Telehealth CBT to increase engagement in pain treatment

among Veterans using prescription opioids

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Abstract

Purpose: Chronic pain and negative consequences of long-term opioid therapy are related public health concerns associated with significant functional impairment, high psychiatric comorbidity, and premature mortality, particularly among Veterans. Clinical Practice Guidelines for opioid prescribing and pain management recommend using non-pharmacological approaches as first-line treatments. Psychosocial interventions (e.g., cognitive-behavioral therapy) have strong evidence supporting their ability to improve pain outcomes. Patient beliefs about the stigma associated with psychological interventions, opioid analgesics, ability of psychosocial intervention to improve pain among others can greatly interfere with the patients' ability to initiate and maintain engagement in psychosocial interventions and other non-pharmacological approaches.

Research question: Does Cognitive-Behavioral Therapy for Treatment Seeking (CBT-TS) increase treatment seeking of psychosocial and other types of pain treatments relative to a pain education control condition and what is the downstream impact on clinical outcomes?

Study Aims or hypotheses: The specific aims are to: test the effects of CBT-TS to increase initiation of psychosocial interventions for pain among Veterans receiving opioid analgesics for chronic pain (Aim 1); test the effects of CBT-TS to increase the retention in psychosocial interventions for pain among Veterans receiving opioid analgesics for chronic pain (Aim 2); and evaluate the effects of CBT-TS in improving pain and substance use outcomes among Veterans receiving opioid analgesics for chronic pain (Aim 3). We will also test the effects of CBT-TS on the initiation of and retention to other non-pharmacological pain treatments (Exploratory Aim).

Research Design Overview: Randomized Clinical Trial

Methodology: Participants (N = 300) will be randomized to either the CBT-TS condition or an education control condition. Participants in both conditions will complete assessments on pain, treatment engagement, and opioid use at baseline, and 1-, 3-, and 6-months post-treatments to assess primary, secondary, and exploratory outcomes. Treatment initiation and retention will be assessed primarily through data extraction and chart reviews. Participants will include men and women Veterans who: (a) are English-speaking, (b) are 18 years of age or older, (c) are taking at least 20 mg morphine equivalent daily dose of opioid analgesics per day for $\geq$90 days, (d) have pain that occurs on at least half the days for 6 months or more, and score $\geq$ 4 on each of the three items of the PEG. Veterans will be excluded on the basis of: (a) having used a nonpharmacological approach to pain management in the last 30 days, (b) having cognitive impairment, and (c) being in hospice, undergoing oncology treatment, or having a recent or upcoming surgery

Data Safety Monitoring Plan: To ensure safety of participants in the study proposed and validity and integrity of data collected, the PI (Ashrafioun) will oversee all data and safety monitoring functions and the research team will be advised that he will be the primary contact overseeing these activities. The investigators will meet regularly to monitor study progress and discuss the implementation of monitoring procedures. He will also meet regularly with the research coordinator and staff to review monitoring procedures and ensure all efforts are being taken to minimize risks to participants. A Data Safety & Monitoring Board was not required by VA HSR&D.

Data Analysis: Aim 1 Hypothesis: A Cox Proportional Survival Analysis will be conducted to examine treatment initiation by the 6-month follow-up. Condition will be entered into the model as a predictor of whether a participant reported attending treatment by the 6-month follow-up. A secondary logistic regression analysis will be conducted to examine treatment initiation by the end of the 6-month follow-up using worst case imputation of missing outcome to test robustness of any effects. **Aim 2 Hypothesis:** The outcome will be sessions of psychosocial pain treatment attended during the 6-month follow-up period. Analyses will be conducted using MRM within a multilevel modeling (MLM) framework as this method allows for appropriate modeling of the covariance matrix when measures are repeated over time and can easily account for normal, skewed, and categorical data. MRM will be used, including treatment condition, follow-up time (centered on 6-month follow-up), and a condition by time interaction term as predictors of number of sessions of treatment attended. **Aim 3 Hypotheses:** The outcomes will be pain severity, pain interference, physical functioning, opioid dose, and risk of misuse. MRM will again be used. Treatment condition, follow-up time (centered on 6-month follow-up), and a condition by time interaction term will be included as predictors as will the relevant baseline autoregressors. Additional secondary analysis to demonstrate treatment robustness will involve centering time at the 1-month and 6-month follow-ups, allowing for examination of treatment differences at these timepoints.

List of Abbreviations

ACT – Acceptance and Commitment Therapy

ASSIST – Alcohol, Smoking, and Substance Involvement Screening Test

BHS – Beck Hopelessness Scale

CBT – Cognitive Behavioral Therapy

CoE – VISN 2 Center of Excellence for Suicide Prevention

COMM – Current Opioid Misuse Measure

CPG – Clinical Practice Guidelines

ITT – Intent-to-treat

MAR – Missing at random

MBQ – Medication Beliefs Questionnaire

MBSR – Mindfulness-based stress reduction

MCAR – Missing completely at rando

MEDD – Morphine equivalent daily dose

OUD – Opioid use disorder

PCS – Pain Catastrophizing Scale

PROMIS – Patient Reported Outcome Measures Information Syste

PSEQ – Pain Self-Efficacy Questionnaire

PTWS – Pain Treatment Willingness Scale

SEM – Structural Equation Modeling

SBIRT – Screen, Brief Intervention, and Referral to Treatment

TSK – Tampa Scale for Kinesiophobia

TUF – Treatment Utilization Form

VREB – Veterans Research Engagement Board

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Study Protocol

Protocol Title:

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2.0 Introduction

Chronic pain is a significant public health problem. In the United States, the estimated annual cost burden of chronic pain on healthcare, disability, lost wages and productivity exceeds $500 billion.[1] Low back pain, neck pain, and other musculoskeletal conditions are each among the leading contributors to disability.[2] Veterans are vulnerable to develop chronic pain[1] and report higher pain severity relative to the general population.[3] Health record data from the Veterans Health Administration (VHA) indicate that 55% of almost 10 million Veterans in VHA care between 2000 and 2011 had a diagnosis of a musculoskeletal condition.[4] Veterans with pain conditions report poorer psychosocial functioning, exhibit high rates of psychiatric and medical comorbidity, and are at increased risk of suicide.[4,5]

Opioid misuse: A National Public Health Emergency. There is overwhelming evidence of premature mortality and other significant adverse outcomes associated with opioid analgesic use.[6] There were nearly 50,000 opioid overdoses in the United States in 2019 representing greater than a 4-fold increase from 2002.[7] Suicides involving opioids nearly tripled from 1999 to 2014.[8] Studies among Veterans indicate that higher doses of opioid analgesics increase risk of suicide,[9] and overdose risk is increased by over seven-fold with higher doses of opioid analgesics.[10] Longitudinal studies indicate that long-term opioid analgesic use (i.e., greater than 90 days) is associated with depression onset and recurrence,[11,12] the development of opioid use disorders, and aberrant drug-related behaviors (e.g., illicit substance use, alternative routes of administration)[13] among individuals experiencing chronic pain.

Overall, the long-term use of opioid analgesics to manage chronic pain is guided by little evidence and is associated with increased morbidity and mortality. In most cases, safe and effective alternatives to opioid analgesics are preferred in managing chronic pain.[14,15] Many non-pharmacological pain treatments have good evidence and are associated with lower risk and similar, if not greater, potential for improvement.[16] There is a need to identify ways to engage Veterans in non-pharmacological pain treatment prior to the onset of the adverse outcomes of opioids, after the onset of adverse outcomes, or even prior to starting opioid analgesics to prevent the poorer prognosis associated with long-term opioid analgesic use.

Using psychosocial pain treatments to reduce reliance on opioid analgesics. The VA/Department of Defense Clinical Practice Guidelines (CPGs) for opioid prescribing[14,15] recommend non-pharmacological pain treatments as first-line. Among the many non-pharmacological strategies, psychosocial pain treatments—Cognitive-Behavioral Therapy for Chronic Pain (CBT-CP), Acceptance & Commitment Therapy (ACT), Mindfulness-Based Stress Reduction (MBSR)—offer a solid evidence base, promote active participation in care, and emphasize the psychological and social factors that are often neglected in the biomedical intervention of long-term opioid therapy. Psychosocial pain treatments reinforce skills to address negative emotions, and maladaptive thinking and behavioral patterns that impact pain.[17] They are also particularly helpful in opioid tapering and discontinuation.[18]

Psychosocial pain treatments are effective for improving pain outcomes.[19] CBT-CP reduces pain interference by changing maladaptive thinking patterns, increasing activity level, and improving mood.[20] Importantly, across different types of pain, meta-analyses and studies on randomized clinical trials indicate that CBT-CP has strong effects on mood, pain interference, pain severity, and pain catastrophizing compared to non-active controls.[17,21] ACT targets harmful avoidance of experiences (e.g., sensations, thoughts, behaviors), while encouraging acceptance of one's pain and staying in the moment to help Veterans make choices that are consistent with their values. Again, meta-analyses support medium effects on mental and physical health functioning and improved pain outcomes that are comparable to CBT-CP.[22,23] For MBSR, meta-analyses show improvements in pain, depression, pain intensity, physical functioning and quality of life outcomes.[24,25] A large randomized clinical trial also found that MBSR demonstrated clinically meaningful improvements in disability that was comparable to CBT-CP and better than usual care.[26] Taken together, psychosocial pain treatments are considered first-line interventions that demonstrate positive outcomes.

There are several advantages of engaging in these types of interventions in addition to the promising evidence base. Psychosocial pain treatments are particularly attractive under the VHA Stepped Care model because many of their strategies serve to reinforce the self-management skills that are the foundation of the model.[27] Furthermore, rather than be a passive recipient of treatment as with medication management and other non-pharmacological pain treatments, Veterans engaged in psychosocial pain treatments are active participants in their treatment, building confidence to engage in a broader range of activities to improve their functioning. An additional advantage is that they are transdiagnostic in two senses: their strategies improve pain outcomes across various types of chronic pain (e.g., fibromyalgia, musculoskeletal) and they impact a variety of symptoms beyond those that are specific to pain (e.g., depression, anxiety).[17,22,24,25,28] *Overall, psychosocial pain treatments can reduce reliance on opioid analgesics, reduce opioid-related risk, and improve functioning and other key outcomes.*[26,29,30]

Psychosocial pain treatments and other non-pharmacological pain treatments are underutilized, and barriers need to be addressed. Overall, VA experts in psychosocial pain treatments at the HSR&D State-of-the-Art Conference agreed that CBT-CP, ACT, and MBSR have strong efficacy and effectiveness and that research should focus on addressing barriers of implementation.[19] Psychosocial pain treatments and other non-pharmacological pain treatments more broadly are relatively underutilized,[31-34] particularly among individuals prescribed opioid analgesics.[35,36] An Office of Inspector General report found that less than half of Veterans receiving opioid analgesic prescriptions had no history of using *any* psychosocial treatment let alone those that were pain-focused.[37] Edmond and colleagues found that just 22.6% of Veterans had used a psychosocial pain treatment among a cohort of Veterans serving post-9/11.[38] In a study among civilians, *patients receiving opioid therapy were 90% less likely to participate in provider-recommended non-pharmacological pain treatments compared to patients not receiving opioid therapy*. Less than 20% of those receiving opioid therapy did not participate in non-pharmacological pain treatment after being recommended.[35]

There are also apparent disparities in some demographic groups. For example, racial/ethnic minorities relative to those who are White non-Hispanic are under-engaged in pain treatment

despite often reporting higher pain severity and greater interference in activities.[39] Among the general population, adults 65+ years are more than twice as likely to have prescription opioid fills and have had the smallest decline in prescriptions over time.[40] They also tend to underutilize CBT-CP and exercise for managing pain and are less like to have a history of using complementary and integrative health services.[41,42] While women are more likely to receive non-pharmacological pain treatment, they are also more likely to receive opioid analgesics and be co-prescribed sedatives increasing the risk adverse outcomes.[40,43]

Barriers of treatment engagement include lack of patient and provider knowledge, poor patient-provider communication, and lack of access and availability.[19,44] Efforts have been led to improve patient-provider communication[45,46] and provider education.[47] To combat access and availability barriers, the Comprehensive Addiction Recovery Act (CARA) required that interdisciplinary pain care teams have access to psychosocial pain treatment, in addition to other non-pharmacological pain treatments (e.g., complementary and integrative health approaches).[48] National dissemination of CBT-CP training has increased the number of providers who deliver CBT-CP.[30] According to the 2019 Pain Management in VHA Survey Report, CBT, ACT, and MBSR were available in 98%, 79%, and 71% of facilities, respectively, demonstrating wide availability across the country.[49] Psychosocial pain treatments can easily be delivered through telehealth (offered at 79% of VHA facilities according to the survey administered pre-COVID).[49,50] This is critical in increasing access for those who have mobility issues, have rural residence, and/or lack transportation.[50] Telehealth delivery also facilitates social distancing measures to reduce the spread of COVID-19.[51] While efforts addressing educational, logistical, and communication barriers are essential, patient beliefs represent another critical barrier that has not received sufficient attention.

Beliefs serve as potent obstacles to engage in psychosocial pain treatments. Beliefs about opioids, non-opioid treatment, the potential of pain severity and interference to change, and stigma all have a profound impact on treatment engagement. Beliefs about opioids reinforce continued use, while reducing the likelihood of trying psychosocial pain treatments and other non-pharmacological approaches. A qualitative study found that some patients fear uncontrolled pain that is “impossible” to cope with without opioids.[52] Krebs et al.[53] found that Veterans recruited for a pain trial perceived opioid analgesics to be more effective than non-opioids at baseline, despite no differences in pain after the trial was completed.[54] Many patients believe that prescription opioids are the most effective treatment and higher doses are needed for adequate pain relief, which mediates prescription opioid misuse.[55] On the other hand, some Veterans are reliant on their opioids and request dose escalations despite being ambivalent about their benefits and disliking side effects.[56]

In addition to beliefs about opioids, people with chronic pain believe that they will be stigmatized if they use psychosocial pain treatments (e.g., people will think I’m crazy).[50,57] Like mental health treatment, Veterans may perceive that they are weak, discriminated against, and judged by others.[58] Other beliefs relate to concerns about pain being dismissed as not actual physical pain if they receive psychosocial pain treatments, which would then be confirmed in their minds if the treatment worked to reduce pain.[57] People also indicate that because they experience pain solely as being physical, only medications or surgery can address it.[50,57]

Pain catastrophizing, which includes helplessness over one's pain (e.g., "There's nothing I can do to reduce the intensity of the pain") is a critical factor that impacts engagement in coping behaviors, treatment adherence, and exercise.[59] Other factors are important in non-initiation and problems with retention of non-pharmacological pain treatments, including low pain-related self-efficacy (e.g., "I can't cope with pain without medications") and fear-avoidance beliefs (e.g., "I'm afraid I will injure myself if I start a walking program").[60,61] Many also believe that non-pharmacological pain treatments lack efficacy, are time consuming, and increase pain or cause harm.[44] For MBSR, patients often cite that they "have no time," they are not aware of potential benefits, and the practices cannot be done because of lack of fitness or ability.[62,63] Additionally, some patients become hopeless and fearful that there are not any treatments that can improve their pain.[64]

Beliefs about treatment may vary as a function of demographics such as racial/ethnic minority status, gender, and age. Racial/ethnic minorities often report believing that pain is a sign of weakness, that pain is inevitable, and that they do not want to be labeled as complainers.[39] Similarly, many older adults believe that showing pain is a sign of weakness and that "treatments won't work."[42,65] Some studies did not find differences in perceived barriers and facilitators of pain treatment engagement among men and women Veterans;[44,66] however, one study found that women identified specific challenges of being female that interfered with treatment engagement. These beliefs included feeling like were not understood or believed by their providers, and that providers perceived that weight was a more central issue to their pain by relative to men.[67]

Overall, beliefs can drive powerful negative emotions (e.g., despair, anxiety, hopelessness) and problematic behaviors (e.g., avoidance) that perpetuate functional impairment and continued use of opioids, despite harm, potential for harm, or lack of improvement. Evidence-based interventions are needed to directly address these patient beliefs that are potential barriers to engaging in psychosocial pain treatments.[68]

CBT is ideally suited to modify beliefs interfering with engagement in psychosocial pain treatment. The mechanism behind CBT's efficacy comes from its demonstrated ability to change beliefs, which serves to change behavior (in the case of the current study, treatment initiation and retention).[69-71] CBT is effective for a wide range of conditions,[21,69,72] is efficacious when delivered via telehealth,[73] and can be administered by individuals other than highly trained mental health professionals.[74] Dr. Tracy Stecker (co-I) has developed CBT for Treatment Seeking (CBT-TS), which specifically targets treatment beliefs that interfere with treatment seeking. CBT-TS is backed by strong evidence that it increases treatment initiation and retention through changing beliefs. The current study will address the need of increasing the initiation of and retention to psychosocial pain treatments by modifying beliefs that are interfering with treatment engagement.

Conceptual Model. CBT-TS targets beliefs interfering with engagement, which will include beliefs about opioid analgesics, exaggerated negative thoughts about one's ability to address pain (i.e., helplessness-related catastrophizing, fear-avoidance beliefs, pain-related self-efficacy), and psychosocial and other non-pharmacological pain treatment. CBT-TS may also

increase the belief that they can manage their pain providing hope that their functioning can improve. By addressing such beliefs (e.g., “opioids are the only thing that helps me sleep”), patients will be more willing to engage in psychosocial pain treatments. Treatment engagement will then reduce their reliance on opioids as well as improve physical functioning, reduce pain severity, and pain-related interference in activity. CBT-TS may also change beliefs about a wide range of treatments including other non-pharmacological pain treatments and non-pain treatment (e.g., SUD, mental health), which may also impact downstream clinical outcomes.

3.0 Objectives

Aim 1: Test the effects of CBT-TS to increase initiation of psychosocial pain treatment among Veterans receiving opioid analgesics for chronic pain. *Hypothesis*: *Participants receiving CBT-TS will be significantly more likely to initiate psychosocial pain treatment than participants in the control condition.*
Aim 2: Test the effects of CBT-TS to increase retention in psychosocial pain treatment among Veterans receiving opioid analgesics for pain. *Hypothesis: Participants receiving CBT-TS will attend significantly more sessions of treatment during the 6-month follow-up period than participants in the control condition.*

Aim 3: Evaluate the effects of CBT-TS in improving pain and opioid outcomes.
Hypotheses: Participants *receiving CBT-TS will have significantly (a) reduced pain severity and interference, (b) improved physical functioning, and (c) reduced opioid dose and risk of misuse compared to participants in the control condition.*

Exploratory Aim: Explore the effects of CBT-TS in increasing the initiation of and retention to other non-pharmacological pain treatments among Veterans receiving opioid analgesics for chronic pain.

4.0 Resources and Personnel

Drs. Ashrafioun and Stecker will train the coordinator to administer verbal consent and administer and score the assessment measures through instruction and observed role play. Interventionists with at least a master’s degree and prior CBT training will deliver CBT-TS and the education control. Drs. Stecker and Ashrafioun will train the interventionists using the published version of the instruction manuals for CBT-TS and the education control. We will monitor treatment fidelity (i.e., adherence and competence) by audio-recording intervention sessions (via Teams or Webex and stored on protected drives noted in the Data Security Plan) and reviewing them in weekly supervision meetings. Weekly meetings will be provided by Drs. Ashrafioun and Stecker. The meetings will focus on all of the issues involved in study tasks including: a) recruiting participants, b) conducting interviews, c) coding interview data, d) communicating between research staff and interventionists, e) contacting participants for follow-up assessment; f) completing documentation, and g) storing and safeguarding data. To maintain blinding, separate meetings among interventionists and the coordinator will be done as needed.

The interventionist will complete intervention sheets to track beliefs identified. These will be monitored, in addition to the recorded sessions, during ongoing supervision.

5.0 Study Procedures

5.1 Study Design

Study sample: We will recruit 300 veterans with chronic pain for this randomized clinical trial. Participants will be randomized to either the CBT-TS condition or an education control condition. Participants in both conditions will complete assessments on pain, treatment engagement, and opioid use at baseline, and 1-, 3-, and 6-months post-treatments to assess primary, secondary, and exploratory outcomes.

Screening: This study aims to recruit 300 eligible participants nationally. Potential participants with at least a 90-day supply of opioid analgesics will be identified through queries of VHA administrative data from the Corporate Data Warehouse. Potential participants will be mailed a personalized letter describing the study and provided with a toll-free number so that they can contact study staff if they are interested in participating as well as opt out of future contact. The project coordinator will call all patients who receive a letter unless the patients call a number to opt out. An advantage of our procedure is the ability to identify gender, race/ethnicity, and high-risk opioid use (e.g., high dose) to help target recruitment of these Veterans. We can accomplish this by sending out recruitment letters to a higher proportion of these groups relative to the overall proportion. Data extraction will occur monthly to identify Veterans who have newly initiated opioid therapy. To reach 300 total participants, we would need to start from a recruitment pool of less than ~5,000-10,000 people based on the following estimates: screened 95% of people, 75-90% ineligibility rate, and 25-60% declining the invitation to participate. Therefore, there is a large enough pool to reach our conservative screening estimate with large numbers of Veterans across demographic characteristics.

Assessments and Intervention: Veterans who are eligible and agree to participate will go through the informed consent process with research staff. Those who agree to participate will be asked to schedule a time to complete a baseline assessment and randomized to the CBT-TS condition or control. Following the baseline assessment, participants will then be scheduled a convenient time to conduct their intervention session (lasting approximately 45 minutes for both the experimental and the control condition). All study activities will be conducted by telehealth. Follow-up assessment will occur 1-, 3-, and 6-months post-treatment. At the conclusion of the 6-month follow-up assessment, participants will complete an exit interview describing their experiences with the study. Participants will receive compensation for their participation in the study. The compensation amount will be based on the following:

Baseline Assessment	$50
1-Month Post-Treatment Follow-Up Assessment	$40
3-Month Post-Treatment Follow-Up Assessment	$40
6-Month Post-Treatment Follow-Up Assessment	$40

Therefore, the total compensation for completing all the study components would be $170.Payments will be made via direct deposit, check, or debit card following each study procedure listed above. Participants who do not complete the entire study for any reason will receive compensation for the components that were completed per the above schedule of payments.

5.2 Recruitment Methods

Recruitment and retention procedure: Potential participants with at least a 90-day supply of opioid analgesics will be identified through queries of VHA administrative data from the Corporate Data Warehouse. Potential participants will be mailed a personalized letter describing the study and provided with a number so that they can contact study staff if they are interested in participating as well as opt out of future contact. The project coordinator will call all patients who receive a letter unless the patients call a number to opt out. Potential participants may be recruited from other studies that are IRB approved following completion of those other studies or if deemed ineligible. Only study staff that are approved on those studies will recruit those participants.

We will use several procedures known to promote retention in longitudinal studies. These strategies include careful hiring, training, and supervision of study personnel; establishing rapport and clarifying procedures with participants from the outset; obtaining locator information (i.e., home address, email address, alternative email, phone number, alternative phone) at the outset; updating locator information as appropriate at each call; obtaining updated contact information via medical record access; remunerating participants for their time and effort; making it easy for participants to contact study personnel (e.g., to ask general study questions); maintaining flexibility and ease in the scheduling and keeping of appointments; using an assessment battery that is not overly long; providing reminders in advance of appointments; and making repeated and varied contact attempts. We will also consult our VREB to enhance our retention efforts as need. Our team has solid experience with retaining high-risk, potentially difficult-to-retain samples of participants.

***Recruitment pool and feasibility of recruitment*:** As of the 3rd quarter of 2020, over 133,000 VHA Veterans were receiving long-term opioid therapy.[80] Using national VHA administrative data extraction, we conducted a preparatory analyses of Veterans receiving at least a 30-day supply of opioids from 05/01/2020-04/30/2021 to further assess recruitment feasibility of a relatively diverse demography (Table 3). To reach 300 total participants, we would need to start from a recruitment pool of less than ~ 5,000-10,000people based on the following estimates: screened 95% of people, 75% ineligibility rate, and 25-50% declining the invitation to participate. Therefore, there is a large enough pool to reach our conservative screening estimate with large numbers of Veterans across demographic characteristics.

5.3 Informed Consent Procedures

There are two phases where informed consent could be obtained, when completing the screening for eligibility and when enrolling into the study following the screening and if eligibility criteria are met. Verbal consent to participate will be obtained for the screening and baseline appointment. Informed consent will be obtained by study personnel trained in human subjects' protections requirements and how to obtain and document informed consent.

5.4 Inclusion/Exclusion Criteria

Inclusion criteria: Participants will include men and women who:

- Are English-speaking
- Are 18 years of age or older
- Are on long-term opioid therapy prescribed opioid analgesics (e.g. ≥20mg morphine, codeine, fentanyl, hydrocodone, hydromorphone, meperidine, methadone, morphine,

oxycodone, oxymorphone, tapentadol, and/or tramadol equivalent daily [MEDD] and at least a 90 day supply)
- Report pain that occurs on at least half the days for six months
- Score at least a 4 on each item of the three items on a brief pain intensity and interference measure (PEG)

Exclusion: Veterans will be excluded on the basis of:
- Does not understand informed consent
- Currently undergoing oncology treatment, hospice patients, and Veterans with a recent or upcoming surgery
- Currently engaged (i.e., within the past month) in non-pharmacological pain treatment

Pregnant women will not be excluded from this study as no invasive medical procedures are being performed and there is no known risk to the mother or the fetus of the proposed interventions. The study will not include prisoners or institutionalized Veterans.

5.5 Study Evaluations

Medical Record Review and Treatment Utilization Form (TUF). Treatment utilization will be assessed through medical record review. The measure can be found in the **Appendix**. CAPRI and Joint Longitudinal Viewer will be used to access medical records. These are used at every VAMC and regional office and are accessible from every VA site of care. We will abstract data related to treatment utilization and medications across VHA facilities, including types of service (e.g., CBT-CP, chiropractic care), dates of service, number of sessions, and type and dose of medications. Non-VA medications known to VA providers and non-VA treatment notes are also included in the medical record. This data will be abstracted as available. Treatment initiation of psychosocial pain treatment is defined as attending at least one session of CBT-CP, ACT, or MBSR. We will also utilize data extraction from the Corporate Data Warehouse (CDW) to initially capture treatment utilization from medical records to assist in the medical record review. CDW contains financial, enrollment, demographic, diagnostic, treatment utilization, and other data across Veterans from 1979 to present. For training of the medical record chart review, the research staff will code 12 charts unrelated to the study and then meet to discuss and resolve differences. During the review for the study, they will overlap on 10 charts to facilitate agreement and ongoing discussion of differences will be addressed as needed. Drs. Dougherty and Ashrafioun will make the final decisions.

We will also collect self-report data on non-VHA care not identified in the medical record. *Self-report data will be exploratory* to evaluate the extent to which treatment was utilized outside the VHA and will not be included in the analyses of the primary and secondary outcomes. Participants will be asked at baseline and each follow-up period whether they have initiated treatments and the number of sessions for each type of treatment they have attended since the previous assessment. We will ask participants to provide information about where the treatment was received, and type of treatment (e.g., CBT-CP, MBSR, chiropractic, acupuncture).

Pain Treatment Willingness Scale (PTWS). Beliefs about psychosocial and other non-pharmacological pain treatments will be assessed using a modified PTWS.[68] The original scale consists of seven items assessing respondents' willingness to use opioids or non-pharmacological approaches using a 6-point rating scale. (1 = "not at all willing" to 6 "extremely willing"). The PTWS will be modified to include CBT-CP, MBSR, and ACT, in addition to those noted in the left column of Table 5. Research supports the reliability and validity of the PTWS.[68]

Table 4. Schedule and content of study assessments

Construct (measure)	Base-line	Follow-ups
Treatment Initiation and Retention		
Treatment uptake (TUF)	X	X
Beliefs		
Hopelessness (BHS)	X	X
Opioid beliefs (MBQ, BMQ)	X	X
Treatment beliefs (PTWS)	X	X
PCS, PSEQ, TSK (pain beliefs)	X	X
Clinical outcomes		
Pain interference/severity (PROMIS-29)	X	X
Opioid misuse (COMM)	X	X
Physical Functioning (PROMIS-29)	X	X
Overdose risk behaviors (ORBQ)	X	X
Paykel Suicide Scale (PSS)	X	X
UCLA Loneliness Scale	X	X
Other key measures		
Other relevant treatment utilization	X	X
Possible OUD, other SUD (ASSIST)	X	X
Anxiety and depression (PROMIS-29)	X	X
Optional Add-on Study Assessments		
Race-Related Events Scale (RES)	X	X
Discrimination in Medical Setting (DMS)	X	X
Racial Trauma Scale-Short Form (RST-SF)	X	X

Medication Beliefs Questionnaire (MBQ). The MBQ[55] uses five items to assess beliefs about one's response to, relief from, and potential for addiction to opioid analgesics. Respondents are asked to select one of five responses for each item (e.g., "None at all" to "Complete", "Much worse" to "Much better"). Previous research indicates that higher MBQ scores are associated with greater substance use problems and mediate the relationship between anxiety and substance use history with medication misuse.[55]

Beliefs about Medicines Questionnaire. We will utilize the BMQ-Specific subscale to assess beliefs about medications specifically prescribed for pain. Previous research has found that scores of BMQ are associated with treatment adherence.[81]

Beck Hopelessness Scale (BHS). The BHS contains true-false items designed to assess beliefs about the future. The BHS has demonstrated high test-retest reliability as well as good concurrent validity.[82]

Pain Catastrophizing Scale (PCS). The PCS[83] is a 13-item measure, with each item rated on a 5-point rating scale (0 = "Not at all" to 4 = "All the time"). The measure is divided into three subscales: magnification, rumination, and helplessness and has strong psychometric properties.[83]

Pain Self-efficacy Questionnaire (PSEQ). The PSEQ assesses one's confidence in performing activities while in pain. The PSEQ has demonstrated good construct and convergent validity along with high test-retest reliability.[84]

Tampa Scale for Kinesiophobia (TSK). The TSK-11 is an 11-item measure assessing pain-related fear of movement or injury. Research supports the scale's psychometric properties.[85]

Loneliness: The 20-item Revised UCLA Loneliness Scale will be used to assess loneliness as both a clinical outcome and factor that may interfere with treatment engagement.[86]

Suicidal thoughts and behaviors: For the 5-item Paykel Suicide Scale,[87] respondents will be asked to indicate (yes or no) if they had: (1) felt that life was not worth living, (2) wished, (3) thought about, (4) seriously considered, and/or (5) attempted suicide in the past year (at baseline)/since last visit (for all other assessments). Participants receive a score equal to the greatest magnitude of suicidal ideation or behavior positively endorsed.

PROMIS-29. The PROMIS-29[88] provides a profile of one's health-related quality of life. Components of the profile include pain (severity and interference) and physical functioning. Anxiety and depression components will provide key data to account for mental health distress. The PROMIS-29 will also provide data on fatigue, sleep, and functioning in social roles. Pain intensity and interference is rated on a scale from 0 to 10 with greater scores indicating greater pain severity and interference in activities due to pain, respectively. The remaining scales are on a 1 to 5 rating scale with higher scores indicating greater problems.

Current Opioid Misuse Measure (COMM). The COMM is a 17-item measure that will be used to assess the frequency of aberrant drug-related behaviors and other behaviors that are prevalent among pain patients who are misusing prescription opioids (e.g., frequent visits to the emergency department). The rating scale on the COMM ranges from 0 ("Never") to 4 ("Very Often"), with higher scores indicating greater risk of misuse of prescription opioids. The COMM has demonstrated strong psychometric support.[89]

Overdose Risk Behavior Questionnaire (ORBQ). The ORBQ assesses the frequency of past-month engagement in behaviors that are associated with overdose. Higher scores on the ORBQ are associated with number of prior overdoses.[90]

Opioid Dose. The TUF will be used to record information on opioid dose. Opioid type, days supply, and dose will be assessed through access to the medical record. Ms. Krapf will assist us in the conversion of dose to MEDD as needed.

Table 5. Assessment of the uptake of other relevant treatment and non-opioid analgesics

Other non-pharmacological pain treatments	Other relevant treatment	Non-opioid analgesics
• Other psychosocial interventions (e.g., hypnotherapy; relaxation training) • Movement-based interventions (e.g., exercise, aquatic therapy, yoga, tai chi) • Manual therapy (e.g., acupuncture, chiropractic care, massage)	• Substance use disorder, including meds • Mental Health, including meds • Nutrition/Diet • Weight loss (MOVE!) • Vocational rehabilitation	• NSAIDs • Muscle relaxants • Anticonvulsants • Anti-depressants • Other analgesics • Medical cannabis

5.5.14. Other relevant treatment utilization. Using a similar data extraction tool as the TUF, we will assess if participants initiate other relevant types of treatment (e.g., mental health, weight loss, substance use interventions; see Table 5). Additionally, we will track if patients start using prescription and non-prescription non-opioid analgesics.

5.5.15. Substance Use Disorder Screener. Lifetime and past three-month possible opioid disorders will be assessed using the NIDA-modified Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST).[91] Respondents are asked to indicate the frequency with which they experience 8 substance-related problems, including "street" opioids and prescription opioids. Scores ranging from 0-3 suggest lower risk, 4-26 suggest moderate risk, and 27 and higher suggest high risk.

5.5.16. Demographics and military background. At screening, we will assess participants' military background (e.g., service branch, years in service, deployment history), gender, age, educational background, employment, income, race, ethnicity, and marital status.

5.5.17. Exit Interview. The exit interview is a combination of self-report measures and a semi-structured interview. Open-ended questions in the semi-structured interview will assess what participants liked most and least about the study experience. Other questions include whether the participant will remember anything specific about the study a year later. Additional questions will include items on a 5-point rating scale that ask about how much participants agree or disagree with statements about the relevance and helpfulness of the intervention. The exit interview will be critical in helping to enhance components of the intervention and identifying barriers/facilitators of implementation. The exit interview can be found in the **Appendix**.

5.6 Optional Study Add-on

Purpose. This add-on study will examine the efficacy and mechanisms of action in CBT-TS to identify factors that facilitate the initiation of psychosocial pain treatment among African American Veterans (AAV) using opioid analgesics for chronic pain management.

Study Sample, Recruitment, Screening, and Eligibility. We will recruit 76 AAV, within the 300 Veterans recruited for the parent study. Participants will need to have already completed the consent for the parent study. Participants of the parent study (inclusion) will be approached about participating in this study if they identify as being African American (inclusion) in the demographic questionnaire that is completed in the baseline assessment.

Consent, Assessments, and Intervention: African American Veterans who are eligible and agree to participate in the optional add-on study will go through an additional verbal informed consent process with research staff. This informed consent will detail the purpose of the optional add-on study and additional time commitment. In addition to assessments and interventions for the parent study, participants who agree to participate in the optional add-on study will be asked to complete three additional assessments at baseline and each of the follow-up assessment visits as well as additional questions in the exit interview (see below in Study Evaluation).

Participants will receive additional compensation for their participation in the study. The compensation amount will be based on the following:

Baseline Assessment	$50
1-Month Post-Treatment Follow-Up Assessment	$50
3-Month Post-Treatment Follow-Up Assessment	$50
6-Month Post-Treatment Follow-Up Assessment	$50

Therefore, the total compensation for completing all the study components for the add-on study would be $200 (Grand total of $370, including the $170 received for participation in the parent study). Payments will be made following each study procedure listed above. Participants who do not complete the entire study for any reason, will receive compensation for the components that were completed per the above schedule of payments.

Study Evaluations. The instruments to be used, addition to those outlined in the parent study, will measure experiences of racial discrimination and race-related stress. These instruments will be added to the assessment battery and administered at baseline and/or during the follow-up assessment at 1-, 3-, and 6-months. These measurements have been included in Table 4. Schedule and content of study assessments.

Race-Related Events Scale (RES). The RES, a 22-item scale that assesses life-time exposure to stressful and potentially traumatizing experiences of racism.[92] Respondents are asked to respond yes to items (e.g., "treated rudely because of my race or ethnicity") if that event was experienced in their lifetime. Higher scores are indicative of experiencing more race-related stressors

Discrimination in Medical Settings (DMS). The DMS was adapted from existing discrimination scales and modified items from the Everyday Discrimination Scale.[93] The DMS is a 7-item scale that assesses prior experiences of mistreatment while getting health care that respondents attribute to race. Example items include, "You feel like a doctor or nurse is not listening to what you were saying," and "A doctor or nurse acts as if he or she things you are not smart." Responses are scored on a 5-point Likert scale (1 = "never" to 5 = "always"). Higher scores indicate more experiences of mistreatment in the medical setting based on race.

Racial Trauma Scale – Short Form (RTS-SF). The RTS-SF is a clinical tool for the measurement of trauma-related symptoms arising from race-based maltreatment of people of color (POC).[94] Symptoms measured are based on DSM-5 post-traumatic stress disorder criteria. The RTS-SF is a 9-item scale scored on 4-point Likert scale (1 = "not at all" to 4 = "extremely"). Participants are asked to think about all the times when they have heard about, seen or experienced racial discrimination, and to respond to how bothered have you been by that experience. Example items include, "Feeling society is unfair to people like me.", "Reacting angrily." Higher scores indicate more trauma-related symptoms.

Exit Interview-Modified. Additional questions were added to the exit interview that will be critical in helping to identify culturally-sensitive components of the treatment and identifying barriers/facilitators of implementation.

5.7 Data Analysis

General. To enhance methodological rigor and to allow for accurate dissemination of our findings, we will follow CONSORT guidelines in the design, analysis, and reporting of this study.[95]

Data Management. Dr Allan, with the assistance of Dr. Ashrafioun, will supervise data management using the following services: Enrollment, randomization, tracking of interviews, and auditing of data. A single enrollment and randomization document will be developed to assign identification codes to participants during the pre-enrollment period to track their eligibility

status, and randomly assign participants. The PI and Co-Is will remain blind to the meaning of participant condition until unblinding, following data analysis. Similar to our prior studies, a tracking system will be developed to assist research personnel in managing follow-up interviews. This information will be covered during weekly staffing meetings involving Drs. Ashrafioun, Stecker, and Allan as well as the research personnel. Data will be audited for: a) data quality control (% of scales returned for corrections after auditing); b) rate of data entry; and c) backlog of data that has not been entered. All scales will be audited for identifiers, item completeness, and consistency of major clinical indicators. We will store and manage data at the VA with access limited to pertinent study personnel. During the study, we will maintain a dialogue on the technical integrity of our procedures and on conceptual aspects of our project.

Randomization. Following consent, participants will be randomly assigned (1:1) to the CBT-TS or the educational control based on a concealed block randomization scheme. Block sizes will be four and overall, 50% of participants will be assigned to each condition.

Preliminary Analysis. For all variables, we will examine the distribution for potential nonnormality and outliers. If necessary, appropriate data transformations or alternative data analysis procedures (e.g., nonparametric, bootstrapping) will be used prior to data unblinding. Prior to outcome analyses, baseline demographic and outcome variables will be assessed for baseline equivalency. Categorical variables will be analyzed using chi-square tests; continuous variable differences will be assessed using pooled t-tests. Per missing data design (see *Missing Data*), if baseline differences are detected, these covariates will then be included in the final model as auxiliary variables to improve the plausibility of assuming data is MAR.[96]

Primary Analyses in Support of the Specific Aims. **Aim 1 Hypothesis:** Participants receiving CBT-TS will be significantly more likely to initiate psychosocial pain treatment than participants in the control condition. Treatment initiation of psychosocial pain treatment will be treated as a binary outcome variable (0|1). A Cox Proportional Survival Analysis.[97] will be conducted to examine treatment initiation by the 6-month follow-up. This approach is like logistic regression except it accounts for missing data across the follow-up timepoints. Condition will be entered into the model as a predictor of whether a participant reported attending treatment by the 6-month follow-up. The assumption of proportionality will be tested in this model. A secondary logistic regression analysis will be conducted to examine treatment initiation by the end of the 6-month follow-up using worst case imputation of missing outcome to test robustness of any effects. Additional secondary analyses to demonstrate treatment robustness will be treatment initiation by the 1-month and 3-month follow-ups.

Aim 2 Hypothesis: Participants receiving CBT-TS will attend significantly more sessions of treatment during the 6-month follow-up period than participants in the control condition. The outcome will be sessions of psychosocial pain treatment attended during the 6-month follow-up period. Analyses will be conducted using MRM within a multilevel modeling (MLM) framework as this method allows for appropriate modeling of the covariance matrix when measures are repeated over time and can easily account for normal, skewed, and categorical data. MRM will be used, including treatment condition, follow-up time (centered on 6-month follow-up), and a condition by time interaction term as predictors of number of sessions of treatment attended.

Aim 3 Hypotheses: Participants receiving CBT-TS will have significantly (a) reduced pain severity and interference, (b) improved physical function, and (c) reduced opioid dose and risk

of misuse compared to participants in the control condition. The outcomes will be pain severity, pain interference, physical functioning, opioid dose, and risk of misuse. MRM will again be used. Treatment condition, follow-up time (centered on 6-month follow-up), and a condition by time interaction term will be included as predictors as will the relevant baseline autoregressors. Additional secondary analysis to demonstrate treatment robustness will involve centering time at the 1-month and 6-month follow-ups, allowing for examination of treatment differences at these timepoints.

Exploratory Analyses: Explore the effect of CBT-TS in increasing the initiation of and retention to other non-pharmacological pain treatments among Veterans receiving opioid analgesics for chronic pain. For treatment initiation and treatment retention, we will employ the same approach as described in Aims 1 and 2. As an additional set of exploratory analyses and consistent with an experimental therapeutics approach, we will explore beliefs as potential mediators of treatment initiation. Structural equation modeling (SEM) will be used to conduct these analyses. Latent variables (BHS, PTWS, PSEQ, PCS, TSK, MBQ, BQ) will be constructed to capture beliefs about opioids, treatment, beliefs that pain can be reduced, and hope. These variables will be included as potential mediators between condition and treatment initiation by month 6 as well as pain and opioid clinical outcomes at month 6. Prior to testing the mediation model, the direct effects of condition on treatment initiation, pain, and opioid outcomes at month 6 will be examined in one model. Next, the latent belief factors at month 3 will be included as mediators. All models will be conducted including relevant baseline autoregressors. Measurement invariance across conditions and across treatment initiation status will be established for the month 3 latent belief factors. All models will be re-analyzed using manifest variables instead of latent variables to test for model robustness. Any differences will be discussed. We will also explore variables such as gender, baseline dose, age, race/ethnicity, parent station type (1a-c, 2, 3) as potential moderators of treatment effect to drive further study.

Analysis in Support of Specific Aims for Optional Add-on Study: **Aim 1 Hypothesis:** African American participants receiving CBT-TS will be significantly more likely to initiate psychosocial pain treatment than African American participants in the control condition, compared to rates of treatment initiation in the rest of the sample. Treatment initiation of psychosocial pain treatment will be treated as a binary outcome variable (0|1). A Cox Proportional Survival Analysis[97] will be conducted to examine treatment initiation by the 6-month follow-up. Race will be dummy coded (0 = African American, 1 = other) and included as an independent variable as well as moderator of treatment condition.

Aim 2 Hypothesis: Treatment initiation for African American participants receiving CBT will be moderated by CBT treatment components, including individualization, non-judgment, self-expert, collaboration, and empowerment. We will restrict these analyses to African American participants and will include treatment condition, CBT treatment components, and condition by components interaction terms.

Exploratory: Explore the effect of race-related stress on treatment initiation and retention to other non-pharmacological pain treatments among African American Veterans receiving opioid analgesics for chronic pain. African Americans participants who experience higher levels/more

race-related stress will be significantly less likely to initiate or complete other non-pharmacological pain treatments for chronic pain.

Missing Data. An intent-to-treat (ITT) approach will be used, including all participants randomized to a treatment condition. Missing data in the full analysis set will occur if participants discontinue prior to the end of the study or do not complete an outcome measure. Participants will not be discontinued from the study because of non-adherence and all will remain in the study unless consent is withdrawn or if there are concerns regarding participant safety. Missing data for the ITT analysis set will be addressed using robust full information maximum likelihood (FIML), which is superior to most alternative missing data approaches even when data is missing completely at random (MCAR) or missing at random (MAR).[96,98] Although the use of FIML will result in the least biased parameters, regardless of data missingness, several approaches will be undertaken to better understand the exact mechanisms for missing data. Little's MCAR test will be applied to all final models to determine whether data can be considered MCAR. Further, the results of analyses using study completers will be compared with results using the ITT approach to test sensitivity of study conclusions to study discontinuations. Baseline differences also will be explored between treatment completers and those that discontinue across study and demographic variables. If baseline differences are detected, these covariates will then be included in the final model as auxiliary variables to improve the plausibility of assuming data is MAR.[96]

Power Analysis and Sample Size. A balanced randomization scheme (1:1) will be used for this trial. Power to detect the primary effects of interest for the Aim 1 Hypothesis involve testing whether CBT-TS, compared to the education control condition, increases treatment initiation of psychosocial pain treatment. Power to detect the primary effects of interest for the Aim 2 Hypothesis involve testing whether CBT-TS, compared to the education control condition, increases treatment retention. Power to detect the primary effects of interest for the Aim 3 Hypothesis involve testing whether CBT-TS, compared to the education control conditions, improves pain and opioid outcomes. Sample size was determined using Monte Carlo simulation studies (with 10,000 replications). For each of the hypotheses, it was determined that with a sample size of $N = 250$ we would have at least 80% power with an $\alpha = 0.05$ to find small effects of condition on treatment initiation and small-to-moderate effects on all other direct effects. This includes adequate power to detect all significant indirect effects. To adjust for potential attrition, the sample size was increased by 20%, resulting in a final sample of $N = 300$. Power analyses for the mediation models ($\alpha = .05$, $1 - \beta = .80$) indicates that with 300 participants we will be adequately powered to find mediation in the presence of small-to-medium paths from condition to the potential mediators and from the potential mediators to the primary (treatment initiation) and two secondary outcomes (pain and opioid clinical outcomes).

Type 1 Error Protection. To help control for Type 1 error, the Benjamini-Hochberg method will be used to adjust for the multiple comparisons proposed in the current study.[99] This method adjusts for multiple comparisons by controlling false discovery rate instead of family-wise error rate. It is less conservative than the more traditional Bonferroni methods, yet still provides adequate protection against Type 1 error and is the optimal solution to the multiple comparison problem in most practical situations.

Data storage, security, and confidentiality

Several procedures for protecting participant confidentiality will be implemented to reduce the risk of revealing participant identity. All informed consent forms will contain identifying information. To ensure confidentiality, each consent form will be labeled with a numeric identifier and will be stored in a double-locked file. These will be stored in separate double-locked files from other study materials. As noted in the Data Transport Memorandum, locked courier bags will be used to transport any sensitive study information (e.g., consents) outside VA.

The VA Informatics and Computing Infrastructure (VINCI) will be used for the storage of study data. VINCI is a major informatics initiative of the Department of Veterans Affairs (VA) that provides a secure, central analytic platform for performing research and supporting clinical operations activities. It is a partnership between the VA Office of Information Technology (OI&T) and the Veterans Health Administration Office of Research and Development (VHA ORD). VINCI includes a cluster of servers for securely hosting suites of databases integrated from select national VA data sources. VINCI servers for data, applications. and virtual sessions are physically located at the VA Austin Information Technology Center (AITC), located in Austin, Texas. This secure enclave with 105 high-performance servers and 1.5 petabytes of high-speed data storage has multiple layers of security and disaster recovery to prevent data loss.

Study data will be kept in accordance with the Department of Veterans Affairs Record Control Schedule 10-1 (RCS 10-1). Storage and transfer of any Personally Identifiable Information (PII) or Protected Health Information (PHI) must be done in accordance with applicable VA and VHA policies and directives, state and federal regulations, and applicable statutes including the Health Insurance Portability and Accountability ACT (HIPAA). Unless explicitly requested and approved by data stewards, all sensitive patient data must remain on VINCI project servers and only aggregate data without PII / PHI may be transferred from VINCI.

Prior to being uploaded to VINCI for analysis, data will be stored on a secure VA server to which only IRB approved VA research personnel have access. Should any identifiable information need to be shared between research team members, we will utilize a secure, SharePoint site or electronic communication with PKI encryption. Any identifiable paper data will be stored in two separate locked file cabinets (one for informed consents and the other for paper questionnaire data) in the offices of the Center for Excellence for Suicide Prevention at the Canandaigua VAMC a. After a participant completes the study, any identifiers will be removed from the paper questionnaire data immediately. Data analysis will occur in the VINCI framework.

5.8 Withdrawal of Subjects

Participants who wish to withdraw may do so at any time without affecting their medical care or participation in any other study. Participants will be informed of any new information throughout the duration of the study which may affect their condition or influence their willingness to continue in this study. Finally, based on decisions made by the Principal Investigator, participants may be taken out of the study because of unanticipated circumstances such as extreme distress. That is, they may be withdrawn from the study if we judge that participating is not in their best interest.

6.0 Protection of Human Subjects

Protection of Human Subjects

Risk to Participants

Human Subjects Involvement and Characteristics. The purpose of the study is to test the effects of Cognitive-Behavioral Therapy for Treatment Seeking (CBT-TS) CBT-TS in increasing the initiation of psychosocial pain treatment among Veterans using opioid analgesics for chronic pain. Secondary goals are to assess the effects of CBT-TS on treatment retention and its downstream effects on pain and opioid use outcomes. We will also explore CBT-TS effects on treatment engagement of other non-pharmacological pain treatments and mechanisms of change to identify barriers to engagement in non-pharmacological pain treatment. A total of 300 veterans will be recruited nationally and randomized to receive either CBT-TS (n = 150) or an Education control (n = 150). Over 50% of Veterans in the Veterans Health Administration (VHA) have received a diagnosis of a musculoskeletal condition (the majority of which are associated with chronic pain) between 2000 and 2011. Of these individuals, over one-third are over 65 years of age, nearly three-quarters are White and fewer than 10% are women. Hypertension occurs in approximately half of these Veterans and other medical conditions including diabetes, coronary artery disease, and chronic obstructive pulmonary disease occur in over 10% of Veterans with a musculoskeletal condition. We expect to have a greater proportion of women and racial/ethnic minorities relative to the above as we will target them in recruitment.

Inclusion criteria: Participants will include men and women Veterans who:

- Are English-speaking
- Are 18 years of age or older
- Are taking at least 20 mg morphine equivalent daily dose of opioid analgesics per day for ≥90 days
- Pain that occurs on at least half the days for 6 months or more
- Score ≥ 4 on each of the three items of the PEG
- Optional Add-on Study: Identify as African American

Exclusion: Veterans will be excluded on the basis of:

- Used a nonpharmacological approach to pain management in the last 30 days
- Has cognitive impairment
- Being in hospice, undergoing oncology treatment, or has a recent or upcoming surgery

Pregnant women will not be excluded from this study as no invasive medical procedures are being performed and there is no known risk to the mother or the fetus of the proposed interventions. The study will not include prisoners or institutionalized veterans.

Source of Materials. Study materials will include self-report questionnaires. The materials will be collected for study purposes only. Information collected will be stored in a locked filing cabinet in a locked office at the study sites that can only be accessed by members of the study team. *All electronic data* will be stored on VA Informatics and Computing Infrastructure (VINCI) project servers. Only approved study team personnel who will be involved in data entry, management and analyses will be granted access to this data. All computers are password protected.

Potential risks.

Psychological distress. Anticipated risks to the participants from assessment procedures and therapy are minimal; however, participants may experience psychological distress, frustration, and/or fatigue. The semi-structured interviews, assessments associated with the intervention, and therapy sessions encourage participants to recall personal events and life stressors that

may evoke distress. Additionally, confidentiality may need to be breached if a participant poses a threat to him or herself or others, including child abuse.

Adequacy of Protection from Risk
Recruitment and Informed Consent.
All research staff conducting recruitment and informed consent will have completed appropriate and up-to-date training in research, research ethics and the proper conduct of research that includes common issues related to recruitment and informed consent.

Veterans will be identified using structured queries of VA administrative datasets. Research staff will use these lists to identify potentially eligible participants and to enhance the number of Veterans at high risk, women and/or minorities recruited into the study. Research staff will mail an IRB-approved letter describing the study to the Veteran. Research staff will call all patients who receive a letter unless the patients call a number to opt out. These are Syracuse VA IRB-approved procedures that are used by researchers at the Center of Excellence for Suicide Prevention and Syracuse VAMC. There is no more than minimal risk to the participants and the rights of the participants, or their welfare, will not be adversely affected. Recruitment and informed consent procedures were designed to ensure patients do not feel like participation is required. Patients unable to understand the informed consent process will be excluded from participating. Screening interviews will be completed initially over the telephone (using a script) to assess eligibility criteria. Verbal consent will be obtained at this time to complete the screening. Participants screening positive for exclusion criteria will not be included in the study. Veterans who report suicidal intent with a plan will be transferred to the Veteran's Crisis Line (as detailed below in Protection Against Risk). For eligible and interested participants, a research assistant will review the consent form and complete a brief questionnaire to ensure the potential participant understands the study.

Participants will receive compensation for their participation in the study. The compensation amount will be based on the schedule that follows:

Baseline Assessment	$50
1-month Assessment	$40
3-month Assessment	$40
6-month Assessment	$40

Therefore, the total compensation for completing all the study components would be $170. Payments will be made following each study procedure listed above. Participants who do not complete the entire study for any reason, will receive compensation for the components that were completed per the above schedule of payments.

Optional Add-on Study: In addition to the compensation provided for participation in the parent project, participants who consent to participate in this add-on project will receive additional compensation for their participation. The compensation amount will be based on the schedule that follows:

Baseline Assessment	$50
1-month Assessment	$50
3-month Assessment	$50
6-month Assessment	$50

Therefore, the total compensation for completing all the study components for the add-on study would be $200 (Grand total of $370, including the $170 received for participation in the parent study). Payments will be made following each study procedure listed above. Participants who do not complete the entire study for any reason, will receive compensation for the components that were completed per the above schedule of payments.

Protection Against Risk.
Psychological distress. The potential risks are negligible. There are no known risks associated with interview procedures. Participants will be informed that they may feel slightly uncomfortable discussing some of their symptoms. Mild discomfort may occur during the intervention session; however, this is unlikely to have a serious negative impact on the participant's well-being. Participants will be told they can withdraw from the study at any time. Participation or withdrawal from the study will not affect any benefits to which they are otherwise entitled. Special precaution will be taken to safeguard confidentiality. During assessments, if the interviewer is concerned about thoughts and planning of a suicide attempt, the interviewer will ask two follow-up questions: Do you have a desire to kill yourself that you think you might act on and Do you have a plan for killing yourself and intend to carry the plan out? With this information and available suicide assessment measures, the interviewer will evaluate the severity of the participant's suicide risk. If the participant is deemed to be at imminent risk, a safety plan will be initiated. All study staff will receive adequate training in suicidal ideation and risk assessment, and all work will be supervised by Drs. Ashrafioun or Stecker, who are licensed clinicians.

Psychological distress. The potential risks are negligible. There are no known risks associated with interview procedures. Participants will be informed that they may feel slightly uncomfortable discussing some of their symptoms. Mild discomfort may be likely during the intervention session; however, this is unlikely to have a serious negative impact on the participant's well-being. Participants will be told they can withdraw from the study at any time. Participation or withdrawal from the study will not affect any benefits to which they are otherwise entitled. Special precaution will be taken to safeguard confidentiality. During assessments, if the interviewer is concerned about thoughts and planning of a suicide attempt, the interviewer will ask two follow-up questions: Do you have a desire to kill yourself that you think you might act on and Do you have a plan for killing yourself and intend to carry the plan out? With this information and available suicide assessment measures, the interviewer will evaluate the severity of the participant's suicide risk. If the participant is deemed to be at imminent risk, a safety plan will be initiated. All study staff will receive adequate training in suicidal ideation and risk assessment, and all work will be supervised by Drs. Ashrafioun or Stecker.

All assessors and interventionists will have a specific protocol to follow regarding emergency care and will have the clinical back-up of Dr. Ashrafioun and Stecker. This study will use safety procedures that have been previously approved by the IRB in several of our protocols. All research staff will be thoroughly trained on these procedures. These include written procedures for handling emergencies, a written procedure for conducting a full suicide risk assessment whenever suicidality is endorsed, procedures for participants endorsing a suicidal plan or intent (including staying with a patient until they are connected with a mental health provider or 911 help), and a written warm-handoff guideline to connect Veterans to the National Veterans/Military Crisis Line (VCL).

Besides responses on study assessment instruments, participants may also allude to suicide or make other provocative statements, irrespective of the scale rating, and in these instances the research assistant may also decide to transfer the participant to the VCL. A participant's

answers to other questions in the research battery may also persuade the research assistant to transfer the participant to the VCL, irrespective of the scale rating.

For example, a participant may score in the severe depression range on the PHQ-9 depression scale and, together with other information obtained during the call, the research assistant may perceive acute risk and decide to transfer the participant to the VCL.

In any of the above instances, the research staff member will read (or paraphrase) the following statement to the participant at the end of the call:

> *I am concerned about your safety and so at this time I am going to transfer you to speak with one of our mental health clinicians at the Veterans/Military Crisis Line. There will be a moment of silence as I connect you. If for some reason we get disconnected please dial 1-800-273-8255 and press #1 to reach the Lifeline. I will stay on the line with you until the transfer is complete. I am now going to transfer you. Please stay on the line.*

The researcher will briefly summarize the participant's situation to orient the VCL responder to the nature of the call (the participant will hear a moment of silence at this time0, and then the participant will be transferred to the VCL.

If the participant hangs up or becomes disconnected, the researcher will call the VCL immediately, and the VCL staff will take necessary actions as appropriate according to the VCL safety protocol and/or direct the researcher what actions to take. These actions may include initiating a "rescue" that involves calling 911 at the participant's local jurisdiction and having emergency personnel come to the participant's home to ensure their safety. The VCL staff performs rescues every day, and all rescues are done in collaboration with a supervisor. We have ongoing collaborations with the VCL and have substantial experience working with responders and supervisors. Our approach to participant safety will be applied to all participants including control participants and is guided by ongoing clinical and research experience in suicide prevention, including our Center Director's affiliation with the VCL.

We will collaborate closely with the VCL during the study start-up phase to review these safety protocol steps. As a reminder, the VCL, which was established in 2007 at the Canandaigua VAMC, can be reached anytime by calling 1-800-273-8255. The VCL has grown to be one of the largest in the world, with a full-time staff of more than 600 full-time responders. VCL responders are paid professional staff and nearly all have a Master's degree in a relevant field (e.g., mental health counseling), distinguishing the VCL from others in the U.S. that are staffed primarily with volunteers.

VCL resources will be available as back-up at all times during study sessions. VCL responders are arguably the foremost experts in managing acute suicidal crises via telephone. They have in place protocols for locating suicidal individuals, identifying the closest police and emergency medical services, and monitoring and documenting "rescues." Moreover, VCL responders have the ability to look up call histories based on callers' phone numbers, a capability that since implemented has greatly aided the ability of responders to rapidly assess callers' needs.

All participants will be provided the VCL phone number at the end of each baseline assessment and at each follow-up assessment and encouraged to call the number should they become suicidal, simply wish to talk with someone, or would like assistance in obtaining a referral for mental health treatment. In situations in which potential suicide risk is identified during a phone call, we plan to use two levels of response: 1) researcher transfers the individual to the VCL

(used in acute crises requiring emergency intervention or “rescue”); 2) researcher offers the participant a transfer to the VCL, but does not perform the transfer if he/she does not wish to be transferred (used in non-emergency situations).

Breach of Confidentiality. Statistical data files will be kept VINCI project servers maintained by VINCI OI&T personnel and only summarized data without protected health information (PHI) will be downloaded from VINCI to local storage media. Research staff will use an audited VINCI download utility to move summarized data for reports, presentations and publications from VINCI servers to local storage media. The VINCI download utility provides an audit path including a copy of the downloaded material. The data extraction tool will be adapted for use with software directly available on the VINCI platform (e.g. Microsoft Word and Excel) and study data will be stored and maintained on VINCI. All study team personnel with access to sensitive patient data will stay current on their VA approved information security training and VA approved privacy policy training.

Adverse Events (AE). AEs may include, but are not limited to: worsened physical or mental health, or inadvertent disclosure of confidential research information. Serious Adverse Events (SAE) may include: death, hospitalization due to worsening psychiatric symptoms or suicidal ideation, or all life threatening or disabling/incapacitating events among research participants. Per IRB regulations, SAEs, any event resulting in a deviation from the study protocol (e.g., emergency hospitalization to address suicidal behaviors) or death will be reported to the PI within 24 hours and to the IRB in 48 hours. This will be completed in order to assess significance and determine an appropriate response. AEs that involve temporary distress will be noted by interviewers and provided to the IRB in an annual report.

Confidentiality of Records: Numerous protections are in place to reduce the likelihood of loss of confidentiality. All research data will be kept in locked filing cabinets in secure areas, absent of identifying information, and coded by research number only. Files containing consent forms and other items with identifying information will also be kept in locked filing cabinets, but these will be separate from cabinets containing data from this study. All electronic files, including therapy notes, will be maintained on a secure study folder behind the VA firewall. Only approved study team personnel will be granted access to this data. All identifiable information will be stored in a separate folder behind the firewall from the de-identified study ID and data.

Potential Benefits of Research to Participants and Others. There may be direct and/or indirect benefits of study participation. Participants may initiate a psychosocial or other nonpharmacological pain treatment, or a related treatment that may help improve physical and/or mental well-being. Dissemination of the findings from the study will contribute to the extant literature and will inform future implementation efforts.

Importance of Knowledge to be Gained. Chronic pain conditions are among the most common and disabling in the United States and management of chronic pain with opioid analgesics increases risk of premature death. The latest Clinical Practice Guidelines detail utilization of nonpharmacological approaches, including psychosocial pain treatments as front-line treatment. Beliefs regarding the utility of such treatment often act as a barrier to patients initiating and engaging in such treatment. The proposed study is a one-session, cognitive-behavioral intervention that is delivered by phone targeting treatment initiation and engagement through reducing thoughts that act as barriers. Patients receiving such treatment may be more likely to initiate psychosocial and other nonpharmacological pain treatments that are safer alternatives to opioid analgesics. Additionally, there is less patient and provider burden to help

increase treatment initiation given it is one session and can be delivered by phone. Knowledge gleaned from this study will help inform future implementation and dissemination efforts.

Data Safety & Monitoring Plan

Data Safety. To ensure safety of participants in the study proposed and validity and integrity of data collected, the PI (Ashrafioun) will oversee all data and safety monitoring functions and the research team will be advised that he will be the primary contact overseeing these activities. The investigators will meet regularly to monitor study progress and discuss the implementation of monitoring procedures. The PI will also meet regularly with the research coordinator and staff to review monitoring procedures and ensure all efforts are being taken to minimize risks to participants. As indicated below, the PI will track all negative outcomes and incidents as well as conduct interim data analysis every 12 months after the study has started. The study design will be significantly modified if the study is creating potential harm to our participants.

The PI and Dr. Stecker will regularly oversee all aspects of the study, including participant recruitment, informed consent, data collection, management, and analysis, as well as regularly assess the risk/benefit ratio associated with participation in the study. All research staff will participate in an intensive training to help them understand the importance of reducing the risk for participants and learning how to recognize and report any AE or SAE. SAEs may include: death, hospitalization due to worsening psychiatric symptoms or suicidal ideation, or all life threatening or disabling/incapacitating events among research participants. AEs may include, but are not limited to: physical injuries, worsened physical or mental health, or inadvertent disclosure of confidential research information.

If an SAE occurs, the PI will immediately contact the IRB, followed by a written report in 24 hours. He will make a decision whether there is sufficient evidence to suspend data collection, allow for further IRB review, modify the protocol, or make other changes to reduce potential risk to participants. The study will resume based on agreement of the PI, and an IRB member (the chair will recuse himself because he is a co-I on the study). Immediate evaluation will occur to determine if any extra steps can be taken to minimize the likelihood of that type of AE occurring again. If changes can be made, a report/amendment will be written and submitted to the IRB.

As part of a standard practice, the PI will supervise the implementation of one audit within 4 months after study recruitment and one regularly per year afterwards of the materials collected and produced as part of the study at each site to ensure proper confidentiality and compliance with ethical principles, including informed consents, questionnaire data, and to make sure that the research staff are following established protocols. The PI will provide an annual summary report of all AEs to the IRB as part of the annual review. If no adverse events have occurred, the report will state, “No adverse events affecting human participants have occurred during this project year.”

Data Monitoring. To ensure adequate participant recruitment and enrollment, each week, the PI will discuss the current number of participants contacted, screened, and enrolled from each site and compare those numbers to the expected based on our preliminary data. If after the first 4 months, it appears we are not reaching our expected number of participants, the PI will discuss potential barriers/obstacles and solutions with the research team and we will enact contingency plans as needed.

7.0 References

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