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Study design for a randomized clinical trial of cognitive-behavioral therapy for posttraumatic headache

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ABSTRACT

Posttraumatic headache (PTH) is a common debilitating condition arising from head injury and is highly prevalent among military service members and veterans with traumatic brain injury (TBI). Diagnosis and treatment for PTH is still evolving, and surprisingly little is known about the putative mechanisms that drive these headaches. This manuscript describes the design of a randomized clinical trial of two nonpharmacological (i.e., behavioral) interventions for posttraumatic headache. Design of this trial required careful consideration of PTH diagnosis and inclusion criteria, which was challenging due to the lack of standard clinical characteristics in

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test-Self Report; B-IPF, Brief Inventory of Psychosocial Functioning; CAP, Consortium to Alleviate PTSD; CAPS-5, Clinician-Administered PTSD Scale for *DSM-5*; CBT, cognitive-behavioral therapy; CCBT, clinic-based cognitive-behavioral therapy intervention for headache; CEQ, Credibility and Expectancy Questionnaire; CGRP, calcitonin gene-related peptide; CPRS, Computerized Patient Record System; CPT, Cognitive Processing Therapy; CRIS, Community Reintegration of Injured Service Members; DoD, U.S. Department of Defense; DRRI-2-D, Deployment Risk and Resilience Inventory-2-Deployment Environment; DRRI-2-P, Deployment Risk and Resilience Inventory-Postbattle Experiences; DSI-SS, Depressive Symptom Index-Suicide Subscale; GAD-7, Generalized Anxiety Disorder Screener; GLM, general linear mixed; HIPAA, Health Insurance Portability and Accountability Act; HIT-6, Headache Impact Test; HMSE, Headache Management Self-Efficacy Scale; HSLC, Headache-Specific Locus of Control Scale; ICHD-2, International Classification of Headache Disorders, 2nd Edition; ICHD-3, International Classification of Headache Disorders, 3rd Edition; IRB, institutional review board; ISI, Insomnia Severity Index; ITT, intent to treat; LEC-5, Life Events Checklist for *DSM-5*; NIH, National Institutes of Health; NSI, Neurobehavioral Symptom Inventory; OSU TBI-ID-SF, Ohio State University TBI Identification Method-Interview Form; PHQ-9, Patient Health Questionnaire-9 Item; PHQ-15, Patient Health Questionnaire-15; PCL-5, PTSD Checklist for *DSM-5*; PRC, Polytrauma Rehabilitation Center; PP, per protocol; PROMIS, Patient-Reported Outcomes Measurement Information System; PTCI, Posttraumatic Cognitions Inventory; PTH, posttraumatic headache; PTHA Study, posttraumatic headache and PTSD study; PTSD, posttraumatic stress disorder; QDS, Quick Drinking Screen; RSES, Response to Stressful Experiences Scale; SDIH-R, Structured Diagnostic Interview for Headache-Revised, Brief Version; SITBI, Self-Injurious Thoughts and Behaviors Interview – Short Form; STOP, Snoring, Tired, Observed, Blood Pressure; TAU, treatment as usual; TBI, traumatic brain injury; VA, U.S. Department of Veterans Affairs; VHCS, Veterans Health Care System; VR-12, Veterans RAND 12-Item Health Survey.

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PTH unique from other types of headaches. The treatments under study differed in clinical focus and dose (i.e., number of treatment sessions), but the trial was designed to balance the treatments as well as possible. Finally, while the primary endpoints for pain research can vary from assessments of pain intensity to objective and subjective functional measures, this trial of PTH interventions chose carefully to establish clinically relevant endpoints and to maximize the opportunity to detect significant differences between groups with two primary outcomes. All these issues are discussed in this manuscript.

1. Introduction

Posttraumatic headache (PTH) is the most common and disabling symptom of traumatic brain injury (TBI), and federal agencies have dedicated significant resources to its diagnosis, management, and treatment [1,2]. The International Classification of Headache Disorders, 3rd Edition (ICHD-3) defines PTH as persistent or acute headache attributable to a head or neck injury [3,4]. Persistent posttraumatic headache is prevalent among military veterans with TBI, with up to 97% reporting headache after head injury [1,5–7]. These headaches are not defined by any specific clinical characteristics, making them difficult to treat. For example, most PTH presents with migraine-type symptoms (e.g., unilateral, throbbing pain quality, premonitory aura), but up to one fourth of PTHs are characterized as tension-type headache (e.g., bilateral, pressing quality) and a minority as cluster headache [8]. For this same reason, PTH is difficult to study. The exact mechanisms driving and maintaining PTH remain unknown, and in clinical practice the treatment for PTH tends to default to traditional treatments of primary headaches. Evidence of predominant migraine characteristics in PTH have led some to explore migraine treatments for PTH [9], but prophylactic and abortive agents for migraines (including non-vasoconstrictor agents like CGRP antagonists and 5-HT1F agonists) are not always effective [1]. Also, long-term use of medication can worsen headache symptoms, resulting in medication overuse headache [10].

Nonpharmacological interventions are increasingly used to address complex pain conditions, but the vague definition of PTH makes it difficult to tailor interventions. Posttraumatic headache often presents in the context of comorbid trauma conditions like TBI and posttraumatic stress disorder, so treatment should include comprehensive nonpharmacological treatment strategies that can address both PTH and comorbid trauma symptoms concurrently [8,11–13]. Posttraumatic stress disorder (PTSD) plays a significant role in headache chronicity and intensity [11,14,15] and can play a greater role in maintaining headache than that of more proximal causes like TBI [5,16,17]. Thus, established PTSD interventions may improve PTH by ameliorating PTSD symptoms. Broad-spectrum nonpharmacological interventions (e.g., cognitive and behavioral therapies; CBT) may be uniquely suited to the indistinct PTH presentation because CBT addresses the various dimensions of pain through multiple mechanisms, including coping, social activity, and comorbid mood symptoms [12].

The present study is designed to test the efficacy of a clinic-based CBT headache intervention compared to a gold-standard nonpharmacological intervention for PTSD in the treatment of posttraumatic headache. This manuscript describes (1) the methods and rationale for PTH inclusion criteria (to homogenize the sample), (2) implementation of the two treatments despite differences in treatment dose and duration, and (3) planning the analyses of multiple primary outcomes (e.g., headache-related disability and PTSD symptoms). The two interventions under study were compared to treatment as usual (TAU) in a large VA Polytrauma Rehabilitation Center to assess the best approach for managing military veterans with comorbid PTH and PTSD symptoms. The trial described in this manuscript is the largest study of nonpharmacological treatment for PTH, and it will be the first to document the contribution of comorbid PTSD to headache treatment outcomes.

2. Materials and methods

2.1. Study design

This study was the first of 11 nationwide research projects supported by the Consortium to Alleviate PTSD (CAP). Headquartered at The University of Texas Health Science Center at San Antonio, the CAP was jointly funded in 2013 by the U.S. Department of Defense (DoD) and the U.S. Department of Veterans Affairs (VA) to focus on developing and evaluating effective interventions for the prevention and treatment of combat-related PTSD and comorbid conditions, such as posttraumatic headache. The CAP is part of a National Research Action Plan jointly issued by the Department of Defense, Department of Veterans Affairs, Department of Health and Human Services, and Department of Education. Additional details about the CAP are available at www.ConsortiumToAlleviatePTSD.org.

The posttraumatic headache and PTSD study (PTHA Study) is a Phase III, three-arm, randomized clinical trial examining the efficacy of nonpharmacological interventions for headache and PTSD on headache-related disability. Participants include United States military veterans who meet International Classification of Headache Disorders, 3rd edition (ICHD-3 [3]) criteria modified for posttraumatic headache and report at least moderately impactful symptoms of comorbid PTSD. The sample is limited to veterans with *persistent* posttraumatic headache because these headaches are significantly more disabling and more difficult to treat than acute PTH and because up to 40% of individuals with acute PTH will later meet criteria for persistence [18].

Veterans enrolled in the study complete a comprehensive battery of assessments over 9 months of study participation including the CAP Common Data Elements [36], measures of headache-related disability, PTSD, TBI, mood disorders, health behaviors, cognitive functioning, and blood-based biomarkers. Due to the lack of studies exploring behavioral interventions for PTH, this research is designed as a three-armed randomized clinical trial to compare (1) an eight-session, manualized, clinic-based, cognitive-behavioral therapy intervention for headache (CCBT), (2) a 12-session Cognitive Processing Therapy (CPT) intervention for PTSD, and (3) treatment as usual (TAU) for patients with comorbid symptoms of PTH and posttraumatic stress following military deployment and combat trauma. Because both interventions require a different dose of treatment (i.e., eight sessions for CCBT and 12 sessions for CPT), the research team yoked the treatments at 6 weeks in duration. Outcomes variables were selected to add significantly to the extant research by supporting the efficacy of a manualized, nonpharmacological intervention for PTH based on a functional self-report outcome (i.e., headache-related disability) and highlighting potential mechanisms of change in PTH as a function of changes in PTSD symptoms, mood, sleep, pain coping, and serum-based biomarkers. Assessments occur at four different time points: prior to treatment (baseline) and at 1, 3, and 6 months following treatment completion. Blood was collected prior to treatment, during two of the sessions of the 6-week treatment phase for all participants, and at 1 and 6 months following treatment to allow examination of gene expression profiles linked with PTH that may be predictive of treatment outcomes. Veterans randomized to the TAU group have the option to be treated clinically with either CCBT or CPT after their 6-month follow-up assessment is complete.

2.2. Defining the clinical phenotypes

2.2.1. Posttraumatic headache phenotype

The ICHD-3 criteria offer no defining clinical characteristics of PTH (e.g., no diagnostic requirements for headache laterality, presence of aura symptoms, headache duration, or quality of head pain), and patients presenting with PTH may report symptoms that are indistinguishable from primary headaches such as migraine and tension-type headache [9]. Some diagnostic precision is needed, however, to separate PTH from phenotypically similar headaches because the suspected underlying role of head injury may alter headache mechanisms, prognosis and treatment response [19,20]. The ICHD-3 criteria make this distinction through a 7-day onset criterion that was established as an arbitrary onset latency that reasonably assures diagnosing providers that the headache (regardless of clinical phenotype) is causally linked to a head or neck injury. Unfortunately, many patients (approximately 28%) with head or neck injury report *de novo* or worsening headache up to 3 months after the injury [9,21]. Limiting diagnosis of PTH to a 7-day onset latency window could exclude up to one third of veterans with PTH, so we expanded our PTH inclusion criterion to include veterans with headache onset up to 3 months after a head or neck injury if the patient and provider agreed that the headache was likely linked to the injury. Most PTH will abate before 3 months, but those that persist beyond 3 months have a 71% likelihood of persisting for 1 year [22]. We chose to only include *persistent* PTH in this study to ensure that we are addressing the patients with the greatest need for treatment and that headache improvement after treatment can be attributable to the treatment intervention rather than spontaneous recovery. There is little information describing mechanistic differences in PTH with different clinical phenotypes (e.g., migraine-similar PTH versus tension-type-similar PTH), and the underlying mechanism of head injury in PTH is expected to be the same regardless of clinical characteristics of the headache. Thus, we did not specify clinical characteristics as part of our headache inclusion. A summary of the PTH inclusion criteria modified for this study is outlined in Table 1.

2.2.2. Posttraumatic stress disorder phenotype

There is growing evidence that posttraumatic stress disorder (PTSD) has a significant mechanistic impact on posttraumatic headache. PTH patients with comorbid PTSD symptoms report greater headache-related disability than those without PTSD, and PTSD symptoms are a stronger predictor of headache disability than either TBI or demographic variables [13]. Limiting PTHA study participation to veterans who meet diagnostic criteria for PTSD would ensure adequate levels of PTSD symptoms in the sample to meaningfully affect PTH but would ignore many veterans who are subsyndromal for PTSD but still have significant trauma symptoms that affect headache. Thus, we established an inclusion definition of PTSD for this trial that allowed enrollment of veterans with subsyndromal PTSD. Veterans are included if they endorse a clinically significant level of PTSD with a baseline score of 25 or more on a gold-standard posttraumatic stress symptom survey (PTSD Checklist for *DSM-5*; PCL-5). To ensure adequate representation of different PTSD symptom clusters, we also required documented exposure to a traumatic event, at least one intrusion symptom, and at least one avoidance symptom as documented in a structured clinical interview for PTSD (i.e., the Clinician Administered PTSD Scale for *DSM-5*; CAPS-5 [23]).

Table 1
Inclusion criteria for posttraumatic headache in PTHA study.

Diagnostic criteria:
A. Any headache fulfilling criteria C and D
B. Traumatic injury to the head has occurred
C. Headache is reported to have developed within 3 months after one of the following:
1. the injury to the head
2. regaining of consciousness following the injury to the head
3. discontinuation of medication(s) impairing ability to sense or report headache following the injury to the head
D. Agreement between patient and provider that headache is due to head injury
E. Headache persists for >3 months after its onset
F. Not better accounted for by another ICHD-3 diagnosis

Note: ICHD-3 = International Classification of Headache Disorders, 3rd Edition; PTHA = Posttraumatic Headache and PTSD Study. Differences from ICHD-3 criteria are noted in bold text.

2.3. Study objectives

The PTHA study was designed to address two primary objectives and two secondary objectives. First, we plan to assess differences between CCBT for headache and TAU on headache-related disability and posttraumatic stress symptoms at posttreatment and long-term follow-up (3 and 6 months posttreatment). We also plan to assess differences between CPT, a gold-standard PTSD intervention, and TAU on headache-related disability and posttraumatic stress symptoms at posttreatment and follow-up. There are two planned secondary objectives. The first objective is to determine whether the CCBT group experiences greater decreases in headache-related disability and has lower PTSD symptom scores posttreatment compared to the CPT group. This analysis will directly test the extent to which PTSD symptoms contribute to PTH disability. The second objective is to assess between-group differences related to longitudinal change in average headache frequency, reported twice daily over a 14-day period as a secondary outcome. Participants are asked to report the number of headaches they experienced since the last reporting period at each assessment and complete standardized headache diaries. The two primary outcomes for headache-related disability and PTSD symptoms are defined as follows:

Headache disability (Headache Impact Test [HIT-6]; [24,25]): The HIT-6 is a six-item assessment that measures headache-related interference and disability. Participants answer the six items on a 5-point Likert scale ranging from "Never" to "Always." Sums are used as scale scores, and items are coded as follows: "Never" = 6; "Rarely" = 8; "Sometimes" = 10; "Very Often" = 11; and "Always" = 13, for a total score range of 36–78. Scores greater than 50 represent significant headache disability. The HIT-6 has excellent reliability and validity for headache disability assessment and was administered at all four assessment intervals.

PTSD symptoms (PCL-5; [26]): The PCL-5 is a self-report, 20-item assessment measuring each symptom of PTSD as defined by the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5)* on a 5-point Likert scale: "Not at All" = 0; "A little bit" = 1; "Moderately" = 2; "Quite a bit" = 3; "Extremely" = 4. Items are summed for a total scale score. Participants who are randomized into the CPT arm complete the PCL-5 once a week (i.e., at even-numbered sessions) as part of their clinical protocol.

Primary analyses will compare CCBT for headache and CPT for PTSD to TAU. To adjust the alpha level for these joint hypotheses, we plan to interpret both outcomes at the alpha = 0.025 significance level. Secondary analyses will examine differences between the two experimental interventions as well as sensitivity analyses of the primary outcomes considering missing data, adherence to the protocol, or imbalances between the groups at baseline. Additional analyses will consider the secondary outcomes and differences between the groups at other time points.

2.3.1. Rationale for chosen outcomes

Headache is a challenging research topic because headache-related pain is often assessed across numerous dimensions (e.g., headache frequency, duration, intensity), and there is little consensus on how to prioritize, balance, or combine these dimensions to establish a reliable index of headache experience [27]. Furthermore, longitudinal assessment of headache dimensions using a headache diary can be unreliable and risks high levels of missing data [28]. Self-report measures of headache-related disability (e.g., the HIT-6 and the Migraine Disability

Assessment) significantly correlate with headache frequency and intensity [29] and demonstrate strong relationships with headache comorbidities like depression and anxiety that likely affect how patients cope with their pain [30]. These measures are generally brief and can be completed with much less time and effort than prospective headache diaries [25]. Validated, headache-specific measures of impairment/-disability are recommended for use in clinical trials examining behavioral interventions [27]. Thus, we chose to use the 6-item HIT-6 as our primary headache endpoint and will examine headache dimensions based on pain diaries as secondary outcomes.

PTSD can be assessed using self-report symptom inventories and structured diagnostic interviews, all of which account for contemporary diagnostic criteria for PTSD listed by the American Psychiatric Association in the *DSM-5* [31]. Although both self-report inventories and diagnostic interviews may be used to diagnose PTSD, it is recommended that clinicians use structured diagnostic interviews (e.g., CAPS-5 [26]) to reliably establish a PTSD diagnosis. Self-report PTSD symptom inventories (e.g., PCL-5 [32]) are best used to track changes in PTSD symptoms over time (based on their ease of use and sensitivity to change). Our study objective is to assess change in PTH outcomes as a function of change in PTSD symptoms over time, and we are less interested in PTSD caseness in this headache trial. Thus, we chose the PCL-5 as our primary PTSD outcome for this study. The schedule of all study assessments are shown in Table 2.

2.3.2. Study duration and flowchart

The treatment plans for CCBT for headache and CPT for PTSD prescribe different doses (i. e., number of sessions) of therapy (CCBT = 8 sessions; CPT = 12 sessions). Although one could add content to CCBT to make the treatment sessions and durations equivalent, there was some concern that doing so would deleteriously alter the treatment (which is already used as an efficacious intervention for migraine headache), increase dropout from treatment, and erode outcomes. Thus, both interventions were limited to a 6-week treatment window with no other modifications, allowing an additional 1-month window for veterans who failed to complete treatment in the allotted 6 weeks. Manualized treatments for PTSD (e.g., CPT) maintain efficacy and decrease dropouts when treatment is delivered in a relatively short timeframe [33], so there was little concern about delivering CPT twice a week for this study. All participants are screened for suitability for this study after providing informed consent, and those meeting inclusion and exclusion criteria are randomized to one of the three study arms in a 1:1:1 ratio. Veterans randomized to CCBT or CPT are asked to begin treatment at a large Veterans Health Care Center within 2 weeks of randomization. TAU participants are asked to access care in their usual fashion and are assessed for any notable changes to headache or PTSD symptoms or treatment at the same intervals as those in the CCBT and CPT study arms. All participants complete blood draws twice during the treatment period (at weeks 2 and 4). Posttreatment outcomes (including blood draws) occur 1 month after the 6-week treatment period to allow a 4-week window for veterans who cannot complete CCBT or CPT in the allotted 6 weeks. Additional follow-ups occur at 3 and 6 months after treatment completion. Fig. 1 shows a timeline of study events.

3. Study procedures

3.1. Eligibility and study recruitment

Participants are recruited from the Polytrauma Rehabilitation Center at a large VA medical facility in the southern United States, from regional military medical treatment facilities, and from the local community. Recruitment efforts target veterans and active duty military personnel having returned from a post-9/11 deployment with persistent PTH (based on ICHD-2 and ICHD-3 criteria) and symptoms of post-traumatic stress.

Table 2
List of study assessments.

Assessments	Baseline	During Treatment	1 Month F/U	3 Month F/U	6 Month F/U
Headache Assessments					
Structured Diagnostic Interview for Headache –Revised (SDIH-R)	x		x	x	x
Headache Impact Test (HIT-6)	x		x	x	x
Headache Management Self-efficacy Scale (HMSE)	x		x	x	x
Headache-Specific Locus of Control Scale (HSLC)	x		x	x	x
Daily Headache Diary*	x		x	x	x
TBI Assessments					
History of Head Injuries and History of Head Injuries Addendum	x		x	x	x
Ohio State University TBI Identification Method-Interview Form (OSU TBI-ID-SF)	x				
NIH Cognition Battery (by computer)	x		x	x	x
PTSD Assessments					
Life Events Checklist-5 (LEC-5)	x		x	x	x
PTSD Checklist List for *DSM-5* (PCL-5)	x	x	x	x	x
Clinician Administered PTSD Scale for *DSM-5* (CAPS-5)	x		x	x	x
Selection of Index Event for the CAPS-5	x				
Comorbid Condition Assessments					
Patient Health Questionnaire-9 (PHQ-9)	x	x	x	x	x
Generalized Anxiety Disorder-7 (GAD-7)	x		x	x	x
Insomnia Severity Index (ISI)	x		x	x	x
CAP Common Data Elements					
Deployment Risk and Resiliency Inventory-2-Deployment Environment (DRRI-2-D)	x				
Demographics and Military Questionnaire	x				
Deployment Risk and Resiliency Inventory-2-Postbattle Experiences (DRRI-2-P)	x				
Deployment Risk and Resiliency Inventory-2-Combat Experiences (DRRI_2_C)	x		x	x	x

(*continued on next page*)

Table 2 (*continued*)

Assessments	Baseline	During Treatment	1 Month F/U	3 Month F/U	6 Month F/U
Depressive Symptom Index–Suicide Subscale (DSI-SS)					
Quick Drinking Screen (QDS)	x		x	x	x
Neurobehavioral Symptom Inventory (NSI)	x		x	x	x
Alcohol Use Disorders Identification Test–Self Report (AUDIT)	x				
Pretreatment Health Interview	x				
Posttreatment Health Interview			x	x	x
Posttraumatic Cognitions Inventory (PTCI)	x		x	x	x
Response to Stressful Experiences Scale (RSES)	x				
Patient Health Questionnaire-15 (PHQ-15)	x		x	x	x
Veterans RAND 12-Item Health Survey (VR-12)	x		x	x	x
PROMIS Sexual Function	x		x	x	x
Brief-Inventory of Psychosocial Functioning (B-IPF)	x		x	x	x
PROMIS Sleep-Related Impairment and Disturbance	x		x	x	x
Snoring, Tired, Observed, Blood Pressure (STOP)	x				
Community Reintegration of Injured Service Members (CRIS)	x		x	x	x
Self-Injurious Thoughts and Behaviors Interview–Short Form	x		x	x	x
Supplemental Assessments					
Credibility and Expectancy Questionnaire (CEQ)		x	x		
PTHA Study Missing Data Assessment					x
* Diary Includes: 1. Daily Headache Diary 2. Profile of Mood States 3. Sleep Quality/ Quantity 4. Daily Stress Inventory					

Note: TBI = traumatic brain injury; TBI = traumatic brain injury; NIH = National Institutes of Health; PTSD = posttraumatic stress disorder; CAP = Consortium to Alleviate PTSD; PROMIS = Patient-Reported Outcomes Measurement Information System; PTHA = posttraumatic headache and PTSD.

3.1.1. Inclusion criteria

Veterans are enrolled in the PTHA study if they meet the following inclusion criteria: adult (ages 18 and above); U.S. military veteran or active duty personnel who performed military service during a post-9/11 deployment; have sustained a traumatic head injury; and have been diagnosed or report symptoms consistent with persistent (>3 months) posttraumatic headache attributed to a traumatic head injury.

We chose to focus on persistent PTH due to the very low likelihood of spontaneous headache remission after 3 months, the high levels of disability associated with persistent PTH, and the high prevalence of persistent versus acute PTH in the U.S. military and veteran populations. A positive PTH diagnosis is indicated for individuals with *de novo* headache onset after a concussion or exacerbation of pre-existing headache symptoms (increased frequency, duration, or intensity), which is consistent with existing ICHD-3 diagnostic criteria for PTH. Headache-related symptoms are assessed using the Structured Diagnostic Interview for Headache-Revised, Brief Version (SDIH-R [34]). Study staff confirm PTH diagnosis with the study principal investigator and a VA Polytrauma Rehabilitation Center (PRC)/Polytrauma System of Care physician (two of whom are co-investigators for this study) if symptoms consistent with chronic PTH are reported but the diagnosis is not already documented in the participant's medical record.

If taking headache medication, participants are asked to work with their prescriber(s) to remain on stable doses of any headache medications for the duration of the intervention and through the follow-up assessment intervals as much as possible and as medically indicated. Participants also must report an exposure to a traumatic event (Criterion A) and at least one intrusion symptom (Criterion B) on the CAPS-5 to be enrolled in this study. There is some evidence suggesting 40% comorbidity between PTSD and new onset headache [13], so it was reasonable to assume that at least half of all PTH participants recruited for this study would have PTH and comorbid posttraumatic stress symptoms.

3.1.2. Exclusion criteria

Criteria that exclude an individual from study participation are as follows: report of a recent and significant change in the nature of headache symptoms during the 6 weeks prior to screening (as determined by the investigators); undergoing treatment with CPT or prolonged exposure for PTSD at the time of enrollment or plans to engage in these PTSD treatments during study participation; diagnosed medication overuse headache at baseline based on the SDIH-R [34] and clinical judgment; inability to read or speak English at a 6th grade level; psychiatric hospitalization in the 6 months prior to enrollment; pregnancy or plans to become pregnant during the trial (due to concerns about pregnancy-induced headache that may obscure findings); an ongoing psychiatric problem at enrollment that warrants immediate treatment as indicated in the VA electronic health record (i.e., VA Computerized Patient Record System; CPRS), flagged by an independent evaluator during evaluation, or confirmed by a clinician through screening or review of CPRS notes; or demonstrated, significant cognitive impairment that could impact treatment adherence/benefit.

3.1.3. Study recruitment

Initial contacts for patient recruitment are made through various mechanisms. Under an institutional review board-approved Health Insurance Portability and Accountability Act authorization waiver, PRC physicians and/or study staff identify candidates who may benefit from and qualify for the study. This is done by reviewing CPRS appointment schedules and CPRS medical records of Veterans Health Care System (VHCS) and PRC patients with pending clinical appointments. A "qualified" candidate is a PRC/VHCS patient presenting with a primary diagnosis of headache and a history of diagnosis for TBI and/or persistent postconcussive symptoms (e.g., tinnitus, dizziness) as noted in the CPRS record. The PRC physician or study staff contacts the veteran's VA healthcare provider prior to their next clinic visit to inform the provider that his or her patient may qualify for the study and to ask if study staff

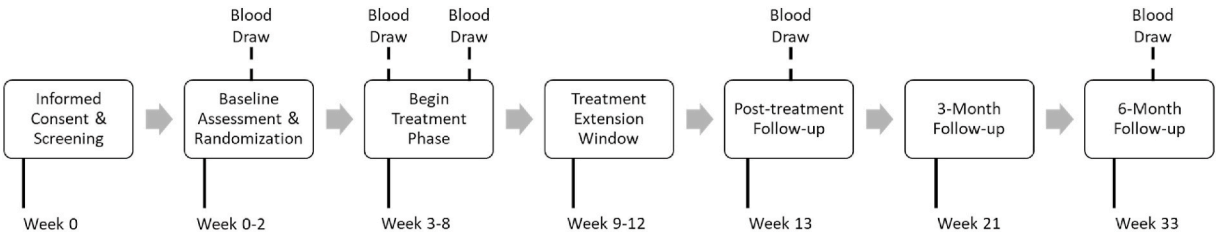

Fig. 1. Timeline of PTHA study participation. PTHA = posttraumatic headache and posttraumatic stress disorder.

could speak to the patient about the study after the next clinical appointment. Candidates are given information about the study from their medical provider, and interested veterans are consented by study staff who were housed in the PRC. If study staff are unavailable to meet with potential participants at the time of their clinical appointment, interested patients can give permission for study staff to contact them by signing a "consent to contact" form. Providers in all the VA and local military clinics that treat veterans with headache and/or TBI are briefed on study goals and the inclusion/exclusion criteria to help guide their referrals. We also recruit participants through other local trauma and TBI research trials (see Fig. 2).

Study investigators meet regularly with treatment providers at local military treatment facilities who may see patients who could benefit from the study interventions, and the study team accepts direct referrals from these providers. Individuals also are referred by other Consortium to Alleviate PTSD (CAP) and VA studies or are self-referred in response to recruitment information on the CAP website (maintained through the South Texas Research Organizational Network Guiding Studies on Trauma and Resilience [STRONG STAR] at www.strongstar.org). Interested persons can call or walk into the STRONG STAR offices. STRONG STAR also recruits via various social media sites (e.g., Facebook, Twitter, LinkedIn, etc.), and web search engines (e.g., Google Ads, Bing, etc.). In addition, there are events where information about STRONG STAR studies is provided, and those interested may fill out a "consent to contact" form indicating that they would like a member of the research team to contact them later to learn more about the study and schedule or complete prescreening. Research staff field incoming phone calls and walk-ins. News media coverage of the study or involving the study staff also generates self-referrals. Recruitment letters are mailed to veterans or active duty service members registered at the South Texas Veterans Health Care System with a history of post-9/11 military service through collaboration with the local VA Transition and Care Management Team or through research registry databases (or other open research studies) of willing veteran or service member research participants who have consented to be contacted about further study opportunities. Recruitment materials provide information about the study and contact information for both the study PI and study coordinator.

3.2. Screening, consent and randomization

Individuals interested in participating are given information about the study including inclusion and exclusion criteria and are screened using a telephone prescreen questionnaire to determine the possible presence of chronic PTH, the presence of posttraumatic stress symptoms, and the presence of any indicators that would exclude them from participation. Interested and qualified participants then receive additional information about the study, meet with the study coordinator to be formally consented into the study, and undergo formal screening and a baseline assessment. Baseline assessment follows consenting in a private room at the Polytrauma Rehabilitation Center. Participants not meeting inclusion criteria are informed and referred to appropriate care either as part of another study or through the local VA, military providers, and/or civilian resources, as appropriate. Individuals who met criteria were enrolled in the study and block randomized into one of the three treatment arms in a 1:1:1 ratio.

Participants who meet inclusion/exclusion criteria return to the clinic to have blood drawn as part of the baseline assessment, are oriented to online assessments and, if randomized to CPT, undergo a trauma interview conducted by the therapist who will be providing the CPT treatment. Appointments are made for participants to start treatment approximately 2 weeks later. All participants complete online headache diaries daily for 14 days following baseline assessment. If participants miss a headache diary entry, they receive a phone call from research staff to remind and encourage them to complete the diary.

3.3. Treatments

Treatment takes place at the South Texas Veterans Healthcare System or The University of Texas Health Science Center at San Antonio STRONG STAR clinic.

- *Clinic-Based Cognitive Behavioral Therapy (CCBT).* The CCBT headache treatment is based on a cognitive and behavioral model of headache management [35] and consists of eight 1-h sessions that participants are asked to complete in 6 weeks (participants are seen once or twice each week). The eight CCBT treatment sessions cover a variety of headache self-management topics and techniques including the following: relaxation training, identifying stress and analyzing stressful situations, planning for long-term stress management, solving problems that impact headaches, dealing with thoughts about headache, specific headache coping-skills training, and recommendations on how to maintain gains from treatment.

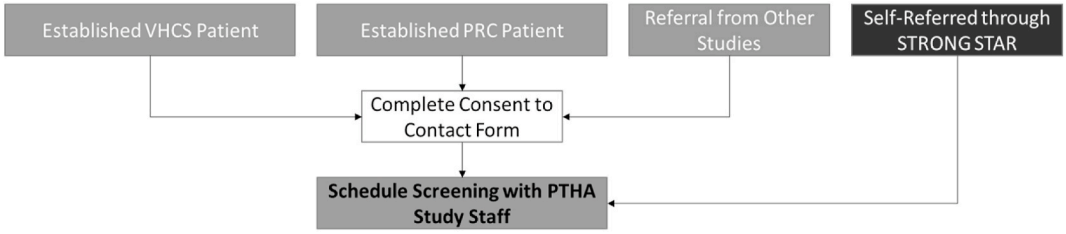

Fig. 2. PTHA study recruitment mechanisms. PTHA = posttraumatic headache and posttraumatic stress disorder; VHCS = Veterans Health Care System; PRC = Polytrauma Rehabilitation Center; STRONG STAR = South Texas Research Organizational Network Guiding Studies on Trauma and Resilience.

- *Cognitive Processing Therapy (CPT)*. CPT is a trauma-focused treatment that involves helping patients learn to recognize and challenge thoughts related to their traumatic brain injury in addition to the traumatic event(s) they experienced and their PTSD. Participants assigned to this treatment arm are asked to meet with a study therapist twice a week for 6 weeks for a total of 12 1-h sessions. During this treatment, participants are asked to think about their trauma and about the meaning of the event as well as their current beliefs about themselves and others. Topics such as safety, trust, control, self-esteem, and intimacy are discussed. Participants are expected to complete progressive worksheet assignments outside of session to practice skills learned in treatment.
- *Treatment as Usual (TAU)*. Participants assigned to the TAU condition receive treatment by their primary providers according to their established clinical treatment plan and recommendations. TAU includes primary care and specialty care through the Polytrauma Rehabilitation Center at a large VA hospital. TAU also often includes medication management, palliative care, complementary and integrative health interventions, and interventional pain medicine procedures.

3.4. Study assessments

Assessments were chosen to assess the major clinical domains of interest, e.g., PTH and PTSD symptoms, as well as comorbidities that could affect response to therapy (e.g., lifespan and warzone exposure to potentially traumatizing events, depression, anxiety, alcohol use, sleep, head injury, suicidal ideation, and functional impairment). Because this study is part of the Consortium to Alleviate PTSD, the CAP Common Data Elements [36] are administered as well as additional measures specific to head injury and PTHA.

3.4.1. Summary of assessment measures

Demographics and Military Questionnaire – The Demographics and Military Questionnaire was developed by STRONG STAR and the CAP to assess research participant demographics, military service variables (e.g., branch of service, rank, deployment) and VA data (employment, service-connected disability) in a self-report format.

History of Head Injuries – The History of Head Injuries Questionnaire was developed by STRONG STAR for military trauma studies with four self-report items covering the presence, cause and outcomes of head injury. The History of Head Injuries form covers military deployment-related head injuries and up to two head injuries that are not deployment-related. If a research participant endorses more than two nondeployment-related head injuries, these are tracked using the History of Head Injuries Addendum.

Deployment Risk and Resiliency Inventory 2 (DRRI-2; [37]). The Deployment Risk and Resiliency Inventory (version 2) includes 17 different scales describing different trauma risk factors associated with military service and deployment. The present study included DRRI-2 scales for Deployment Environment, Postbattle Experiences, and Combat Experiences. The DRRI-2 Deployment Environment scale includes 14 items rated by frequency on a 5-point numeric scale assessing conditions of day-to-day life during deployment. The Postbattle Experiences scale lists 13 items rated by frequency on a 6-point numeric scale assessing exposure to consequences of warfare during deployment. The Combat Experiences scale lists 17 items rated by frequency on a 6-point numeric rating scale assessing exposure to various combat circumstances. Higher scores indicate more frequent exposure for all DRRI-2 scales.

Life Events Checklist-5 (LEC-5; [26]). The LEC-5 is a self-report questionnaire allowing individuals with trauma to identify exposure to 16 different types of events that may have contributed to trauma symptoms and posttraumatic stress.

Patient Health Questionnaire – 9 Item (PHQ-9; [38]). The PHQ-9 is a nine-item module of the Patient Health Questionnaire [38] assessing depression symptoms consistent with clinical depression. Items are rated by frequency using a 4-point numeric rating scale and the scores are summed for a total depression score. The PHQ-9 has been established as a highly valid assessment of depression severity [39].

Depressive Symptom Index – Suicide Subscale (DSI-SS; [40]). The DSI-SS is a four-item self-report suicide screening tool with each item rated on a 4-point numeric rating scale ranging from 0 to 3. Item scores are summed for a total score between 0 and 12 with higher scores representing more severe suicidal ideation. The DSI-SS has strong content validity, with a cutoff score of 3 or more representing clinically significant ideation [40].

Generalized Anxiety Disorder Screener (GAD-7; [41]). The GAD-7 is a self-report anxiety screening tool derived from the PRIME-MD that uses seven items representing anxiety symptoms that are scored on a 4-point numeric rating scale. Item scores are summed for a total anxiety score ranging from 0 to 21. The GAD-7 showed strong sensitivity and sensitivity and was dimensionally distinct from depression [41].

Alcoholic Use Disorder Identification Test – Self-Report (AUDIT; [42]). The self-report AUDIT is a 10-item questionnaire designed to identify problematic or hazardous drinking with strong convergent validity with other measures of problematic alcohol use.

Quick Drinking Screen (QDS; [43]). The QDS is used to summarize average alcohol consumption over a specified timeframe with comparable psychometric precision with the AUDIT. It is recommended for alcohol use assessment in addition to the AUDIT because it provides information on drinking severity that may not be present in the AUDIT.

Headache Management Self-Efficacy Scale (HMSE; [44]). The HMSE comprises 51 self-report items that assess thoughts and beliefs that a headache sufferer can prevent headache onset when confronted with headache triggers. The measure has good construct and discriminant validity.

Headache-Specific Locus of Control Scale (HSLC; [45]). The HSLC is a 33-item self-report headache questionnaire designed to assess attribution of headache to behaviors, healthcare, or chance. Individuals who attribute headache to chance demonstrate worse outcomes.

Neurobehavioral Symptom Inventory (NSI; [46,47]). The NSI is a 22-item, self-report inventory of common symptoms accompanying mild traumatic brain injury. NSI symptoms fit a three-cluster model of somatic, affective and cognitive symptoms [48].

Credibility and Expectancy Questionnaire (CEQ; [49]). The CEQ is a brief assessment of treatment expectancy and rationale credibility with high internal consistency and good reliability. CEQ items assess both cognitive and emotional reactions to treatment.

Pre- and Post-Treatment Health Interview. The Pre-Treatment and Post-Treatment Health Interviews are semistructured interviews of common comorbid health and psychiatric conditions that often accompany military trauma and headache. The interviews include a list of a priori conditions, and participants are asked if they experienced problems or treatment related to each condition. There is also an open-ended response option for participants to add conditions that may have affected trauma or headache but were not on the a priori list.

Structured Diagnostic Interview for Headache (SDIH; [50]). The SDIH is a clinician-administered diagnostic interview for primary headaches and posttraumatic headache. The SDIH was originally developed using ICHD-2 headache criteria but was updated by our study team to be consistent with the ICHD-3 criteria for posttraumatic headache.

Ohio State University TBI Identification Method Interview (OSU TBI-ID; [51]). The OSU-TBI-ID is a brief, semistructured interview assessing the frequency and mechanism of head injury across a patient's lifetime. Respondents are asked to describe the date and circumstances of head injuries and can rate the severity of the head injury based on the associated duration of loss of consciousness. The OSU TBI method has solid reliability and predictive validity for cognitive performance and emotional functioning related to head injury [51].

Clinician Administered PTSD Scale for *DSM-5* (CAPS-5; [23]). The CAPS-5 is a structured diagnostic interview for PTSD based on *DSM-5*

diagnostic criteria. The interviewing clinician uses a standard form to select an index trauma event as the primary target of the CAPS-5 assessment. The CAPS-5 has excellent reliability and validity for both PTSD symptom severity and diagnosis.

Self-Injurious Thoughts and Behaviors Interview – Short Form (SITBI; [52]). The SITBI assesses past and recent suicidal thoughts and behaviors with excellent reliability and strong convergent validity with other measures of suicide risk in military veteran samples [53].

Response to Stressful Experiences Scale (RSES; [54]). The RSES is a trait measure of resilience. It is a 22-item questionnaire developed by a team of experts at the National Center for PTSD to assess trait-related cognitive, emotional, and behavioral resilience [54]. It asks participants to assess how well each statement describes them, both during and after stressful events in their lives. Responses are given on a 5-point scale, with anchors 0 (not at all like me) to 4 (exactly like me). Factor analysis revealed a six-factor model of resilience including subscales for active coping, meaning-making, cognitive flexibility, spirituality, self-efficacy, and restoration with good internal consistency and test-retest reliability.

Patient Health Questionnaire-15 (PHQ-15; [55]). The PHQ-15 is an abbreviated version of the original PHQ that asks about somatic symptoms and symptom clusters that account for more than 90% of physical complaints reported in an outpatient setting. The 15-item measure asks patients to report symptom severity on a scale ranging from 0 ("not bothered at all") to 2 ("bothered a lot"). The PHQ-15 has excellent internal reliability ($\alpha = 0.80$) and good convergent validity with other measures of symptom severity and functionality (e.g., SF-12, sick days, healthcare utilization and symptom-related difficulty [55]).

Veterans RAND 12 Item Health Survey (VR-12; [56]). The VR-12 is a 12-item health questionnaire that was developed from, and explains 90% of the reliable variance of, the longer VR-36 [57]. Its items are sampled from each of the eight health domains from the VR-36: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, energy/vitality, social functioning, role limitations due to emotional problems, and mental health resulting in two summary scales: a physical component summary (PCS) and a mental component summary (MCS). Each item includes a 5-point response scale ranging from "no, none of the time" to "yes, all of the time." Higher scores indicate better health.

PROMIS Sleep Disturbance and Sleep-Related Impairment short forms [58]. The PROMIS Sleep Disturbance and Sleep-Related Impairment short forms are self-report measures of past-week sleep disturbance and past-week, sleep-related impairment, respectively, derived from the larger PROMIS item banks [59]. Each short-form measure includes eight items, with most items (symptoms) scored in intensity from 1 ("not at all") to 5 ("very much"). Each measure has shown strong reliability and construct validity.

Brief Inventory of Psychosocial Functioning (B-IPF; [60]). The Brief Inventory of Psychosocial Functioning is a seven-item, self-report instrument measuring respondents' level of functioning in seven life domains: romantic relationship, relationship with children, family relationships, friendships and socializing, work, training and education, and activities of daily living [60]. Respondents indicate the degree to which they had trouble in the last 30 days in each area on a 7-point scale ranging from "0 = Not at all" to "6 = Very much."

Insomnia Severity Index (ISI; [61]). The ISI [61] is a seven-item, self-report measure that assesses perceived severity of insomnia. Each item uses a 5-point Likert type scale from 0 to 4, with higher numbers corresponding to greater sleep problems. The items sum to produce a total score (range 0–28). The ISI has an internal consistency alpha coefficient of 0.74, and it has shown convergent validity with other measures such as the Pittsburgh Sleep Quality Index ($r = 0.67$), the Dysfunctional Beliefs and Attitudes about Sleep ($r = 0.55$), and sleep diaries (r ranges from 0.32 to 0.91) [62].

Missing Data Assessment. The study team developed a brief, structured questionnaire to administer to study participants who drop out of treatment. The questionnaire asks about reasons for dropout and assesses headache and PTSD symptoms to be used for multiple imputation.

Electronic data were stored on a Federal Information Security Management Act-compliant, secure, research database at The University of Texas Health Science Center at San Antonio. Blood samples were collected at the following timepoints: prior to treatment (e.g., at baseline assessment) for all participants; at two treatment sessions for CCBT and CPT participants; within 6 weeks after baseline for TAU participants; and at 1 month and 6 months following treatment completion for all participants. A skilled phlebotomist drew the samples.

4. Data analysis

The primary aim of the study is to compare two nonpharmacological therapies—a clinic-based, cognitive-behavioral intervention for headaches (CCBT) and Cognitive Processing Therapy (CPT)—to treatment as usual (TAU) in their capacity to decrease headache-related disability scores (HIT-6) and posttraumatic stress scores (PCL-5) at a clinically meaningful level.

Treatment groups will be compared on baseline variables. Dropout during treatment resulting in lack of outcome data can bias analyses. If attrition can be successfully modeled with logistic regression based on baseline characteristics, and if there is evidence of differential attrition, strategies such as inverse probability weighting can supplement outcome analyses. To address this potential source of bias, we developed a standardized missing data assessment form that we used to assess reasons for dropout and/or missing data, PTH and PTSD symptoms at the time of reassessment, and satisfaction with research participation for all participants who dropped out of this study. Data from the missing data assessment will be used to assess reasons for data missingness that can guide multiple imputation of missing data in the final analyses.

4.1. Sample size justification and power analysis

Two recent studies helped to guide our determination of what constitutes a clinically meaningful change in perceived headache disability, and the proposed study was powered in light of these differences [32,63]. In the primary care setting, HIT-6 changes ranging from 2.5 (95% CI: 3.3 to −1.7) were perceived as "somewhat better" and changes up to 5.9 (95% CI: 7.6 to −4.1) were perceived as "much better." We considered a meaningful change as somewhere between these two global impressions and used this marker as an index of clinically significant between-group differences. For the PCL-5, we identified a total score change of 10 points as a clinically significant change in PTSD symptoms. Our study was powered to detect an effect size of 2.8 points between groups after controlling for baseline scores (i.e., a residualized change), an effect that would be meaningful to most headache sufferers. Assuming an alpha level of 0.025, group sample sizes of n = 64 (N = 192), and a moderate correlation between the baseline scores and final endpoints ($r = 0.50$), we will have power = 0.80 to detect an effect size of $d = 0.52$ between both of the joint primary comparisons. In realistic terms, this will allow us to detect a difference of 2.8 points on the HIT-6 and 11.0 points on the PCL-5 between the active treatment and the controls after controlling for baseline scores. Differences smaller than this magnitude are unlikely to be clinically meaningful.

4.2. Primary analysis

Assuming that headache disability data (HIT-6; our primary outcome for this research) is reasonably normally distributed across the sample, treatment effects of the clinical interventions (CCBT and CPT) over the TAU control condition will be analyzed using a general linear mixed (GLM) model using baseline scores as a covariate. Unlike ANOVA, mixed effects models permit heterogeneity of variance in the treatment groups. If HIT-6 data are non-normal, a generalized linear model will be used (e.g., Poisson regression). There are no interim analyses planned.

Confidential review by a Data Safety Monitoring Board will occur routinely, and we will not apply stopping rules for futility or superiority.

Planned analyses will include both intent-to-treat (ITT) and per protocol (PP) population sets. The primary analysis will be conducted on a modified ITT set defined as randomized individuals who receive one or more treatment sessions. The PP set will be restricted to those individuals who complete 75% or more of treatment sessions (i.e., six sessions of CCBT and nine sessions of CPT) and complete the relevant assessment occasions.

4.3. Planned secondary analyses

Planned secondary analyses were developed to identify important secondary questions to address based on a priori hypotheses that would minimize bias in data analytic planning based on exposure to primary study outcomes. The research group established a formal secondary analysis planning document and required all planned secondary analyses to be reviewed by the investigator team based on a one-page summary document. Secondary analyses were discussed, amended and ratified by the investigator team. The primary and secondary analyses will be conducted on both the ITT and PP sets, and sensitivity analyses will estimate differences in primary and secondary outcomes conditional on the population.

5. Discussion

Research on posttraumatic headache is rapidly evolving, and PTH studies confront difficulties related to sparse evidence of PTH-specific mechanisms that can guide the design of research, vague definitions of the PTH phenotype (which lacks specification of clinical headache characteristics and includes an arbitrary criterion for headache onset), and a paucity of clinically relevant research endpoints. Surprisingly, research on the mechanisms of PTH date back almost 100 years [64], but there is still significant uncertainty about both how PTH develops and how persistent PTH is maintained [65]. Most studies of PTH find that military PTH resembles migraine headache, and some studies suggest migraine-specific mechanisms that may underlie PTH progression (e.g., calcitonin gene-related peptide, CGRP [66]). Interestingly, CGRP mechanisms have also been identified in studies of other primary headache (e.g., tension-type headache [67]), so CGRP pathways may lead to robust treatments across the varied clinical characteristics of PTH. Contemporary models of PTH mechanisms highlight the complex network of genetic, inflammatory, neurological, and behavioral factors that likely interact to produce and perpetuate headache after traumatic brain injury [68]. Thus, interventions with broad effects, like behavioral treatments based on cognitive and behavioral therapies (CBT; cf. [69]), show significant promise for PTH, leading this study to test two CBT-based interventions as experimental PTH treatments.

The inclusion of PTSD assessment and a gold-standard treatment for PTSD, CPT, is an important component of this study. Although the index event chosen as the focus in CPT may not be the same event that caused the PTH, CPT is sufficiently flexible to incorporate any dysfunctional thoughts about the meaning of the headaches as well as other traumatic events. CPT is a cognitive therapy that teaches patients to examine their thoughts, assumptions, and conclusions by teaching them how to examine the evidence for their beliefs with progressive worksheets and to develop meaningful and more accurate alternative thoughts that they can practice. CPT has been found to reduce reported health symptoms [70] but has not yet focused on posttraumatic headache specifically. This treatment is a good comparison condition for a headache-focused treatment among those who also have PTSD symptoms. Cognitive and behavioral therapies are mainstays of primary headache treatment, and they could effectively address headache through cognitive, behavioral and emotional pathways that directly affect headache-related disability [71]. Although CPT and CBT for headache (called CCBT in this study) differ in number of sessions, previous studies of CBT-based pain interventions found similar effects of psychosocial pain treatments with differing dose and duration [69]. Thus, there is little concern about systematic differences in headache outcomes between the two treatments based on dose or frequency of treatment.

As noted above, studying PTH is difficult due to the lack of definition in diagnostic criteria for these headaches. Systematic review of psychosocial and integrative treatments for posttraumatic headache reveal high heterogeneity in published study samples that significantly undermine synthesis of PTH research findings [72]. Much of this heterogeneity is attributable to the relatively broad diagnostic criteria for PTH as defined in the ICHD-3 [3]. Our investigative team carefully considered the definition of PTH before designing our inclusion criteria for the study. Team members also consulted with national experts to identify criteria that would balance sample homogeneity with enough clinical breadth to ensure meaningful translation of study findings into the population of veterans with PTH. We chose to allow for headache onset within 3 months of head injury and limited enrollment to veterans with persistent (instead of acute) PTH. These decisions ensured that we are not using a mixed sample of acute and persistent PTH and that we are being sensitive to veterans who are experiencing a mechanistic PTH with delayed onset. Onset latency criteria for PTH have varied over time (the first edition of the ICHD criteria required a 14-day onset latency), and the existing 7-day criterion in the ICHD-3 is widely acknowledged as arbitrary [18]. As research continues to improve our understanding of PTH, evidence of headache attributable to head injury with onset beyond 7 days will be crucial in the reevaluation and evolution of the onset latency criterion. Data resulting from our trial should include participants who meet and exceed the established latency criterion for PTH, which will allow for preliminary analyses on how or whether differences in headache onset latency affect headache phenotype and response to common treatments.

Because PTH is putatively driven by head injury and trauma mechanisms, we chose not to enroll based on clinical characteristics resembling primary headaches. Our resulting sample is likely to include a majority of participants with migraine-like symptoms. However, this trial is likely to include a substantial number of tension-type and cluster headache phenotypes as well as more complex "mixed" phenotypes (which include symptoms consistent with multiple primary headaches). Little is known about how differing clinical characteristics affect PTH, so heterogeneity in clinical characteristics in our trial may offer preliminary evidence of any differences that may exist. Until more is known, an assumption of clinical equipoise between different clinical characteristics is the only reasonable assumption for PTH. Similarly, we chose not to stratify our sample based on the mechanism of head injury resulting in posttraumatic headache.

It is difficult to determine the extent to which the findings from this trial will extrapolate to civilians with posttraumatic headache. Military veterans are more likely than civilians to experience head injury associated with blast exposure (i.e., barotrauma) or overpressure associated with discharge of firearms. Some suggest that barotrauma may have unique effects on the brain that could result in characteristically different rates and presentations of headache [73], though the body of research is equivocal, with some reporting evidence that head injury mechanisms have little differential impact on brain functioning [74]. Unfortunately, the body of literature describing unique contributions of barotrauma to TBI (and TBI-related headache) is sparse and does not provide enough information to lead to a reasonable stratification of head injury type (i.e., barotrauma versus blunt trauma). Approximately 26% of service members with TBI are exposed to blast trauma (compared to 44% with blunt force injury due to physical assault or motor vehicle accident) [75], so we anticipate that our sample will include multiple head injury types, allowing for subanalyses that may lead to further research on the unique contribution of injury type to headache presentation and treatment response. Unfortunately, very little is known about how differences in head injury mechanism and the unique context of military head trauma (which is more likely to appear with comorbidities

like posttraumatic stress disorder than civilian TBI [76]) affect response to treatment. So, it is recommended that any treatment that works well for one population (migraine) be applied to another (civilian or military PTH resembling migraine) until better research is available to guide treatment [76].

Posttraumatic headache is a significant and impactful consequence of traumatic brain injury for which there are few, if any, well-supported treatments. The clinical and research communities have made some progress in understanding and defining this complex phenomenon, but more work is needed to develop a robust research literature describing the mechanisms and treatments for posttraumatic headache. The present study was developed to directly assess nonpharmacological interventions for PTH and the influence of a common trauma comorbidity, PTSD, on PTH course and outcome. We hope that this trial will represent a meaningful step toward better understanding PTH and will provide some of the first Level II evidence supporting PTH treatment.

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Declaration of competing interest

None to report.

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