Title

Telemedicine-based Cognitive Behavioral Therapy (TENACITY) for Veterans with Chronic Migraine: Study protocol of a pilot randomized controlled trial

Trial registration

ClinicalTrials.gov: NCT04613362

Trial registration: data set

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Funding

Veterans Health Administration VA Health Services Research and Development
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Introduction

Background and Rationale

1. Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention

Individuals with chronic migraine routinely face barriers that limit their access to evidence-based (EB) behavioral headache treatment. With the Veterans Health Administration (VHA) infrastructure dedicated to efficient telehealth delivery into patient homes, the delivery of a behavioral intervention for headache (HA) via the telehealth platform is primed to address barriers of in-person care delivery and holds considerable promise to reach and reduce Veteran patients' headache days.

An evidence base of over 300 studies addressing behavioral headache interventions has exerted a substantive influence on contemporary headache pain management.(Rains, Penzien, McCrory, & Gray, 2005) Behavioral treatments have consistently been shown to be significantly more effective than control conditions and yield clinically-meaningful benefit,(Campbell & Penzien, 2000) and have been found to be similarly efficacious to preventive pharmacotherapy,(Holroyd et al., 2001; Holroyd & Penzien, 1990; Powers et al., 2013) leading numerous professional practice organizations to recommend behavioral headache treatments as front-line interventions for chronic migraine (CM). For example, drawing upon evidence from an Agency for Healthcare Research and Quality (AHRQ)-funded meta-analysis(Goslin et al., 1999), the U.S. Headache Consortium, a multidisciplinary assemblage of seven professional organizations including the American Headache Society,(Silberstein & Consortium, 2000) recommended use of cognitive behavioral therapy (CBT) for CM.(Campbell & Penzien, 2000) Thus, the efficacy and value of behavioral headache interventions has been unequivocally demonstrated—their effect sizes are comparable to pharmacotherapy, the observed improvements are durable, they are essentially free of adverse events, and their use is strongly endorsed by multiple headache medicine stakeholders.

Despite strong empirical support and endorsement by professional practice organizations, behavioral interventions are not widely available to headache patients. (Penzien, Irby, Smitherman, Rains, & Houle, 2015)Even when trained practitioners are available, clinic-based behavioral treatments remain inaccessible to many, given time restraints for patients. Considerable effort has been devoted to making behavioral headache therapies more accessible through development of limited therapist-contact formats (3-5 clinic appointments). Self-management skills are introduced in clinic by a therapist, whereas skills-training occurs at home. This research suggests behavioral self-management interventions for headache can prove highly beneficial if delivered in a compelling format designed to enhance patients' sustained engagement, thereby reducing treatment attrition. Despite the burgeoning empirical evidence that a broad variety of interventions are efficiently and effectively delivered via telemedicine approaches, this strategy has not yet been empirically studied for headache pain management. Therefore, we aim to implement and test a telemedicine-based delivery of CBT for CM employing our manualized migraine treatment protocol.

Background and rationale: choice of comparators

TENACITY's manualized CBT sessions are adaptable through the delivery medium (telehealth vs in person), by number of sessions, and by the clinical role of the interventionists. The EHUT comparator was chosen to allow each site the flexibility of delivering an appropriate behavioral therapy(Grinberg et al., 2023) alternative.

Objectives

The objective of this study is to conduct a pilot randomized controlled trial (RCT) and determine the feasibility of the implementation of a cognitive behavioral therapy (CBT-HA) protocol for headache delivered via telemedicine (TENACITY) compared to enhanced headache usual treatment (EHUT).

The investigators will recruit Veterans diagnosed with chronic migraine during the one-year recruitment period across the 3 VAMCs. The investigators will randomize eligible Veterans to participate either in the TENACITY intervention (n=50) or treatment as usual (n=50).

The specific aims are threefold:
Aim 1: To develop a bundle of evidence-based practice (EBP) implementation strategies to engage 3 VA Medical Centers [2 Headache Centers of Excellence HCoEs and 1 general neurology service] and facilitate their local adaptation and implementation of Cognitive Behavioral Therapy (CBT) (TENACITY) through the vehicle of telehealth services.

Aim 2. To conduct a pilot RCT and determine the preliminary efficacy and feasibility of TENACITY compared to TAU across 3 VA sites. We will conduct a superiority analysis.

Hypothesis 2: Veterans receiving TENACITY will experience a statistically significant reduction in routine clinical headache metrics: headache frequency [headache days per month] (primary outcome), headache-related impairment and psychological symptoms (secondary outcomes) compared to enhanced headache usual treatment at 3 and 6 months.

Aim 3: The investigators will conduct exploratory cost analysis of TENACITY from the Veteran's perspective, using inputs from the pilot RCT, and a two-year budget impact analysis from the VHA's perspective, incorporating the costs of implementation as well as direct costs (and cost-savings,) of providing the TENACITY intervention over all HCoEs to VHA.

Hypothesis 3: TENACITY will be cost-effective and provide value to Veterans and VHA.

Trial Design

TENACITY is a single-blind, randomized, controlled, pilot trial with a single intervention arm and an enhanced headache usual treatment (EHUT) control arm analyzed as intention-to-treat. This multi-site study has a 31-day run-in/screening period to confirm chronic migraine and an approximately 12-week treatment period. Follow-up assessments are conducted at 3 and 6 months post-treatment initiation.

Methods: Participants, interventions, and outcomes

Study Setting

Participants will be recruited from three geographically distinct VA medical centers. Site one hosts a large, multidisciplinary HCoE, and is neurology-led with a strong health psychology program. Site two hosts a smaller VA Headache Consortium Center, is neurology-led, and has a developing health psychology program. Site three has no established HCoE and is a large-volume site with no health psychology program for headache.

All study procedures will be conducted via telehealth, with no in-person, face-to-face communication.

Eligibility Criteria

Inclusion criteria. Veteran participants within the VHA medical system with an ICD-10 diagnosis of chronic migraine who complete at least 28 days of headache diary at baseline with a confirmed frequency of ≥8 headache days per month at baseline are eligible for this study.

Exclusion criteria. Veteran patients with any of the following diagnoses are ineligible for this study: post-traumatic headache, cluster headache, other primary headache, post-whiplash headache, and trigeminal autonomic cephalalgia diagnosis. Also excluded are participants who have received ≥ 90 days opioid therapy from the date of chart screening; have a current diagnosis of severe cognitive impairment indicated by Short Portable Mental Status Questionnaire (SPMSQ); have a diagnosis of traumatic brain injury ≤ 1 year before diagnosis of chronic migraine or worsening of chronic migraine as indicated by post-traumatic headache screening tool; suffer from a disabling psychiatric illness (as noted by clinician); have had a psychiatric hospitalization in the last 6 months; relate daily suicidal ideation within the last 2 weeks as indicated by the PHQ-9 with an answer of "3" to question nine; have severe depression, as indicated by PHQ-9 score ≥ 20; are terminally ill (life expectancy of <12 months as noted by clinician); decline to or cannot use the Annie App; have been treated by a HCoE clinical health psychologist in last two years.

Interventionists: Two clinical psychologists employed by 2 of the 3 VAMCs trained to deliver CBT for Headache manualized behavioral treatment will provide the intervention. One of the psychologists will provide a telehealth clinic to the third site (VAMC) which is without any clinical psychologist trained in CBT-HA in addition to the local site. The two psychologists met to coordinate the treatment protocol prior to the start of the intervention.

Interventions: description

The TENACITY intervention consists of protocolled, manualized, short-term cognitive behavioral therapy for headache (CBT-HA) sessions which are administered via a telehealth delivery platform. Each session is approximately 50 minutes and follows a similar structure: (1) agenda setting (2) home practice check-in (3) learning a new skill (4) goal setting for home practice. The treatment will be delivered over approximately six biweekly sessions.(Grinberg et al., 2023)

The enhanced headache usual treatment (EHUT) intervention consists of a referral to behavioral pain therapy contingent on the specific site. The therapies available are cognitive behavioral therapy for chronic pain (CBT-CP), integrated pain mindfulness, and dialectical behavioral therapy. Depending on which format is offered at the specific site, these therapies will be delivered either individually or in a telehealth group setting.

Interventions will be initiated after patient randomization and subsequent scheduling with the appropriate clinician using the VHA clinical scheduler. Treatment will be administered using the VA telehealth platform, VA Video Connect (VVC) and/or telephone in one to one clinical visits.

Interventions: modifications

i. Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)

Treatment length and content is able to be modified and adjusted based on clinician discretion and mutual agreement with the participants.

Interventions: adherence

i. Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)

Clinicians have the option of scheduling participants for subsequent sessions ahead of time to potentially improve adherence. Post-hoc chart abstractions will be conducted to assess intervention adherence.

Interventions: concomitant care

i. Relevant concomitant care and interventions that are permitted or prohibited during the trial

There is no prohibited concomitant care during the course of the study. Participants will be asked to continue their usual medical headache care.

Outcomes

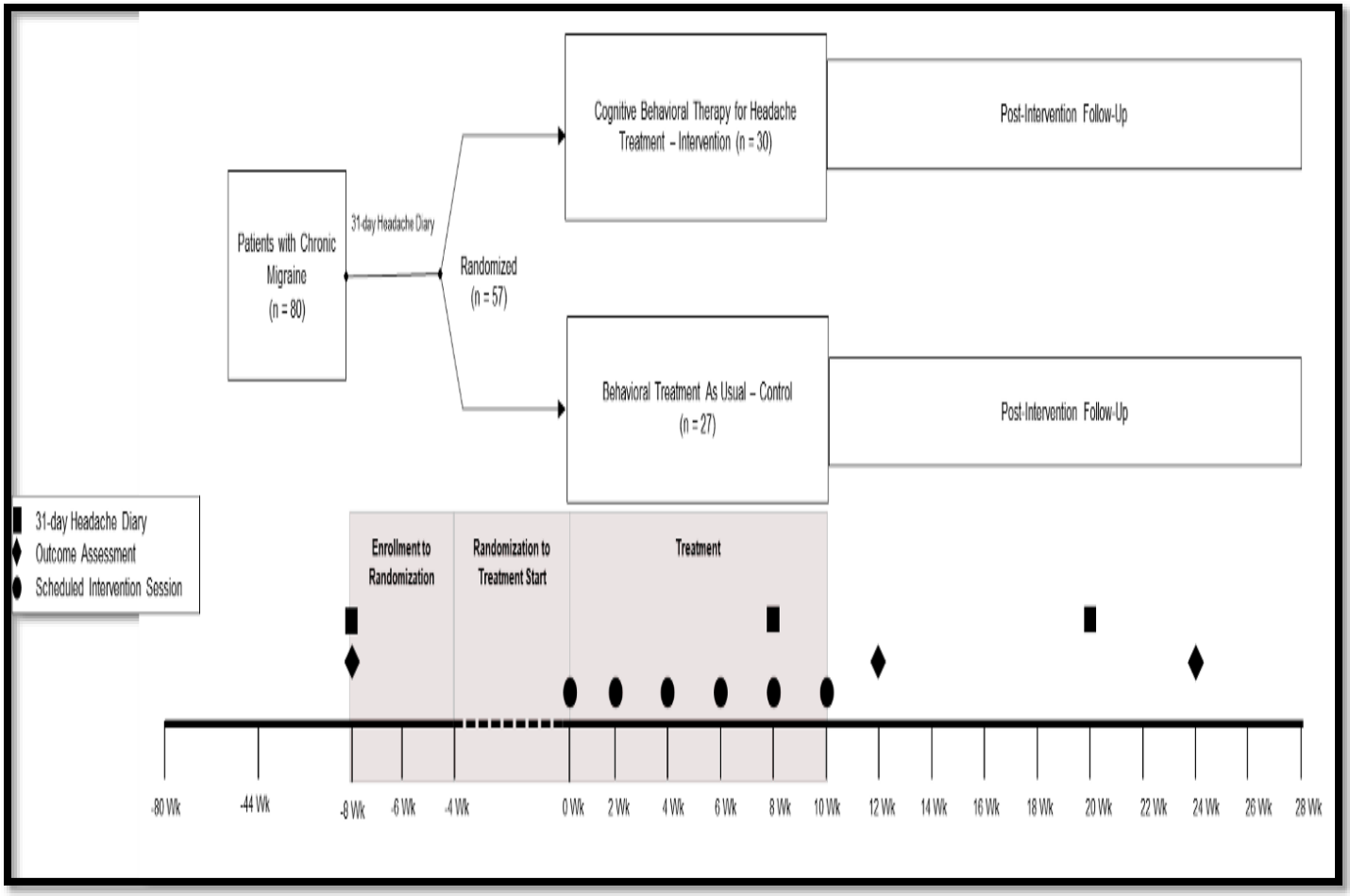
The primary outcome to be evaluated is change in the number of self-reported headache days during the past 31 days at 3 months compared to baseline. This outcome is considered the gold standard for prospective migraine research.

Secondary outcomes include the change in headache-related impairment and psychological symptoms at 3 and 6 months compared to baseline. These include a battery of well-validated health questionnaires of functioning and symptoms that are tracked as part of routine headache care services both in VA and non-VA healthcare systems and include the following: Migraine-Specific Quality of Life Questionnaire (MSQ); MIDAS; Headache-specific Pain Catastrophizing Scale (HPCS); Headache Management Self-Efficacy Scale (HMSE); Post Traumatic Stress Disorder (PCl-5); PHQ-9; GAD-7; Veterans RAND VR-12; Insomnia Severity Index (ISI).

Participant timeline

i. Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)

Upon enrollment, participants will begin a run-in period of a 31-day electronic headache diary. Participants will be asked to participate in a baseline interview and to complete health questionnaires. On completion of baseline headache diary, if all inclusion criteria are met, participants will be randomized to either CBT-HA (TENACITY) or EHUT. Consults will be placed to the appropriate clinical providers, with clinics contacting participants to schedule treatment. Participants will complete the 31-day headache diary and health questionnaires again at approximately 3 and 6 months after treatment initiation, along with an additional treatment satisfaction survey.



Sample size

i. Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations

We will recruit Veterans until we have reached 100 eligible participants across the three VAMCs. We will randomize eligible Veterans to participate either in the TENACITY intervention (n=50) or enhanced headache usual treatment (EHUT) which may include outpatient clinic-based health psychology (n=50). This is a pilot feasibility demonstration to provide preliminary efficacy. The sample size estimate was based upon the staff resources available to screen, invite and recruit patients to reach 100 subjects over a 15-month period.

Recruitment

i. Strategies for achieving adequate participant enrolment to reach target sample size

This study will recruit participants from three geographically distinct VA medical centers. All recruitment procedures will be conducted via phone, with no in-person communication, which will allow for greater reach to include entire VAMC catchment areas and eliminate any potential barriers due to COVID.

Potential participants will be identified by either direct referral from a clinician or from a HCoE-generated recruitment list which utilizes the VHA Headache Data cohort(Sico et al., 2022). The cohort is constructed using VHA electronic clinical and administrative data for Veterans with a headache diagnosis. Research staff will review each Veteran's electronic health record in order to determine if they meet study inclusion criteria. If inclusion criteria are met, the Veteran is sent a recruitment letter by mail which describes patient incentives for participation ($25) per assessment period and will receive a follow-up phone call. During the phone call, research staff will provide a study overview and conduct further screening if the Veteran indicates interest.

Methods: Assignment of interventions (for controlled trials)

Allocation: sequence generation

i. Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions

We will use a computer-generated random assignment stratified by 3 sites with no blocking.

Allocation concealment mechanism

i. Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned

We will use a password protected computer file to conceal random assignment.

Allocation: implementation

i. Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions

Program manager will designate the random assignment upon participant completion of the baseline assessment and notify the respective clinical program and schedulers to contact the participants for their respective treatments.

Blinding (masking)

A TENACITY protocol evaluation will be conducted with participants at approximately 3 months post-treatment initiation in order to evaluate the study arms and exercises used in treatment. To protect research personnel blindness, the research staff member who is responsible for randomization will be the sole staff member to conduct these evaluations and collect self-reported medical care received during the prior 3 months.

Blinding (masking): emergency unblinding

i. If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial

Methods: Data collection, management, and analysis

Data collection plan

i. Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol

Participants will complete a baseline interview and health questionnaires via phone or electronically using VA Qualtrics. They will be assigned a 31-day headache diary using VA Annie app. Research staff will obtain Veteran permission to audio-record the interviews. Each interview will be recorded and transcribed. The health questionnaires and headache diary will also be completed at 3-month and 6-month post-treatment initiation, along with a treatment satisfaction survey.

At the end of the 31-day run-in period, the participants will be contacted by phone to review the headache diary. If the participant self-reported ≥8 headache days over the course of the prior 31 days and completed the first question of the headache diary on at least 28 days, s/he will remain eligible for the study. If the participant did not meet these criteria, they will be invited to complete an additional 31 days of headache diary, with the same stipulations applied. If they choose not to complete the headache diary a second time, they will be considered ineligible, removed from the study and sent back to the HCoE clinical provider to review other treatment options. Participants enrolled in the study will then be randomized to either the TENACITY arm or the EHUT control arm of the study.

Screening Assessments

Short Portable Mental Status Questionnaire (SPMSQ)

The SPMSQ(Pfeiffer, 1975) will be utilized to screen potential participants for cognitive impairment. The SPMSQ is a 10-item measure with scoring guidelines as follows: intact intellectual functioning (0-2), mild intellectual impairment (3-4), moderate intellectual impairment (5-7), and severe intellectual impairment (8-10).

American Migraine Study/American Migraine Prevalence and Prevention (AMS/AMPP) Diagnostic Module

The AMS/AMPP will be utilized to assess Veterans for chronic migraine according to International Classification of Headache Disorders (ICHD-2) criteria. Respondents meet criteria for chronic migraine if at least 2 of 4 pain features are scored as a 3 or more, and nausea or both photophobia and phonophobia are scored 3 or more. The AMS/AMPP has a sensitivity of 91% and specificity of 80% for CM diagnosis.(Lipton, Diamond, Reed, Diamond, & Stewart, 2001)

Post-Traumatic Headache (PTH) Screener

The PTH will be utilized to determine if the participant meets criteria for post-traumatic headache.

Patient Health Questionnaire (PHQ-9)

The PHQ-9(Kroenke, Spitzer, & Williams, 2001) is a reliable and well-validated self-report measure of depressive symptom severity and suicide risk based on Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria. Items are rated from 0 to 3 (0 = not at all, 3 = nearly every day). Total scores range from 0 to 27. Totals are categorized as follows: none-minimal (0-4), mild (5-9), moderate (10-14), moderately severe (15-19), and severe (20-27). Daily suicidal ideation is indicated by a response of “3” to question nine.

Primary Outcomes Collection

Reduction of headache days in the 31 days prior to the 3-month post-start of treatment mark is the primary outcome; reduction in headache days in the 30 days prior to the 6-month post-start of treatment mark will allow for measurement of cumulative benefit and persistence of efficacy.

The VA Annie mobile application (Saleem et al., 2020) will be utilized as the platform for a daily headache diary. A protocol has been designed (Table 1) to send daily automated text messages to each participant for a total of 31 consecutive days. Participant responses are stored in the Annie system and are accessible by study staff. If a participant responds that they had a headache, eight additional questions are asked as indicated in Table 1. After being prompted with an Annie question, if the participant does not respond, a reminder message is sent every twenty minutes, with a maximum of three reminders per question.

Q	Text	Response Options	Action
1	Hello, it's Annie. Did you have a headache today?	Yes – HA 2 No – HA 1	If HA 2 → Q2 If HA 1 → Q9
2	On a scale from 0-10, with 0=none and 10=worst, how severe was the headache?	PN 0 – PN 10	If response → Q3
3	Was the pain worse on one side of your head?	Yes – SD 2 No – SD 1	If response → Q4
4	Was the pain pounding/throbbing?	Yes – PD 2 No – PD 1	If response → Q5
5	Did light bother you?	Yes – LT 2 No – LT 1	If response → Q6
6	Did sound bother you?	Yes – SO 2 No – SO 1	If response → Q7
7	Did you feel nauseated or sick to your stomach or vomit?	Yes – VO 2 No – VO 1	If response → Q8
8	Was the pain made worse with routine activities such as walking or climbing stairs?	Yes – MV 2 No – MV 1	If response → Q9
9	On a scale from 0-10, with 0=none and 10=worst, how much did the headache interfere with your life today?	IN 0 – IN 10	

Secondary Outcomes Collection

Migraine Disability Assessment (MIDAS)

The MIDAS(Stewart, Lipton, Dowson, & Sawyer, 2001) is a 5-item, self-report measure of disability related to headache based on number of missed or significantly limited activity days due to headache in school or paid work, household work, and family, social, or leisure activities. Responses are categorized as follows: little or no disability (0-5), mild disability (6-10), moderate disability (11-20), and severe disability (21+).

Patient Health Questionnaire (PHQ-9)

The PHQ-9(Kroenke et al., 2001) is a reliable and well-validated self-report measure of depressive symptom severity and suicide risk based on Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria. Items are rated from 0 to 3 (0 = not at all, 3 = nearly every day). Total scores range from 0 to 27. Totals are categorized as follows: none-minimal (0-4), mild (5-9), moderate (10-14), moderately severe (15-19), and severe (20-27). Daily suicidal ideation was indicated by a response of "3" to question nine.

Generalized Anxiety Disorder Screener (GAD-7)

The GAD-7(Spitzer, Kroenke, Williams, & Löwe, 2006) is a reliable and validated 7-item, self-report measure of anxiety. Items are rated from 0 to 3 (0 = not at all, 3 = nearly every day). Total scores range from 0 to 21 and are categorized as follows: none-minimal (0-4), mild (5-9), moderate (10-14), and severe (15-21) anxious symptoms.

Post-Traumatic Stress Disorder Checklist (PCL)

The PCL(Blevins, Weathers, Davis, Witte, & Domino, 2015) is a validated 17-item, self-report measure of PTSD symptoms based on DSM criteria. Items are rated from 0 to 4 (0 = not at all, 4 = extremely). Total scores range from 17-85. Higher scores indicate higher post-traumatic stress symptoms. This measure was only collected at baseline.

Insomnia Severity Index (ISI)

The ISI(Bastien, Vallières, & Morin, 2001; Morin, Belleville, Bélanger, & Ivers, 2011) is a 5-item measure of the respondent's perceptions of their insomnia, such as severity of sleep-onset and sleep maintenance difficulties. Items are rated from 0 to 4 (0 = not at all, 4 = very much). Total scores range from 0 to 28. Totals are categorized as follows: no clinically significant insomnia (0-7), subthreshold insomnia (8-14), clinical insomnia (moderately severe) (15-21), clinical insomnia (severe) (22-28). The ISI has demonstrated good reliability and validity, particularly in detecting changes in perceived insomnia.

Headache Pain Catastrophizing Scale (HPCS)

The HPCS(Sullivan, 1995; Wheeler, Williams, & Morley, 2019) is a modified version of the validated Pain Catastrophizing Scale (substitutes "headache" for "pain" in the questions). The HPCS is a 13-item measure used to assess catastrophic thinking related to headache with three subscales: rumination, magnification, and helplessness. Item responses range from 0 to 4 (0 = not at all, 4 = all the time). Total scores range from 0 to 52, with higher scores indicating higher levels of catastrophizing. A total score of 30 or higher indicates clinically significant catastrophizing.

Headache Management Self-Efficacy Scale (HMSE)

The HMSE(French et al., 2000) is a 25-item measure used to assess a respondent's perception of their ability to take actions to prevent and manage their headaches and headache-related disability. Item responses range from 1 to 7 (1 = strongly disagree, 7 = strongly agree). Total scores range from 25 to 175 with higher scores indicating higher levels of headache management self-efficacy. The HMSE has demonstrated excellent reliability and construct validity.

Veterans RAND-12 Health Status Inventory (VR-12)

The VR-12(Selim et al., 2009) is a 12-item measure used to assess health related quality of life and to produce physical and mental health component scores.

Migraine-Specific Quality of Life Questionnaire (MSQ)

The MSQ(Martin et al., 2000) is a 14-item measure of headache-related quality of life with three dimension scores: role restrictive, role preventive, emotional. It has demonstrated evidence of construct validity and reliability.

Data collection plan: retention

i. Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols

Participants will be eligible to receive a total of $150 in gift cards for completion of all data collection measures.

Data management

i. Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol

Research staff will enter participant assessment data directly into a secure database. In addition, we will use a secure database (QUALTRICS) for participants to enter their self reported outcome data directly into a database.

Statistics: outcomes

i. Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol

Analyses comparing the TENACITY and EHUT control groups on primary and secondary outcomes will be completed using linear mixed models for hierarchical and longitudinal data (patients are nested within site). The mediating and/or moderating effects of patient-level (e.g., age, gender, and depression) and facility-level variables will be examined.

We will conduct an intention-to treat analysis. A generalized mixed effects model will evaluate the primary outcome of number of headache days and fixed effect of study arm, Visit (time) (Month 3 vs Baseline) and their interaction. Days will be clustered within Veteran and a first order autoregressive structure will be used for the relationship between adjacent days.

Statistics: additional analyses

i. Methods for any additional analyses (eg, subgroup and adjusted analyses)

We will adjust for participant sex.

Statistics: analysis population and missing data

i. Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

We will evaluate missing data and will employ imputation for participants who complete at least 28 of 31 days of headache diary for our primary outcome.

Methods: Monitoring

Data monitoring: formal committee

i. Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

We have established a Data Safety Monitoring Committee that is comprised of two clinical psychologists employed by the VHA one of which is also a research scientist and an

epidemiologist employed by VHA. This committee is independent from the sponsor and the research team.

Data monitoring: interim analysis

i. Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial

No interim analysis will be conducted.

Harms

i. Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

Oversight for assessing potential harms or adverse events will be provided by Dr. Teresa Damush (PI) and co-investigator, Dr. Jason Sico MD, a board-certified headache specialist and Director of the West Haven VAMC Headache Center of Excellence, and Dr. Emily Lane Schlitz, a site PI and Dr. Doyle Yuan, a site PI .

Research staff are trained to report any adverse events promptly to the PI and the project manager. Participants will be encouraged to report any adverse events they have experienced. We anticipate that using this active identification method will allow us to identify all adverse events in a timely manner.

The project manager will be responsible for reviewing the adverse events reports of all participants each day, reporting the information to the PI, and if needed, reporting the adverse event to the IRB. As per VA policy, we will notify the IRB promptly using the appropriate form when a serious, study-related adverse event occurs. If the adverse event is serious, unanticipated or requires revision of the Project Description or Consent Form, we will notify the IRB by telephone as soon as possible and always within 24 hours. A formal report will be provided within 2 business days. All adverse events will be reported yearly to the IRB for review regardless of seriousness or relationship to the research. Because of this policy, the IRB will be providing parallel review of adverse events along with the PI. We believe this will ensure stringent oversight and early identification of any unexpected risks to human subjects.

All adverse events will be monitored by the principal investigators and graded as “expected” or “unexpected” and graded for severity. All unexpected and serious adverse events will be reported to the IRB within 24 hours. Adverse events will be discussed and graded by the entire study team at the weekly team meetings.

All study personnel will have access to community mental health contacts (local phone numbers, 1-800 numbers) and will be trained on emergency plans for subjects found to be actively suicidal. All patients who have scores indicating depression diagnosis and who have not been diagnosed or treated will be advised to contact their primary care provider for evaluation. We will also contact the primary care providers of all undiagnosed/untreated subjects whose scores indicate severe depression and/or suicidality.

Auditing

i. Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

This study is subject to triennial audits and any additional audits according to the policies of the local IRB at each study site.

Ethics and dissemination

Research ethics approval

i. Plans for seeking research ethics committee / institutional review board (REC / IRB) approval

Approval by local site ethics committees, IRBs, and R&D committees will be obtained prior to any study procedures taking place. Any relevant modifications to the study requiring review by these entities will be submitted and approved before implementing them.

Protocol amendments

i. Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)

All protocol modifications will be agreed upon by investigators and submitted to the appropriate IRBs for approval. Should the modifications potentially affect a participant's willingness to participate in the study, the modifications will be discussed with participants and an updated informed consent will be signed if applicable.

Consent or assent

i. Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)

Trained research staff will obtain consent from potential trial participants. Potential participants will be sent the following documents via mail or DocuSign: Informed Consent, HIPAA Authorization, Patient-facing health questionnaires, Headache Diary Script. Once the patient receives the documents, research staff will conduct a formal consent process via telephone. Dependent on individual IRB regulations, either verbal or written consent will be obtained.

Consent or assent: ancillary studies

i. Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

Confidentiality

i. How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial

Identifiers will be removed from the identifiable private information that is collected. Research staff will treat personal information with professional standards of confidentiality. Study

standard operating procedures for data collection and data management have been designed to protect against data loss and maintain patient confidentiality. Computer files will be password protected. Files containing names or other personal identifiers will have a separate password and will be accessible only to personnel who need to contact participants. Study data will be maintained on VHA network servers which are secured and backed-up on a nightly basis. Access to these servers is controlled by network administrators. There is little risk to loss of privacy or confidentiality given these measures, and there has been no instance of a problem in this area in prior trials conducted by this investigative team.

Audio files will be stored on a password-protected, restricted-access server at the Richard L. Roudebush VA Medical Center, 1401 W. 10th Street, Indianapolis, Indiana 46202. All recording devices used for this study are encrypted for security and once the files are uploaded to the server, the files are deleted from the device. Recordings are then transferred to a VA-contracted transcription service where the recordings are transcribed or are transcribed by Indianapolis VA HSR&D center staff and cleaned of any information that would identify a participant. Each participant is assigned a unique study identification number at the time of enrolment. This will be the only identifier on the transcripts and research documents. Only research staff on this study will have access to the coding system.

Research records will be maintained by the investigator in accordance with the VHA Records Control Schedule. Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the investigator and his/her research associates, the study sponsor, the Indiana University Institutional Review Board or its designees, the VA Research and Development Committee's designees, and federal agencies, including but not limited to the Office for Human Research Protections (OHRP), the Office of Research Oversight (ORO), VA Office of the Inspector General (OIG). A description of this clinical trial will be available on ClinicalTrials.gov, as required by U.S. law.

Declaration of interests

i. Financial and other competing interests for principal investigators for the overall trial and each study site

There are no financial or competing interests for the principal investigator and at each site.

Data access

i. Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

Information collected for this study may be used for future research studies or shared with other researchers for future research. If this happens, information which could identify participants will be removed before any information is shared.

Ancillary and post trial care

i. Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

The VA medical facilities shall provide necessary medical treatment to a research subject injured as a result of participation in a research project approved by a VA Research and Development

Committee and conducted under the supervision of one or more VA employees in accordance with applicable federal regulations (38 CFR 17.85). This does not apply to (1) treatment for injuries due to noncompliance by a subject with study procedures; or (2) research conducted for VA under a contract with an individual or a non-VA institution. Financial compensation for research-related injuries is not available.

Dissemination policy: trial results

i. Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions

The study team will disseminate results publicly through professional conferences and publications.

Dissemination policy: authorship

Authorship eligibility guidelines and any intended use of professional writers
We will follow standard guidelines by professional publications for authorship eligibility.

Dissemination policy: reproducible research

i. Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials

i. Model consent form and other related documentation given to participants is available upon request.

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