Prazosin and CSF Biomarkers in mTBI

MIRB# 00914

VA Rehabilitation Research and Development Service (RR&D)

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Version 4, Revised 11/02/2018

Abstract

Background and Rationale: A majority of neurodegenerative dementing disorders, including Alzheimer's disease, (AD), dementia with Lewy bodies (DLB) and chronic traumatic encephalopathy (CTE), now appear to be caused by the accumulation and aggregation of proteins that cause progressive damage to the brain. Recent preclinical results suggest that clearance of such neurotoxic proteins from the brain may be greatly increased during states where noradrenergic (NA) tone is decreased or blocked, such as anesthesia and normal sleep, but impaired in animal models of Traumatic Brain Injury (TBI). These results also suggest that clearance through this mechanism, which has been termed the 'glymphatic' system, is likely to be decreased in conditions where NA signaling is inappropriately maintained during sleep, such as posttraumatic stress disorder (PTSD).

Importantly, the rate at which toxins are cleared through the glymphatic system has been found to be under alpha-1 adrenergic receptor (AR) control, and the application of noradrenergic blockers such as the alpha-1 AR antagonist drug, prazosin, has been shown to increase waking clearance of these proteins to levels normally found during sleep or anesthesia. This suggests two important possibilities: first, that conditions in which the brain NA signaling is increased and sleep is impaired, such as posttraumatic stress disorder (PTSD) and TBI, may predispose people to decreased clearance of neurotoxic proteins associated with the development and progression of dementia; and second, that the use of prazosin may be able to prevent such effects.

Study Objectives, Specific Aims, and Hypotheses: We propose a two phase proof-of-concept pilot study in Veterans with PTSD and/or a history of mild or moderate TBI; phase I will be open label, and phase II will be randomized placebo controlled. It is hypothesized that prazosin (but not placebo) will decrease cerebrospinal fluid (CSF) concentrations of three established biomarkers of neurodegeneration: amyloid beta$_{42}$ (Aβ_{42}), total tau (tTau), and phosphorylated tau$_{181}$ (p-tau$_{181}$). Such a finding would be consistent with prazosin resulting in increased glymphatic clearance of neurotoxic molecules from the brain, and provide a rationale for larger scale studies of clinical evaluation of prazosin. Further, we will also characterize predictors and correlates of any observed effect, both in terms of the baseline characteristics of the participants showing an effect, and any clinical changes which correlate with change in CSF biomarkers.

Study Design: Sixty Veterans with a history of PTSD and/or mild or moderate TBI will receive either prazosin or placebo for a titration period plus 5 weeks. The first 22-37 of these participants will comprise phase I, and will receive open-label prazosin; in phase II, participants will be randomized to prazosin or placebo. CSF will be collected by lumbar puncture (LP) at pretreatment baseline and again after completion of 5 weeks of steady-dose study drug treatment. Unstable or serious medical conditions, conditions that are contraindications for LP, and conditions that are relative contraindications for the use of prazosin (hypotension, orthostatic hypotension, severe peripheral edema) will be exclusionary.

Relevance to VA Mission: If we find that prazosin increases clearance of potentially neurotoxic proteins, we will move towards confirmation in a larger sample and with additional endpoints, such as incidence of dementia. If confirmed, these results would provide the first rational pharmacologic treatment strategy for prevention of neurodegeneration and dementia following TBI and PTSD. They would also hold the potential of generalizing to the prevention of dementia related to other risk factors.

List of Abbreviations

ACT	Auditory Consent Trigrams
ACTH	Adrenocorticotropic hormone
AD	Alzheimer's disease
ADRA1A	Alpha-1a adrenergic receptor
ADRA2A	Alpha-2a adrenergic receptor
AEs	Adverse events
APOE	Apolipoprotein E
AQP4	Aquaporin 4
AR	Adrenoreceptor
AUDIT-C	Alcohol Use Disorders Identification Test - Consumption
Aβ	Amyloid beta
$A\beta_{42}$	Amyloid $beta_{42}$
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
BP	Blood pressure
BPH	Benign prostatic hypertrophy
CALHM1	Calcium homeostasis modulator 1
CAPS	Clinician-Administered PTSD Scale for DSM-V
CBOC	Community-based outpatient clinics
CBTi	Cognitive Behavioral Therapy for Insomnia
CCK	Cholecystokinin
CNS	Central nervous system
CoC	Federal Certificate of Confidentiality
COMT	Catechol-O-methyltransferase
CPRS	Computerized Patient Record System
CPT	Cognitive Processing Therapy
CRF	Corticotropin-releasing factor
CRFs	Case report forms
CRHR1	Corticotropin Releasing Hormone Receptor type 1
CRP	C-reactive protein
CRU	Clinical research unit

CSD-E	Consensus Sleep Diary-E
CSF	Cerebrospinal fluid
CTE	Chronic traumatic encephalopathy
CVLT	California Verbal Learning Test II
CYP19A1	Cytochrome P450, Family 19 Subfamily A polypeptide 1
DLB	Dementia with Lewy Bodies
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
DVBIC	Defense and Veterans Brain Injury Center
DVPRS	Defense and Veterans Pain Rating Scale
EKG	Electrocardiogram
EMDR	Eye Movement Desensitization and Reprogramming
FDA	Food and Drug Administration
FTLD	Frontotemporal Lobar Dementia
GAD-7	General Anxiety Disorders – 7
GAO	Government Accountability Office
GRIN2B	Glutamate receptor, ionotropic, N-Methyl D-Aspartate 2B
HA	Headache
HAM-D	Hamilton Depression Rating Scale
HIPAA	Health Insurance Portability and Accountability Act of 1996
HR	Heart Rate
IFIS	Intraoperative floppy iris syndrome
IGF-1	Insulin-like growth factor-1
IRB	Institutional Review Board
LP	Lumbar puncture
LRP-1	Low density lipoprotein receptor-related protein 1
MAO	Monoamine oxidase
MAPT	Microtubule-associated protein tau
MHP	Mental Health Professional
MIRECC	Mental Illness Research, Education, and Clinical Center
MoCA	Montreal Cognitive Assessment
mTBI	Mild traumatic brain injury

N3	NREM 3 sleep
NA	Noradrenaline
NCAM	Neural Cell Adhesion Molecule
NGF	Nerve growth factor
NMDA	N-Methyl D-Aspartate
NPY	Neuropeptide Y
NREM	Non-REM sleep
NSI	Neurobehavioral Symptom Inventory
OEF	Operation Enduring Freedom
OHRP	Office of Human Research Protections
OIF	Operation Iraqi Freedom
OIG	VA Office of the Inspector General
OND	Operation New Dawn
ORO	VA Office of Research Oversight
p-tau	Phosphorylated tau
p-tau$_{181}$	Phosphorylated tau$_{181}$
PCL	PTSD Checklist
PDR	Physicians' Desk Reference
PE	Prolonged Exposure therapy
PHQ-9	Patient Health Questionnaire-9
PLPHA	Post-lumbar puncture headache
PSQI	Pittsburgh Sleep Quality Index
PTSD	Posttraumatic stress disorder
PVT	Psychomotor Vigilance Test
QCC	Quantification of Cannabis Consumption
R&DC	Research and Development Committee
RCT	Randomized clinical trial
REM	Rapid eye movement sleep
SAE	Serious adverse event
SCID	Structured Clinical Interview for DSM-5
SDMT	Symbol Digit Modalities

SLC6A2	Solute carrier family 6 member 2 (gene name)
SMs	Servicemembers
SUCLG2	Succinyl-CoA ligase subunit beta
TLEQ	Traumatic Life Events Questionnaire - Modified
TOMM40	Translocase of outer mitochondrial membrane 40
tTau	Total Tau
VA	Department of Veterans Affairs
VR-12	Veterans RAND-12
WTAR	Wechsler Test of Adult Reading

Contents

1.0 Study Personnel

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2.0 Introduction

Although the exact cause of neurodegenerative dementing disorders varies, a majority of them – including Alzheimer's disease (AD), dementia with Lewy bodies (DLB), frontotemporal lobar dementia (FTLD), and chronic traumatic encephalopathy (CTE) – now appear to be caused by the accumulation of abnormal aggregates of insoluble proteins that cause progressive damage to the brain parenchyma[1, 2]. Recent evidence has suggested that the clearance of many such proteins from the brain may occur primarily during sleep[3-5], and may in particular be dependent on the dramatic decrease in noradrenergic (NA) tone known to occur during rapid eye movement (REM) and non-REM slow wave sleep, particularly what is most commonly referred to as stage III, or "N3", sleep[4].

These findings suggest that pathologic states that lead to inappropriately preserved NA tone during sleep, such as PTSD[6, 7], may predispose to development of neurodegenerative dementing disorders by impairing clearance of neurotoxic proteins[8-10] – but that reversal of the inappropriately preserved NA tone may be protective against this increased risk. Furthermore, these findings suggest that even in individuals without pathologically increased NA tone during sleep, further lowering of NA tone during both wake and sleep may be able to increase protein clearance above even baseline levels, and by doing so decrease the risk of AD or other forms of dementia in individuals with increased protein accumulation due to other predisposing factors, such as due to increased aberrant tau accumulation in TBI.

Prazosin is a selective α_1 AR antagonist that has been used widely for many years to treat hypertension and urinary outflow restriction secondary to benign prostatic hypertrophy (BPH), and, more recently, as a treatment for trauma nightmares and other hyperarousal symptoms in PTSD and for reducing alcohol consumption in alcohol use disorders[11-13], as well as for ameliorating post-concussive headaches[14, 15] and managing disruptive agitation in dementia[16]. Prazosin has long been FDA approved, is widely available as inexpensive generic preparations, and has a long track record of safety. Thus, prazosin is a rational choice for interrupting

inappropriately high NA tone during sleep, and for seeking to convert low waking levels of neurotoxic protein clearance to that seen during sleep, in humans with or without inappropriately high NA tone during sleep. In addition, prazosin was in fact one of the alpha-blocking medications used in the original research linking the blocking of NA signaling to increased CSF flow through the brain[5], and has since been shown to be the specific NA blocking mediator of increasing CSF flow and neurotoxin clearance (Nedergaard, personal communication), further validating its use in this context. However, there is nothing currently known in humans about the potential of prazosin for increasing clearance of neurotoxic proteins and thus providing a preventive strategy for neurodegenerative dementias.

Given the potential importance of this potential neuroprotective strategy and the safety and likelihood of efficacy of this intervention, we are proposing an initial proof-of-concept clinical trial of the feasibility and efficacy of prazosin as an intervention to ameliorate risk factors for neurodegenerative dementia. We hypothesize that prazosin will antagonize NA activity during sleep and waking to increase clearance of neurotoxic proteins. This is a biomarker-based proof-of-concept study in which we will measure concentrations of widely-accepted CSF biomarkers of neurodegeneration as our primary outcome measure. Our trial design will additionally allow us to characterize baseline patient characteristics that are predictive of the presence or magnitude of change in CSF biomarkers, as well as any clinical changes, such as changes in sleep or behavioral, cognitive or somatic symptoms, that correlate with the presence or magnitude of change in CSF biomarkers.

3.0 Objectives

We are proposing an initial, biomarker-based proof-of-concept pilot trial of prazosin as a pharmacologic intervention to ameliorate PTSD and/or mild or moderate TBI as risk factors for neurodegenerative dementia. In phase I, participant will receive open-label prazosin; in phase II, participants will be randomized to double-blind prazosin or placebo. CSF $A\beta_{42}$, total tau, and p-tau_{181} will be measured prior to study drug initiation and following a titration period plus 5 weeks of steady-dose treatment with study drug. Quantitative and qualitative biologic measures likely to have predictive value for identifying individual variations in efficacy, including genetic markers, known or suspected indicators of central NA tone, and data on sleep, will also be collected.

Specific Aims and Hypotheses:

Aim 1: We will test for an effect of prazosin in decreasing CSF biomarkers of neurodegeneration and dementia. Specifically, we will test the primary hypothesis that prazosin administration over a titration period plus 5 weeks of steady-dose treatment will produce a consistent change across all groups in CSF concentrations of $A\beta_{42}$, total tau and p-tau_{181}.

Aim 2: We will characterize predictors and clinical correlates of any observed effect of prazosin on the CSF concentrations of $A\beta_{42}$, total tau and p-tau_{181}. Specifically:

- Aim 2a: We will test the primary hypothesis that the magnitude of any observed effect will correlate across all groups with the degree of quantitative evidence of baseline sleep disruption – either short total sleep time or fragmented sleep – as measured by actigraphy.
- Aim 2b: We will carry out an exploratory analysis of the relationship of any observed effect of prazosin on both CSF biomarkers of neurodegeneration and dementia and symptomatic rating scales with genetic markers associated with increased risk and/or progression of neurologic disorders and brain injury, as well as genetic markers associated with the uptake

and biologic distribution of orally consumed drugs.

- Aim 2c: We will carry out exploratory analyses of correlations between any observed efficacy of prazosin and additional baseline and post-treatment clinical assessments, including psychiatric symptom rating scales, pupillometry measurements, and baseline blood pressure and heart rate.

4.0 Resources and Personnel

Research procedures will be conducted at VA Puget Sound, Seattle Division. Study personnel as listed on the Institutional Review Board (IRB) and Research and Development Committee (R&DC) applications will have access to protected health information, will be involved in recruiting participants, will obtain consent, will conduct study interviews, and will administer study instruments. Generally, the staff includes Clinicians, Raters, Psychometrists, Study Coordinator(s), and Research Assistant(s) as described below.

Description of Study Personnel:
Study Clinicians: will perform safety assessments and examinations, make decisions regarding the dose titration schedule for individual participants, and make any necessary unscheduled dose changes. The Study Clinician will be a physician, physician assistant, or nurse practitioner with experience conducting clinical research in Veterans with TBI and with PTSD.

Study Raters: will administer all interview-based assessments. Raters will be master's level social workers or other study professionals who have extensive experience in performing these assessments in this study population.

Psychometrists(s) and/or Neuropsychologists: will administer all neuropsychological testing (as described in the study procedures section below). Psychometrists will be experienced and will have been trained by a neuropsychologist.

Study Coordinator(s) and Research Assistant(s): will be responsible for scheduling visits, conducting the portions of study visits that do not require clinicians, maintaining case report forms (CRFs), preparing reports for the IRB and subcommittees, and assisting the data manager.

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 on a weekly basis by a study Research Assistant under the supervision of the Database Manager. The Database Manager will generate weekly 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 on a weekly basis.

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.

5.0 Study Procedures

Overview: We are proposing an initial, biomarker-based proof-of-concept pilot randomized clinical trial (RCT) of prazosin as a pharmacologic intervention to ameliorate PTSD and/or mild to moderate TBI as a risk factor for neurodegenerative dementia in Veterans. There will be two phases. In phase I, participants will all receive open-label prazosin. In phase II, participants will be randomized to double-blind prazosin or placebo. In each case, the study drug will be maintained for 5 weeks once full dose is reached. The first 5-8 weeks will be a titration period,

where the dose of prazosin or placebo will be increased at regular intervals to a maximum dose of 25 mg in divided doses (see section 5.5 below for detailed description of dose titration). All procedures for this study are research procedures; none are standard of care.

Study Population: Participants will be Veterans from any conflict with a history of mild or moderate TBI, plus Veterans from any conflict with a current diagnosis of PTSD. Persons of all races, ethnicities, and genders are eligible to participate. Some participants may be VA employees. However, we are not targeting employees as a study population. Any VA employee will complete study visits on their off-duty time. Based on previous experience we expect a screen-failure and dropout rate of 30% each, requiring for phase I 29 participants to be screened in order to obtain an enrollment of 22, and requiring for phase II 120 participants to be screened in order to obtain an enrollment of 90 participants with at least 60 completers.

Procedures: Participants will undergo a lumbar puncture (LP) and will have blood samples collected prior to initiation of study drug and following 5 weeks at maximal dose of study drug. Blood collection for DNA analysis will also be done at the time of the first LP. Symptom assessments, neurocognitive testing, and quantitative and qualitative biologic measures likely to have predictive value for identifying individual variations in efficacy, including data on autonomic functioning and sleep, will also be collected both at baseline and at the time of completion.

Samples will be used for measurement of CSF biomarkers (total tau, p-tau181, Aβ42, F2-isoprostanes, brain-derived neurotrophic factor [BDNF], neuropeptide Y [NPY], corticotropin-releasing factor [CRF], hypocretin, nerve growth factor [NGF], Cholecystokinin [CCK], dynorphin, a cytokine panel, catecholamines [norepinephrine, epinephrine, and dopamine], indoleamines [serotonin] and their precursors and metabolites), serum and plasma biomarkers (fasting lipids, C-reactive protein [CRP], adrenocorticotropic hormone [ACTH], cortisol, total testosterone, insulin-like growth factor-1 (IGF-1), and catecholamines), RNA, microRNAs, and proteomics.

Proteomics, similar to genomics, is an unbiased method that simultaneously assesses thousands of proteins. There are several CSF biomarkers that reflect particular facets of neurodegeneration. Conducting a large-scale survey of potential CSF biomarkers will allow us to define a panel of biomarkers that may discriminate treatment effects and provide insight into as yet unknown mechanisms of action.

We will be studying the following genes: *APOE*, *MAPT*, *AQP4, LRP-1, SUCLG2, GRIN2B, ADRA1A, NCAM, CYP19A1, TOMM40, CALHM1*, *MAO-A* and *COMT* (see below for more detailed discussion of each gene's connection to the study); overall, each gene has been implicated in the mechanism or regulation of glymphatic flow, the progression of AD, the regulation of biomarkers of AD in CSF, and/or the metabolism of NA.

At the conclusion of the study, participants who have obtained relief of symptoms they may be experiencing during the study and who are interested in continuing on the medication will be provided with appropriate referrals to providers to prescribe prazosin for clinical care purposes, and will be provided with a bridging supply of the medication at the dose on which they had been stabilized.

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. All study medications will be shipped to the investigational pharmacist at VA Puget Sound. Study drug may be stored at room temperature. Unused drug will be disposed of by the investigational pharmacist 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 IND 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 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, and requirement v. is satisfied in that we are not promising any benefit from the use of prazosin in this study.

Foreseeable Risks:

Venipuncture and i.v. placement: May cause transient pain and bruising at the site of the needle stick. Infrequently, participants may experience fainting or dizziness and there is also a slight risk of infection at the site of the needle stick.

Genetic Studies: We will be studying the following genes: *APOE, MAPT, AQP4, LRP-1, SUCLG2, GRIN2B, ADRA1A, NCAM, CYP19A1, TOMM40, CALHM1, MAO-A,COMT, CRHR1, SLC6A2,* and *ADRA2A*. *APOE* and *MAPT* have been associated with increased risk and/or progression of various neurological disorders as well as brain injury. The *APOE-4* allele has been implicated as a risk factor for development of AD in later life. However, *APOE* type should not be considered a genetic test for AD since the results will not conclusively determine whether a person or any of his/her relatives have or might develop AD. *MAPT* codes for the microtubule associated protein tau, whose transcript gives rise to a variety of splicing variants including the

[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.

tau protein that accumulates in multiple neurodegenerative diseases. The rest of the genes we are studying have even less clear clinical interpretation at present, and are considered entirely experimental / investigational in their interpretation.

Participants are informed that currently, the results of these genetic tests do not have any clinical relevance and will be used for research purposes only. Participants will not be informed of their genotyping results. Participants will be told that if they wish to know their *APOE* genotype, that they can have the testing done at a commercial lab at their own expense.

The Genetic Nondiscrimination Act of 2008 protects participants against risks to employability and access to health insurance due to participation in genetic studies. However, it is theoretically possible that participation in genetics studies may jeopardize access to life insurance, disability insurance, or long-term care insurance if involvement and/or results of the study become part of the medical record. Procedures to minimize such risk are described below.

Clinical Assessment and Neuropsychological Testing, including pupillometry: Risks due to clinical assessment procedures are modest. Participants may experience stress similar to that of a standard clinical evaluation for memory complaints or dementia. Participants may also receive information that they are cognitively impaired. Such information may be distressing to a participant. The neuropsychological assessment battery may cause fatigue and/or unpleasant affective states due to the large number of individual tests. For the pupillometry portion of the neurocognitive testing, participants will be expected to keep their head relatively still, with their chin resting on a chin-rest platform, for approximately 15 minutes, which can be mildly uncomfortable. Some of the clinician and self-administered assessment instruments may cause participants to focus their attention on traumatic war-zone related experiences and as a result may produce transient subjective distress. However, these war-zone experiences are routinely assessed and discussed as part of standard clinical care.

Actigraphy, Ambulatory blood pressure (BP) and heart rate (HR) measurement: Wearing an Actiwatch for actigraphy measurements can be uncomfortable. Wearing the ambulatory BP monitor can be uncomfortable, and the intermittent inflation of the cuff can be both uncomfortable and can cause anxiety by occurring at unexpected times.

Wearing the ambulatory HR monitor can be uncomfortable as well. Some people find that the leads irritate their skin over time. The leads can also cause discomfort at the time of removal if they are placed over chest hair.

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 which may have interactions with other medications, it will be documented in the participant's medical record that they may be taking prazosin. We plan on obtaining a Federal Certificate of Confidentiality (CoC) to protect information collected. The study team will have access to VA Computerized Patient Record System (CPRS) records from initial consent until 30 days beyond the end of study participation. Results of clinically indicated screening labs will be placed in the participant's CPRS record and will be available to any of the participant's other VA health care providers or any health care providers to whom a participant releases his/her medical records.

Prazosin: There are no known absolute contraindications to prazosin. In clinical trials of prazosin, the most frequent adverse reactions were: dizziness (10%), drowsiness (8%), headache (8%), lack of energy (7%), weakness (7%), palpitations (7%), and, nausea (5%). Less frequent

adverse reactions (1-4%) reported in clinical trials were: vomiting, diarrhea, constipation, edema, orthostatic hypotension, dyspnea, syncope, vertigo, depression, nervousness, rash, urinary frequency, blurred vision, reddened sclera, epistaxis, dry mouth, and nasal congestion. Fewer than 1% of patients have reported the following (causal relations sometimes not established): abdominal discomfort or pain, liver function abnormalities, pancreatitis, tachycardia, paresthesias, hallucinations, pruritus, alopecia, lichen planus, incontinence, impotence, priapism, tinnitus, diaphoresis, fever, positive ANA titer, and arthralgia.

Prazosin may cause syncope. 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.

Headache (HA) is listed in the Physician Desk Reference (PDR)[17] as a potential adverse reaction to prazosin, reported in as many of 8% in early clinical trials. However, in our experience, the incidence of this is lower. In a placebo-controlled pilot study evaluating use of prazosin for treatment of PTSD in Iraq and Afghanistan active-duty servicemembers (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 these 22 had worsening of their HAs, and 1 of 4 participants with no prior HAs developed HAs. In contrast, 11 of the 22 with baseline HAs had improvement or complete resolution of their HAs while on prazosin.

Regarding mood alterations, although depression is listed in the PDR 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. Ham-D scores actually improved more in the prazosin vs. placebo group (5.3 vs. 0.7, $t=1.9$ [2-tailed], $p=0.07$)[18]. 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 participants have reached their stable dose, erectile dysfunction medications will be allowed at 1/2 the usual clinical dose.

In our current study of prazosin in active duty service members 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.

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.

Lumbar Puncture: The risk of serious effects from LP (infection, nerve root damage) is extremely low. Rarely, patients may experience transient local pain either at the site of the puncture or in the distribution of the sciatic nerve if the nerve roots of the *cauda equina* are stimulated. Because the LP is performed well below the termination of the spinal cord and because the nerve roots readily move aside from the spinal needle, the possibility of permanent damage to a nerve root is very remote. Participants with blood clotting abnormalities, on anticoagulant medications, or with inadequate platelet function will be excluded. A previously common (approximately 20% in young persons) adverse effect was post-LP headache. The incidence of headache is a function of the diameter and type of spinal needle used and not the amount of fluid removed.

We have instituted use of the 24g Sprotte atraumatic bullet tip spinal needle. Use of the Sprotte needle has been recommended in the American Academy of Neurology practice parameter on post-lumbar puncture headache[19]. Both the literature and our experience in performing over 1000 LPs with the Sprotte 24g needle indicate that we may anticipate a low risk of post-LP headache of less than 1% [20-23]. Among the approximately 1000 LPs with the Sprotte 24g needle, we have had only 2 severe post-LP headaches that required intervention with epidural blood patch.

In addition, it should be noted that removal of up to 30 cc of CSF does not increase the incidence of headache since CSF is rapidly produced. Since CSF is produced normally at the rate of 0.35cc/5 minutes, it is estimated that the amount of CSF withdrawn will be replaced in about 6-7 hours. Post-LP headache is thought to occur due to a persistent leak of CSF from the hole left in the dura by the larger bore (18-20g) Quincke cutting spinal needle used in commercial LP kits, rather than the amount of CSF removed acutely. This leads to a depletion of the normal CSF hydraulic "cushion" and leads to a headache the day after the procedure. Use of the noncutting 24g Sprotte atraumatic spinal needle greatly reduces post-LP headache risk. We further reduce the risk of CSF leak by having participants remain in a recumbent position for one hour after the procedure, having them increase their fluid intake, and by instructing them to not engage in any exertion for the 48 hours following the procedure. All investigators performing LPs are very experienced in performing this procedure in these subject populations.

Headaches following LP, if they occur, are usually mild to moderate and may last for 24-48 hours; such headaches are successfully managed with acetaminophen and caffeine. In unusual cases, typical post-LP headache, which is posturally sensitive, may occur; these may be fairly severe and can last as long as a week with conservative management. Our approach to treatment of severe typical post LP headache is the epidural blood patch, performed on the first morning of severe post-LP headache (usually the day following LP). Epidural blood patch consists of the injection of 30 ccs of the participant's own blood into the epidural space over the lumbar puncture site. This procedure is done by an anesthesiologist and usually provides immediate relief of post-LP headache. The Anesthesiology Service at VA Puget Sound Health Care System has agreed to perform these procedures if necessary and has quite graciously and successfully performed them in the past.

There is also a small risk of infection at the site of the LP, although sterile technique will be used. Participants will be given the option to have lidocaine used in placement of the IV catheter used before LP, and lidocaine will be used to provide local anesthesia at the LP site. Occasionally, an allergic reaction to the lidocaine such as transient stinging (less than 1 minute)

at site of injection and rare dermatitis can occur. Participants will be asked if they have a history of lidocaine allergy.

We analyzed data from 428 research LPs performed on 342 subjects (67 with AD or MCI, and 275 cognitively normal adults). The frequency of any adverse event (11.7%), clinically significant adverse events (3.97%), and typical post-lumbar puncture headache (PLPHA) (0.93%) was low. Risk of PLPHA was unrelated to age, gender, position during LP, mls CSF collected, or minutes of recumbent rest following LP[22].

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 (see below). A study clinician 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.

Risk management for prazosin: vital signs, including orthostatic BP and HR will be performed at all study visits. Systolic and diastolic BP and HR will be obtained following 10 minutes of supine posture, and repeated following 2 minutes of standing. Occurrences of lightheadedness, dizziness on standing, palpitations, drowsiness, nausea, nasal congestion, peripheral edema, headache, and other adverse effects will be rated by the clinician. For vital signs parameters, unacceptable side effects will include supine 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 participants 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 (BPH). It has been safely prescribed to large numbers of middle-aged and older people over the past 35 years. The following information regarding the side effect profile and safety record or 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. 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.

Female participants of childbearing potential will have a urine pregnancy test at screen. Urine pregnancy test must be negative within one week of taking the first dose of study medication. If more than one week has elapsed since the screening visit, urine pregnancy test will be repeated. Women of childbearing potential with either positive pregnancy test at screen or refusal to avoid activities that may result in pregnancy or take precautions to avoid the possibility of becoming pregnant while participating in this study will be excluded. Contraception is not required after completion of study. Contraception is not required for male participants.

Risk management for LP: Women of childbearing potential will have a negative urine pregnancy test before undergoing any LP procedures. Pain at the needle insertion site will be minimized by adequate local anesthesia with subcutaneous injection of 1% lidocaine. We will use an atraumatic 24g Sprotte spinal needle which is associated with a reduced risk of adverse events, including post-LP headache. The Sprotte needle has been recommended in published guidelines for reducing risk of post-LP headache. We have performed over 1000 LPs since we began using the Sprotte spinal needle and in our hands, risk of post-LP headache is 0.5%.

We reduce the risk of CSF leak by having the participant lie in bed for one hour after the procedure, having them increase their fluid intake, and by instructing participants not to engage in any strenuous activity for the 48 hours following the procedure. All investigators performing LPs are very experienced in performing this procedure in these subject populations.

We provide a snack of chips and a mountain dew (or other caffeine-containing beverage) to participants after the LP. We have found in the past that giving participants something salty and something with caffeine lowers the risk of mild-moderate headaches. Participants will also be given the choice of lunch or a voucher to use in the VA cafeteria after the LP if they wish.

Lastly, if the participant wishes, the participant's spouse, other family member, or friend may be present in the room during the LP, and is able to help keep the participant relaxed and comfortable.

Risk Management for venipuncture and i.v. placement: All such procedures will be performed by experienced study staff using sterile technique.

Risk management for Actigraphy and ambulatory BP and HR measurement Some people find that wearing a sweatband under the wrist strap of the Actiwatch helps. Participants will be instructed to remove the Actiwatch if it interferes with sleep. The overall comfort of wearing the BP cuff for an extended period of time is maximized by providing disposable covers designed to reduce irritation and rubbing of the cuff against the skin. The anxiety and discomfort of the periods of inflation are minimized through the use of a "comfort setting" on the Actiwave monitor, which shapes the waveform of the initial pressure inflation to minimize both sudden increases in and peak pressures. The intermittent inflation of the cuff can also disrupt sleep briefly around each assessment, the impact of which is minimized by taking only the minimum number of measurements to provide a representative assessment of blood pressure during sleep, and by minimizing the total number of nights of recording.

Discomfort from the HR measurement equipment can be addressed by minimizing the total amount of recording time as well as allowing participants to move the leads to alternate locations on the chest if necessary. For some participants, we may recommend that participants remove chest hair at the specific recording locations.

When these devices are returned to study staff, the information will be downloaded immediately. If any abnormal readings are discovered, they will be reviewed by a study physician. If the physician, based on their review and possibly additional information gathered from the subject, believes the results to be clinically significant, the participant will be notified of the finding, and referred for follow up with their primary care provider.

The Actiwatch and HR monitors can be worn in the shower, but should not be submerged in water for long periods of time. The ambulatory blood pressure monitor should not get wet, as it would ruin the equipment. All devices can be safely and easily removed by participants at any point if they find them too uncomfortable or wish to do so for any other reason.

Risk Management for questionnaires and assessments: To prevent the development of fatigue and/or unpleasant affective states due to the subject matter and the large number of individual tests, participants will be able to take breaks between individual tests. Snacks and water will also be available to participants during the longer study visits. Participants are free to refuse to answer any question.

Risk Management for loss of confidentiality: We plan on obtaining a Federal Certificate of Confidentiality to protect against compelled disclosure of answers to the questionnaires. We will keep study records and data in a secure location, either in locked filing cabinets in locked rooms or on restricted-access, password-protected computers which meet all VA-mandated data security standards. Identifying information will not be stored with study data.

Safety procedures specific to the war zone 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 patient or others. For participants enrolled in the study, requiring psychiatric interventions to manage deterioration of clinical status will result in early study termination, and appropriate crisis management by a study clinician, in conjunction with the participant's primary mental health care provider and referral to outpatient or inpatient psychiatric care at each study site.

In addition, due to the increased scrutiny surrounding studies of persons with comorbid depression, we will specifically ask about suicidal ideation at each study visit. Participants who endorse suicidal ideation will be assessed as to their level of risk and the level of care required to keep themselves or others from harm. If a patient requires inpatient treatment in order to prevent harm but is unwilling to accept that care, referral will be made to the county-designated Mental Health Professional (MHP) and the patient will be supervised in a safe setting in the VA Puget Sound emergency department until evaluated by the MHP and appropriate disposition made. In a similar fashion, patients that are found to have symptoms of disorganized thought processes secondary to psychosis would be accompanied by study personnel for emergency psychiatric evaluation at VA Puget Sound.

Safety Monitoring: We do not intend to establish a data safety monitoring board for this study. However, all adverse events (AEs) and serious AEs (SAEs) will be recorded and communicated to the study PI or other study clinician as soon as they are discovered. If AEs occur at a greater

rate or with greater severity than previously encountered in our other prazosin studies, the study will be suspended and the IRB notified. We will then work with the IRB to determine if and when the study should be re-started.

Unanticipated AEs (physical complaints that are not present at baseline and which may be related to study procedures) and AEs which are more serious than anticipated, but are not SAEs will be reported to the IRB at the time of the annual report. SAEs (defined as any untoward medical occurrence which may be related to study participation at any time during the study that results in participant death, is life threatening, requires hospitalization, or results in persistent or significant disability/incapacity) will be reported to the IRB within 5 business days of being reported to the PI.

Adverse Events: all treatment for adverse events related to the study will be provided free of charge. The Department of Veterans Affairs (VA) authorizes treatment for any study approved by a VA R&DC. Participants who seek treatment for study-related adverse events in a non-VA facility will be reimbursed for treatment costs. We have adequate personnel and equipment to respond to expected and unexpected adverse events.

Specimen Banking: Participants may be asked to sign a separate consent form to allow us to bank any samples leftover after study analyses for future research. This consent form will be approved under a different IRB application. Information about potential specimen banking is included in the consent form for this study. Participants may decline specimen banking and still participate in this study.

Consideration of Potential Risks vs. Potential Benefits: All components of this study (use of the medication prazosin, LPs, IV line placement, clinical assessments, cognitive assessments, and actigraphy) are procedures routinely used in a wide variety of clinical settings in diverse populations. There is currently no established or suspected intervention available to increase clearance of neurotoxic protein biomarkers of neurodegeneration and dementia. This is an adjunct study, so no usual care or alternative intervention will be avoided or delayed through participation in this study.

Participants will not benefit from study procedures. Through participation in this research, all participants will receive thorough medical and psychiatric assessments, which may benefit them by providing them information about these assessments. Society at large will benefit if treatments to increase clearance of neurotoxic proteins are discovered through this research.

If we can demonstrate that prazosin increases clearance of potentially neurotoxic proteins, this will provide perhaps the first rational pharmacologic treatment strategy for prevention of post repetitive mTBI CTE, and a novel approach for reducing the long-term increased risk of Alzheimer's disease following both TBI and PTSD.

5.1 Recruitment Methods

Description of the Recruitment Process: Participants will be recruited via referrals from VA outpatient clinics, including MIRECC mTBI/Behavioral Specialty, Neurology, Primary Care, Mental Health, Neuropsychology, Rehabilitation Medicine, Polytrauma, and others; VA community-based outpatient clinics (CBOCs); local area Veterans centers; National Guard and Reserve units; hospital health fair and hallway information tables; advertisement on VA electronic reader-boards; public outreach presentations; posted IRB-approved advertising in highly trafficked areas and clinic waiting rooms; advertisements in newsletters, local

newspapers, radio, and the Internet; presentations to appropriate clinical services (such as grand rounds presentations or service staff meetings); and word-of-mouth. All recruitment materials will be submitted to and approved by the IRB before use.

Interested potential participants will contact the study team for more information. In addition, if a clinical provider documents in their clinical note that a Veteran has expressed interest in receiving information about the study, and the provider notifies us of this, we will contact that Veteran directly; the request for contact (documentation in a CPRS note and co-sign to study team) and the outcome will be documented in the pre-screen log. Please note that the note will only say that the provider spoke to the patient about research, and that the patient has given permission for the team to contact him/her, but will not include details about the type of research. We may also contact a Veteran directly if they are in the BNG registry and have indicated that they would like to hear about future research opportunities, or we have sent them the mailing with opt-out information, but have not received an opt-out request. When we make contact with a Veteran who has expressed interest, the study will be described privately either over the phone 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 for an initial screening visit. The study consent form will be sent to potential participants for their review prior to that visit.

Compensation: Participants will be compensated per the table below:

Type of Visit	**Amount of reimbursement per visit**	**Total Reimbursement**
Screen	$100	$100
Behavioral/Cognitive testing and questionnaires	$50 (2 visits)	$100
Sample Collection (LP, blood)	$200 (2 visits)	$400
Titration and safety visits	$25 (up to 7 visits)	up to $175
Potential extra titration visits	$25 (0-3 total visits)	up to $75
Total for completed study **without** extra titration visits:		$775
Total for completed study **with** extra titration visits:		up to $850

Payments will be pro-rated, based on the number of completed study visits and weeks of actigraphy. In addition, 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. This rate of compensation complies with the VA Puget Sound IRB guidelines for prevention of research study participant financial coercion.

Small snacks (such as trail mix or granola bars) and water will be available for participants during and/or following visits involving sample collection and neurocognitive testing. Participants will be given lunch or a voucher to use in the VA cafeteria after LPs.

Payments for the screen and baseline 1 and 2 visits will be contingent on the return of all equipment loaned to the participant for home use prior to these visits. Payments for the two parts of the End of Study visits will be similarly contingent on the return of all loaned equipment prior to the end of the study.

At the end of the study, participants will be given a certificate of appreciation and a tote bag to thank them for study participation.

5.2 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 participant'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 CPRS. If we require non-VA medical records, a written Release of Information will be obtained.

Personnel who will be obtaining Informed Consent: Before co-Investigators and study staff are considered qualified to obtain consent, they must first undergo all VA 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 co-Investigator or 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, PA, or nurse practitioner) 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 Screening visit before study procedures are performed. If an investigator is also the potential participant's primary health provider, an alternate will conduct the consent 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 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 60%/30% chance of being randomized to either treatment (active medication or placebo)
- Participation is entirely voluntary and that the participant 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 IRB before any study procedures are performed. A progress note will be written in the participant's study chart to document the consent discussion was conducted and all questions were answered to the participant's satisfaction. A note will also be placed in CPRS records per current VA Puget Sound guidelines.

A copy of the informed consent form can be given or mailed to interested potential participants to review and discuss with family members or their primary physician without any time limit.

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

5.3 Inclusion/Exclusion Criteria

Inclusion criteria:

- Age ≥ 21 years
- Veteran of the U.S. Armed Forces
- Ability to complete psychometric and other clinical assessments in English
- No clinically significant laboratory abnormalities at screen
- Platelet count >100,000/mm2 within two weeks of lumbar puncture (LP)
- Body mass index (BMI) between 18 and 36 inclusive (BMIs outside this range may make LPs for CSF collection difficult to perform). If a potential participant has a BMI over 36 but still in the 30s, they may be included if the clinician determines an LP would not be difficult to perform.
- Women 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 study clinician during the study. Men are not required to use contraception during the study
- Meeting criteria for at least one of the following:
  1. History of mild or moderate TBI:
     - Exposure to at least one blast or experiencing at least one collision of the head associated with acute symptoms that meet VA/DoD criteria for mild or moderate TBI (loss of consciousness, if present, <24 hours; posttraumatic amnesia, if present, <1 week; Glasgow Coma Scale (if available) 9-15)
     - >6 months since last TBI.
  2. Documented diagnosis of PTSD related to combat trauma (from any conflict)

Exclusion criteria:

- Medical
  - History of severe TBI (Glasgow Coma Scale (if available) <9, loss of consciousness >24 hours, posttraumatic amnesia >1 week)
  - Acute or unstable chronic medical illness, including unstable angina, recent myocardial infarction (within 6 months), congestive heart failure, preexisting hypotension (systolic <110) or orthostatic hypotension (systolic drop > 20mmHg after two minutes standing or any drop accompanied by dizziness), autoimmune disorders; insulin-dependent diabetes;

HIV.
  - Chronic renal or hepatic failure, acute pancreatitis, Meniere's disease, benign positional vertigo, narcolepsy, or diagnosed untreated sleep apnea (sleep apnea currently being treated is not exclusionary).
  - Contraindications to LP (e.g., spinal cord injury; deformity, severe disease or infection in the region of the lumbosacral spine; bleeding tendency, clotting abnormalities, use of anticoagulant medications, or platelet count <100,000/mm2); trauma or infection in the 4 weeks before LP
  - Current pregnancy or lactation. Women 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 study clinician during the study. Men are not required to use contraception during the study.

Note: Wounds requiring surgery, embedded shrapnel, and recent surgical amputation do not comprise an exclusion if the individual is otherwise medically eligible.

- Psychiatric/Behavioral
  - Meets DSM(IV or 5, depending on what evaluative method was used in this subject) criteria for current schizophrenia, schizoaffective disorder, other specified or unspecified psychotic disorder, delirium, or any DSM cognitive disorder
  - Current substance use disorder (except caffeine-related disorders, tobacco-related disorders, or cannabis intoxication) other than in remission for at least 3 months. The use of cannabis other than that meeting criteria for cannabis use disorder is not exclusionary. Use of cannabis will be documented.
  - Current use of any stimulant, including prescribed stimulant medications
  - Current use (within the past 1 month, ongoing, or expected during the study period) of any drugs that are illegal under Washington state law.
  - Severe psychiatric instability or severe situational life crises, including evidence of being actively suicidal or homicidal, or any behavior which poses an immediate danger to participant or others.

Note: Nonsuicidal depression comorbid with PTSD will not be exclusionary. Participants may continue in any stable concurrent psychotherapy in which they are participating with the exception of the evidence based trauma- and sleep-focused psychotherapies listed below. Participants with active suicidal ideation or with depression severe enough to require psychiatric hospitalization will be excluded.

- Medications/Therapies
  - Current use of prazosin or other alpha-1 antagonist or trazadone, or use of such agent within the 3 month period prior to when the baseline 2 visit would be scheduled (a 3-month washout is required due to the potential effects it may have on the biomarker measurements).
  - Allergy or previous adverse reaction to prazosin or other alpha-1 antagonist
  - Use of exclusionary medications in the 4 weeks prior to screening: selected CNS-acting medications; antipsychotics, anti-Parkinson's disease medications and CNS stimulants; Coumadin or other medications affecting coagulation and/or inflammation (low-dose aspirin and use of NSAIDs for pain will not be exclusionary); potent immune-modulating medications, such as hydrocortisone or methotrexate.
  - Use of avanafil (Stendra), sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra)

will be not be permitted during the study dose titration period because of increased risk of hypotension in combination with alpha-1 blockers, but will be allowed at 1/2 the usual starting dose following dose titration
  - Current use of stimulants or nitrates, or of alternative medications or supplements with stimulant properties (e.g., ephedra) or vasodilatory properties (e.g., nitrate containing supplements)
  - Recent evidence based trauma- or sleep-focused psychotherapy, such as Prolonged Exposure therapy (PE), Cognitive Processing Therapy (CPT), Eye Movement Desensitization and Reprogramming (EMDR), Cognitive Behavioral Therapy for Insomnia (CBTi) or Image Rehearsal and Rescripting therapy for nightmares. These therapies must have been completed > 4 weeks before first baseline assessment visit (study visit 2).

  Note: Other psychotropic medications and/or maintenance psychotherapy at a stable dose for at least 5 weeks prior to the Baseline-1 visit and ambulatory monitoring will not be exclusionary.

- Other
  - Allergy or previous adverse reaction to prazosin or other alpha-1 antagonist
  - Receiving another medication in another interventional study (except as described in section 5.5 below).

5.4 Study Evaluations

Study Visits and Procedures: This is a two phase study. In phase I, all subjects will receive open-label prazosin; in phase II, it will be an RCT where participants will be randomized 2:1 to take prazosin or placebo, have samples collected for biomarker, and genetics, undergo sleep and activity monitoring, and have cognitive and behavioral testing. 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. A detailed description of study instruments follows the description of study visits.

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 time to read the consent form and ask questions. If an Investigator is also the potential participant's primary health provider, an alternate study staff member will conduct the consent process.

Screening Procedures: At the screening visit, we will review the potential participant's list of medications; medical, psychiatric, military, and head trauma histories; including mechanisms and circumstances of trauma (using the Traumatic Life Events Questionnaire [TLEQ] and Combat Exposure Scale [CES]). Potential participants will be interviewed using the Structured Clinical Interview for DSM-5 (SCID-5), SCID-IV, or MINI to rule out disqualifying major psychiatric disorders and the Clinician-Administered PTSD Scale (CAPS) to diagnose and assess severity of PTSD.) A short measure of cognitive function will be administered (Montreal Cognitive Assessment [MoCA]):

Screening medical and neurologic exams will be performed. 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, vitamin B_{12}, thyroid function, and coagulation (PT and PTT/INR) tests and a routine urinalysis will be performed. Female participants of childbearing potential will have a urine pregnancy test, which must be negative in order to continue study participation. If it is found that a potential participant does not meet the inclusion criteria, follow-up care will be coordinated.

Participants who remain eligible after screening will be asked to undergo the following study procedures:

At-home BP monitoring and monitoring of sleep activity (description of equipment and sleep logs below after the description of study visits): At the end of the screen visit, we will place the at-home BP monitoring equipment on the study participant. The participant will remove the BP monitoring equipment after 24 hours and will bring it back at Baseline visit 1. We will also give the study participant an Actiwatch to wear until Baseline visit 2 (typically 9-14 days total, although possible alterations in this timing are discussed under "Potential exceptions to visit schedule" below). Instructions for wearing the Actiwatch and filling out a sleep diary during this time will also be given to participants.

Baseline visit 1—Clinical and Cognitive Assessments, pupillometry, placement of HR monitor: Health history and list of medications will be updated as needed. Vital signs will be taken. Behavioral, functional, and cognitive instruments/questionnaires will be administered as outlined in the schedule of study visits. If it has been longer than 2 weeks since screen (or if BL visit 2 is expected to be longer than two weeks from screen), about 5-10 ml of blood will be collected for blood count and coagulation tests.

Participants will return the BP monitoring equipment and will have an ambulatory HR monitor placed. When possible, the HR monitor will be placed at a point in the visit prior to the completion of the neurocognitive testing, in order to allow the degree of correlation between the results of the heart rate variability analysis and the pupillometry analysis to be assessed; this will then count as the beginning of 24 hours of use, after which the participant may remove the HR monitor. Participants will continue wearing the Actiwatch and filling out sleep diaries until the baseline 2 visit.

Baseline Visit 2—Collection of samples for DNA and biomarker measurements (LP, and blood collection): This visit will take place in the Clinical Research Unit (CRU) at the VA in Seattle. Participants will be asked to arrive at the CRU at 8 am. They will have been fasting (nothing to eat or drink except water) from midnight the night before the study. If participants take medications in the morning, they will be asked to bring the medications with them to take after the LP is done (usually by 11 am). This study visit will take approximately 3-3.5 hours. Participants will be given lunch (or a voucher to use in the VA cafeteria) and instructions for what to do for 24 hours post-LP before they leave. The day after the LP, our research nurse or clinician will call the participant to make sure there are no adverse events.

Participants will return the HR monitor, Actiwatch, and sleep diaries. We will ask about the participant's health and current medications to make sure the participant has not had an acute illness within the past two weeks. A urine sample will be collected from women of childbearing potential. If the pregnancy test is positive, the participant will be withdrawn from the study.

Next, participants will lie in bed, at which point an indwelling i.v. catheter will be placed in an

antecubital vein and kept patent with a slow (50 ml/hr) infusion of normal saline. A small amount of blood will be collected right away to test platelet levels. The i.v. allows us to infuse fluids if needed and to collect 150 ml of blood for DNA and measurement of plasma and serum biomarkers and proteomics.

Following blood collection, CSF will be obtained by LP. All LPs will be performed by a physician credentialed to perform LPs and trained in our specific research procedures. The participant will be placed in the lateral decubitus position (asked to lie on his or her side with knees curled up toward the chest). The L3-4 or L4-5 interspace will be infiltrated with 1% lidocaine to provide local anesthesia. The LP will be performed atraumatically with a 24g bullet-tip Sprotte spinal needle and 28cc of cerebrospinal fluid will be withdrawn with sterile syringes. Use of the 24g Sprotte atraumatic spinal needle is recommended by published guidelines on prevention of post-lumbar puncture headache and greatly reduces frequency of post-lumbar puncture headache (<1%). We have been using this technique for 8 years with very low incidence of adverse events. After the LP, the i.v. catheter will be removed. The participant will remain in bed for one hour following the LP to reduce the chance of post-LP headache.

Randomization and Study Drug Titration: Following collection of the samples, participants will receive the first week's supply of study drug and will be instructed in dosing procedures and safety precautions to prevent potential adverse effects. They will be instructed to start taking the study drug the **third** night following LP. The starting dose for all participants will be 1 mg taken at bedtime (qhs) for the first 2 nights. The dose will be increased to 2 mg qhs on days 3-7.

Titration Schedule			
	AM dose (morning)	**PM dose (afternoon)**	**QHS dose (bedtime)**
Days 1-2			1 mg
Days 3-7			2 mg
Week 2	1 mg	1 mg	4 mg
Week 3	1 mg	1 mg	6 mg
Week 4	2 mg	2 mg	10 mg
Week 5	2 mg	2 mg	15 mg
Weeks 6-10	5 mg	5 mg	15 mg

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 treatment with a low dose, then titrating upward gradually, per the table above.

Participants will be seen at each dose increase after completion of the first week to evaluate for adverse effects, record any new medications and interval medical problems, monitor supine and standing BP and HR, to assess drug compliance, determine whether proceeding to the next step of the dose titration is appropriate, and to provide additional study drug for the scheduled dose increase, decrease, or dose maintenance.

Occurrence of lightheadedness, dizziness on standing, palpitations, drowsiness, headache, nausea, nasal congestion, peripheral edema, and other adverse effects will be rated by a clinician as absent, present, ongoing, worsening or unacceptable. The clinician will also assess if these side effects are due to factors that may be unrelated to the medication (i.e., if the participant has been ill or is dehydrated) For vital signs parameters, unacceptable side effects will include supine hypotension (supine systolic BP<100) and clinically meaningful orthostatic hypotension (≥ 20

mmHg drop in systolic BP accompanied by dizziness, lightheadedness or syncope).

For participants maintained on other antihypertensive medications, their primary care provider will be informed of clinically significant blood pressure reductions at any time during the study to allow adjustment of the participant's antihypertensive regimen. As a further precaution, male participants will be advised to sit on the toilet for urination during the first night of medication use. Participants will be asked to call a study clinician the day after the first dose to make sure there was no occurrence of postural dizziness.

If a participant has unacceptable side effects, the dose will be reduced to the previous titration step. Participants who cannot tolerate the dose of 1mg morning, 1 mg afternoon and 4 mg bedtime will be reduced to the dose of 1 mg morning, 1 mg afternoon and 2 mg bedtime. If the participant is unable to tolerate a minimum dose of 1 mg morning, 1 mg afternoon, and 2 mg bedtime, he/she will be terminated from the study.

If a participant is unable to make it to a titration visit (due to illness, scheduling, etc.), the participant will be offered the option of completing the visit via the telephone; this visit will include all of the elements of a regular titration visit except for those that must be done in person, such as vital sign assessment. Alternatively, if the participant is not able to complete the study visit at all, the study clock will be "stopped" temporarily and his/her dose will be maintained at the current level until he/she is able to come for another titration visit. The titration period can be extended up to an additional three weeks in that manner.

Study Treatment Period: Once the participant has reached his/her highest tolerated dose, he/she will enter the Study Treatment Period. The participant will maintain this dose for a minimum of 5 weeks. A clinic visit will take place at one and four weeks after stable dose is achieved to assess for adverse events. Concomitant medications and health status will be updated. Study drug adherence will be tracked by pill counts.

At the 4 week stable dose visit, we will place the ambulatory blood pressure monitoring equipment, and the participant will be sent home with the Actiwatch and sleep diaries and told to wear them as before.

After 5 weeks at stable dose, participants will undergo cognitive/behavioral testing and sample collection visits just as in baseline visits 1 and 2 (with the exception that blood will not be collected). Ambulatory heart rate measurements will be collected during and following the end of study 1 visit, again as during the baseline period.

Potential exceptions to visit schedule:
If the content of either the screening or a baseline part 1 assessment visit cannot be completed in the expected time, or the participant wishes, the visits can be divided into separate visits.

If CSF cannot be collected at an LP visit, and the participant is willing, an additional LP visit will be scheduled. Participants will be compensated for the time and effort involved for any extra LP visit. Additional safety visits may be required if participants have laboratory abnormalities or adverse events (AEs) that require continued follow-up (we will follow until abnormality/AE is resolved).

If the participant is unable for some reason to wear the ambulatory monitoring equipment during the usual periods of time, their use may be delayed for up to two weeks. To accommodate this, the participant may take the equipment home early and be trained in placing the equipment on themselves; alternatively, if the participant or clinician are for any reason concerned about the

participant's ability to place the monitoring devices on themselves, or simply for participant preference, the participant may visit the clinic for an extra 1-2 brief visits for the devices to be placed on the participant.

If upon return of ambulatory monitoring equipment it is discovered that user or technical error prevented sufficiently high quality data from being collected, the ambulatory monitoring attempt may be repeated if the participant is willing and the involved clinicians believe there is a reasonable chance of success with a second attempt. In such cases, the ambulatory monitoring periods may also extend for up to two weeks beyond their usual time windows.

At times, for any of these reasons or to accommodate the participant's scheduling constraints for the baseline visits, the period of actigraphic monitoring may be extended to up to 30 days in order to encompass both the periods of ambulatory blood pressure and heart rate monitoring and the week prior to the two baseline visits.

However, ambulatory monitoring will not be done any more than two weeks past baseline LP nor once prazosin has been started, and end of study measures will not be completed any more than two weeks past baseline LP nor once prazosin has been stopped. If necessary, an additional period of up to two weeks delay after the baseline LP but prior to the initiation of prazosin may be added to accommodate this or other scheduling difficulties in obtaining baseline ambulatory monitoring data, and an additional period of up to two weeks of taking the achieved stable prazosin dose may be added to the end of the study in order to accommodate this or other scheduling difficulties in obtaining end of study ambulatory monitoring data. Overnight blood pressure monitoring will not be performed within the 7 day period immediately prior to an LP, to ensure that this procedure does not change the results of the laboratory results via an impact on sleep.

Although all efforts will be made to complete study visits in person, it may be necessary to obtain assessments by telephone. The following actions will be attempted (as appropriate per visit schedule): 1) adverse events will be assessed, 2) assessments shall be completed by telephone interview with the raters, 3) self-rated measures will be provided to participants, then returned by mail using prepaid envelopes, and 4) dispensing of study drug shall be done by trackable shipment. No-show, missed visits and actions taken will be documented in the study record.

In general, we expect that ambulatory monitoring equipment will be returned by participants in person at subsequent visits. If, however, a schedule change, early termination or other unplanned alteration (e.g., a participant forgets to bring it to a visit as planned), there will be two alternative methods for collecting the equipment: first, a member of the study team may go to the participant's location in the community to receive the item from them, or, second, the item can be mailed back using postage-paid, self-addressed packing.

<u>Potential exceptions to study procedures:</u>
Participants already randomized to prazosin versus placebo prior to approval of the protocol modification instituting an initial, phase I open-label phase will continue to receive prazosin versus placebo in a double-blind fashion without alteration. Similarly, an individual who is participating in the study only via dual-enrollment (where the prazosin versus placebo is being administered as part of another study, and it is only assessments being conducted as a part of this study), will continue to be directly enrolled in the phase II version of the trial. All changes in study procedures will only apply to subjects who have not yet been randomized.

Phase I is designed to run until at least 22 participants have completed the full protocol, and their data has been analyzed. As discussed below in the data analysis section, if at the end of phase I the results are potentially consistent with a clinically significant effect, but do not yet meet statistical significance, we will continue the open label portion until we have 37 subjects who have completed the study (15 subjects beyond the initial 22), which is expected to involve 26 additional subjects screened when allowing for expected screen failure and dropout rates.

Some participants may also be (or have been in) in another study longitudinal study of mTBI that is being conducted by the MIRECC research group. If these participants have also agreed to have samples and data stored in the Behavioral Neurosciences Group (BNG) research repository (MIRB #00891, Elaine Peskind PI), many screening/study assessments and the baseline sample collection may not need to be repeated (as described below).

The MIRECC research group is also conducting a study of the potential efficacy of prazosin in relieving post-traumatic headaches in Veterans with mTBI. Some of these participants will also be eligible for participation in this study. We wish to allow these participants to be in both studies simultaneously in order to maximize scientific learning and medical advances while minimizing participant burden. It also limits potential bias in the results of this study that might come if participants that qualified for competing local studies were enrolled at lower rates than their prevalence in the local community.

In this case, once the potential participant is recruited and enrolled into the related headache study and the BNG repository, and if the potential participant and both study PIs agree, we will alter the schedule of this study as described below and will place information gathered in each study in the BNG repository in real time so that it will be possible to share information between studies so that participants may be able to be in both studies at the same time without having to repeat study evaluations and other procedures.

1. Screen: All items **except study consent and vital signs** that are scheduled for the screening visit may be taken instead from the same item previously carried out within the prior year with the following exceptions:
   a. a previously completed TLEQ will only be used if it contains the modifications that include collection of information on the timing of events;
   b. updates will be obtained for medical and psychiatric history and current medications;
   c. physical and neurological exams will be repeated if they were last done more than 3 months ago, or 4 weeks ago if there are any elements in the medical or psychiatric history, vital sign data, or on previous physical/neurologic exam that suggest the Veteran may have increased risk for adverse outcomes with prazosin;
   d. a general screening question will be asked to ascertain whether there may have been any potentially traumatic experiences since the SCID, CAPS, and TLEQ were last completed, and if so, they will be redone as indicated.
2. Baseline 1:
   a. Any previously completed WTAR may be substituted for the WTAR for the baseline 1 visit of this study.
   b. Any other component of the baseline 1 visit may be taken instead from an equivalent item previously carried out as long as it is completed within one month of the baseline LP. Although we will try to carry out these assessments in an order and configuration that is consistent across participants, this will not be an absolute requirement; for example, if

a participant has completed the WTAR two years ago and the ACT and SDMT one week ago, we will only include the CVLT, dot counting test, emotional Stroop test, and PVT for the baseline 1 neurocognitive testing, as the repeated-measure effects from repeating the ACT and SDMT so close together would be more of a concern than the variability in administration context.

3. Baseline 2: Any LP completed in the two weeks prior to scheduled randomization date and with sufficient CSF sample collected for our primary outcome measures will be allowed to substitute for the baseline LP. Any previous genetic testing from the prior 10 years may be substituted for equivalent genetic testing in this study.
4. Prazosin or placebo titration and maintenance: If a participant is concurrently enrolled in MIRECC prazosin vs. placebo study with overlapping inclusion/exclusion criteria the dosing schedule and data collected from stable dose study treatment period of the **other** study will be used (instead of the schedule for this study), if the following conditions are met:
   a. The target dose per day of study drug is within 25% of the target dose per day in our study
   b. The procedures performed at end of study visits 1 and 2, including the associated ambulatory monitoring, will be completed after the participant completes the study treatment period of the concurrent study. We will attempt to coordinate study schedules so there is a mid-point visit that matches when our Stable Dose week 4 visit would be scheduled.
5. End of study assessments: substitutions will be allowed as with the baseline assessments, described above.

Any non LP visit-related adverse events will be reported to the IRB for both studies, and it will be noted that the participant is in both studies simultaneously.

Schedule of Study Visits[a]:

	Screen	At home, prior to baseline visits	Baseline part 1	Baseline part 2	Standard titration/ follow up visits	Optional titration visits[c]	Stable dose, Week 1	Stable-dose, Week 4	At home, prior to end of study visits	End of study visits part 1	End of study visits part 2
Visit Number	**1**		**2**	**3**	**4-8**		**9**	**10**		**11**	**12**
Study Week		**-1**	**0**	**0**	**1-5**		**6**	**9**	**9-10**	**10**	**10**
Obtain Consent	X										
Medical and Psychiatric History	X										
Physical exam, Neurological exam	X										
Urine pregnancy test (women of childbearing potential)	X			X							X
Screening labs	X		X[b]							X[b]	
EKG (if clinically indicated)	X										
Demographic Information, Military History, Combat Experiences Scale	X										
SCID/MINI	X										
Quantification of Blast Exposure	X										
CAPS	X		X							X	
TLEQ	X										

	Screen	At home, prior to baseline visits	Baseline part 1	Baseline part 2	Standard titration/ follow up visits	Optional titration visits[e]	Stable dose, Week 1	Stable-dose, Week 4	At home, prior to end of study visits	End of study visits part 1	End of study visits part 2
STOP-BANG Sleep Apnea Screening	X										
MoCA	X		X							X	
WTAR			X								
ACT			X							X	
SDMT			X							X	
CVLT			X							X	
Dot Counting Test			X							X	
Emotional Stroop Test			X							X	
PVT			X							X	
PHQ-9			X				X			X	
GAD-7			X				X			X	
PSQI			X		X[g]	X[g]	X	X[g]		X	
VR-12			X				X			X	
DVPRS			X				X			X	
AUDIT-C			X				X			X	
QCC			X				X[d]			X[d]	
CSN			X				X			X	
PCL			X				X			X	
NSI			X				X			X	
Vital Signs	X		X	X	X	X	X	X		X	X
Review Concurrent Medications			X	X	X	X	X	X		X	X
Review Adverse Events			X	X	X	X	X	X		X	X
Dispense/collect study drug				X	X	X	X	X			X
Wear Actiwatch, Complete Sleep Diary		X							X		
Wear blood pressure/heart rate monitor		X							X		
Lumbar Puncture				X[c]							X
Blood collection for biomarkers/DNA				X[c]							X[f]
Estimated Time of Visit (hrs.)	4.5-6.5		2.5	3	.5	.5	1.5	.5	.5	3	3

[a] This schedule may be revised if procedures have been done for a different study within a certain period of time or if participating in two studies simultaneously. Participants will be informed if their existing data can be reused.

[b] If more than two weeks will have passed between screen LP visit, then platelet count and clotting time labs will be drawn at these visits.

[c] If DNA is already available in a research repository, it will not be collected. If an LP has been performed within two weeks of randomization, and sample is available in the repository, LP will not be done at baseline visit 2.

[d] For second and third QCC, an abbreviated follow up version will be used

[e] There may be up to three additional titration visits, which would add three weeks to the total length of the study.

[f] Blood and saliva for DNA will only be collected at first biomarker collection visit.

[g] At routine titration / follow up visits, an abbreviated, 1 page version of the PSQI will be used.

Detailed Descriptions of Study Assessments:

- *Structured Clinical Interview for DSM-5 Axis I Disorders (SCID5)*[24]*:* A widely used structured interview that assesses Axis I psychiatric history. The SCID has very good reliability and validity. The SCID will be used at the screen visit to rule out exclusionary diagnoses and to describe the subject sample.

- *Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-IV):* Previously version of the same widely used structured interview that assesses Axis I psychiatric history. The SCID has very good reliability and validity. The SCID will be used at the screen visit to rule out exclusionary diagnoses and to describe the subject sample. If clinically or logistically more accessible, due to previous assessments undergone by this particular subject or new information on the relative utility of the different instruments, we may carry out and/or accept the SCID for DSM-IV or the MINI in place of the SCID5. The SCID for DSM-IV has been a widely used structured interview that assesses Axis I psychiatric history according to the DSM-IV criteria, and is still administered in many of the ongoing research studies here at the MIRECC. The Mini International Neuropsychiatric Interview (MINI)(Sheehan et al., 1998) is a widely used alternative that is also designed to take into account the International Classification of Disease (ICD) 10 criteria, and is widely used internationally.
- *Clinician-Administered PTSD Scale for DSM-5 (CAPS)*[25]*:* A structured clinical interview designed to assess the symptoms of PTSD outlined in the DSM-5. The CAPS allows the interviewer to make current (past month) and lifetime diagnoses of PTSD. The frequency and intensity of each symptom on the CAPS is rated on separate 0-4 scales. The CAPS has become the standard for psychopharmacologic outcome trials in PTSD.
- *Combat Experiences Scale (CES)*[26]: Will be used to describe the degree of combat trauma exposure in the study sample. Scores range from 1-18. The CES has been utilized in many studies evaluating combat Veteran samples and is relevant to any war zone setting from WWII to OEF/OIF/OND.
- *Traumatic Life Events Questionnaire (TLEQ) – modified*[27]*:* A 23-item self-report measure of 22 types of potentially traumatic events including natural disasters, exposure to warfare, childhood abuse, and community violence, developed and validated by VA researchers. Traditionally this scale was designed around the DSM-IV, and for each event, respondents are asked to provide the number of times it occurred and whether fear, helplessness or horror was present. However, with the criterion for the experience of fear, helplessness or horror having been removed from the definition of PTSD in DSM-5, and with our interest in potential physiologic impacts of traumatic exposures, which may vary based on the age at which an event was experienced and the time since the event, we have modified the TLEQ to replace the questions about the experience of fear/helplessness/horror with the question "At approximately what age(s) did this happen?"
- *STOP-Bang Sleep Apnea Screening*[28]*:* 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. In addition, those who screen positive for an elevated risk of OSA and who have not been evaluated for OSA will be provided with appropriate referral options for further evaluation, either by referral to the VA sleep medicine service (for Veterans) or by referral to community providers (non-Veterans and requesting Veterans).
- *Montreal Cognitive Assessment (MoCA)*[29]*:* 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. Test-retest reliability is high, with less than one point variation. Internal consistency is good (Cronbach alpha=0.83). To correct for education, 1 point is added for those with less than 12 years of education.

- *Patient Health Questionnaire-9 (PHQ-9)*[30]*:* The 9-item depression module of the Patient Health Questionnaire, a self-report version of the PRIME-MD used to diagnose major mental disorders. The PHQ-9 items correspond with DSM-IV criteria for depression, with each item scored from "not at all" to "nearly every day." Items of the PHQ-9 are internally consistent (alpha = 0.86-0.89) and the questionnaire exhibits high test-retest reliability coefficients. Agreement between the PHQ-9 and clinician-based interview diagnosis of major depression is high, with a sensitivity of 88% and a specificity of 88% using a PHQ-9 score $\geq$ 10.
- *General Anxiety Disorders-7 (GAD-7)*[31]*:* A 7-item self-report questionnaire assessing generalized anxiety symptoms that has been broadly assessed for reliability and validity as a measure of anxiety across the general population. Each item assesses the participant's frequency of experiencing a different common anxiety symptom over the past two weeks on a scale of "not at all" / "several days" / "over half the days" and / "nearly every day". Each response can be assigned a number from 0-3, and the responses can be summed to provide a simple quantification of overall anxiety.
- *Pittsburgh Sleep Quality Index (PSQI)*[32]: A self-report questionnaire assessing 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 sleeping medication, and daytime dysfunction. A global score may be obtained by summing the seven component subscales (total score range: 0-21).
- *Veterans' RAND-12 (VR-12)*[33]*:* A shorter version of the Veterans SF-36, which was based on the administration of the Medical Outcomes Study SF-36 to a large sample of Veterans. The Veterans SF-36 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 SF-12V assesses the same 8 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 7 of the 8 scales. Results are expressed as physical and mental component summaries. Scores on the SF-12V have been shown to correlate strongly with the Veterans SF-36. The SF-12V is the "gold standard" for measuring health related quality of life, owing to its established reliability, validity, and widespread adoption in clinical treatment trials.
- *Defense and Veterans Pain Rating Scale (DVPRS)*[34]*:* A visual pain rating scale assessing the severity of pain in various areas of the body and how much pain affects the participant's daily activities, sleep, mood, and stress.
- *PTSD Checklist for DSM-5 (PCL) without Criterion A*[35]*:* A well validated 20-item self-report measure assessing severity of PTSD symptoms consistent with DSM-5 criteria, with scores ranging from 0 to 80.
- *Alcohol Use Disorders Identification Test-Consumption (AUDIT-C)*[36]*:* A 3-item modification of the AUDIT questionnaire that enquires about frequency and quantity of typical alcohol consumption, and the frequency with which the respondents report an episode of heavy drinking in the past year. The AUDIT-C demonstrates excellent sensitivity and specificity for detection of heavy drinking and is used as a standard screening tool for alcohol problems in VA primary care settings.

- *Quantification of Cannabis Consumption (QCC):* A brief questionnaire developed by our research group in consultation with local cannabis researchers that enquires about frequency, quantity and methods of typical cannabis consumption. The questionnaire has been designed around local consumption patterns since the state-level legalization of cannabis use in Washington state, assessing the use of edible and concentrated forms of cannabis as well as smoked forms. The questionnaire also includes questions about subjects' experiences with the effects of cannabis on their mental health and daily functioning.
- *Caffeine, Sugar and Nicotine (CSN) assessment:* A 1 page questionnaire developed by our research group that draws two items from the Fagerstrom test for nicotine dependence and adds a general frequency of use assessment of different sources of nicotine, caffeine and sugar and some of the primary motivations for this use. This assessment is designed to rapidly accomplish two things: first, to assess for levels of caffeine and nicotine use that are likely to be directly affecting sleep structure or quality, and second, to detect any large changes in patterns of use over the course of the study.
- *Neurobehavioral Symptom Inventory (NSI)*[37]*:* A 22-item questionnaire designed to assess the presence and severity of common cognitive, emotional, sensory, and somatic symptoms that can occur after traumatic brain injury. Patients rate on a 5-point scale the extent to which each symptom has affected them (rated from "absent" to "very severe"). Anchor descriptions are provided for level of severity. This scale is widely used in VAs across the country as part of the standardized TBI Comprehensive Evaluation.
- *Wechsler Test of Adult Reading (WTAR)*[38]*:* Will be used to assess premorbid intellectual ability. This measure has excellent internal consistency (0.90 to 0.97), high test-retest reliability (>0.90), and it correlates highly with WAIS-III Verbal IQ (r=.75) and Full Scale IQ (r=0.73). This test typically takes 5 minutes or less to complete.
- *Auditory Consonant Trigrams Test (ACT)*[39]*:* A measure of short term working memory in which individuals will be asked to recall a series of items after a delay. During the delay, they are asked to complete an interference task (like mental arithmetic). This test takes approximately 5 minutes to complete.
- *Symbol Digit Modalities Test (SDMT)*[40]*:* Will be used to measure processing speed and divided attention. The participant is provided with a coding key that contains 9 abstract symbols, each paired with a number. Then the participant is asked to fill in empty boxes with the correct number, using the key described above. In part 1 of the task, the participant writes down the answers. In part 2 of the task, they say the answers out loud. This test takes approximately 5 minutes to complete.
- *California Verbal Learning Test-II (CVLT)*[41]*:* A measure of verbal learning and memory. It has also been shown to be a reliable measure of learning and memory (with internal consistency values ranging from .78 to .94). This measure takes 15-20 minutes to complete.
- *Dot Counting Test:* Developed in the 1940s as a test of effort and used with minimal modification since this time, this test consists of 12 cards with differently grouped patterns of dots, which subjects are asked to count as quickly as possible. The test has been assessed for validity in a wide variety of populations including those with MCI or mild AD, depression, brain injuries, stroke, and populations with learning disabilities. This measure typically takes less than 5 minutes to complete.

- *Emotional Stroop Test*[42]*:* This test is a widely used measure of the extent to which affective arousal interferes with cognitive processing. It can be tuned to different categories of emotionally arousing stimuli, including combat-related terms, and has been found to be particularly sensitive to the presence of PTSD in combat Veterans, including OEF/OIF Veterans. It is a computerized test where an individual is shown one word at a time and asked to identify the color of the word being shown, and the reaction time as a function of whether the word presented is one with a positive affective tone, a negative affective tone, is neutral, or is combat related, is assessed. It is compatible with simultaneous recording of pupil diameter (pupillometry) to correlate results with an independent physiologic measure of affective arousal, vigilance, and locus ceruleus activity in particular. It takes 15-20 minutes to complete this task.
- *Psychomotor Vigilance Test (PVT)*[43]: This test is a widely used measure of behavioral alertness, with high sensitivity to both acute and chronic sleep deprivation, as well as sensitivity to restoration of healthy sleep. It is a computerized test that is given in 5-minute or 10-minute versions, where subjects are asked to press a button each time a visual stimulus appears on the computer screen. The stimulus appears at random inter-stimulus intervals, and both response time and false starts are recorded. The 10-minute PVT has been shown to be highly reliable across a wide variety of populations, and has no measurable learning effects with repeat administration. It is compatible with simultaneous recording of pupil diameter (pupillometry) to correlate results with an independent physiologic measure of affective arousal, vigilance, and locus ceruleus activity in particular.
- *Pupillometry*: Pupil diameter provides a noninvasive real-time physiologic measure of affective arousal, vigilance and locus ceruleus activity. Pupil diameter will be recorded using an eyetracking-based pupillometry system both at rest and during the performance of the computer-based neurocognitive tests (the PVT and the Emotional Stroop). This equipment monitors pupil diameter using a camera placed at a distance from the participant's eye and carries no additional risk to the participant.
- *Actigraphy:* The Actiwatch Spectrum Plus (Philips Respironics, Bend, OR) 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. 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, OR), and analyzed using standard statistical software. 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.
- *Blood Pressure (BP) monitoring*: The SpaceLabs OnTrak ambulatory blood pressure monitoring system consists of a blood pressure cuff connected to a small computerized device that is programmed to inflate the cuff and take and record a BP measurement at preprogrammed intervals. The previous version of this same device has been used by researchers to demonstrate a connection between PTSD and/or trauma exposure, and a failure to display the normal nighttime drop in BP that occurs during sleep[44].
- *Heart Rate (HR) Monitoring:* The CamNTech Actiwave cardio ambulatory single channel ECG waveform recorder consists of two electrodes connected by a short lead, which clip onto two standard ECG pads worn on the chest; the entire unit weighs only 10.3g, and can

record up to 31 hours of data at 128Hz resolution. A tri-axial accelerometer is built into the unit as well, to facilitate correlation of the recorded data with sleep and activity states. The recorded data can be used to assess baseline HR during wake and sleep states, as well as HR variability, a measurement frequently used to provide an indication of both sympathetic and parasympathetic activity during both wake and sleep.

- *Consensus Sleep Diary-E (CSD-E)*[45]*:* A pre-printed form in calendar format used for self-report of quantitative and subjective measures of sleep quality, completed on a daily basis during the same periods that the participant is wearing an actigraph. 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.

5.5 Data Analysis

Power calculations were carried out for the primary endpoint of CSF Aβ42. For both phases, an estimated mean baseline value of 294 ng/L with a baseline standard deviation of 54 ng/L, based on previous findings from a group of boxers with repetitive mTBI[46], and the previously reported Pearson's coefficient of .98 for the stability of CSF Aβ42 measurements within a single individual but based on CSF samples collected six months apart[47] were used. With these numbers, we can estimate an expected standard deviation of the change from baseline of 10.8 ng/L.

For phase I, our goal is to rapidly test whether there is a reasonably high likelihood of efficacy based on the first, smaller series of subjects. To achieve this, we will formally examine the data at the point where we have an 80% power to detect a decrease in the prazosin group as compared to the placebo group of approximately 5%, which is the minimum we expect to have the potential to be clinically significant. Using a one-sample t-test with a 5% Type I error rate, this means we will require 22 patients to complete the study. Based on previous experience, we expect a screen-failure rate and dropout rate of 30% each, suggesting that we will need 38 participants to be screened in order to obtain an enrollment of 39 participants with at least 22 completers.

If the results of the initial phase I portion are positive, we will continue on to phase II. Here, our goal is to provide a stronger, randomized controlled test of the effect of prazosin on biomarkers of neurodegeneration and dementia. Setting our Type II error rate now at 10%, using a two-sample, two-sided t-test using a 5% Type I error rate, this means we will require 60 total patients, with 40 receiving prazosin and 20 receiving placebo, in order to have a 90% power to detect a decrease in the prazosin group as compared to the placebo group of approximately 5%, which is the minimum we expect to have the potential to be clinically significant. Based on previous experience we expect a screen-failure and dropout rate of 30% each, which suggests that we will need 120 participants to be screened in order to obtain an enrollment of 90 participants with at least 60 completers.

If at the end of phase I the results are potentially consistent with a clinically significant effect, but do not yet meet statistical significance, we will continue the open label portion until we have enough subjects who have completed the study to increase the power from 80% to 95%. Again using a one-sample t-test with a 5% Type I error rate, this would require 15 additional completers above the 22 initially planned, or 26 subjects screened when allowing for the same expected screen failure and dropout rates.

Participant Randomization: Participants in phase II will be randomly assigned 2:1 to prazosin or

placebo, stratified by gender and group (TBI only, PTSD only, or both). Permuted block randomization codes within each stratum will be generated by a MIRECC staff member uninvolved with this study using statistical software. This person will create one card per subject number specifying treatment assignment and will prepare double envelopes labeled with the subject number and containing the treatment group assignment card. These envelopes will be used for purposes of breaking the blind when necessitated by medical emergency when a computer and the Internet may not be available, and following study termination assessments (see section 5.7 below). In addition, the investigational pharmacist will have access to the randomization codes. No other study personnel will have access to the randomization codes.

Descriptive statistics of baseline characteristics will be calculated: demographic variables, vital signs, number and cause of TBI, mental health and substance use assessment scales, cognitive testing scores, total sleep time by participant report and by actigraphy, and sleep fragmentation index as measured by actigraphy.

Primary outcome measures will be CSF total-tau, p-tau$_{181}$, and Aβ_{42}. For each outcome, we will use a linear regression model to compare, between treatment groups, the within-subject changes in biomarkers from baseline. The model will include concentration at study completion as the response (dependent) variable, and the concentration at baseline and treatment group as the predictor (independent) variables, along with the covariates age, gender, *APOE**4 status, and blast exposure quantification. To account for dropouts and subjects who have their final biomarker assessment prior to 10 weeks, we will also use a linear mixed-effects regression model[48] with biomarker concentration as the response variable, and the predictor variables time, treatment group, and a time by treatment group interaction term, along with the same covariates as for the linear regression model. Exploratory analyses will be conducted of the interaction among biomarkers; sleep and ambulatory monitoring variables; participant-reported symptoms of PTSD, depression, and postconcussive symptoms; and cognition.

Data will be analyzed by co-investigator Rebecca Hendrickson, with consultation as necessary with the MIRECC biostatistician, Steven Millard, PhD, regarding the analysis plan and interpretation.

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 participant 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 to 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 on a weekly basis at VA Puget Sound by the study Research Assistant under the supervision of the MIRECC Database Manager. The Database Manager will generate weekly 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 on a weekly basis. Database maintenance includes nightly backup of hard drives 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: CRFs will be kept at VA Puget Sound. Data 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. Exceptions are if a participant agrees to specimen/data banking, data will be retained indefinitely. The link between study code and participant identity will be retained for the duration of data retention.

5.6 Withdrawal of Subjects

There are three conditions under which participants will be withdrawn from the research independent of participant request:

1. If the participant is not able to tolerate a minimum dose of 1 mg morning, 1 mg afternoon, and 2 mg bedtime of prazosin, he or she will undergo early termination. Such participants will be referred back to their primary or referring providers for further management; if they do not have such providers, Veterans will be offered a referral to an appropriate VA provider, and non-Veterans and requesting Veterans will be provided with appropriate community referrals. Reasons for early discontinuation or withdrawal will be recorded.
2. Participants may be discontinued prematurely from study treatment to manage deterioration of clinical status. Any participant who: (1) reports active suicidal ideation with intent and/or with plan, (2) displays a marked deterioration of clinical and/or functional status, or (3) is otherwise judged by the study clinician to be not stable enough to continue participation, including due to any other indication of severe participant distress or presentation of immediate danger to self or others, will be discontinued from the study for management of acute or unstable symptoms. For participants whose status necessitates emergent care, study termination will be followed by a warm hand-off to appropriate VA Emergency Department personnel for emergent care. For participants who are discharged from the study due to acute symptoms or clinical deterioration that does not require emergent care, referral to appropriate VA personnel for Veteran participants or referral for appropriate community care for non-Veteran or requesting Veteran participants will be provided.
3. Participants who are unable to come to regularly scheduled visits or who are noncompliant with study procedures or taking medication will also be withdrawn from the study. Reasons for early discontinuation or withdrawal will be recorded.

Participants may remain in the study despite declining ambulatory heart rate or blood pressure monitoring, genetic testing, and/or quantification of cannabis consumption, as long as the study staff working with the participant continue to feel he or she is able to continue in good faith and it remains clinically appropriate. However, a participant cannot decline any screening procedures, the PCL, the PVT and emotional Stroop, the PSQI, the LP, or the prazosin titration and remain in the study (except in the circumstance that the participant is already participating in an allowed substituting prazosin titration as described above). In these cases, any participant will be considered withdrawn from the study.

Participants who withdraw early from the study due to their own decision will be thanked for participation. They will be asked to undergo the two final study visits (for ITT analysis purposes) but will not be required to have these visit (prazosin may be discontinued abruptly without adverse consequences). They will be asked why they decided to withdraw early so we can record

the reason. The participant will be notified that any data and/or samples collected will be continued to be used in the analyses unless the participant specifically requests that samples and data not be used. If the participant requests, samples (including DNA) will be destroyed.

Participants who withdraw from the study or are withdrawn by the PI will be reimbursed on a pro-rated basis for the visits they have completed, as long as all ambulatory monitoring equipment has been returned; if this equipment is not returned, all payments outstanding will be placed on hold until it is returned.

For participants completing the entire trial, the blind will be broken by a Study Clinician at the end of the study (except if they are participating in a simultaneous prazosin study: in those cases, the blind will be broken when the longer study period ends). 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 wishing to continue, 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.

Once the blind has been broken for a participant, they will be provided a written report describing the information from their ambulatory blood pressure and actigraphic monitoring data. These will be provided as a standardized report, generated by the analysis software for these systems. The participant will be informed that these are not being conducted as medical tests but rather as experimental data collection, and the data is being provided for their interest, rather than as the result of a medical test. We will be able to discuss the reports with the participants and refer them to their primary care provider if follow-up is warranted.

6.0 Reporting

Collection of adverse event information will begin at the screening visit.

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 participant 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 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 the IRB per local guidelines. Expected adverse events, which are not serious and possibly related to research participation, will be reported 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 the IRB per local guidelines.

Adverse events or problems that the PI determines are unrelated to research participation will not be reported.

A summary of all above reports will be sent to 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. 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, phone number, address, medical record 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 3 digit screening code, and if randomized a 1 letter + 3 digit randomization code (those in phase I will still receive a 3 digit code prior to the initiation of study drug). The crosswalk between participant identities and code number are kept electronically on the VA research drive. The list is only accessible to the personnel listed on the R&DC application.

Data which are recorded on paper case report forms are kept a restricted access area (VA Puget Sound, Seattle Division, Building 1, rooms B22 and B25). 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 these locked areas. File cabinets are also 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 R&DC application.

Risks to Confidentiality: There is a risk of loss of confidentiality. We will be creating/updating VA medical records. All clinical labs will be ordered through CPRS and results will be placed automatically in CPRS. We are not ordering any clinical labs which would contain sensitive information (i.e., are not performing drug, HIV, or hepatitis testing). The study team will have access to CPRS records from initial consent until 30 days beyond the end of participant study participation to monitor for adverse events

Reduction of risk due to loss of confidentiality: We plan on obtaining a Federal Certificate of Confidentiality to protect against compelled disclosure of answers to the questionnaires.

8.0 Communication Plan

N/A—this is not a multi-site study.

9.0 Information Security and Data Storage/Movement

All data collection, management and analysis procedures will take place at VA Puget Sound. Study personnel will have access to protected health information. All data are coded. Participants are given a sequential code number. The crosswalk between participant identities and code number are kept electronically on the VA research drive. The list is only accessible to the personnel listed on the R&DC application.

VA Committees that oversee research (VA IRB, R&DC) 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), and the Government Accountability Office (GAO).

The VA Puget Sound Fiscal Department and U.S. Department of the Treasury will be provided with the full name, address, phone number, and social security number of participants in order to authorize payment for participation in the study

Physical transportation of Identifying or Sensitive Data: There will be no physical transportation of identifying or sensitive data.

Electronic Transmission of Data: There will be no electronic transmission of data outside the VA servers.

Final Disposition of Data: Data 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. Exceptions are if a participant agrees to specimen/data banking, data will be retained indefinitely. The link between study code and participant identity will be retained for the duration of data retention.

10.0 References

1. Ross CA, Poirier MA. Protein aggregation and neurodegenerative disease. Nat Med. 2004;10 Suppl:S10-7. doi: 10.1038/nm1066. PubMed PMID: 15272267.
2. Taylor JP, Hardy J, Fischbeck KH. Toxic proteins in neurodegenerative disease. Science (New York, NY). 2002;296(5575):1991-5. doi: 10.1126/science.1067122. PubMed PMID: 12065827.
3. Iliff JJ, Chen MJ, Plog BA, Zeppenfeld DM, Soltero M. Impairment of glymphatic pathway function promotes tau pathology after traumatic brain injury. 2014;34(49):16180-93. doi: 10.1523/jneurosci.3020-14.2014. PubMed PMID: 25471560.
4. Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, Benveniste H, Vates GE, Deane R, Goldman SA, Nagelhus EA, Nedergaard M. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta. Science translational medicine. 2012;4(147):147ra11. doi: 10.1126/scitranslmed.3003748. PubMed PMID: 22896675; PubMed Central PMCID: PMCPMC3551275.
5. Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, O'Donnell J, Christensen DJ, Nicholson C, Iliff JJ, Takano T, Deane R, Nedergaard M. Sleep drives metabolite clearance from the adult brain. Science (New York, NY). 2013;342(6156):373-7. doi: 10.1126/science.1241224. PubMed PMID: 24136970; PubMed Central PMCID: PMCPMC3880190.
6. Mellman TA, Hipolito MM. Sleep disturbances in the aftermath of trauma and posttraumatic stress disorder. CNS Spectr. 2006;11(8):611-5. PubMed PMID: 16871127.
7. Germain A. Sleep disturbances as the hallmark of PTSD: where are we now? Am J Psychiatry. 2013;170(4):372-82. doi: 10.1176/appi.ajp.2012.12040432. PubMed PMID: 23223954; PubMed Central PMCID: PMCPMC4197954.
8. Greenberg MS, Tanev K, Marin MF, Pitman RK. Stress, PTSD, and dementia. Alzheimers Dement. 2014;10(3 Suppl):S155-65. doi: 10.1016/j.jalz.2014.04.008. PubMed PMID: 24924667.

9. Berezuk C, Ramirez J, Gao F, Scott CJ, Huroy M, Swartz RH, Murray BJ, Black SE, Boulos MI. Virchow-Robin Spaces: Correlations with Polysomnography-Derived Sleep Parameters. Sleep. 2015;38(6):853-8. doi: 10.5665/sleep.4726. PubMed PMID: 26163465; PubMed Central PMCID: PMCPMC4434551.
10. Justice NJ, Huang L, Tian JB, Cole A, Pruski M, Hunt AJ, Jr., Flores R, Zhu MX, Arenkiel BR, Zheng H. Posttraumatic stress disorder-like induction elevates beta-amyloid levels, which directly activates corticotropin-releasing factor neurons to exacerbate stress responses. J Neurosci. 2015;35(6):2612-23. doi: 10.1523/JNEUROSCI.3333-14.2015. PubMed PMID: 25673853; PubMed Central PMCID: PMCPMC4323535.
11. Broese M, Riemann D, Hein L, Nissen C. alpha-Adrenergic receptor function, arousal and sleep: mechanisms and therapeutic implications. Pharmacopsychiatry. 2012;45(6):209-16. doi: 10.1055/s-0031-1299728. PubMed PMID: 22290201.
12. Calohan J, Peterson K, Peskind ER, Raskind MA. Prazosin treatment of trauma nightmares and sleep disturbance in soldiers deployed in Iraq. Journal of traumatic stress. 2010;23(5):645-8. Epub 2010/10/12. doi: 10.1002/jts.20570. PubMed PMID: 20931662.
13. Group MoP-TSW. Va/DOD clinical practice guideline for management of posttraumatic stress. In: Department of Veterans Affairs DoD, editor. Washington, DC2010.
14. 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):1071-84. Epub 2009/01/01. PubMed PMID: 20437313.
15. Ruff RL, Riechers RG, 2nd, Wang XF, Piero T, Ruff SS. For veterans with mild traumatic brain injury, improved posttraumatic stress disorder severity and sleep correlated with symptomatic improvement. J Rehabil Res Dev. 2012;49(9):1305-20. Epub 2013/02/15. PubMed PMID: 23408213.
16. Wang LY, Shofer JB, Rohde K, Hart KL, Hoff DJ, McFall YH, Raskind MA, Peskind ER. Prazosin for the treatment of behavioral symptoms in patients with Alzheimer disease with agitation and aggression. Am J Geriatr Psychiatry. 2009;17(9):744-51. doi: 10.1097/JGP.0b013e3181ab8c61. PubMed PMID: 19700947; PubMed Central PMCID: PMCPMC2842091.
17. Physicians Desk Reference. 55th ed. Montvale, NJ: Medical Economics Company; 2001.
18. Raskind MA, Peterson K, Williams T, Hoff DJ, Hart K, Holmes H, Homas D, Hill J, Daniels C, Calohan J, Millard SP, Rohde K, O'Connell J, Pritzl D, Feiszli K, Petrie EC, Gross C, Mayer CL, Freed MC, Engel C, Peskind ER. 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):1003-10. Epub 2013/07/13. doi: 10.1176/appi.ajp.2013.12081133. PubMed PMID: 23846759.
19. Evans RW, Armon C, Frohman EM, Goodin DS. Assessment: prevention of post-lumbar puncture headaches: report of the therapeutics and technology assessment subcommittee of the american academy of neurology. Neurology. 2000;55(7):909-14. PubMed PMID: 11061243.
20. Brattebo G, Wisborg T, Rodt SA, Roste I. Is the pencil point spinal needle a better choice in younger patients? A comparison of 24G Sprotte with 27G Quincke needles in an unselected group of general surgical patients below 46 years of age. Acta Anaesthesiol Scand. 1995;39(4):535-8. PubMed PMID: 7676793.
21. Hopkinson JM, Samaan AK, Russell IF, Birks RJ, Patrick MR. A comparative multicentre trial of spinal needles for caesarean section. Anaesthesia. 1997;52(10):1005-11. PubMed

PMID: 9370847.
22. Peskind ER, Riekse R, Quinn JF, Kaye J, Clark CM, Farlow MR, Decarli C, Chabal C, Vavrek D, Raskind MA, Galasko D. Safety and acceptability of the research lumbar puncture. Alzheimer Dis Assoc Disord. 2005;19(4):220-5. Epub 2005/12/06. PubMed PMID: 16327349.
23. Vallejo MC, Mandell GL, Sabo DP, Ramanathan S. Postdural puncture headache: a randomized comparison of five spinal needles in obstetric patients. Anesth Analg. 2000;91(4):916-20. PubMed PMID: 11004048.
24. 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). Arlington, VA: American Psychiatric Association; 2015.
25. Weathers FW BD, Schnurr PP, Kalupek DG, Marx BP, Keane TM. Clinician-Administered PTSD Scale for DSM-5. In: PTSD NCf, editor.
26. 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. doi: 10.1056/NEJMoa040603. PubMed PMID: 15229303.
27. Kubany ES, Haynes SN, Leisen MB, Owens JA, Kaplan AS, Watson SB, Burns K. Development and preliminary validation of a brief broad-spectrum measure of trauma exposure: the Traumatic Life Events Questionnaire. Psychol Assess. 2000;12(2):210-24. PubMed PMID: 10887767.
28. Nagappa M, Liao P, Wong J, Auckley D, Ramachandran SK, Memtsoudis S, Mokhlesi B, Chung F. Validation of the STOP-Bang Questionnaire as a Screening Tool for Obstructive Sleep Apnea among Different Populations: A Systematic Review and Meta-Analysis. PLoS One. 2015;10(12):e0143697. doi: 10.1371/journal.pone.0143697. PubMed PMID: 26658438; PubMed Central PMCID: PMCPMC4678295.
29. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53(4):695-9. Epub 2005/04/09. doi: 10.1111/j.1532-5415.2005.53221.x. PubMed PMID: 15817019.
30. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606-13. Epub 2001/09/15. doi: jgi01114 [pii]. PubMed PMID: 11556941; PubMed Central PMCID: PMCPMC1495268.
31. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006;166(10):1092-7. doi: 10.1001/archinte.166.10.1092. PubMed PMID: 16717171.
32. 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. Epub 1989/05/01. doi: 0165-1781(89)90047-4 [pii]. PubMed PMID: 2748771.
33. Iqbal S, Rogers W, Selim A, Lee A, Ren X, Rothendler J, Miller DR, Kazis L. The veterans RAND 12-item health survey (VR-12): What it is and how it is used.
34. Buckenmaier CC, 3rd, Galloway KT, Polomano RC, McDuffie M, Kwon N, Gallagher RM. Preliminary validation of the Defense and Veterans Pain Rating Scale (DVPRS) in a military population. Pain Med. 2013;14(1):110-23. doi: 10.1111/j.1526-4637.2012.01516.x. PubMed PMID: 23137169.
35. Weathers FW LB, Keane TM, Palmieri PA, Marx BP, Schnurr PP. The PTSD Checklist for

DSM-5. In: PTSD NCf, editor. 2013.
36. 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):1789-95. Epub 1998/09/17. PubMed PMID: 9738608.
37. Cicerone K, Kalmar K. Persistent post-concussive syndrome: Structure of subjective complaints after mild traumatic brain injury. J Head Trauma Rehabil. 1995;10:1-17.
38. WTAR. Corporation TP, editor. San Antonio, TX: Harcourt Asessment; 2001.
39. Stuss D, Stethem L, Poirer C. Comparison of three tests of attention and rapid information processing across six age groups. The Clinical Neuropsychologist. 1987(1):139-52.
40. Smith A. Symbol Digit Modalities Test : manual. Los Angeles, CA: Western Psychological Services; 2007.
41. Delis DC, Kramer JH, Kaplan E, Ober BA. California Verbal Learning Test-Second Edition, Adult Version. 2nd ed. San Antonio, TX: The Psychological Corporation; 2000.
42. Cisler JM, Wolitzky-Taylor KB, Adams TG, Jr., Babson KA, Badour CL, Willems JL. The emotional Stroop task and posttraumatic stress disorder: a meta-analysis. Clin Psychol Rev. 2011;31(5):817-28. doi: 10.1016/j.cpr.2011.03.007. PubMed PMID: 21545780; PubMed Central PMCID: PMCPMC3132173.
43. Lim J, Dinges DF. Sleep deprivation and vigilant attention. Ann N Y Acad Sci. 2008;1129:305-22. doi: 10.1196/annals.1417.002. PubMed PMID: 18591490.
44. Mellman TA, Brown DD, Jenifer ES, Hipolito MM, Randall OS. Posttraumatic stress disorder and nocturnal blood pressure dipping in young adult African Americans. Psychosom Med. 2009;71(6):627-30. doi: 10.1097/PSY.0b013e3181a54341. PubMed PMID: 19483123.
45. Carney CE, Buysse DJ, Ancoli-Israel S, Edinger JD, Krystal AD, Lichstein KL, Morin CM. The consensus sleep diary: standardizing prospective sleep self-monitoring. Sleep. 2012;35(2):287-302. Epub 2012/02/02. doi: 10.5665/sleep.1642. PubMed PMID: 22294820; PubMed Central PMCID: PMC3250369.
46. Neselius S, Brisby H, Theodorsson A, Blennow K, Zetterberg H, Marcusson J. CSF-biomarkers in Olympic boxing: diagnosis and effects of repetitive head trauma. PloS one. 2012;7(4):e33606. Epub 2012/04/13. doi: 10.1371/journal.pone.0033606. PubMed PMID: 22496755; PubMed Central PMCID: PMC3319096.
47. Blennow K, Zetterberg H, Minthon L, Lannfelt L, Strid S, Annas P, Basun H, Andreasen N. Longitudinal stability of CSF biomarkers in Alzheimer's disease. Neurosci Lett. 2007;419(1):18-22. doi: 10.1016/j.neulet.2007.03.064. PubMed PMID: 17482358.
48. Pinheiro J, Bates D. Mixed Effects Models in S and S-Plus. New York: Springer; 2000.