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Rationale and design of a multisite randomized clinical trial examining an integrated behavioral treatment for Veterans with co-occurring chronic pain and opioid use disorder: The Pain and Opioids Integrated Treatment In Veterans (POSITIVE) Trial

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Abstract

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Declarations: Kevin Vowles has consulted with Angelini Pharmaceuticals and has provided paid chronic pain treatment training and supervision for organizations that provide treatment services for chronic pain and substance use disorders, including Kaiser Permanente Southern California (USA) and Connect Health Ltd (UK). Katie Witkiewitz is a member of the Alcohol Clinical Trials Initiative (ACTIVE) Workgroup, which has been supported previously, but not in the past 36 months, by Abbott/Abbvie, Amygdala Neurosciences, Arbor Pharmaceuticals, GSK, Indivior, Janssen, Lilly, Pfizer, and Schering Plough, but in the past 36 months its activities were supported by Alkermes, Dicerna, Ethypharm, Lundbeck, Mitsubishi, and Otsuka. Dr. Witkiewitz is also on the Scientific Advisory Board for Pear Therapeutics and has consulted with and collaborated on scientific presentations with Alkermes. The other authors have no conflicts of interest to declare.

Trial registration:
ClinicalTrials.gov Identifier: NCT04648228

Trial status
The trial is currently recruiting under Protocol version 7.0, date 20 October 2021; and began recruitment on 01 July 2021. We anticipate recruitment to be completed 30 June 2023.

Background: Chronic pain and opioid use disorder (OUD) individually represent a risk to health and well-being. Concerningly, there is evidence that they are frequently co-morbid. While few treatments exist that simultaneously target both conditions, preliminary work has supported the feasibility of an integrated behavioral treatment targeting pain interference and opioid misuse. This treatment combined Acceptance and Commitment Therapy (ACT) and Mindfulness-Based Relapse Prevention (ACT+MBRP). This paper describes the protocol for the adequately powered efficacy study of this integrated treatment.

Methods: A multisite randomized controlled trial will examine the efficacy of ACT+MBRP in comparison to a parallel education control condition, focusing on opioid safety and pain education. Participants include veterans (n = 160; 21 – 75 years old) recruited from three Veterans Administration (VA) Healthcare Systems with chronic pain who are on a stable dose of buprenorphine. Both conditions include twelve weekly 90 minute group sessions delivered via telehealth. Primary outcomes include pain interference (Patient Reported Outcome Measurement Information System - Pain Interference) and hazardous opioid use (Current Opioid Misuse Measure), which will be examined at the end of the active treatment phase and through 12 months post-intervention. Secondary analyses will evaluate outcomes including pain intensity, depression, pain-related fear, and substance use, as well as treatment mechanisms.

Conclusion: This study will determine the efficacy of an integrated behavioral treatment program for pain interference and hazardous opioid use among veterans with chronic pain and OUD who are prescribed buprenorphine, addressing a critical need for more integrated treatments for chronic pain and OUD.

Keywords

Chronic Pain; Opioid Use Disorder; Medication for Opioid Use Disorder (MOUD); Veterans; Acceptance and Commitment Therapy; Mindfulness-Based Relapse Prevention; Pain Education

INTRODUCTION

Chronic pain affects 20% - 33% of adults[1,2] and reliability reduces quality of life and engagement in personally important activities[3,4]. The harmful impacts of chronic pain were worsened by opioid prescription practices, particularly in the United States (US), as morbidity and mortality associated with chronic pain were exacerbated by exponential increases in prescribed opioids[5,6]. Prescription rates have decreased moderately over the past few years[7,8], although they remain elevanted in the US and significant adverse consequences related to opioid use have persisted[9,10]. Potentially harmful opioid use behaviors, such as using more opioids than prescribed and use associated with overdose risk[11,12], occur in a clinically significant minority of patients with chronic pain[13–15]. In those with a diagnosis of opioid use disorder (OUD), there is also evidence of significant comorbidity with chronic pain, ranging from 49% to 64%[16,17].

In US military veterans, chronic pain and problematic opioid use complications are pronounced, with veterans being nearly twice as likely to experience a fatal accidental overdose compared to the general population[18]. Chronic pain is common among veterans, with prevalence estimates as high as 68%[19–23] and opioids were increasingly used for the

treatment of chronic pain during the early part of this century[19,24]. The US Department of Veterans Affairs (VA) Opioid Safety Initiative[25] and other efforts have led to decreasing prescription rates, yet 2018 VA Opioid Prescribing Data indicate opioid prescribing rates remain a clinically significant issue[26]. Furthermore, there is evidence of a vicious cycle of chronic pain, opioid use, and adverse events in veterans[27,28].

Buprenorphine (including buprenorphine-naloxone) is increasingly prescribed for patients with chronic pain[29]. While there is a limited evidence that it is helpful in decreasing pain [30], it may not be sufficient on its own in relation to other important areas. For example, a recent meta-analysis indicated that buprenorphine is not effective in reducing opioid use or disability[31]. Furthermore, in a separate meta-analysis examining treatment in non-chronic pain OUD treatment settings, the addition of psychosocial intervention improved outcomes[32] while the experience of pain represents a risk for relapse to hazardous opioid use[33]. Therefore, a need exists for an intervention that combines buprenorphine for hazardous opioid use with a behavioral intervention that addresses *both* pain interference and also important behavioral risks for relapse such as craving, distress, and stressful circumstances.

A recent pilot study presented results of one promising integrated treatment[34]. A randomized design was used to assess the feasibility and initial efficacy of integrating two empirically supported interventions: (1) Acceptance and Commitment Therapy for chronic pain and (2) Mindfulness-Based Relapse Prevention for opioid misuse (ACT+MBRP). Participants were randomized to treatment as usual (TAU), which involved care through a VA co-occurring disorders medical clinic to treat chronic pain and opioid misuse, or to TAU plus ACT+MBRP. In total, 37 participants were randomized and included in intent to treat analyses. Primary outcomes included pain interference, hazardous opioid use, and frequency of pain behavior (i.e., behavioral indicators that one is experiencing pain) which were assessed at six-month follow-up. Results indicated a significant and large effect in favor of ACT+MBRP plus TAU across all three outcomes. Further, feasibility indicators were positive, as retention and treatment completion were excellent. Given these positive results of the pilot study[34], a fully powered trial is needed.

Objectives and trial design

This study is a phase 3 multisite, randomized clinical trial (RCT) of ACT+MBRP for comorbid OUD and chronic pain compared to an active education control (EC) consisting of pain and opioid/buprenorphine education. The Pain and OpioidS – Integrated Treatment In VEterans (POSITIVE) Trial will recruit a total of 160 veterans with chronic pain who are receiving buprenorphine for the treatment of OUD within one of three VA Healthcare Systems (VAHCS). Participants will be randomized and followed for a total of 15 months (3-month active treatment period, 6-month follow-up, 12-month follow-up). All study interventions will be delivered via 12 weekly 90 minute group sessions via telehealth using the VA's secure online video appointment system, VA Video Connect (VVC). We followed the SPIRIT reporting guidelines for reporting details in this clinical trial protocol[35].

Hypotheses and aims

Aim 1: The primary aim is to determine the efficacy of the 12 week ACT+MBRP group treatment in comparison to a 12-week education control (EC) group treatment for reducing pain interference and hazardous opioid use (primary outcomes), as well as a number of secondary outcomes (as detailed in the methods section). It is hypothesized that the ACT+MBRP group will demonstrate significant improvements in primary and secondary outcomes in comparison to EC at post-treatment, 6 month, and 12 month follow-up.

Aim 2: Weekly progress on specific mechanisms will be examined, including pain acceptance, values-based activity, and opioid craving, to identify potential mechanisms of change in relation to treatment outcomes. It is hypothesized that changes in treatment mechanism variables will significantly mediate improvements in outcome variables.

METHODS

Study setting and eligibility criteria

Participants will be recruited from three VAHCS, including New Mexico, Puget Sound, and San Francisco. Individual approval for each study site's Institutional Review Board (IRB) is in place as of May 2022. Participants will be eligible if they are: (1) prescribed a stable dose of buprenorphine for the treatment of OUD for a period of one to six months, (2) willing to comply with all study procedures and be available for the duration of the study, (3) aged between 21 and 75 years old, (4) enrolled as a patient in one of the participating VAHCS, (5) diagnosed with chronic pain (per VA electronic health record), and (6) able to read and understand English. Participants will be excluded if they are experiencing a current episode of: (1) schizophrenia, delusional disorder, psychotic or dissociative disorders, or (2) a substance use disorder requiring a higher level of care than outpatient treatment (e.g., severe alcohol use disorder requiring inpatient detoxification).

Study recruitment, screening and enrollment

Primary recruitment efforts include: (1) engagement with clinicians via advertisement, (2) live informational sessions led by the on-site study team, and (3) participant outreach. Awareness methods comprise physical and digital approaches (e.g., posters, flyers, website: https://www.positivestudy.org/). All materials were created with the Vanderbilt Recruitment Innovation Center's (RIC) guidance regarding best practices for health communication, including plain language, readability at sixth-grade level, cultural adaptation, and summary of key facts. Potentially eligible participants will be identified through clinic databases and then mailed an invitation letter which includes an opt out/in postcard/email response card.

Individuals who meet screening criteria will be followed up for a formal assessment, which will include confirmation of inclusion/exclusion criteria and informed consent. Appendix A displays the model consent form, which is individualized according to the specifications of the individual VAHCS. After providing informed consent, participants will be randomized to treatment condition, complete baseline assessments, and provide a sample for a urine drug screen (UDS). All self-reported data will be collected via REDCap.

Assignment of interventions

Randomization.—A block randomization method, stratified by site and gender, will be used with a random block size based on group scheduling, where groups will start with a group size of 3 to 8. Given that the expected participant pool is ~90% male [based on the pilot study[34] and existing epidemiological data of VA patients[20]], stratification by gender will be "male" or "other". This method of stratification allows the study to include non-binary genders and still account for the anticipated male majority in the sample. A randomization list was established prior to the beginning of participant enrollment.

Blinding.—The study principal investigators (KEV, KW) are fully blinded, as are study statisticians and research assistants who complete assessments. Co-investigators and study clinicians in the treatment and control conditions are not blinded as they deliver the intervention. The VA research coordinators are not blinded as they are involved in coordinating participant screening and randomization. Study participants will not interact across study arms.

Intervention details

Both intervention arms include 12 weekly group-based sessions, each lasting 90 minutes, with group sizes ranging from three to ten. All sessions are delivered via VVC and will begin with an introductory session (Session 0) in which connectivity and other potential procedural issues will be addressed.

ACT+MBRP—As noted, ACT and MBRP have evidence supporting their effectiveness. In the treatment of chronic pain, ACT is graded as having strong research support by the US American Psychological Association's Division of Clinical Psychology[36] and it is a recommended intervention within the guidelines issued by the United Kingdom's National Institute of Health and Care Excellence[38]. Relatedly, MBRP has good evidence for reducing risk of relapse in those with substance use disorders[37] with a recent meta-analysis indicating a small, significant, effect in favor of MBRP over alternative treatments for craving and negative consequences of substance use[38].

For the present trial, session content for the ACT+MBRP condition was taken from existing validated treatment protocols[39,40]. In summary, within ACT, participants identify areas of meaningful functioning that have been adversely impacted by pain (e.g., relationships, productivity, self-care), learn methods to enhance willingness to have chronic pain in the service of these meaningful areas, and practice present-focused awareness skills. Group sessions include discussions of the impact of pain and distress avoidance, identifying alternatives to this avoidance and establishing plans for behavior change, demonstration, role-playing exercises, and homework assignments.

The MBRP portions build upon this content by focusing on reactivity to substance use cues, improving awareness of the present moment, and facilitation of nonjudgmental awareness. Further, participants are instructed in mindfulness techniques aimed at increasing concentration, improving awareness, and cultivating a nonjudgmental and accepting attitude toward craving and automatic thought patterns. Group sessions will include discussions

of mindfulness as a means of coping with craving and painful cognitions, role-playing exercises, meditation practice, and homework assignments.

Education Control (EC)—The active comparator control group, EC, will follow a protocol that combines two extant manualized education programs offered at all study VAs: Opioid/buprenorphine education sessions and psychology-led pain education. The EC group will include pain neuroscience education, which has been shown to improve pain knowledge and decrease fear of pain, but which has negligible effects on pain intensity and pain interference (disability)[41] and no known effects on opioid risk.[46–48]. Session topics will include specific sessions on nociceptive processing, ascending/descending pain modulation, acute versus chronic pain, the biopsychosocial model of chronic pain (including discussions of anxiety, mood, and trauma), and sleep education. Opioid education will include materials taken from the VA's Opioid Safety Initiative toolkit[42], including discussion of opioid and non-opioid analgesic options for pain relief including buprenorphine, opioid overdose signs and symptoms, and overdose prevention. Group discussions will be primarily didactic and informational.

Intervention fidelity and monitoring—Therapist fidelity to treatment materials will be assessed using the ACT Core Competency Rating Form (ACT-CCR)[43] and MBRP Adherence and Competence Scale (MBRP-AS)[44]. Inter-rater reliability of adherence ratings will be ascertained by double coding randomly selected practitioner audiotapes at least once per month throughout the course of the 12-week treatment. Fidelity to the EC condition will be assessed by identifying key learning objectives and evaluating therapist adherence to addressing all identified objectives.

Plans to promote participant retention—Participants will be contacted before each week's treatment session with a reminder by the VA research staff. The coordinator will also remain in contact with participants through the study follow-up period to remind them of urine drug screens and assessment scheduling. Participants will receive compensation for the time and effort taken to complete study assessments. Our previous pilot trial[34] used a similar strategy and achieved a 78% retention rate (just under our expected retention rate of 80%).

Confidentiality—No personally identifiable information will be collected as part of study procedures. VA research coordinators will maintain paper consent forms in a locked suite. To further protect the privacy of study participants, the Secretary of the Department of Health and Human Services has issued a Certificate of Confidentiality to all researchers engaged in biomedical, behavioral, clinical, or other human subjects research funded wholly or in part by the federal government.

Measures

Measurement timeline

From randomization, participants will be enrolled in the study for a total duration of 15 months. During that time, participants will complete primary and secondary outcomes on four occasions (enrollment, post-treatment, 6-month follow-up, 12-month follow-up), treatment mechanism measures on 12 occasions (following weekly treatment sessions), and

exploratory measures monthly throughout study enrollment. Supplementary Table 1 contains the assessment schedule.

Demographic and pain-related information

Participant demographics (e.g., biological sex, gender, age, ethnicity, marital status, income, educational achievement) and pain-related information (e.g., duration, location, opioid history) will be collected during the baseline enrollment assessment. Information collected at baseline regarding treatment history will include assessment of healthcare utilization, including average number of outpatient visits regardless of reason, number of visits related to pain, types of treatments received, number of disability days due to pain, injury recurrence, medication use (including opioid and non-opioid analgesics and psychotropic medication), and work status.

Primary outcomes

Pain interference.—The National Institutes of Health (NIH) PROMIS Pain Interference short form (Version 8a; 58) will be used to assess pain interference [46]. This measure was responsive to ACT+MBRP in the pilot study[34].

Hazardous opioid use.—The Current Opioid Misuse Measure (COMM) will be used to assess opioid-related behaviors[47]. The COMM has demonstrated relations with pain-related function and substance use[48] and was also responsive to ACT+MBRP in the pilot study[34].

Secondary outcomes—*Pain intensity.* Pain intensity, including current and least/most/usual over the past week, will be assessed via a 0 (no pain) to 10 (maximum possible pain) Numerical Rating Scale.

Depression.—The Patient Health Questionnaire-9 (PHQ-9)[49] will be used to assess depression. The PHQ-9 is both a valid and reliable measure of depression severity and has been used with veteran populations in previous research and clinic settings[50].

Pain-related fear.—Pain-related fear will be measured by the Pain Anxiety Symptom Scale-20 (PASS)[51]. Pain related fear is reliably related to increased pain-related distress and disability and has demonstrated reliable relations with pain-related functioning[52–54].

Substance use.—Substance use (including alcohol, opioids, cannabis, stimulants, sedatives, hallucinogens, and any other substances) over the past 7 days will be assessed via the Timeline Followback[55]. Number of substance use days, number of days misusing substances, and number of days of polysubstance use (using more than one substance) will be calculated. The TLFB is a gold standard method of collecting retrospective reports of substance use and has demonstrated excellent reliability and validity in numerous studies of clinical and nonclinical populations, as well as correspondence with collateral reports and biomarker data[56–59]. We will also administer the Tobacco, Alcohol, Prescription medication and other Substance use Tool (TAPS)[60] at each assessment, which assesses substance use in the prior 12-months.

Urine drug screening and confirmation.—Urine drug testing will be performed by the VA approved laboratories. Samples will be collected monthly throughout the 15 months of participation at the same time each month. Screening will test for the presence of opioids, cannabis, cocaine, amphetamines, benzodiazepines, and barbiturates. For every positive drug screen, confirmatory testing will be performed via gas chromatography/mass spectrometry.

Treatment mechanism measures

Pain acceptance.—The short form of the Chronic Pain Acceptance Questionnaire (CPAQ)[61] will be used to measure pain acceptance.

Values-based action.—The Values Tracker (VT)[62] will be used to quantify changes in valued activities over the course of treatment. Valued activities are defined as actions taken that contributed to improved quality of life or that allowed progress in personally meaningful areas of living.

Opioid craving.—A modified version of the *Penn Alcohol/Drug Craving Scale (*PACS[63]) will be used to assess opioid craving. The PACS has demonstrated good psychometric properties in our prior studies, including internal consistency reliability (α=.87) and criterion validity[64].

Analytic details and plan

Power calculations

The statistical power for efficacy analyses was estimated using a Monte Carlo simulation study. Consistent with our own pilot work and work on effectiveness of behavioral treatments for pain interference[65–68], a medium effect size (Cohen's d = 0.75) was assumed for primary outcomes at the initial post-randomization assessment. Given two primary outcomes, power was estimated with a Holm procedure to correct for multiplicity of two primary endpoints at the post-randomization. Per this procedure, we would test the smallest p-value at alpha of 0.025, and the largest p-value at alpha of 0.05. The Holm procedure tests the smallest p-value at the same alpha as the Bonferroni test, but given a statistically significant result on that endpoint, it tests subsequent p-values at higher significance levels. With an n=160, power is 80% to detect a minimum effect size of 0.56 for the primary endpoint with the smallest p-value (tested at alpha <0.025) and power of 80% to detect a minimum effect size of 0.50 for the primary endpoint with the largest p-value (tested at alpha <0.05). Given we anticipate a medium effect size of 0.75 for both effects, we will have power greater than 90% to detect this effect. Six covariates (baseline level of the outcomes, site, sex, buprenorphine dose, buprenorphine formulation, and treatment attendance [e.g., number of sessions attended]) were also incorporated.

Statistical power for the mechanism analyses was based on parameter estimates from prior mediation studies following ACT for chronic pain[67] and MBRP for substance use disorders[64,69] to estimate the effect sizes. Following ACT, acceptance and values significantly mediated changes in disability, depression, pain-related anxiety, medical visits, and number of classes of prescribed analgesics, with large mediation effect sizes. Studies

of MBRP indicate that craving significantly mediated the association between treatment and changes in substance use ($\alpha = -0.20$; $\beta = 0.71$). Based on these effect sizes and power estimates for testing mediation derived from a simulation study[70], we will have power of 0.90 to detect significant mediating effects with the proposed sample size of 160.

Data management

All variables in the analytic database will be evaluated to detect gaps, patterns, outliers, and inconsistencies in the data.

Statistical methods

Analysis of outcomes.—Primary analyses will include all randomized participants (intent-to-treat analyses) and will be supplemented with per-protocol analyses (defined as participants who completed at least 75% of treatment sessions; for example, 9 of 12 sessions in the ACT+MBRP and EC groups). Differences between study conditions on outcomes will be examined using a mixed effects model with fixed effect of treatment and time, as well as a random intercept and random slope for the time x treatment interaction. Sex-, site-, and treatment-relevant variables that are known to influence outcomes (including attendance, predictors of attrition, buprenorphine formulation, and buprenorphine dose), as well as baseline levels of the primary outcomes will be covaried. The mixed models will examine the effects on primary outcomes at the end of the active treatment (3-month post-randomization assessment; intercept) and change in primary outcomes over time across the 12-month follow-up (slope). These models will also test secondary outcomes of the effects of treatment on secondary outcomes at the 3-month post-randomization assessment (random intercept in the mixed models) and on change in the secondary outcomes over time across the 12-month follow-up (random slope in the mixed models). A normal distribution with an identity link function will be used.

Attrition analyses will determine whether there are any differences in study variables between those with missing and complete data. Study variables associated with missing data will be covaried in all analyses. It will also be examined whether there is any within-group correlation and adjust the model parameters if the intraclass correlation coefficient is less than 0.1 using a sandwich estimator to adjust the standard errors for clustering within groups. If the intraclass correlation coefficient exceeds 0.1 for the effect of group membership, group membership as an additional level of analysis in the mixed effects models will be incorporated.

Analyses to test treatment mechanisms.—The primary goal of mechanism analyses will be to examine potential mechanisms of change. This goal will be accomplished by examining initial level and changes in targeted mechanisms over time, as well as the association between changes in targeted mechanisms during treatment and clinical outcomes at follow-up. Targeted mechanisms will include (1) pain acceptance, (2) values-based action, and (3) opioid craving. These mechanisms will be examined using latent growth mediation models. Specifically, it will be examined whether initial level (intercept) or changes (slope) in the targeted mechanisms during treatment mediate the effect of treatment on primary

outcomes. Sex-, site-, and treatment-relevant variables that are known to influence outcomes, as well as baseline levels of the primary outcomes will be covaried.

Mediation models will be estimated using the product of coefficients method[71], which provides an estimate of the mediated effect by multiplying regression coefficients for the regression of the mediators (e.g., slope of targeted mechanism) on treatment condition (i.e., a-path or α) and for the regression of the clinical outcome on the mediators (i.e., b-path or β). We will use bootstrapping to obtain 95% confidence intervals of the mediated effect[72]. We will use maximum likelihood estimation for all analyses, which provides the variance-covariance matrix for all available data and is the preferred method for estimation when some data are missing[73].

Planned subgroup analyses.—Outcome models by gender, buprenorphine dose, and buprenorphine formulation will be examined, and gender and buprenorphine dose and formulation will also be examined as a moderator of treatment effects. Models will be estimated using a weighted maximum likelihood function.

Missing data analyses.—Participant characteristics, including gender, race/ethnicity, age, substance use history, pain duration and intensity, educational achievement, baseline buprenorphine dose, and previous treatment experiences, will be compared for those participants retained in the study versus those lost to attrition. Further, the data will be examined for both missing cases and outlier scores on measures. Variable distributions will be checked for normality and, if necessary, transformations will be performed to normalize the distributions. Further, the data will be examined for both missing cases and outlier scores on measures. For all models, it will be assumed that data are missing at random and use maximum likelihood estimation, which provides the variance-covariance matrix for all available data even when some data are missing. Maximum likelihood estimation applies to every form of censored or multi-censored data. Sensitivity analyses will be used to test the influence of missing data and missing data assumptions, including the assumption that data are missing at random. We will use missing not at random methods, including pattern mixture and selection models, to test the missing data assumptions.

Plans to give access to the full protocol, participant level-data and statistical code

This study will comply with all applicable NIH Data Sharing Policies. After last subject enrollment and all follow-up procedures have been completed, the HEAL Pain Management Effectiveness Research Network Data Coordinating Center (DCC) at the University of Utah will prepare a final releasable database that will be completely de-identified in accordance with the definitions provided in HIPAA.

Oversight and monitoring

Composition of the Coordinating Center and Trial Steering Committee

This trial forms part of the National Institutes of Health (NIH) Helping to End Addiction Long-Term (HEAL) initiative, within the Pain Effectiveness Research Network, for which trial coordination is provided by the Recruitment and Trial Innovation Centers (TIC) in the

Trial Innovation Network (TIN). The Duke/Vanderbilt TIC provides project management, site monitoring, and communications support. The Johns Hopkins/Tufts TIC serves as the Safety and Biostatistics core. The Utah TIC serves as the Data Coordinating Center (DCC). The Vanderbilt RIC provides support and guidance in recruitment and retention of study participants.

Composition of the Data Monitoring Committee, its role and reporting structure

The Data and Safety Monitoring Board (DSMB) will act in an advisory capacity to the NIH leadership to monitor participant safety, evaluate the progress of the study, to review procedures for maintaining the confidentiality of data, the quality of data collection, management, and analyses. The DSMB will be independent of the study sponsors and trial investigators. A detailed description of the DSMB, including roles, purpose, structure can be found in the study's DSMB charter.

Adverse event reporting and harms

The study team will document unsolicited adverse events (AEs) and serious adverse event (SAEs). Serious adverse events include any events that result in death or are life threatening (including fatal or non-fatal overdose), results in inpatient or prolonged hospitalization, causes a persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, or is an important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Adverse events of special interest (AESI) will also be collected, including suicide attempt, suicide, arrest, imprisonment, and violence to others. All AEs, SAEs, and AESIs will be followed until resolution or until the study site physician deems the event to be chronic or the participant is lost to follow-up. Any AE's meeting local site reporting will be addressed immediately to the IRB following VA guidelines.

Dissemination plan

Results will be disseminated through presentations and manuscripts, with the latter submitted to PubMed Central immediately upon acceptance for publication. There are no plans to use professional writers in any dissemination efforts. The study is a clinical trial and will comply with the NIH policy that establishes the expectation that all investigators conducting clinical trials funded in whole or in part by the NIH will ensure that these trials are registered at ClinicalTrials.gov, and that results of these trials are submitted to ClinicalTrials.gov.

DISCUSSION

Opioid prescription in the treatment of chronic pain is frequent and carries a consequent risk of poor treatment outcome, as well as higher morbidity and mortality in a clinically significant number of patients, particularly those who meet criteria for OUD. Despite the alarming increases in opioid mortality and OUD, there are few treatment options available that target both pain-related interference *and* OUD in an integrated fashion. In military

veterans, this issue is particularly important as numerous reports indicate continued frequent opioid prescription use, as well as continued high levels of opioid-related morbidity and mortality. To date, there are no evidence-based treatment options that aim to minimize pain interference while simultaneously addressing OUD among veterans. The current study will address this gap in the field.

If the trial's hypotheses are supported, then evidence for an integrated and efficacious approach in chronic pain will be available with training and treatment materials ready for dissemination. Furthermore, the issue of chronic pain in substance use disorder treatment settings is also prevalent[74,75] and it is possible that this same treatment approach may be of use in those settings as well. Finally, we elected to limit the trial to individuals with chronic pain prescribed buprenorphine for the treatment of OUD as clinical experience indicates that buprenorphine is preferred in chronic pain treatment settings over alternative medications for OUD, such as methadone. If hypotheses are supported, it is possible that the testing of this approach in substance use disorder treatment settings may also include participants on different medications for the treatment of OUD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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