965.

Madigan Collaborators:

Paul J. Savage, MD; Physician, TBI Program, Madigan Army Medical Center. paul.j.savage.civ@mail.mil, 253-968-9028.

2.0 Introduction

Overview: Headaches (HAs) following combat-related mild traumatic brain injury (mTBI) are common, and can persist and worsen to become a debilitating chronic pain syndrome. These posttraumatic HAs (PTHAs), which often have migraine features, can be refractory to standard prophylactic treatment. Here, we propose a randomized controlled trial (RCT) to evaluate the medication prazosin as a prophylactic treatment for postconcussive PTHAs in active-duty Service Members (SMs) and Veterans at Madigan Army Medical Center/Joint Base Lewis-McChord (Madigan/JBLM) and Veterans at VA Puget Sound Health Care System (VA Puget Sound). Prazosin, a brain-active clinically available alpha-1 adrenoreceptor (AR) antagonist, has shown promise in preliminary studies for efficacy with good long-term tolerability and no addictive potential for prophylaxis of combat mTBI-related PTHAs in this population. An RCT to confirm these encouraging results is necessary to evaluate definitive prazosin efficacy for prophylaxis of frequent persistent PTHAs.

Persistent PTHA Following Concussion in Iraq/Afghanistan SMs and Veterans: An estimated 19% of Iraq/Afghanistan Veterans have sustained deployment-related mTBI,[1] the majority of these cases the result of explosive blast concussive injury.[2-4] Irrespective of the cause of injury, the prevalence of HAs associated with mTBI is high, ranging from 22% to 97%.[3-6] While these PTHAs often resolve within a year, they may persist and worsen in frequency and severity, becoming treatment-refractory and leading to significant disability.

The International Classification of Headache Disorders, 3rd edition (beta version) (ICHD-3 beta)[7] defines PTHA as a secondary HA syndrome precipitated by an inciting event of head, neck, or facial trauma, with onset occurring within 7 days of the trauma or within 7 days of regaining the capacity to perceive and report HA following the trauma. These time of onset criteria have been criticized as being arbitrary,[8,9] and in practice onset of HAs within weeks or months of trauma with no other evident precipitating factors is often observed.[8,10,11] HAs that continue for more than 3 months are defined by ICHD-3 beta criteria as being persistent[7] (previously termed “chronic” in ICHD-2[12]).

Clinically, HAs precipitated by trauma do not have unique defining characteristics and are treated empirically based on their resemblance to primary HA disorders.[13] In the civilian TBI population, for whom injury is by far most often due to mechanisms other than blast, PTHAs tend to be tension-type, migraine, or mixed,[13] whereas in the military combat population, particularly in the setting of blast TBI and physical injury, HAs with migraine features predominate.[11,14-16] These blast-related PTHAs seem to be more refractory to standard prophylactic pharmacotherapies than those following non-blast TBI, as demonstrated in a retrospective cohort study evaluating medical treatments of PTHAs in SMs conducted by study Consultant, COL Jay Erickson, MD, at the Madigan Neurology Clinic.[17] HA frequency was determined at initial clinic visit and again at 3 months after starting HA prophylactic medications. Only 29% of blast-TBI PTHA patients compared to 57% of non-blast TBI PTHA patients had a 50% or greater decline in HA frequency (P=0.023) with treatment. This reduced rate of response is concerning for an increased risk for development of long-term HA persistence (chronification). This concern is supported by findings from a recent cross-sectional study.[18] Among 978 soldiers with deployment-related concussion, 20% met criteria for chronic daily HA (at least 15 HAs per month), which is 4- to 5-fold higher than that seen in the general population.[19] In this group, 66% had HA with migraine features. Chronic daily HA, particularly with migraine features, is considered to be one of the most disabling and difficult to treat HA syndromes.[20,21]

HA disorders are one of the top reasons for military disability evaluation.[22] Theeler et al[23] found that migraine HAs tended to persist after return from deployment, and were associated with substantial disability. Seventy-seven percent of all migraine attacks interfered with duty performance on a mean of 2.4 days per month. Of particular concern is a recently reported association between migraine and suicide in Veterans.[24] Based on a large-scale retrospective analysis of noncancer pain conditions and risk of suicide in Veterans, the investigators found a suicide mortality hazard ratio of 1.34 (1.02-1.77) for migraine, after controlling for comorbid psychiatric conditions.[24]

Clearly, interventions are needed that will reduce the suffering and disability caused by frequent persistent PTHAs in the active-duty SM and Veteran populations. Successful management of persistent HAs can be a trial-and-error time-consuming process entailing substantial effort to optimize effective treatment for an individual patient. Even with careful management, HAs following mTBI often are treatment-refractory and difficult to control. Inadequate or inappropriate medication regimens used in attempts to preemptively abort impending HAs or treat HA pain can not only increase vulnerability to HA chronification, but can also lead to superimposed rebound or “medication over-use” HAs (MOHs) in some patients, particularly those with frequent HAs at baseline.[20] MOHs occur in 19-42% of patients with PTHAs.[9,25] The injudicious use of opioids is particularly problematic, with the added risk of opioid dependence. The role of effective prophylactic (preventive) agents is thus particularly important in reducing the need for abortive or analgesic treatment.

Preliminary data (see below) support prazosin as a rational candidate medication for PTHA prophylaxis. Prazosin has a well-characterized pharmacologic profile with minimal side effects, no major interactions with other medications, and no addictive potential, based on over 30 years of clinical experience since its Food and Drug Administration (FDA) approval. As previously noted, common co-morbidities in the combat head trauma population, notably PTSD, depression, and sleep disruption, may be coexistent conditions or may be contributory to HA genesis and/or exacerbation.[26] A common physiologic substrate for these conditions may be over-activation of the central noradrenergic system, as suggested by their responsiveness to the centrally acting alpha-1 AR antagonist, prazosin.

Prazosin blocks alpha-1 ARs; it is the most lipid soluble of the alpha-1 AR antagonists, and it is the only one empirically demonstrated to cross the blood-brain barrier (BBB) to block norepinephrine (NE)

effects in the brain when administered peripherally.[27] Prazosin was originally marketed as an antihypertensive agent and was subsequently found to be beneficial for treating benign prostatic hypertrophy (BPH). Project Principal Investigator (PI) Murray Raskind, MD, pioneered the use of prazosin for combat-trauma PTSD. He hypothesized that the noradrenergic (NA) hyperarousal adaptive in combat persisted and became maladaptive following return to civilian life, and further, that blocking postsynaptic alpha-1 ARs with prazosin would decrease NA hyperactivity. Based on this concept, prazosin was proposed as a potential treatment for PTSD[28] and has since been shown in double-blind RCTs to relieve PTSD symptoms, including sleep disturbance and nightmares, and to improve global clinical status in Vietnam Veterans,[29,30] in active-duty SMs and Veterans of Iraq and Afghanistan, and in civilians.[31] In addition, prazosin has been found to reduce daytime hyperarousal symptoms of PTSD, including hypervigilance and irritability/anger.[32]

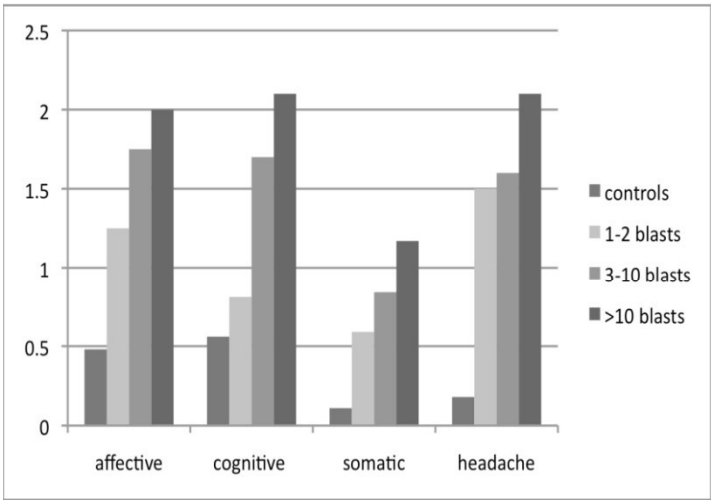
Prazosin Effects on Sleep and Actigraphic Monitoring of Sleep/Wake Activity: We demonstrated that an important effect of prazosin treatment of PTSD is normalization of rapid eye movement (REM) sleep and an increase in total sleep time.[31] Because improving sleep quantity and quality can be an important component of both migraine[33] and PTHA prophylaxis,[26] prazosin may be particularly helpful in treating persistent PTHA with its high prevalence of comorbid PTSD sleep disruption. In this study, we will monitor sleep/wake activity using wrist actigraphy (described in detail below). Studies have shown actigraphy correlates well with polysomnography in most sleep measures, including in a study of Iraq/Afghanistan Veterans with PTSD and mTBI.[34,35]

Current Status of the Field: Currently available agents used for HA prophylaxis may be poorly tolerated and/or contraindicated for certain conditions; none of these agents are effective in all patients. For example, beta blockers are contraindicated in patients with bronchospasm, congestive heart failure, cardiac arrhythmias, or a history of depression.[36] Tricyclic antidepressants may be sedating and are contraindicated in patients with some cardiac arrhythmias. Valproic acid causes weight gain, hair loss, and tremor, and its use may lead to hepatotoxicity, or rarely, pancreatitis.[37] Topiramate has shown some benefit in reducing HA frequency in soldiers with PTHA, but it may cause sedation, decreased energy, and worsening of depression.[38] More recently, onabotulinumtoxinA (Botox®) has shown efficacy for migraine prophylaxis in some patients,[39] but this medication, like the others, has not been evaluated for PTHAs, and its effectiveness for chronic migraine prophylaxis, as for topiramate, is modest.[39,40] A recent placebo-controlled trial assessing addition of propranolol to topiramate in treating chronic migraine HAs unresponsive to topiramate alone showed no evidence of benefit of combined therapy.[41] Thus, there is an imperative for research to identify more effective treatment options.

Although practice guidelines for managing PTHAs following military-related TBI have been established by the Department of Defense (DoD) and Department of Veterans Affairs (DVA), recommended treatments have not been validated by RCTs in the active military SMs and Veteran population.[42] This study is intended to address this need, with the express goal of providing a validated treatment option to a common refractory condition, and to do so in a timely manner. Anecdotal and case reports of the use of prazosin or other alpha-1 blockers for prophylaxis of HA have been identified in the literature;[43-45] however, no Level I RCTs have been performed.

Preliminary Studies

Blast mTBI and Postconcussive HAs: Data on the relationship of number of blast mTBIs and chronic postconcussive symptoms are available from Co-Investigator, Dr. Peskind's, study of multimodal neuroimaging and CSF biomarkers of neurodegeneration in 34 Iraq/Afghanistan Veterans with blast concussion mTBI and 19 Iraq/Afghanistan Veterans with no lifetime history of TBI. The mTBI Veterans experienced an average of 14 blast exposures with acute symptoms that met American Congress of



Rehabilitation Medicine (ACRM) criteria for mTBI[46] and were an average of 4 years since their last blast exposure. Postconcussive symptoms were self-rated using the Neurobehavioral Symptom Inventory (NSI).[47] The figure to the left shows the relationship between the number of blast exposures and mean **NSI** symptom severity for the affective, cognitive, and somatic symptom clusters as well as for HAs as a single symptom. The symptom clusters show a dose-dependent relationship to number of blast exposures. HA shows more of a threshold effect, with even 1-2 blast exposures having a similar NSI HA rating compared to 3-10 blast exposures, and then increasing with > 10 blast exposures.

Evidence for Benefit of Prazosin for PTHAs: Retired DVA Director of Neurology and study Consultant Robert Ruff, MD, performed a large open-label trial of prazosin in Iraq and Afghanistan combat Veterans who had blast-related mTBI and persistent PTHAs; most of these Veterans also had PTSD.[26] The study examined whether prazosin plus sleep hygiene would improve sleep, PTHAs, and cognitive performance. Seventy-Four Veterans (71 who met diagnostic criteria for PTSD) with persistent blast-related PTHA were treated with open-label prazosin and sleep hygiene counseling for 9 weeks: a 5-week dose titration period and 4 weeks at constant dose. HA pain severity and frequency decreased, daytime sleepiness decreased, and cognitive function improved (Table 1). By week 9, more than half of the study subjects had a >50% reduction in pain, and more than three quarters had a >50% decrease in both HA frequency and Epworth Sleepiness Scale scores. These changes all were highly statistically significant (all p values <0.001).[26]

Table 1. Effect of 9 weeks of prazosin and sleep hygiene counseling on HAs, daytime sleepiness, and cognitive function.[26]

Performance of Veterans (n=74)	**HA Frequency (No./Month)**	**HA Pain Intensity (0-10)**	**ESS Score (0-24)**	**MoCA (0-30)**
Baseline (mean ± SE)	12.40 ± 0.94	7.28 ± 0.27	16.10 ± 0.28	24.50 ± 0.49
After intervention (mean ± SE)	4.77 ± 0.34	4.08 ± 0.19	7.28 ± 0.34	28.60 ± 0.59
p-Value by ANOVA	<0.001	<0.001	<0.001	<0.001
ESS = Epworth Sleepiness Scale, MoCA = Montreal Cognitive Assessment, SE = standard error of the mean, ANOVA = Analysis of Variance				

Further evidence supporting prazosin for treatment of PTHAs comes from the observation of beneficial effects on HAs among active-duty soldiers in the RCT of prazosin for combat-trauma PTSD recently completed by our group at Madigan/JBLM (M. Raskind, PI).[48] HA was queried among potential anticipated side effects of prazosin, with presence/absence noted at baseline and at conclusion of 15 weeks of prazosin or placebo. Of the 22 soldiers with HA at baseline randomized to prazosin, 11 (50%) reported improvement or complete resolution of their HAs. In the placebo group, 4 of 19 (21%) had improvement or resolution of their HAs. The small group of women in the study appeared to benefit

particularly well from prazosin. Of the 4 female soldiers in the prazosin group, all had HA at baseline. With prazosin treatment, 3 of the 4 had complete HA resolution.

3.0 Objectives

Objectives: The objective of this study is to evaluate the efficacy of the alpha-1 AR antagonist drug prazosin as a prophylactic medical treatment for frequent persistent PTHA. This objective will be accomplished by conducting a double blind RCT of prazosin in active-duty SMs and Veterans with persistent PTHAs.

Specific Aims and Hypotheses:

- 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.
  - *Hypothesis 1*: Prazosin will be more effective than placebo in ameliorating the effects of persistent PTHA, specifically: a) prazosin will reduce HA frequency, as compared to placebo; and b) prazosin will reduce HA severity and duration, use of abortive/analgesic medications, and HA-related disability, as compared to placebo (secondary outcome measures).
- 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 (secondary outcome measures).
  - *Hypothesis 2a:* Prazosin will improve sleep quality, PTSD symptom severity, mood, moderation of alcohol consumption, cognitive function, health-related quality of life, and global clinical status
  - *Hypothesis 2b*: Improvement in HA parameters will be associated with improvement in sleep quality, PTSD symptom severity, mood, moderation of alcohol consumption, cognitive function, health-related quality of life, and global clinical status.

4.0 Resources and Personnel

Overview: The study will take place at two sites: VA Puget Sound (the study Coordinating Center and one of the Clinical Sites) and at Madigan Army Medical Center (Clinical Site). The Coordinating Center and each Clinical Site will all have separate Institutional Review Board (IRB) and subcommittee approvals, as appropriate.

Description of Coordinating Center and Personnel: The study Coordinating Center will be the MIRECC at VA Puget Sound. Murray Raskind, MD is the PI of the overall study and of the Coordinating Center. All data management and analysis procedures will take place at VA Puget Sound. Coordinating Center Personnel will have access to protected health information (PHI), but will not be involved with study procedures, excepting personnel that have roles at both the Coordinating Center and Clinical Sites. The MIRECC regulatory team at the Coordinating Center will also maintain records of all IRB and subcommittee submissions and approvals, and will coordinate communication between sites, as described in section 8.0 below.

Data Management: Database design, any required computer programming, and maintenance of computer hardware and software will be performed by the Data Management team. Initial and second data entry will be performed at VA Puget Sound by the study Research Assistant under the supervision of the MIRECC Database Manager. The Database Manager will generate reports of data discrepancies. The study Research Assistant under the supervision of the Study Coordinator and Data Manager will be responsible for rectifying data entry errors.

Database maintenance includes nightly backup of servers and storage of backups at a safe off-site location. Only personnel having the correct user name, password, and signing on from a computer with the appropriate IP address will have access.

Disposition of Data: Original Source Documents and case report forms (CRFs) will be kept at each clinical site. Copies of CRFs will be kept at VA Puget Sound. Copies of CRFs from Madigan will either be shipped to VA Puget Sound via trackable method (i.e. Fed-Ex, UPS) or will be transported to VA Puget Sound by one of the study staff in HIPAA-compliant locked containers. CRFs will be stored in locked offices. Data managers and analysts will not have access to the link between study code numbers and subject identities.

There is a subcontract between Seattle Institute of Biomedical and Clinical Research (SIBCR) and the Henry M. Jackson Foundation for the Advancement of Military Medicine (HJF) at Madigan. This subcontract will outline the work to be done at each location, disposition of data, and storage of documents.

Description of Study Clinical Sites and Personnel: The clinical study will take place at two facilities, VA Puget Sound and Madigan.

Study Visits will be performed at VA Puget Sound under the supervision of Cynthia Mayer, DO and Elaine Peskind, MD; and at Madigan under the supervision of Paul Savage, MD.

Study personnel as listed on the IRB applications at each site will have access to protected health information, will be involved in recruiting subjects, will obtain consent, will conduct study interviews, and will administer study instruments. Generally, the staff at each site includes clinicians, RN(s), Clinical Research Coordinator(s), Study Coordinator(s), and Research Assistant(s).

Clinicians Prescriber –will perform safety assessments and examinations, make decisions regarding the dose titration schedule for individual participants, and make any necessary unscheduled dose changes. The Clinician Prescriber will be a physician, physician assistant, or nurse practitioner with experience conducting clinical research in active-duty SMs and Veterans with mTBI and/or PTSD.

Raters –will administer the SCID-5 at the Screen visit. The Raters have extensive experience in performing interview-based assessments in Veterans and SMs with mTBI and/or comorbid PTSD. A female Rater will be available if requested by female participants.

RN, Clinical Research Coordinator – will perform duties as assigned by the Site Investigator.

Study Coordinator(s) and Research Assistant(s) - will be responsible for scheduling visits, conducting the portions of study visits that do not require the Clinician Prescriber, maintaining CRFs, preparing reports for appropriate IRBs and subcommittees, communicating between sites as described below in section 8.0, assisting the data manager, and performing duties as assigned by the Site Investigator.

5.0 Study Procedures

5.1 Study Design

Overview: The study is a prospective double-blind placebo-controlled RCT to evaluate the efficacy of prazosin for prophylactic treatment of frequent persistent HAs following blast and/or impact mTBI in a convenience sample of male and female SMs and Veterans aged 18 and older who have a history of mTBI with chronic PTHAs and who meet inclusion/exclusion criteria as described further below. We anticipate enrollment of 228 participants to achieve 160 randomized -- an average of approximately 4-5 participants randomized per month divided approximately equally across the 2 sites.

All study procedures are investigational; none are standard of care. The total trial length is up to 24 weeks, including a 5-week Preliminary Screening Period during which the participant will keep a HA log, eligibility for randomization will be determined, and baseline data (including 1 week of sleep/activity monitoring using actigraphy and keeping a sleep log) will be collected; a 5-7week Titration Period, during which optimal dose will be determined; and a 12-week Steady-Dose Period, as detailed in section 5.5 below and in the schedule of study visits table.

Participants who remain eligible after the Preliminary Screening period will be randomly assigned 2:1 to prazosin or placebo and will then begin the study drug dose Titration Period. During the Titration Period, the dose of study drug will be gradually increased to a maximum dose of 5 mg each morning and 20 mg each evening or to the maximum tolerated dose. Once the maximum (or maximum tolerated) dose has been attained, the participant will continue on this dose for 12 weeks. Evaluations to be performed are described in section 5.5 below and on the Schedule of Study Visits table.

Investigational Drug: This study will be conducted using the drug, prazosin, which has been approved by the FDA for treatment of hypertension but is being used off-label for investigational purposes in this study. Prazosin and indistinguishable placebo will be obtained from commercial sources. Investigational pharmacists at each study site will procure the study drug. Study drug may be stored at room temperature. Unused drug will be disposed of by the investigational pharmacists once notification has been made by the PI that the study has been completed.

Pursuant to 21 CFR 312.2(b)(1), the clinical investigation of a marketed drug or biologic does not require submission of an Investigational New Drug (IND) application if all six of the following conditions are met:

(i) it is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;

(ii) it is not intended to support a significant change in the advertising for the product;

(iii) it does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

(iv) it is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];

(v) it is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7][1]; and

(vi) it does not intend to invoke 21 CFR 50.24 (Exception From Informed Consent Requirements for Emergency Research).

We do not intend to use the results of this research in support of a new indication for prazosin, nor do we intend to support significant change in advertising for prazosin. The route of administration, dosage level, and subject population are all the same as in general clinical practice, and do not increase the risks

[1] *Promotion of an investigational new drug.* A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.

usually associated with prazosin. Thus, we have satisfied requirements i., ii., and iii. Requirement iv. is satisfied through the approval of this study by the appropriate Institutional Review Boards. Requirement v. is satisfied in that we are not promising any benefit from the use of prazosin in this study. Requirement vi. is satisfied as we will not be conducting emergency research.

Foreseeable Risks: Venipuncture may cause transient pain and bruising at the venipuncture site, along with a small risk of infection.

Administered and subject-rated assessment instruments may cause participants to focus their attention on traumatic experiences and as a result may produce transient subjective distress. However, these combat experiences are routinely assessed and discussed as part of standard clinical care.

There is a risk of loss of confidentiality. We will take all due care so that responses to questionnaires are not commingled with patient medical records. However, because we are administering medications that may have interactions with other medications, it will be documented in the subject's medical record that they may be taking prazosin. We have obtained a Federal Certificate of Confidentiality (CoC) to protect the participant's name or other identifying information from being disclosed in any civil, criminal, administrative, legislative, or other proceedings, whether at the federal, state, or local level. Because of Military regulations, there are some activities that must be reported regarding Active Duty SMs. In those cases, we will be following the OTSG-MEDCOM Policy: Release of PHI to Unit Command Officials. This information is included in the Madigan consent form.

There are no known absolute contraindications to prazosin. The most common side effects of prazosin include dizziness, drowsiness, lightheadedness, headache, nausea, lack of energy, weakness, and palpitations. Other side effects, which occur in less than 4% of patients when compared to placebo, include vomiting, diarrhea, constipation, orthostatic hypotension, dyspnea, syncope, vertigo, depression, nervousness, rash, increased urinary frequency, blurred vision, reddened sclera, dry mouth, nasal congestion, and epistaxis.

Prazosin may cause syncope with sudden loss of consciousness. In most cases, this is believed to be due to excessive postural hypotension although occasionally the syncopal episode has been preceded by severe tachycardia with heart rates of 120-180 beats per minute. Syncopal episodes have usually occurred within 30-90 minutes of the initial dose. The incidence of the syncopal episodes is 1% if the initial dose is 2 mg or more. Clinical trials suggest that syncopal episodes can be minimized by starting with a dose of 1 mg and slowly titrating up to the final dose, as we are doing in this study.

HA is listed in the Physician Desk Reference[49] as a potential adverse reaction to prazosin, reported in as many of 8% of subjects in early clinical trials. However, in our experience, the incidence of this is lower. In the previously described placebo-controlled pilot study evaluating use of prazosin for treatment of PTSD in Iraq and Afghanistan active-duty SMs in which HA was monitored as a potential side effect of prazosin, 22 of 26 participants had HA at baseline. Among those randomized to prazosin, 1 of the 22 with baseline HA had worsening of their HAs, and 1 of 4 participants with no prior HA history developed HAs. In contrast, 11 of the 22 with baseline HAs had improvement or complete resolution of their HAs while on prazosin. Among those randomized to placebo, 3 of 9 participants with no prior HA history developed HA.

Regarding mood alterations, although depression is listed in the Physician Desk Reference[49] as occurring in 1-4% of patients, we have found little evidence for prazosin precipitating or worsening symptoms of depression. In 33 participants administered the Hamilton Depression Rating Scale (Ham-D) in our recently completed placebo-controlled study of prazosin for PTSD,[48] Ham-D scores actually improved

more in the prazosin vs. placebo group (5.3 vs. 0.7, t=1.9 [2-tailed], p=0.07). However, for safety reasons, participants will be carefully monitored for signs and symptoms of depression and other mood disorders.

Prazosin should not be taken concurrently with trazodone. Potential participants who are taking trazodone for sleep and who are willing to discontinue will be washed out before starting this study. Care should be taken when alpha-1 blockers are combined with erectile dysfunction medications. We will be following VA pharmacy prescribing guidelines regarding these medications. They will not be allowed during the Titration Period. Once the Stable Dose Period has been reached, erectile dysfunction medications will be allowed at 1/2 the usual clinical dose.

In our current study of prazosin in active duty SMs at Madigan, we have noticed an increased use of dietary supplements containing nitrates. In one case, a participant experienced three episodes of priapism while taking one of these supplements with prazosin. Therefore, use of these supplements and supplements containing stimulants (such as ephedra) will be exclusionary for the duration of the study. Participants who take these supplements will be asked to discontinue them before the Preliminary Screening Period begins.

In post-marketing experience, intraoperative floppy iris syndrome (IFIS) has been observed during cataract surgery in some patients who are taking or have taken alpha-1 blockers. The patient's ophthalmologist should be prepared for possible modifications to the surgical technique to reduce the surgical risk of IFIS. If a patient needs to have cataract surgery, he/she should tell his/her eye surgeon that he/she may have taken prazosin in a research study.

Risk Management and Emergency Response: Evaluation for adverse effects and review of concurrent medications will be completed at all study visits. Participants are asked about suicidal ideation at each in-person visit. If endorsed, participants will be assessed as to their level of risk and the level of care required to keep them or others from harm. If a participant requires inpatient treatment in order to prevent harm or is found to have symptoms of disorganized thought processes secondary to psychosis, mental health personnel will be notified immediately to assist with appropriate triage and referral. Vital signs, including orthostatic blood pressure (BP) and heart rate (HR) will be performed at all study visits. Systolic and diastolic BP and HR will be obtained following 10 minutes of rest, and repeated following 2 minutes of standing. Occurrences of lightheadedness, dizziness on standing, palpitations, drowsiness, nausea, nasal congestion, peripheral edema, worsening of HA, and other adverse effects will be rated by the clinician. For vital signs parameters, unacceptable side effects will include resting hypotension (systolic BP<100 mm Hg) and clinically meaningful hypotension (20 mm Hg or more drop in systolic BP accompanied by dizziness, lightheadedness, or syncope).

For participants taking other antihypertensive medications, their primary care provider will be informed of clinically significant BP reductions at any time during the study, to allow adjustment of the participant's antihypertensive regimen. As a further precaution, male subjects will be advised to sit on the toilet for urination the first two nights to avoid orthostatic hypotension secondary to micturition syncope.

Safety monitoring is based on long-term clinical experience with prazosin. Prazosin was first introduced in 1976 under the trade name Minipress (Pfizer) for clinical management of hypertension, and later became widely prescribed for urinary outflow obstruction secondary to benign prostatic hypertrophy. It has been safely prescribed to large numbers of middle-aged and older people over the past 40 years. The following information regarding the side effect profile and safety record of prazosin is a synopsis from the Minipress package insert: "The most important adverse effect to be considered when prescribing

prazosin is a “first dose effect” manifested by syncope with sudden loss of consciousness believed to be due to postural hypotension in approximately 1% of patients given an initial dose of 2 mg or greater. This rare adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration. However, patients should always be started on 1 mg of prazosin. In clinical trials of prazosin, most frequent adverse reactions were dizziness (10%), HAs (8%), drowsiness (8%), lack of energy (7%), weakness (7%), palpitations (5%), and nausea (5%). Less frequent adverse reactions (1-4%) were: vomiting, diarrhea, constipation, edema, orthostatic hypotension, dyspnea, syncope, vertigo, depression, nervousness, rash, urinary frequency, and nasal congestion. Fewer than 1% of patients have reported the following (causal reactions sometimes not established): abdominal discomfort or pain, tachycardia, paresthesias, hallucinations, pruritus, incontinence, impotence, and priapism…”

Through extensive experience of our group, including open-label clinical studies, placebo-controlled trials, and clinical application, prazosin has demonstrated a favorable safety profile. Several thousand active-duty SMs and Veterans with PTSD have now been treated with prazosin at VA Puget Sound and Madigan, as well as at other centers, including the Spokane, Portland, and Cleveland VA Medical Centers. It has been estimated that over 70,000 Veterans nationwide are being treated with prazosin for PTSD. Approximately 5% of those treated with prazosin have discontinued it secondary to subjectively unpleasant side effects, most commonly transient orthostatic dizziness, nasal congestion, or exercise-induced tachycardia.

Regarding other participant safety issues, procedures relevant to the war-zone trauma and TBI population include exclusion of participants with severe psychiatric instability or severe situational life crises, including evidence of being actively suicidal or homicidal, or any behavior that poses an immediate danger to the participant or others. A female Rater will be available to perform interview-based assessments, if requested by female participants. Trained personnel will be on call at all times to receive calls from participants regarding any adverse events; participants will be provided with 24-hour emergency contact numbers.

All treatment for adverse events related to the study will be provided free of charge. The DoD authorizes treatment for adverse events related to study participation in DoD Health Readiness Platform (formerly known as a Medical Treatment Facility) for DoD supported research and the DVA authorizes treatment for any study approved by a VA Research and Development Committee (R&DC). Subjects who seek treatment for study-related adverse events will be reimbursed for treatment costs. Both study sites have adequate personnel and equipment to respond to expected and unexpected adverse events. Any adverse event will be managed by the study team as clinically appropriate. If necessary, a participant will be referred for treatment of an adverse event.

Participants of childbearing potential will have a urine pregnancy test at screen. Urine pregnancy tests must be negative within one week of taking the first dose of study drug. If more than one week has elapsed since the screening visit, a urine pregnancy test will be repeated. If it is not possible to collect a urine sample during a study visit, a urine pregnancy test may be ordered in the EHR system or mailed to the participant to complete at home. If mailed to the participant, the results of the test will be verified via telehealth. Participants of childbearing potential with either positive pregnancy test at screen or refusal to abstain from sexual relations that could result in pregnancy or refusal to use an effective method of birth control acceptable to both participant and the clinician prescriber while participating in this study will be excluded. Contraception is not required after completion of study. Contraception is not required for participants who are not of childbearing potential.

A research monitor at Madigan will be appointed by the Madigan IRB per DoD requirements. The Research Monitor may not be a member of the study team but may be a member of the Data Safety Monitoring Board (DSMB). Duties of the Research Monitor include (but are not limited to): a) Monitoring the conduct of the protocol per the approval plan and ensuring protection of human subjects. This may involve periodic review of medical records of enrolled subjects and the research files being maintained by the PI. b) Reviewing and keeping abreast of adverse events and protocol deviations that occur during the research and c) If there is concern about the welfare of enrolled subjects, the Research Monitor has the authority to stop a research study in progress, remove individual subjects from a study, and take whatever steps necessary to protect the safety and well-being of research subjects until the Madigan IRB can assess the Research Monitor's report. Notification of such actions must be forwarded to the Madigan IRB via Madigan Department of Clinical Investigation (DCI) within one (1) working day of receipt of knowledge of actions prompting human subject welfare concerns. Any report of the Research Monitor will be forwarded to the Madigan and VA Puget Sound IRBs.

In addition to the Research Monitor, a DSMB will be established for this study, and will meet periodically following study completion by 40, 80, 120, and 160 participants. Data will be prepared for review by the DSMB by the study Data Manager. At each DSMB meeting, the safety profile of the study will be reviewed. Periodic reports following each meeting will be provided by the DSMB Chair to the PI and the IRBs. The DSMB will 1) review un-blinded data, as needed during the trial; 2) identify problems relating to safety during the study; 3) identify needs for additional data relevant to safety issues, and request these data from the study investigators; 4) propose appropriate analyses and periodically review developing data on safety and endpoints; and 5) consider the rationale for continuation of the study, with respect to progress of randomization, retention, protocol adherence, data management, safety issues, treatment efficacy, and outcome data, and make recommendations for or against the trial's continuation.

Specimen Banking: Participants at VA Puget Sound only will be asked to provide a blood sample (approximately 65 ml each) for measurement of potential headache-related biomarkers at the baseline and end of study visits. These participants may also be asked to sign a separate consent form to allow us to bank any leftover sample for future research. This consent form is approved under a separate IRB application. Information about potential specimen banking will be included in the consent form for this study.

Potential Benefits: Subjects who are assigned to the prazosin arm of the study may find it helpful for treatment of their symptoms. Subjects on the placebo arm of the study will not directly benefit from participation.

This project addresses treatment of a prevalent disabling chronic pain syndrome, specifically headache, occurring in association with or due to mTBI. If results from this study are positive, it may promote a viable treatment option for this difficult-to-treat condition.

5.2 Recruitment Methods

Description of the Recruitment Process: Recruitment will be based on convenience sampling using available participants from Madigan/JBLM and VA Puget Sound. We anticipate enrollment of 228 participants to achieve 160 randomized -- an average of approximately 4-5 participants randomized per month divided approximately equally across the 2 sites.

At VA Puget Sound, participants will be recruited via referrals from VA outpatient clinics, including Neurology, Primary Care, Mental Health, Neuropsychology, Rehabilitation Medicine, Deployment Health, Polytrauma, and others; periodic, informational e-mail to providers and clinics summarizing the

study, eligibility criteria, study PI, study staff contact information, and instructions for proper referral of potentially eligible participants; VA community-based outpatient clinics (CBOCs); local area Veterans centers; National Guard and Reserve units; hospital health fair and hallway information tables; public outreach presentations; posted IRB-approved advertising in highly trafficked areas and clinic waiting rooms; advertisements in newsletters, local newspapers, radio, and the Internet (including social media); presentations to appropriate clinical services (such as grand rounds presentations or service staff meetings); e-mail and presentations to local non-VA providers and community groups (e.g., TBI support groups); and word-of-mouth.

Similar recruitment strategies will be employed at Madigan/JBLM on and off-site facilities, with the addition of the TBI Program, the Warrior Transition Battalion, educational outreach to the brigades, JBLM Family & Morale, Welfare & Recreation Facilities, JBLM Education Center and a large banner at the gates into JBLM.

Interested potential participants will contact the study team for more information. The study will be described privately either over the telephone, via VA or DoD approved telehealth applications, or in person; eligibility requirements will be explained, preliminary eligibility will be determined, and any questions will be addressed. Those meeting initial eligibility criteria will be scheduled - SMs and Tricare-eligible Veterans who receive care at Madigan will be seen at Madigan and Veterans who are eligible for care through the VA will be seen at VA Puget Sound for an initial screening visit. Written study information and consent forms will be sent to potential participants for their review prior to that visit whenever scheduling time allows.

Compensation:
Veteran participants (at VA Puget Sound and Madigan sites) will be compensated $100 for each of 2 weeks of actigraphy monitoring and $50 per in-person study visit to defray transportation costs and inconvenience, up to a total of $950. In addition, participants may receive a blood pressure cuff to use for remote visits that require an orthostatic vital signs assessment, which participants will keep at the conclusion of their participation. Veterans will be compensated for extra study visits that may be required per clinician judgement (i.e., extra safety visits or extra titration visits). Payments will be pro-rated, based on the number of completed study visits and weeks of actigraphy. In addition, Veteran participants will be compensated an additional $25 per visit if they must travel between 50-100 miles round trip and $50 per visit if they must travel over 100 miles round trip to attend study visits, to defray travel costs.

For visits done remotely (by telephone or telehealth), Veterans will be compensated according to the guidelines below, based on the level of burden placed on the participant per visit:

- Participants will not be paid for the telephone safety checks, such as P1.5, P2.5, and SD3.5 visits.
- For lower-burden visits, such as the P2, P3, T2-T8, and SD1 visits, participants will receive $20 per remote visit
- For higher-burden visits, such as the P1, T1, and SD2-SD4 visits, participants will receive $50 per remote visit.

This rate of compensation complies with the VA Puget Sound IRB guidelines for prevention of research study participant financial coercion.

Active-duty and Federal Personnel participants at Madigan: Per Section 30 of Title 24, U.S.C.:

- Active-duty SMs and Federal personnel cannot be reimbursed for any of the study procedures, except for $50 compensation if a blood draw is performed. In this study, Madigan participants may have one blood draw if laboratory evaluations are clinically indicated.
- SMs and Federal personnel while off duty may be compensated for research participation other than blood draws in the same way as human subjects who are not Federal personnel. If a Madigan participant is off duty while completing study procedures, they will be compensated as detailed for VA Puget Sound participants above.

All payments will occur through one of the foundations overseeing the grant. No payments will be made directly by a government source.

5.3 Informed Consent Procedures

We will be performing a Medical Records Review before obtaining written study consent as follows: potential participants will contact the study team as described above, or may be referred to the study by their health care provider (the provider would either obtain permission from his/her patient to release the potential subject's name and contact information to the study team, or the provider will give the study team's contact information to the potential participant). After the potential participant has spoken to a member of the study team and given verbal permission to have medical records reviewed, a trained study team member will review the records to screen for exclusionary medical conditions and medications. We will first obtain a waiver of the requirement to obtain Health Insurance Portability and Accountability Act of 1996 (HIPAA) authorization and consent in order to pre-screen medical records from the VA Electronic Health Record (EHR) system or the Madigan EHR system. If we require non-VA/Madigan (i.e., private medical provider) records, a written Release of Information (ROI) will be obtained.

If the potential participant remains eligible following initial chart review, an appointment will be scheduled for the Consent and Preliminary Screening Visit. The written informed consent process will take place prior to performing any study procedures.

Personnel who will be obtaining Informed Consent: Before study staff are considered qualified to obtain consent, they must first undergo all VA and/or Madigan-mandated trainings and will also undergo internal training. They must become familiarized with MIRECC procedures regarding obtaining consent, must be familiar with the study protocol, and must be familiar with the risks and benefits of study participation. Once the PI is satisfied that a study staff member is competent to obtain consent, he will formally delegate authority to obtain consent to that person. Because this is a clinical trial, a clinician (physician, physician assistant, or nurse) will be available either in person or by telephone to answer any of the potential participant's questions regarding the study drug.

Description of the Informed Consent Process: The PI or another qualified study staff member will explain the consent form at the first visit before study procedures are performed. If an investigator is also one of the potential participant's care providers, an alternate study staff member will conduct the consent process. Any pressure or appearance of pressure to participate in the study will be carefully avoided. No person in a SM's direct chain of command shall be present during the consenting process. The consent discussion will be conducted in a private location. If the potential participant wishes to have a relative or friend present during the consent process, we will accommodate the potential participant. The person obtaining consent will give the potential participant adequate time to read the consent form and ask questions. The following elements will be discussed with the potential participant:

- The purpose and objectives of the study

- The length of the study
- Any potential risks, discomfort and inconvenience
- The importance of following study procedures
- The importance of compliance with all assessments and study visits
- The possibility of the need for unscheduled visits
- Randomization – there is a 2-1 chance of being randomized to either prazosin or placebo
- Participation is entirely voluntary and that the subject may withdraw from the study at any time without loss of benefits to which he/she may otherwise be entitled
- Alternative treatments
- Compensation schedule for visits
- The participant's social security number (SSN) is required in order to maintain a medical record and to reimburse participants. Participants will be informed that if they do not wish to give us their SSN, they cannot participate in the study.
- Provisions for keeping study data confidential and exceptions to confidentiality
- That adverse events are treated at no cost to the participant

The participant must sign an informed consent and HIPAA authorization as approved by the appropriate (Madigan or VA Puget Sound) IRB before any study procedures are performed. A progress note will be written in the participant's study chart to document that the consent discussion was conducted and all questions were answered to the participant's satisfaction. A note will also be placed in the EHR of participants at VA Puget Sound per current guidelines.

If the safety of a potential participant would prevent the participant from travelling to the study clinic location, initial consent may be obtained over approved VA or DoD telehealth applications. Telehealth consenting will be done according to the following steps:

1) All appropriate consent and HIPAA document(s) will be sent to participants via mail or secure e-mail (e.g., Azure RMS) for the participant to print.
2) Participants will be given as much time as desired to review the document(s) prior to the consent discussion.
3) A qualified study team member will review all elements of the consent and HIPAA document(s) with the participant.
4) If signed, the study team member will take a screenshot of the signature page(s) of all signed study documents. The screenshot(s) will be saved in an approved, secure study folder.
5) The study team member will document the consenting process and enroll the participant in the study.
6) Participants will mail the signed document(s) to the study team using a provided pre-paid envelope.
7) Once the signed documents are obtained by the study team, the documents will be retained according to policy.

If an error in the signing process or documents is discovered, the error will be corrected and properly documented prior to any further study procedures.

A copy of the informed consent form can be provided to interested potential participants to review and discuss with family members or their medical provider without any time limit.

All participants will be able to provide consent on their own behalf. Because all assessments are conducted in English, all subjects will be sufficiently fluent in English to read and understand the consent form. We do not anticipate enrolling any illiterate volunteers.

5.4 Inclusion/Exclusion Criteria

Inclusion Criteria:

- Male and female Active-duty SMs or Veterans aged 18 or older who are in good general health.
- History of blast and/or impact head trauma mTBI meeting Defense and Veterans Brain Injury Center (DVBIC) mTBI criteria.
  - Mild TBI is defined as an injury to the head causing at least one of the following: alteration in consciousness (for up to 24 hours after the injury), loss of consciousness (0-30 minutes), and/or post-traumatic amnesia (up to 1 day post-injury). If available, the Glasgow Coma Scale score must be 13-15, and head imaging findings (if imaging was performed) must be negative.
- Frequent HAs that started within 3 months after a head injury or marked worsening (a two-fold or greater increase in frequency and/or severity) of pre-existing headaches within 3 months of head injury.
  - HAs either 1) must last 4 or more hours a day and reach a moderate to severe intensity at any point during the headache, or 2) may be of any severity or duration if the participant takes a medication or other agent in an effort to stop or treat a headache.
  - HAs meeting these criteria must have been present on average at least 8 days per 4-week period, starting within 3 months after head injury and occurring at a stable level by self-report for at least 3 months prior to the Initial Screening Visit. The 4-week HA frequency/severity criteria must be confirmed during the Preliminary Screening Period.
- Participants of childbearing potential must agree to abstain from sexual relations that could result in pregnancy or use an effective method of birth control acceptable to both participant and the clinician prescriber during the study. Participants who not of childbearing potential are not required to use contraception during the study.
- Participants must have English fluency sufficient to complete study measures.

Exclusion Criteria:

- Participation in other interventional research.
- History of penetrating head injury
- History of TBI more severe than mild by DVBIC criteria
- A primary non migraine and/or tension-type HA disorder (for example hemicrania continua; cluster) that accounts for the majority of current symptoms.
- HAs of any kind of moderate or severe intensity on an average of more than 4 days per month preceding the concussive trauma
- Acute or serious medical illness or unstable chronic medical illness (e.g., unstable angina, myocardial infarction within 6 months, congestive heart failure, clinically significant or concerning cardiac arrhythmias; preexisting hypotension [systolic blood pressure<110] or orthostatic hypotension [systolic drop >20 mm Hg after 2 min standing accompanied by lightheadedness], chronic renal or hepatic failure, or acute pancreatitis. The eligibility of potential participants having acute serious and/or chronic medical illnesses other than those listed will be evaluated on a case-by-case basis by a study physician, PA-C, or ARNP.

- Use of prazosin or other alpha-1 antagonist (including but not limited to alfuzosin, doxazosin, silodosin, tamsulosin, terazosin) for any purpose in the 2 weeks prior to initial screen (P1) visit and prohibited throughout the study
- Any prior use of prazosin at a dose of more than 4 mg per day
- Allergy or previous adverse reaction to prazosin or other alpha-1 antagonist
- Active psychosis or psychotic disorder, severe depression (as determined per clinician prescriber judgment), severe psychiatric instability or severe situational life crisis (including evidence of being actively suicidal or homicidal).
- Meets Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria for any Substance Use Disorder except caffeine-related disorders, or tobacco-related disorders.
- History of delirium within the prior 3 months, epilepsy, stroke, dementia, psychotic disorder, or bipolar disorder
- Structural brain abnormalities on any prior imaging with associated clinically evident manifestations
- Current participation in transcranial magnetic stimulation studies
- Women of childbearing potential must not be pregnant, planning to become pregnant during the study period, or nursing.
- Participation in a HA support group or other activity such as meditation or yoga intended to mitigate HA or other chronic pain must be stable at least 4 weeks prior to beginning the initial screen (P1) visit and may not be started during the study
- Failure to record HA data for at least 80% of days during the Screening Period
- Not suitable for study per clinician judgement.

Medication-and other Treatment-Related Considerations:

- The use of HA rescue or symptom-relieving medications will be allowed during the study. This includes triptans, ergotamines, opioids, simple analgesics (e.g. acetaminophen, aspirin, or non-steroidal anti-inflammatories [NSAIDS], and combination analgesics. Their use will be recorded on the concurrent medication CRF during the Preliminary Screening Period (P1) and throughout the remainder of the study. Randomization of participants will be stratified based on whether their use of HA medications meets ICHD-3 beta criteria for overuse of these medications, as described in section 5.5 below.
- Opioid Medications: Use of opioids for treatment of HA or non-HA-related pain or for any other purpose is allowed during the study. Any opioid use would ideally be excluded due to potential confounding effects on interpretation of response to treatment. However, in this population, particularly in Veterans with chronic pain or undergoing minor orthopedic or dental procedures, opioid use is common. Use of opioids, including frequency and dose, will be recorded on the concurrent medication CRF.
- Cannabis: The use of cannabis in any form is not excluded unless its use meets criteria for Cannabis Use Disorder. All use of cannabis will be documented.
- Other Medications: Participants who are using other medications or treatments on a routine basis must be on a stable dose for at least 4 weeks prior to the Preliminary Screening Period (P1), and

must intend to continue the medication at the same regimen for the duration of the trial unless lack of efficacy, safety, or tolerability dictates otherwise. The following medications and treatments are **not** excluded:

- Psychoactive drugs (for example, anticonvulsants, benzodiazepines, antidepressants, sedative/hypnotics),
- Antihypertensive medications (including beta-blockers, calcium channel blockers, angiotensin converting enzyme [ACE] inhibitors, and angiotensin receptor blockers),
- The use of magnesium in any dose that is prescribed for the purpose of HA prevention or treatment. The incidental use of magnesium in multi-vitamins, laxatives, etc. is permissible but must be documented.
- Hormones (for example, testosterone, estrogen, or progesterone) in any form.
- Onabotulinum toxin A and nerve block injections for the purpose of HA prevention is permissible if the treatment response has been stable during the two most recent treatment cycles.
- The "as-needed" (prn) use of any non-exclusionary medications is allowed; however, such use must be discussed with a clinician prescriber and documented.

- The use of butalbital in any form within 4 weeks of beginning the Preliminary Screening Period (P1) through the end of the participant's study involvement is exclusionary.
- Participants who have been taking trazodone will undergo a 2-week washout period before the Preliminary Screening Period (P1 visit). Combining prazosin and trazodone may increase the risk of priapism. We have decided to begin the washout period before the Preliminary Screening Period in order to remove any confounding variables while on the headache log and actigraphy.
- Sildenafil (Viagra), tadalafil (Cialis), vardenafil (Levitra), and avanafil (Stendra) will not be permitted during the study drug dose Titration Period, because of increased risk of hypotension in combination with alpha-1 blockers, but will be allowed at half the usual starting dose following the study drug dose Titration Period, per VA prescribing guidelines.
- Use of supplements containing nitrates and supplements containing stimulants (such as ephedra) are exclusionary in the two weeks prior to initial screen (P1) visit and prohibited throughout the study. Participants who take these supplements will be asked to discontinue them for a minimum of two weeks before the Preliminary Screening Period (P1 visit).
- Use of prescribed stimulants (such as amphetamine or dextroamphetamine containing medications) is exclusionary in the 2 weeks prior to the initial screen (P1) visit and prohibited throughout the study. Participants who take these medications will be asked to discontinue them for a minimum of 2 weeks before the Preliminary Screening Period.
- Participants may also be excluded at the discretion of PI or study clinicians if they appear to be unsuitable for this research study for a reason not detailed here. This may include risk factors for COVID-19 infection that are considered to present excessive risk given background local COVID-19 transmission rates and available safety protocols at the time of evaluation.

5.5 Study Evaluations

Study Visits and Procedures: the schedule of study visits table at the end of this section provides a summary of study visits, procedures that will be performed at each visit, and the estimated time required per visit.

Screening Period (Consent, Initial Screening, Screening HA Log, Final Screening): Written informed consent will be obtained from potential participants prior to any study procedures. The PI or another qualified study staff member will explain the study procedures and will review the consent form with the potential participant in a private setting. The potential participant will be given adequate time to read the consent form and ask questions. If an Investigator is also the potential participant's primary provider, an alternate study staff member will conduct the consent process. Any pressure or appearance of pressure to participate in the study will be carefully avoided. No person in a SM's direct chain of command will be present during the consent process.

Following written informed consent, participants will undergo preliminary screening procedures: review of medications; medical, psychiatric, military, and head trauma histories; evaluation of headaches, and headache treatment history. Potential participants will be interviewed using the Structured Clinical Interview for DSM-5 (SCID-5) to rule out disqualifying major psychiatric disorders.

Screening medical physical and neurologic exams will be performed. A scratch-and-sniff test of smell (Brief Smell Identification Test™) will be done. The physical exam will include orthostatic BP and HR. A 12-lead electrocardiogram (EKG) will be obtained, if clinically indicated. Laboratory studies, including but not limited to complete blood count, chemistry panel, and thyroid function tests will be performed, if clinically indicated. A routine urinalysis will be performed, if clinically indicated. Participants of childbearing potential will have a urine pregnancy test, which must be negative in order to continue study participation.

The initial screen visit may occur over several visits as needed.

Participants will begin keeping the HA log at the beginning of the Preliminary Screening period and will continue for the duration of the Preliminary Screening Period. If they are determined to be eligible to continue in the study (see below), they will continue keeping the HA log for the remainder of the study phases, including the Titration and Steady-Dose Periods. The Screening HA log data will be used to both confirm that participants are eligible to continue into the Titration Period of the study and to provide baseline data that will be used for comparison with data from the Steady-Dose Period to address the primary and secondary outcome measures.

Participants will be called for a brief telephone visit during weeks 1 and 3 of the screening period. The calls will answer any questions about the HA log keeping and encourage compliance. Medication and health changes will be queried.

At the end of 4 weeks of HA log keeping, the HA log will be reviewed at the Final Screening Visit to determine participant eligibility to continue in the study. Eligibility criteria include 8 or more HA days in the 4-week period of log keeping. A HA day is defined as a calendar day in which the participant had HAs that either 1) lasted for 4 or more hours and reached a pain intensity of moderate to severe at any point during the HA or 2) were of any severity or duration if the participant took a medication or other agent (e.g., caffeine) in an effort to stop or treat a headache. HA log entries must be recorded for at least 80% of the days, and there must be no exclusionary medication or supplement use. Vital signs (BP and HR) will be checked to ensure absence of orthostatic hypotension. Participants will be scheduled for the Baseline Visit, which will optimally occur 7 days later, but not more than 14 days later. During the interim week between the Preliminary Screening Period and the Baseline Visit, participants will

continue keeping the HA log and will undergo baseline sleep/activity monitoring with 7 days of actigraphy and keeping a sleep diary.

If it is found that a potential participant does not meet the inclusion criteria, follow-up care will be coordinated when needed with the appropriate clinic at the study site, either Madigan or VA Puget Sound.

Participants who fail screen for a reason that may change (e.g., stabilization of medications or treatment) may resume the screening process following stabilization. Previously collected information will be verified followed by resumption of headache logging for 4 weeks. Participants who screen fail for any reason may be rescreened if the reason for the screen fail has changed.

Randomization: before the Baseline Visit, participants will be randomized 2:1 to prazosin or placebo. Randomization will be stratified based on study site, gender, and whether participants meet the following criteria for medication overuse:

1. The regular use of ergotamine, triptans, opioids, or combination analgesics on 10 or more days during the Preliminary Screening Period. The term “combination analgesic” is used for formulations designed to treat migraine HAs that combine drugs of two or more classes, each with an analgesic effect or acting as adjuvants (e.g., Excedrin migraine, which contains aspirin, acetaminophen, and caffeine).
2. The regular use of individual “simple analgesics” (acetaminophen, aspirin, and other NSAIDS) on 15 more days during the Preliminary Screening Period.
3. The regular use of any combination of ergotamine, triptans, opioids, combination analgesics, and/or simple analgesics on 10 or more days during the Preliminary Screening Period, without over-use of any single drug or class alone.
4. Caffeine use of 300 mg or more on four or more days per week during the Preliminary Screening Period.

Titration Period (Baseline Visit and Study Drug Titration): At the Baseline Visit, medications will be reviewed, vital signs (BP and HR) will be checked to ensure absence of orthostatic hypotension, and a urine pregnancy test for women of child-bearing potential will be checked and must be negative. For participants who remain eligible for the study, measures will be performed as listed on the schedule of study visits. We will perform a short measurement of the pupillary light reflex. Participants will look into a device that uses an infrared camera to measure the diameter of the pupil at baseline and in response to very brief flashes of light. The measurements take approximately 30 seconds. Including set up and instructions to the participant, the procedure will take approximately two minutes. Blood (approximately 65 ml) will be collected from VA Puget Sound participants only for measurement of potential biomarkers related to headache

After the above procedures are completed, participants will receive the study drug and will be instructed in dosing procedures and safety precautions to prevent potential adverse effects. They will be instructed to continue keeping the daily HA Log, and to start taking the study drug that evening. The prazosin titration schedule is summarized in the Study Drug Titration table. The dosing regimen is based on our experience using prazosin to treat combat-trauma PTSD. The starting dose will be a 1 mg capsule of study drug (prazosin or identical placebo) qhs for the first 2 nights. Then the dose will be increased to 2 mg qhs. For the first week, the study drug will be taken while the participant is in bed for the night, to avoid orthostatic syncope, an uncommon but recognized “first-dose” effect of prazosin. The first-dose effect is avoidable by starting study drug with a low dose, then titrating upward gradually.[49]

The participant will be asked to call the study team the morning after the first dose to make sure there was no occurrence of postural dizziness. The participant will be given a 24-hour contact number in case of adverse events any time the dose is increased.

Dose Titration Visits: Participants will be seen at each dose increase beginning after completion of the first week, according to the titration schedule summarized in the Study Drug Titration Schedule table, to evaluate for adverse effects; record any new medications and interval medical problems; monitor resting and standing BP and HR; confirm that the HA Log is current; determine whether proceeding to the next step of the dose titration is appropriate; and to provide additional study drug for the scheduled dose increase or dose maintenance. A dose increase will occur if the participant does not have unacceptable side effects. Clinical judgement may be used to maintain or decrease the dose as necessary. Dose titration visits are scheduled at the completion of Titration weeks 1 to 5.

If a participant has intolerable side effects, the dose will be reduced to the previously tolerated titration step. If the participant is unable to tolerate a minimum dose of 1 mg/day, he/she will be terminated from the study. Once the maximum dose has been achieved (5 mg qam and 20 mg qhs or the maximum tolerated dose), the participant will continue on that dose for a total of 12 weeks (Steady-Dose Period), unless he or she develops intolerable medication-related side effects. The dose may be re-challenged during the titration period if clinically appropriate.

Study Drug Titration Schedule

		Morning (qam) dose	**Bedtime (qhs) dose**
Week T1	**Days 1-2**		1 mg
	Days 3 -7		2 mg
Week T2	**Days 8 -14**	1 mg	4 mg
Week T3	**Days 15 -21**	2 mg	6 mg
Week T4	**Days 22 - 28**	5 mg	10 mg
Week T5	**Days 29 – 36**	5 mg	15 mg
Week T6	**Day 36 + 12 weeks**	5 mg	20 mg

Steady-Dose Period Visits and Telephone Check: Regular clinic visits will be scheduled. Safety and efficacy visits will be scheduled at the completion of Steady-Dose weeks 1, 4, 8, and 12 to record any interval medical or medication changes, to monitor compliance, and to confirm that the HA Log is current. Participant safety will be assessed at each of these visits, as further detailed in the "Risk Management and Emergency Response" section above. Any adverse symptoms will be recorded, evaluated, and addressed, as appropriate, and safety measures (resting and standing BP and HR) will be performed. The Actiwatch, actigraphy instructions, and the sleep log will be issued to the participant in-person or will be shipped to the participant prior to the week 11 telephone check-in visit. Shipping will occur via trackable method such as Fed Ex or UPS.

At the end of Steady-Dose weeks 4, 8, and 12, in addition to safety assessments and monitoring, all secondary outcome measures will be repeated, as described in the schedule of study visits. At the 12-week visit, approximately 65 ml of blood will be collected from VA Puget Sound participants only for measurement of potential headache biomarkers. In the event of early termination, (see section 5.7 below), a termination visit will be scheduled whenever possible to complete all procedures usually performed at week 12.

Potential Exceptions to study schedule: If a participant delays titration for any reason (e.g., dose maintained and not increased due to temporary AE), up to two additional titration visits may take place

(extending the 5 week titration to 7 weeks). No dose increases may take place after starting the Steady-dose Period.

Study visits windows are up to 6 days before or after each scheduled visit. Outcome rating visits may be done up to 14 days before or after the scheduled outcome rating visit. The screening process (consent visit through completion of all visit P1 procedures) may last as long as 6 weeks due to stabilization of medications and health conditions.

Additional visits (for example, additional titration visits or additional safety visits) may be required per study clinician's discretion. If additional visits are required, participants will be reimbursed as if it were a regular study visit.

Procedures to minimize missing data: It may be necessary to obtain assessments by telephone or by approved VA or DoD telehealth applications throughout any phase of the study. Remote (telephone and telehealth) visits will be conducted in accordance with local policies governing the use of these tools to ensure minimal risk to participant privacy and safety. All visits or parts of visits may be conducted with any of the above methods to address participant safety issues or burden. The following actions will be attempted (as appropriate per visit schedule): 1) adverse event queries and other study assessments will be completed remotely, 2) at-home blood pressure cuffs will be used to capture vital sign safety information, 3) logs for capturing headache and sleep data, instruction forms, contact information sheets, and self-rated measures or any other study document will be provided to participants via secure e-mail, USPS mail, or delivery service. Participants can return any documents using a prepaid envelope provided by the study, via fax to the secured study fax, or at the next in-person visit, and 4) dispensing of study drug shall be done by trackable shipment. Alternate approved telephone/telehealth versions of study assessments will be used as appropriate. Blood draws for biomarkers and Pupillary Light Reflex may be skipped if the participant is unable to be seen in-person for the baseline and SD4 visits. Additionally, the MoCA may be skipped if only a phone visit is possible (MoCA can only be done in person or via video). No-show, missed visits and actions taken will be documented in the study record.

Description of Study Measures:

Structured Clinical Interview for DSM-5 (SCID-5):[50] A semi-structured interview guide for making DSM-5 diagnoses. It is administered by a clinician or trained mental health professional that is familiar with the DSM-5 classification and diagnostic criteria.

Combat Experiences Scale (CES):[51] The 18-item Combat Experiences Scale will be used to describe the degree of combat trauma exposure in the study sample. Scores range from 1-18. The Combat Experiences Scale has been utilized in many studies evaluating combat veteran samples and is relevant to any war zone setting from WWII to OIF/OEF/OND.

HA Log: A pre-printed form in a weekly calendar format used for self-report of the following, on a daily basis: HA pain severity (maximum for the day, rated as none [=0], mild [=1], moderate [=2], or severe [=3]), number of hours of mild, moderate or severe pain (to nearest ½ hour), any medications used in an attempt to treat the HA, including the name, amount, and whether it provided relief, , and a space for comments.

Migraine Disability Assessment Scale (MIDAS):[52] A 5-item self-administered questionnaire used to quantify HA-related disability. The MIDAS queries the number of days of missed or substantially reduced activity caused by HA in the preceding 3 months, taking into account three domains: schoolwork/employment, household work or chores, and non-work activities (family, social, and leisure). Responses are summed and coded into one of four grades of disability ranging from little or no

disability to severe disability.

HA Impact Test-Short Form (HIT-6):[53,54] A 6-item self-administered questionnaire measuring impact on "usual daily activities" including work, school, or social activities, pain intensity, fatigue, and desire to lie down, frustration, and difficulty with concentration in the preceding month. The HIT-6 has shown the ability to discriminate between severity levels and between migraine and other HA diagnoses.

PTSD Checklist (PCL-5)[55]: A 20-item self-report measure that assesses the DSM-5 symptoms of PTSD on a scale ranging from 0 ("not at all") to 4 ("Extremely')

Pittsburgh Sleep Quality Index (PSQI):[56]A self-report questionnaire designed to assess sleep quality and disturbances over a 1-month time interval. Nineteen individual items generate seven subscale scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction. A global score is obtained by summing the seven subscale scores (score range 0-21).

Insomnia Severity Index (ISI): A self-report instrument designed to assess insomnia according to criteria from the DSM-IV and the International Classification of Sleep Disorders that has been validated for clinical as well as research use [57]

Patient Health Questionnaire-9 (PHQ-9):[58] The 9-item depression module of the PHQ, a self-report version of the PRIME-MD used to diagnose major mental disorders. The PHQ-9 items correspond with Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria for depression, with each item scored from "not at all" to "nearly every day".

Alcohol Use Disorders Identification Test-Consumption (AUDIT-C):[59] A 3-item modification of the AUDIT questionnaire that enquires about frequency and quantity of alcohol consumption in the past year, including frequency of episodes of heavy drinking, defined as six drinks in men and four drinks in women, per occasion. The AUDIT-C demonstrates excellent sensitivity and specificity for detecting heavy drinking, and is used in VA clinics as a standard screening tool for evaluating alcohol use. The gender-appropriate version of the AUDIT-C will be used as a secondary outcome measure to quantify the effect of prazosin on alcohol consumption. For administrations of the AUDIT-C subsequent to the baseline evaluation, the AUDIT-C will be modified to enquire about the past month, rather than past year alcohol consumption.

Health-Related Quality of Life: The Veterans RAND 12 (VR-12):[60] A shorter version of the Veterans Short Form 36 (SF-36V), which was based on the administration of the Medical Outcomes Study SF-36 to a large sample of veterans. The SF-36V differs only slightly from the standard SF-36, in that the physical and social role scales are converted from dichotomized choices to 5-point ordinal response options to reduce floor and ceiling effects. The VR-12 assesses the same eight heath concepts (physical functioning, role limitations due to physical problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health) as the SF-36V but uses fewer items for seven of the eight scales. Results are expressed as physical and mental component summaries.

Allodynia Symptom Checklist (ASC): [61] A 12-item self-administered questionnaire that assesses overall cutaneous allodynia (i.e., pain that is provoked by a stimulus to the skin that would not ordinarily cause pain) and subtypes, including thermal, mechanical static, and mechanical dynamic. Cutaneous allodynia is associated with migraine frequency, severity, disability, and other features. ASC is scaled to grade the degree of allodynia as none, mild, moderate, and severe, allowing quantitation of this trait. The ASC is thus used as a quantitative measure to monitor response to therapy in migraine treatment studies.

Montreal Cognitive Assessment (MoCA):[62] A clinician-administered instrument designed to detect mild cognitive impairment, providing a brief assessment of short-term memory recall, executive function, sustained attention, calculation, language, and orientation. Scores range from 0-30, with lower scores indicating greater cognitive impairment.

Consensus Sleep Diary-E (CSD-E):[63] A pre-printed form in calendar format used for self-report of quantitative and subjective measures of sleep quality, completed on a daily basis for one week during the Screening Period immediately preceding randomization (i.e., prior to starting study drug dose titration), and for the last week of the Steady-Dose Period. The CSD-E includes two sections, one to be completed in the morning upon awakening and the other to be completed before bed. This sleep diary is based on consensus recommendations of sleep experts.

STOP-Bang Sleep Apnea Screening*:* A widely used screening tool that uses 8 yes/no questions to screen for individuals having an elevated risk of obstructive sleep apnea (OSA) sufficient to warrant further evaluation. The STOP-Bang will be used to assess for indications of OSA to be used as covariates in later analysis. For participants that screen positive for an elevated risk of OSA, referral options will be discussed with the participant and assistance will be provided as needed.

Brief Smell Identification Test: The Brief Smell Identification Test (B-SIT) is a rapid and effective 5-minute 12-item screening test that assesses an individual's ability to detect odors. It is useful for quantifying olfactory (Cranial Nerve 1) function. Each page has a different scratch and sniff strip embedded with odorant. Multiple choice answers are provided. The odors are well known in most cultures.

Evaluation of sleep patterns with wrist actigraphy and sleep diary: Participants will be asked to wear an Actiwatch 2 (Philips Respironics, Bend, Oregon) on their non-dominant arm continuously for 7 days (as listed on the schedule of study visits). The Actiwatch 2 is a wristwatch-like device that measures gross motor activity, integrates the degree and intensity of motion, and records an activity count per a specified epoch length. A collection epoch of 1 minute will be used. Recorded activity may vary from zero (no activity) to hundreds per epoch (high activity). An activity count for each epoch is downloaded from the device to a computer program (Actiware, Philips Respironics, Bend, Oregon), and analyzed using standard statistical software. The wake threshold value will be set at 40 activity counts per epoch, as has been previously used in a study of Iraq/Afghanistan veterans with PTSD and mTBI.[35] In conjunction with the Consensus Sleep Diary,[63] sleep variables calculated include total sleep time, total time spent in bed, sleep onset latency, number of awakenings, sleep efficiency, and wake time after sleep onset.

Pupillary Light Reflex: This will quantify the pupillary light reflex. Participants will be asked to look into a device that uses an infrared camera to measure the diameter of the pupil both during darkness and following brief pulses of light. The measurements take approximately 30 seconds. The entire process (including set up and instructing participants on the procedure) will take about two minutes.

Neurobehavioral Symptom Inventory (NSI): A 28-item self-report questionnaire designed to assess the presence and severity of common cognitive, emotional, sensory, and somatic symptoms that can occur after traumatic brain injury. It is widely used in VA hospitals across the country as part of the TBI Second Level Evaluation.

TBI History Interview: An 11-item questionnaire that characterizes the participant's traumatic brain injury exposures. Explosion/blast, impact and lifetime injuries are assessed. Dates associated with first TBI, most recent TBI and onset of headaches are captured.

Utah Photophobia Symptom Impact Scale-12-Modified (UPSIS-12M): A 12-item self-administered questionnaire designed to evaluate light sensitivity severity during and between headache attacks, light as a headache trigger, and the impact of light sensitivity on activities of daily living[64]. The UPSIS was

developed with the intention of providing a quantitative tool for assessing effectiveness of treatment interventions. The UPSIS-12 has been validated for internal consistency and reliability against the 17-item UPSIS, the 8-item Korean Photophobia Questionnaire, which emphasizes photophobia only during headaches, and against quantitative psychophysical assessment of light sensitivity thresholds. Minor modifications tailored to the needs of this study have been made and discussed with the UPSIS developers.

-

Schedule of Study Visits

	Preliminary Screening Period					Titration Period[b]			Steady-dose Period				
Visit type	Initial Screening	Phone Check	Review Headache Log	Phone Check	Final Screening[a]	Baseline	Standard Titration	Optional Titration	Safety	Safety/ Efficacy	Safety/ Efficacy	Phone Check	End of Study
Study Week	-5	-4	-3	-2	-1	0	1-5	6-7	1	4	8	11	12
Visit Number	P1	P1.5	P2	P2.5	P3	T1	T2-T6	T7-T8	SD1	SD2	SD3	SD3.5	SD4
Consent	X												
Medical/Psychiatric History	X												
Medication History	X												
TBI history	X												
Physical/Neurological exam	X												
Smell test	X												
12-lead EKG (if indicated)	X												
Routine screening blood tests (if indicated)	X												
UA (if indicated)	X												
Blood draw for headache biomarkers						X							X
Urine pregnancy test (childbearing potential only)	X					X							
Pupillary Light Reflex						X							X
Determine Study Eligibility	X				X								
Resting and orthostatic BP, HR	X		X		X	X	X	X	X	X	X		X
SCID-5	X												
Combat Experiences Scale	X												
Demographic Information/Military History	X												
STOP-Bang	X												
PHQ-9	X					X				X	X		X
NSI						X				X	X		X
MoCA						X				X	X		X
PCL						X				X	X		X
PSQI					X					X	X		X
ISI					X					X	X		X
AUDIT-C						X				X	X		X
Veterans RAND 12						X				X	X		X
HIT- 6						X				X	X		X
MIDAS						X							X
ASC	X												X
UPSIS-12M						X							X
Actigraphy and Sleep Diary					X[c]							X[c]	
Medications review		X	X	X	X	X	X	X	X	X	X	X	X
Dispense/Review Headache Log	X	X	X	X	X	X	X	X	X	X	X	X	X
Review side effects/adverse events							X	X	X	X	X	X	X
Dispense and/or return study drug						X	X	X	X	X	X		X
Approximate length of visit (hrs)	3	¼	½	¼	1 ½	3	½-¾	½-¾	½	3	3	¼	3

[a]There may be up to two weeks between this visit and the Baseline visit.
[b]The titration period can be extended to a maximum of 7 weeks
[c]Actigraph will be worn and sleep log kept for 7 days during these periods of time

5.6 Data Analysis

Sample Size: Our estimate of required sample size for the primary outcome is based on previous studies of chronic migraine HA,[40,65] which reported standard deviations for change from baseline at 16 weeks in number of migraine days/month on the order of 5-6 days for both placebo and active drug groups, and a difference in change from baseline at 16 weeks in mean number of chronic migraine HA days/month between treatment groups of about 4 days (i.e., an effect size of about 0.67). An inclusion criterion for these studies was a minimum of 15 HA days/month, whereas the corresponding inclusion criterion for our proposed study is a minimum of 8 HA days/month. We therefore may see a smaller effect size. A trial with 111 completers (74 in the prazosin group, and 37 in the placebo group) yields 80% power to detect an effect size of 0.57 for a difference in change from baseline based on a standard two-sample t-test using a two-sided 5% Type I error level. Because we will be using linear mixed effects models to analyze this outcome, our power should be greater than 80% to detect an effect size of 0.57.

To arrive at the required number of participants to randomize, we are assuming a 30% dropout rate during the Titration and Steady-Dose Periods, based on the experience of Study Consultant Dr. Erickson in other HA trials in the active-duty SM population. This dropout rate is due mainly to service-related events, such as reassignment or deployment, rather than to adverse drug effects. With a 30% dropout rate, we will need to randomize 160 participants who have met all eligibility criteria. Conservatively assuming a screen-fail rate of approximately 30% based on the Pre-Treatment Screening (e.g., meeting inclusion criteria for HA frequency/severity, adequate compliance with log keeping, voluntary study withdrawal, etc.), 228 potential participants will need to be recruited and enrolled to provide sufficient participants randomized for completion of the study.

The secondary outcomes will be analyzed in the same way as the primary outcome (i.e., using linear fixed effects models), so the power and sample size calculations are the same. For the secondary outcome: 4-week frequency of use of abortive/analgesic medications, Diener et al.[65] saw a difference in change from baseline of 2.7 days (an effect size of 0.5) and Silberstein et al.[66] saw a difference in change from baseline of about 1 day (an effect size of 0.2). For the secondary outcome: MIDAS, Diener et al.[65] observed a difference in change from baseline of 29 (an effect size of 0.7), whereas Silberstein et al.[66] observed a difference in change from baseline of 10 (an effect size of 0.2).

For the secondary outcome PSQI, we have information on the within-subject standard deviation and intraclass correlation (ICC) from our prazosin for combat-trauma PTSD study performed at Madigan/JBLM. For the PSQI, we observed a within-subject standard deviation of 2.5, an ICC of 0.6, and a difference in change from baseline between the prazosin and placebo group of 0.18 per week or 2.8 per 15 weeks (10 weeks at steady-dose). For the proposed study, we should have 80% power to detect a difference in change from baseline between the prazosin and placebo groups of 1.15 at 12 weeks of steady-dose study drug.[70] For the secondary outcome measure PCL, we can use the results from the Clinician Administered PTSD Scale outcome from the prazosin for combat-trauma PTSD study as an approximation. For the Clinician Administered PTSD Scale, we observed a within-subject standard deviation of 13, an ICC of 0.7, and a difference in change from baseline between the prazosin and placebo groups of 0.75 per week or 11.3 per 15 weeks (including a 5-week titration period, thus 10 weeks of steady-dose). Based on the visit schedule, we will have 80% power to detect a difference in change from baseline between the prazosin and placebo groups of 5.25 after 12 weeks of steady- dose study drug. Note

that the inclusion criteria for our prazosin for combat-trauma PTSD study required subjects to meet DSM-IV criteria for PTSD and have a score ≥ 5 (maximum score of 8) on the Clinician Administered PTSD Scale nightmare item, whereas the inclusion criteria for this study do not include these criteria so we do not expect to see as large effect sizes for PCL and PSQI.

Statistical Analysis: We will use summary statistics and graphs (e.g., strip charts, box plots, bar charts, scatter plots) to compare subject demographics at baseline by assigned treatment group (prazosin vs. placebo), and to initially compare outcomes by treatment group. Analyses will follow the intent to treat (ITT) principle. We will use a linear mixed effects model for the analysis of the primary outcome: 4-week frequency of moderate or severe HAs (Hypothesis 1a). We will have 4-week measures at four times during the course of the study: at Baseline, and at three different time points post-randomization (after 4, 8, and 12 weeks of steady-dose study drug). The response (dependent) variable will be 4-week frequency of moderate or severe HAs, and the predictor (explanatory) variables will include treatment group, week and a treatment group by week interaction term, along with the covariates site, gender, baseline age, baseline PSQI, time since onset of PTHAs, and analgesic use. A significant treatment group by week interaction term will indicate a significant difference in change from baseline between treatment groups. Results will include p-values, confidence intervals for change from baseline within each group, the confidence interval for difference in change from baseline between the two groups, and effect sizes.

We will also use linear mixed effects models for the secondary outcomes for Hypothesis 1b, i.e., 4-week average of: HA severity, number of hours of moderate to severe HA, individual HA duration, frequency of migraine days, frequency of non-migraine days, and frequency of use of abortive/analgesic medications (all obtained from the HA log); and for degree of HA-related disability (MIDAS and HIT-6). As for the primary outcome, secondary outcomes obtained from the HA log and the HIT-6 will have observations at four time points during the course of the study: Baseline and after 4, 8, and 12 weeks of steady-dose study drug; MIDAS will have observations at Baseline and week 12. The response (dependent) variable will be the secondary outcome, and the predictor (explanatory) variables will be the same as for the primary outcome.

We will also use linear mixed effects models for the secondary outcomes for Hypothesis 2a, i.e., sleep quality and quantity, PTSD symptom severity, depressive symptoms, alcohol consumption, global cognitive function, health-related quality of life, and global clinical status. The schedule of study visits table shows when these outcomes will be measured during the study. The response (dependent) variable will be the secondary outcome, and the predictor (explanatory) variables will be the same as for the primary outcome and baseline PSQI will be omitted as a predictor variable in models measuring sleep quality and quantity.

For Hypothesis 2b, we will examine the correlations between within-subject change from baseline in HA parameters and within-subject change from baseline in sleep quality, PTSD symptom severity, mood, moderation of alcohol consumption, cognitive function, health-related quality of life, and global clinical status.

Linear mixed effects models easily accommodate missing values. We will compare the rate and timing of dropouts between treatment groups, and also look at graphs to assess the degree by which the prazosin and placebo groups differ in how the outcome variables relate to the predictor variables in order to assess issues related to missingness.[67] If the pattern of missingness is disparate we will explore other methods of analysis such as multiple imputation.[68]

Data Management: All study information will be recorded on standardized CRFs. Forms will be labeled with study code numbers only. Code numbers will be assigned sequentially, and will not include subject initials or any other personally identifiable information. Source documents, which may include identifying information, will be maintained in locked files within a locked office. The study coordinators at VA Puget Sound and Madigan will keep the key between the identity of participants and study code number. The key will not be shared with anyone other than members of the research team.

The VISN-20 Northwest Network MIRECC (Dr. Raskind, Director; Dr. Peskind Co-Director) will supervise database design, double data entry, and any required computer programming. The MIRECC will provide maintenance of computer hardware and software at VA Puget Sound. Initial and second data entry will be performed at VA Puget Sound by the study Research Assistant under the supervision of the MIRECC Database Manager. The Database Manager will generate reports of data discrepancies. The study Research Assistant under the supervision of the Study Coordinators and Data Manager will be responsible for rectifying data entry errors within one week of discrepancy notification. Database maintenance includes nightly backup of hard drives and storage of backups at a safe off-site location. Only personnel having the correct user identification, PIN, and signing on from a computer with the appropriate IP address will have access.

5.7 Withdrawal of Subjects

Study Completion or Discontinuation and Breaking the Blind: Study completion refers to an enrolled participant having completed the full 12 weeks at the constant study drug maintenance dose level. Study discontinuation refers to premature exit from the study by a participant, either voluntarily or at the recommendation of the clinician prescriber.

The clinician prescriber may authorize premature discontinuation of participant involvement for safety reasons or other concerns, discovery of use of excluded medications, or intolerable worsening of existing HAs. Participants who begin any new scheduled prophylactic headache treatment during the study will be discontinued.

The team at the study site will triage any participant to emergency care, mental health support, or clinical care/follow-up as appropriate at any time during the study.

Safety concerns leading to termination of participant involvement may include but are not limited to pregnancy, development of an intolerable adverse reaction to the study drug or inactive constituents, development of an acute serious medical condition, or development of an unstable psychiatric condition. Study discontinuation will also occur if there are unacceptable adverse effects on the lowest study drug dose (1 mg qhs). For the purpose of maintaining participant safety, physical and neurological examinations and urine pregnancy test verification will only be conducted via approved telehealth applications or during an in-person visit. If a participant is unable to comply with these restrictions, then they will be withdrawn or excluded from the study for safety reasons. The reasons for early withdrawal or discontinuation will be recorded. For participants who are prematurely discontinued from the study after randomization, we will attempt to schedule an early termination visit. At this visit, all end-of-study procedures will be obtained in order to include these measures in the Intent-to-Treat (ITT) analyses.

The blind will be broken for participants who are discontinued from the study, whether by voluntary withdrawal or on the advice of the clinician prescriber, on the date of discontinuation.

All reasons for breaking the blind will be recorded, as will the name of the person breaking the blind.

For participants completing the entire trial, the blind will be broken at the end of the 12-week Visit. Maintaining the blind until all participants have completed the protocol and the database has been locked would be ideal; however, previous studies have shown that optimal safety and follow-up patient care argues in favor of breaking the blind for each person when they complete the trial. All participants will be given the option of treatment with open-label prazosin after study completion (an important condition for recruitment, given that prazosin is clinically available). The appropriate and safe method for initiating open-label prazosin differs depending on whether the participant had been randomized to prazosin or placebo. For those randomized to prazosin and having improvement in their HAs, subsequent open-label prazosin should be kept at the maximum achieved dose, and may be titrated further upward, if additional clinical benefit might be obtained. On the other hand, participants randomized to placebo will require titration to effect, as per the study titration schedule, initiated at a low dose (1 mg) to avoid the risk of first-dose hypotension.

6.0 Reporting

Adverse event reporting will begin after the dispensing of the first dose of study drug.

Serious adverse events (SAEs): SAEs (defined as any untoward medical occurrence which may be related to study participation at any time during the study that results in subject death, is life threatening, requires hospitalization, or results in persistent or significant disability/incapacity), will be reported to the PI, or if not available, another clinician investigator immediately upon discovery. SAEs will be reported to the Madigan IRB and DCI per current Madigan policies. The Madigan research monitor and the DSMB will be notified of the submission. A copy of the report will also be sent to the VA Puget Sound IRB per VA guidelines.

Adverse Events (AEs): Unexpected, but not serious, AEs, which the PI determines are related or possibly related to research participation, will be reported to each IRB per local guidelines. The Madigan research monitor and the DSMB will be informed of the event. Expected adverse events, which are not serious and possibly related to research participation, will be reported to the Madigan and VA Puget Sound IRBs on the annual report.

Unanticipated problems: Involving breach of confidentiality or HIPAA violation or any other risk to the health or welfare of participants that the PI determines are related or possibly related will be reported to each IRB per local guidelines. The Madigan research monitor and the DSMB will be informed of the event.

All other adverse events or problems that the PI determines are unrelated to research participation will be reported to the Madigan IRB/DCI with the annual report.

A summary of all above reports will be sent to the Madigan and VA Puget Sound IRBs with the annual report. Departures from the protocol, which do not involve risks to volunteers or affect the scientific integrity of the study, will be reported annually to the Madigan and VA Puget Sound IRBs. Deviations, which involve unanticipated problems involving risks to volunteers or others, will be reported promptly, using the procedures described in reporting of adverse events above.

7.0 Privacy and Confidentiality

The study will both use and disclose PHI. Information to be used are participant name, telephone numbers, address, medical record number (DOD ID number), SSN (for creating or updating a medical record at VA Puget Sound and for purposes of remuneration, and all elements of dates (i.e. birthdate, dates of admission, discharge, and diagnosis).

All data are coded. Participants are given a 1 digit site code, a 3 digit screening code, and if randomized a 2 letter + 3 digit randomization code. The VA crosswalk between participant identities and code number is kept electronically on the VA research drive. The list is only accessible to the personnel listed on the R&DC application. The Madigan crosswalk is kept electronically on a secured site only accessible to Madigan study personnel.

Original Source Documents and CRFs will be kept at each clinical site. Copies of CRFs will be kept at VA Puget Sound. Copies of CRFs from Madigan will either be shipped to VA Puget Sound via trackable method (i.e. Fed-Ex, UPS) or will be transported to VA Puget Sound by one of the study staff in HIPAA-compliant locked containers. CRFs will be stored in locked offices.

CRFs are kept in restricted access areas. Coded data (with no identifiers save study visit date) will be kept on shelves in areas that are locked at all times. Source documents (which contain identifiers) will be kept in file cabinets in locked areas. File cabinets are locked when the rooms are unoccupied. Electronic data will be kept on the VA research server. Access to the Electronic data will be restricted to persons listed on the Coordinating Center IRB application.

We are required by our funding agency to collect TBI Common Data Elements (CDEs). The National Institute of Neurological Disorders and Stroke (NINDS) and several co-sponsoring Federal agencies have the common mission of developing data standards for clinical research. Through the efforts of subject-specific working groups, the NINDS, along with several co-sponsoring Federal agencies developed the first set of CDEs in 2010. To broaden the utility of the TBI CDEs, experts were asked to update the recommendations to make them relevant to all ages, injury severity, and phases of recovery. The second version of the TBI CDEs (v.2) was developed in 2012.

We are required to transmit the CDEs to the Federal Interagency Traumatic Brain Injury Research (FITBIR) informatics system. FITBIR is a biomedical informatics system and data repository, created by the Department of Defense and the National Institutes of Health to assist biomedical researchers working to develop a better understanding of traumatic brain injury and/or to develop more effective methods to diagnose, treat and prevent traumatic brain injuries. Specific information about FITBIR code generation is described in section 9.0 below.

There is a risk of loss of confidentiality. We will be creating/updating medical records in the EHR. Because of this, all clinical labs will be ordered through the EHR systemand results will be placed automatically in it. We are not ordering any clinical labs which would contain sensitive information (i.e., are not performing drug, HIV, or hepatitis testing). When ordered through the EHR, pregnancy test results will be placed in the EHR.

We have obtained a Federal Certificate of Confidentiality to protect against compelled disclosure

of answers to the questionnaires. However, Certificates of Confidentiality do not apply to active duty SMs, due to requirements that information bearing on the SMs health may be required to be reported to appropriate medical or command authorities. In addition, disclosure of any illegal activities or sensitive information, such as drug use, is required to be reported to the SM's Commanding Officer, which may affect the participant's military career. These limits to SM's confidentiality are included in the Madigan consent form.

8.0 Communication Plan

The study Coordinating Center will be the MIRECC at VA Puget Sound. Murray Raskind, MD is the PI of the overall study and of the Coordinating Center. All data management and analysis procedures will take place at VA Puget Sound. The Coordinating Center will also maintain records of all IRB and subcommittee submissions and approvals, and will coordinate communication between sites.

The VA Puget Sound study coordinator will be responsible for ensuring proper conduct of the clinical trial at VA Puget Sound and is a member of the Coordinating Center regulatory team. The Madigan Study Coordinator will have weekly contact with the VA Puget Sound Study Coordinator. The protocol and all amendments are prepared by Coordinating Center Personnel and e-mailed to the Madigan study coordinator for submission to the Madigan IRB. A template consent and HIPAA Authorization form will be given to the Madigan Study Coordinator who will then alter it per Madigan IRB requirements and submit it to the Madigan IRB. Similarly, any changes to the consent form will be e-mailed to the Madigan Study Coordinator by the VA Puget Sound Study Coordinator. All approvals from the Madigan IRB will be submitted to the VA Puget Sound IRB for their records.

The Coordinating Center staff at VA Puget Sound will maintain the IRB files from Madigan and all correspondence from the Army's Human Research Protection Office (HRPO). Because the VA Puget Sound Study Coordinator is a member of the Coordinating Center staff, which prepares all protocol amendments and consent form changes, he/she will be aware of any outstanding submissions and will ensure that all approvals are in place before the study begins and that they remain current during the duration of the study.

Reports of all SAEs, AEs, unexpected, but not serious AEs, unanticipated problems, and expected AEs will be shared between the VA and Madigan teams as they are reported. Detailed reporting criteria are described in section 6.0 above.

9.0 Information Security and Data Storage/Movement

The study Coordinating Center will be the MIRECC at VA Puget Sound. Murray Raskind, MD is the PI of the overall study and of the Coordinating Center. All data management and analysis procedures will take place at VA Puget Sound. Coordinating Center Personnel will have access to protected health information. In addition, Study personnel as listed on the IRB applications at each site will have access to protected health information.

All data are coded. Participants are given 1digit site code, a 3 digit screening code, and if randomized a 2 letter + 3 digit randomization code The crosswalk between participant identities and code number are kept at each site. The VA site will store the crosswalk electronically on the VA research drive. The list is only accessible to the personnel listed on the R&DC application. The Madigan crosswalk will be stored confidentially, accessible only to personnel on the Madigan IRB application per Madigan DCI protocols and approved application.

VA and Madigan Committees that oversee research (VA IRB, R&DC, Madigan Department of Clinical Investigation, Regional Health Command-Pacific IRB (Madigan) the Army Clinical Investigation Regulatory Office [CIRO])as well as the following regulatory bodies may have access to PHI, but will not be able to remove PHI from any facility: other Federal agencies including, but not limited to, the Food and Drug Administration (FDA), the Office for Human Research Protection (OHRP), the VA Office of Research Oversight (ORO), the VA Office of the Inspector General (OIG), Department of Defense (DOD), U.S. Army Medical Research and Materiel Command (USAMRMC) Office of Research Protections (ORP) Human Research Protection Office (HRPO), and the Government Accountability Office (GAO).

SIBCR will be provided with the full name, address, telephone numbers, and social security number of participants in order to authorize payment for participation in the study

Physical Transportation of Identifying or Sensitive Data: Because all data storage, entry, and analysis will take place at VA Puget Sound, copies of CRFs from Madigan subjects will be shipped via trackable method (Fed-Ex, UPS, etc.) or physically transported to VA Puget Sound by study staff in HIPAA-compliant locked containers.

There will be no physical transportation of data collected from participants at VA Puget Sound (only Madigan participants).

Electronic Transmission of Data: We are required by our funding agency to transmit research data and related findings to the FITBIR informatics system as described in section 7.0 above. FITBIR is a restricted access portal to search data relevant to TBI research. A FITBIR account is required to submit or access TBI-related data. Investigators and data managers at research sites are invited to request an account. To provide maximum protection for the confidentiality of research participants whose data is stored in FITBIR, professional credentials are verified by the FITBIR Data Access & Quality Committee (DAQ) during the account request process.

Data submitted to the FITBIR will be de-identified such that the identities of data subjects cannot be readily ascertained or otherwise associated with the data by the FITBIR staff or secondary data users. In addition, de-identified data will be coded using a unique code known as a GUID (Global Unique Identifier). Use of the GUID minimizes risks to study participants because it keeps one individual's information separate from that of another person without using names, addresses, or other identifying information. The unique code also allows FITBIR to link together all submitted information on a single participant, giving researchers access to information that may have been collected elsewhere. The GUID is a computer-generated alphanumeric code [example: TBI 1A462BS] that is unique to each research participant (i.e., each person's information in FITBIR—or each subject's record—has a different GUID). Creating the GUID involves several steps.

- The researcher uses his/her computer to enter pre-defined personal identifiers about research participants (e.g., birth name, date of birth) into a specific computer program provided by FITBIR. The program processes these personal identifiers at the researcher's site into several intermediary codes known as "hash codes." PII cannot be extracted from these hash codes; they are strictly one-way hash algorithms
- The hash codes are then sent from the researcher's institution to the GUID server at FITBIR where they are assigned a GUID. The GUID server also stores the hash code-to-GUID relationship to ensure that the same research participant consistently is assigned

the same GUID irrespective of whether he/she participates in different research studies or at different research sites.

- The GUID server returns the GUID to the researcher, who assigns it to the research participant's information.
- FITBIR cannot accept data without the GUID.

The GUID process has two important attributes: PII is never sent to the FITBIR system, and the GUID is a random number not generated from PII/PHI

Clinical Trials.Gov: A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law.

Final Disposition of Data: The link between study code and participant identity will be retained for six years after study closure, at which point it will be destroyed per guidelines in place at the time of destruction and all study data will become anonymous. Exceptions are if a participant agrees to specimen/data banking, the link will be retained indefinitely.

10.0 References

1. Tanielian T, Jaycox L, eds. *Invisible Wounds of War: Psychological and Cognitive Injuries, Their Consequences, and Services to Assist Recovery.* Santa Monica, CA: RAND Corporation; 2008.
2. Terrio H, Brenner LA, Ivins BJ, et al. Traumatic brain injury screening: preliminary findings in a US Army Brigade Combat Team. *J Head Trauma Rehabil.* 2009;24(1):14-23.
3. Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in U.S. Soldiers returning from Iraq. *N Engl J Med.* 2008;358(5):453-463.
4. Schwab KA, Ivins B, Cramer G, et al. Screening for traumatic brain injury in troops returning from deployment in Afghanistan and Iraq: initial investigation of the usefulness of a short screening tool for traumatic brain injury. *J Head Trauma Rehabil.* 2007;22(6):377-389.
5. Theeler BJ, Flynn FG, Erickson JC. Headaches after concussion in US soldiers returning from Iraq or Afghanistan. *Headache.* 2010;50(8):1262-1272.
6. Nampiaparampil DE. Prevalence of chronic pain after traumatic brain injury: a systematic review. *JAMA.* 2008;300(6):711-719.
7. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia : an international journal of headache.* 2013;33(9):629-808.
8. Evans RW. Expert opinion: posttraumatic headaches among United States soldiers injured in Afghanistan and Iraq. *Headache.* 2008;48(8):1216-1225.
9. Haas DC. Chronic post-traumatic headaches classified and compared with natural headaches. *Cephalalgia : an international journal of headache.* 1996;16(7):486-493.
10. Hoffman JM, Lucas S, Dikmen S, et al. Natural history of headache after traumatic brain injury. *J Neurotrauma.* 2011;28(9):1719-1725.
11. Theeler BJ, Erickson JC. Mild head trauma and chronic headaches in returning US soldiers. *Headache.* 2009;49(4):529-534.
12. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. *Cephalalgia.* 2004;24 Suppl 1:9-160.

13. Lew HL, Lin PH, Fuh JL, Wang SJ, Clark DJ, Walker WC. Characteristics and treatment of headache after traumatic brain injury: a focused review. *Am J Phys Med Rehabil.* 2006;85(7):619-627.
14. Patil VK, St Andre JR, Crisan E, et al. Prevalence and treatment of headaches in veterans with mild traumatic brain injury. *Headache.* 2011;51(7):1112-1121.
15. Ruff RL, Ruff SS, Wang XF. Headaches among Operation Iraqi Freedom/Operation Enduring Freedom veterans with mild traumatic brain injury associated with exposures to explosions. *J Rehabil Res Dev.* 2008;45(7):941-952.
16. Finkel AG, Yerry J, Scher A, Choi YS. Headaches in soldiers with mild traumatic brain injury: findings and phenomenologic descriptions. *Headache.* 2012;52(6):957-965.
17. Erickson JC. Treatment outcomes of chronic post-traumatic headaches after mild head trauma in US soldiers: an observational study. *Headache.* 2011;51(6):932-944.
18. Theeler BJ, Flynn FG, Erickson JC. Chronic daily headache in U.S. Soldiers after concussion. *Headache.* 2012;52(5):732-738.
19. Castillo J, Munoz P, Guitera V, Pascual J. Kaplan Award 1998. Epidemiology of chronic daily headache in the general population. *Headache.* 1999;39(3):190-196.
20. Dodick DW. Clinical practice. Chronic daily headache. *The New England journal of medicine.* 2006;354(2):158-165.
21. Lanteri-Minet M, Duru G, Mudge M, Cottrell S. Quality of life impairment, disability and economic burden associated with chronic daily headache, focusing on chronic migraine with or without medication overuse: a systematic review. *Cephalalgia : an international journal of headache.* 2011;31(7):837-850.
22. Gubata M, Boivin M, Cowan D, et al. *Tri-service disability evaluation systems database analysis and research.* Silver Spring, MD: Accession Medical Standards Analysis and Research Activity, Preventive Medicine Program, Walter Reed Army Institute of Research; 2013.
23. Theeler BJ, Mercer R, Erickson JC. Prevalence and impact of migraine among US Army soldiers deployed in support of Operation Iraqi Freedom. *Headache.* 2008;48(6):876-882.
24. Ilgen MA, Kleinberg F, Ignacio RV, et al. Noncancer pain conditions and risk of suicide. *JAMA Psychiatry.* 2013:1-6.
25. Baandrup L, Jensen R. Chronic post-traumatic headache--a clinical analysis in relation to the International Headache Classification 2nd Edition. *Cephalalgia : an international journal of headache.* 2005;25(2):132-138.
26. Ruff RL, Ruff SS, Wang XF. Improving sleep: initial headache treatment in OIF/OEF veterans with blast-induced mild traumatic brain injury. *J Rehabil Res Dev.* 2009;46(9):1071-1084.
27. Menkes DB, Baraban JM, Aghajanian GK. Prazosin selectively antagonizes neuronal responses mediated by alpha1-adrenoceptors in brain. *Naunyn Schmiedebergs Arch Pharmacol.* 1981;317(3):273-275.
28. Raskind MA, Dobie DJ, Kanter ED, Petrie EC, Thompson CE, Peskind ER. The alpha1-adrenergic antagonist prazosin ameliorates combat trauma nightmares in veterans with posttraumatic stress disorder: a report of 4 cases. *J Clin Psychiatry.* 2000;61(2):129-133.
29. Raskind MA, Peskind ER, Hoff DJ, et al. A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. *Biol Psychiatry.* 2007;61(8):928-934.

30. Raskind MA, Peskind ER, Kanter ED, et al. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. *Am J Psychiatry.* 2003;160(2):371-373.
31. Taylor FB, Martin P, Thompson C, et al. Prazosin effects on objective sleep measures and clinical symptoms in civilian trauma posttraumatic stress disorder: a placebo-controlled study. *Biological psychiatry.* 2008;63(6):629-632.
32. Germaine A. Efficacy of sleep intervention in military veterans in post-deployment adjustment disorders. Military Health Research Forum; 2009; Kansas City.
33. Wilkinson M. Migraine treatment: the British perspective. *Headache.* 1994;34(8):S13-16.
34. Van de Water AT, Holmes A, Hurley DA. Objective measurements of sleep for non-laboratory settings as alternatives to polysomnography--a systematic review. *J Sleep Res.* 2011;20(1 Pt 2):183-200.
35. Wallace DM, Shafazand S, Ramos AR, et al. Insomnia characteristics and clinical correlates in Operation Enduring Freedom/Operation Iraqi Freedom veterans with post-traumatic stress disorder and mild traumatic brain injury: an exploratory study. *Sleep Med.* 2011;12(9):850-859.
36. Welch KM. Drug therapy of migraine. *The New England journal of medicine.* 1993;329(20):1476-1483.
37. Jensen R, Brinck T, Olesen J. Sodium valproate has a prophylactic effect in migraine without aura: a triple-blind, placebo-controlled crossover study. *Neurology.* 1994;44(4):647-651.
38. Theeler BJ, Erickson JC. Posttraumatic headache in military personnel and veterans of the Iraq and Afghanistan conflicts. *Curr Treat Options Neurol.* 2012;14(1):36-49.
39. Dodick DW, Turkel CC, DeGryse RE, et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. *Headache.* 2010;50(6):921-936.
40. Silberstein SD, Lipton RB, Dodick DW, et al. Efficacy and safety of topiramate for the treatment of chronic migraine: a randomized, double-blind, placebo-controlled trial. *Headache.* 2007;47(2):170-180.
41. Silberstein SD, Dodick DW, Lindblad AS, et al. Randomized, placebo-controlled trial of propranolol added to topiramate in chronic migraine. *Neurology.* 2012;78(13):976-984.
42. VA/DoD. Clinical Practice Guideline for Management of Concussion/Mild Traumatic Brain Injury. *J Rehabil Res Dev.* 2009;46(6):CP1-68.
43. Vatz KA. Alpha 1-adrenergic blockers: do they have a place in the prophylaxis of migraine? *Headache.* 1997;37(2):107-108.
44. Bonuso S, Di Stasio E, Marano E, et al. The antimigraine effect of ergotamine: a role for alpha-adrenergic blockade? *Acta Neurol (Napoli).* 1994;16(1-2):1-10.
45. Paterna S, Martino S, Ingurgio NC, Arrostuto A, Correo S, Licata G. [The effects of terazosin hydrochloride and buflomedil in patients with hemicrania without aura]. *Clin Ter.* 1994;144(4):307-319.
46. Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine. Definition of mild traumatic brain injury. *J Head Trauma Rehabil.* 1993;8(3):86-87.
47. Cicerone K. Persistent post-concussive syndrome: Structure of subjective complaints after mild traumatic brain injury. *J Head Trauma Rehabil.* 1995;10:1-17.

48. Raskind MA, Peterson K, Williams T, et al. A trial of prazosin for combat trauma PTSD with nightmares in active-duty soldiers returned from Iraq and Afghanistan. *Am J Psychiatry.* 2013;170(9):1003-1010.
49. *Physicians Desk Reference.* 55th ed. Montvale, NJ: Medical Economics Company; 2001.
50. First MB WJ, Karg RS, Spitzer RL. Structured Clinical Interview for DSM-5—Research Version (SCID-5 for DSM-5, Research Version; SCID-5-RV). In. Arlington, VA: American Psychiatric Association; 2015.
51. Hoge CW, Castro CA, Messer SC, McGurk D, Cotting DI, Koffman RL. Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. *N Engl J Med.* 2004;351(1):13-22.
52. Stewart WF, Lipton RB, Whyte J, et al. An international study to assess reliability of the Migraine Disability Assessment (MIDAS) score. *Neurology.* 1999;53(5):988-994.
53. Kosinski M, Bayliss MS, Bjorner JB, et al. A six-item short-form survey for measuring headache impact: the HIT-6. *Qual Life Res.* 2003;12(8):963-974.
54. Buse DC, Sollars CM, Steiner TJ, Jensen RH, Al Jumah MA, Lipton RB. Why HURT? A review of clinical instruments for headache management. *Curr Pain Headache Rep.* 2012;16(3):237-254.
55. Weathers FW LB, Keane TM, Palmieri PA, Marx BP, Schnurr PP. The PTSD Checklist for DSM-5. In: PTSD NCf, ed2013.
56. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Res.* 1989;28(2):193-213.
57. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med.* 2001;2(4):297-307.
58. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: Validity of a brief depression severity measure. *J Gen Intern Med.* 2001;16(9):606-613.
59. Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. *Arch Intern Med.* 1998;158(16):1789-1795.
60. Iqbal S, Rogers W, Selim A, et al. The veterans RAND 12-item health survey (VR-12): What it is and how it is used.
61. Lipton RB, Bigal ME, Ashina S, et al. Cutaneous allodynia in the migraine population. *Ann Neurol.* 2008;63(2):148-158.
62. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society.* 2005;53(4):695-699.
63. Carney CE, Buysse DJ, Ancoli-Israel S, et al. The consensus sleep diary: Standardizing prospective sleep self-monitoring. *Sleep.* 2012;35(2):287-302.
64. Cortez MM, Digre K, Uddin D, et al. Validation of a photophobia symptom impact scale. *Cephalalgia.* 2019;39(11):1445-1454.
65. Diener HC, Bussone G, Van Oene JC, et al. Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. *Cephalalgia.* 2007;27(7):814-823.

66. Silberstein S, Lipton R, Dodick D, et al. Topiramate treatment of chronic migraine: a randomized, placebo-controlled trial of quality of life and other efficacy measures. *Headache.* 2009;49(8):1153-1162.
67. National Research Council. *The Prevention and Treatment of Missing Data in Clinical Trials.* Washington, DC: National Academic Press; 2010.
68. Little R, Rubin D. *Statistical Analysis with Missing Data, Second Edition.* Hoboken, NJ: John Wiley and Sons; 2002.