Efficacy of Mind-Body Approaches for the Treatment of Chronic Pain with Psychological Comorbidity

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Background and Significance

Chronic Pain and Psychological Comorbidities

Chronic pain (CP), defined as persistent (>6 months), non-malignant, musculoskeletal or generalized pain, is a prevalent and costly public health problem (Institute of Medicine, 2011; Tsang et al., 2008). CP has an astounding economic impact of $600 billion annually in the U.S., including healthcare costs and lost productivity. CP is highly prevalent among Veterans; 30-40% of Veterans have moderate to severe CP (Bair et al., 2008). CP has a significant negative impact on mental health and quality of life. CP is associated with declines in functioning (Kerns et al., 2011), decreased activity levels (van den Berg-Emons et al., 2007), and elevated anxiety (McWilliams et al., 2003) and depression (Knaster et al., 2012). Approximately 1.6 million Veterans Health Administration (VHA) enrolled Veterans have CP and psychological distress associated with mental health comorbidities, including posttraumatic stress disorder (PTSD; ~50%), depression (~25%), and anxiety disorder(s) (~25%; Bair et al., 2008; Outcalt et al., 2015). Furthermore, among Veterans, the co-occurrence of CP and psychiatric disorders (e.g., PTSD & depression) is associated with higher healthcare utilization, medication use, incidence of medication-related adverse events and contraindicated medication use (Outcalt et al., 2014; Seal et al., 2012). Depression, PTSD, and CP are all factors associated with greater risk of suicidal behavior among Veterans (Lee et al., 2018); in a comorbid population, these factors may have an additive effect. Unfortunately, the currently available medical, surgical, and pharmacological interventions for CP are associated with only modest benefit and measurable problems (e.g., opiate abuse, post-surgical complications). There is increasing recognition of the importance of psychosocial aspects of the etiology, maintenance, and treatment of chronic pain (Kerns et al., 2011), and the treatment of Veterans with CP with psychological comorbidity is a high-need area.

The VHA Pain Directive dictates that pain management is a national priority and emphasizes the promotion of quality of life, including physical and psychosocial functioning and treatment satisfaction (DVA, 2009). The VHA strongly recommends against the initiation of long-term opioid treatment for CP (DVA, 2017) and encourages nonpharmacological approaches, such as psychosocial interventions (DVA, 2009, 2017). The presence of psychological comorbidities, especially PTSD, is associated with higher incidence of opioid use, medication-related adverse events, and contraindicated concurrent medications (e.g., benzodiazepines; Seal et al., 2012). Despite this urgent need, there are currently no evidence-based psychosocial interventions that simultaneously target CP interference and common psychological comorbidities in Veterans.

The treatment of CP with mental health comorbidity is often poorly integrated, and gold standard interventions, which are generally disorder-specific, do not always confer significant benefits. For example, although cognitive behavioral therapy (CBT) is the first line psychosocial treatment for CP (Ehde et al., 2014), its efficacy is limited, and it does not address psychological comorbidities. In a recent review, CBT had a significant, but small impact on pain disability and pain catastrophizing, but no effects on pain severity and mood, and there has been a failure to identity mechanisms of change, which stymies the ability to refine theoretical models (Ehde et al., 2014). Furthermore, psychological comorbidities, including depression, have been associated with poorer treatment response in CBT for CP (Turner et al., 2007). Third wave therapies, including Acceptance and Commitment Therapy for CP, have likewise resulted in small effects for depression, disability, and quality of life and medium effects for anxiety and pain interference among individuals with CP (Veehof et al., 2016). Similarly, although CBT is considered a gold standard treatment for both anxiety and depressive disorders, as many as 50% of patients drop out or do not complete CBT, and in one study, only 20% of patients achieved stable remission from depression (Schindler et al., 2013; Taylor et al., 2012). Remission rates of PTSD in military Veterans remain disappointing, even among those receiving gold standard treatments (e.g., Prolonged Exposure, Cognitive Processing Therapy; Steenkamp et al., 2014). Thus, disorder-specific CBT and third wave therapies have failed to result in remission for the majority of individuals with CP, depressive, anxiety, or trauma-related disorders. A recent randomized controlled trial (RCT) of an integrated treatment for PTSD and CP conducted at the VA Boston Healthcare System was inconclusive (Otis et al., 2015), and a recent RCT found that transdiagnostic Acceptance and Commitment Therapy had modest treatment effects and was not superior to control in improving psychological comorbidity (depression or PTSD) among a heterogeneous Veteran sample (60% had depression, 82% had PTSD; Lang et a;., 2017). Therefore, Veterans with CP and psychological comorbidities would greatly benefit from innovative alternative psychosocial interventions.

Complementary and Integrative Health Approaches

We have defined complementary and integrative health as “the incorporation of strategies that currently fall outside of Western medicine into care with the aim of improving wellness as opposed to simply mitigating symptoms” (Malaktaris et al., 2018). Such practices include acupuncture, meditation, relaxation, tai chi and qi

gong, and yoga. The National Center for Complementary and Integrative Health (NCCIH) recently reported that 30% of adults use complementary and integrative health approaches (Stussman et al., 2012). Furthermore, 40% of veterans with CP reported complementary and integrative health use, and over 75% of non-users reported that they would incorporate these approaches if they were offered at the VA (McEachrane-Gross et al., 2006). Consistent with this widespread interest and use, the VA strategic plan 2018-2024 stated "VA will also reinforce health care practices to include incorporating complementary and integrative health care practices to…manage chronic pain, and improve mental health" (DVA, 2012).

Compassion Meditation

Given the insufficient evidence for the use of mindfulness meditation in improving both psychological comorbidities and CP disability, other forms of meditation, such as compassion meditation, should be explored. Compassion meditation is a practice for cultivating compassion for self and others that focuses on the wish to remove suffering. This contemplative practice shows promise for the amelioration of mental and physical health problems as well as improving quality of life. For example, in healthy adults, compassion meditation has been associated with increased mindfulness, positive affect, and self-compassion and decreased worry, perceived stress, and emotion suppression (Jazaieri et al., 2014; Wallmark et al., 2013). Among individuals with CP, compassion meditation is associated with reductions in psychological distress, pain severity, pain-related disability, pain-related anxiety and depression, and pain-related anger as well as increases in self-compassion, pain acceptance, and psychological flexibility (Chapin et al., 2014; Montero-Marín et al., 2018; Parry et al., 2017). A recent meta-analysis found that compassion meditation is associated with improvements in compassion, self-compassion, mindfulness, depression, anxiety, psychological distress, and well-being; these effect sizes were medium (Kirby et al., 2017). However, the majority of previous RCTs of compassion-based interventions were not conducted with clinical samples and did not include well-designed control conditions.

CBCT© (Cognitively-Based Compassion Training), a compassion meditation protocol, was developed in 2004 by Geshe Lobsang Negi, PhD (consultant) at Emory University. In healthy adults, CBCT has been associated with decreases in stress-related subjective and immune responses (Pary et al., 2017), enhanced empathic accuracy and related brain activity (Marasco et al., 2013), and brain activation in areas associated with empathy and positive affect (Engström et al., 2010). CBCT has also shown promise among various clinical samples. For example, CBCT was associated with reductions in depressive symptoms and suicidal ideation among suicide attempters (LoParo et al., 2018).

Rationale for the Present Application

The current study of compassion meditation for CP with psychological comorbidities is motivated by (1) a pressing clinical need, (2) a clear theoretical model (see Figure 1), and (3) initial evidence of its safety, feasibility and potential positive clinical effect for improving psychological *symptom severity* among Veterans (see **Preliminary Studies**). In short, compassion meditation is premised on cultivating mindfulness, positive emotion, and a sense of social connectedness. Mindfulness has positive effects on processes (e.g., pain catastrophizing) that may support recovery from chronic pain and psychological comorbidities. Positive emotion and social connectedness have been shown to enhance well-being both directly and indirectly through developing personal resources (Fredrickson, 1998, 2001). Compassion meditation is also thought to increase chronic pain acceptance while decreasing pain catastrophizing Chapin et al., 2014; Wren et al., 2012). The joint effect is predicted to be reduced psychological symptomatology, and improved chronic pain-related functioning and well-being.

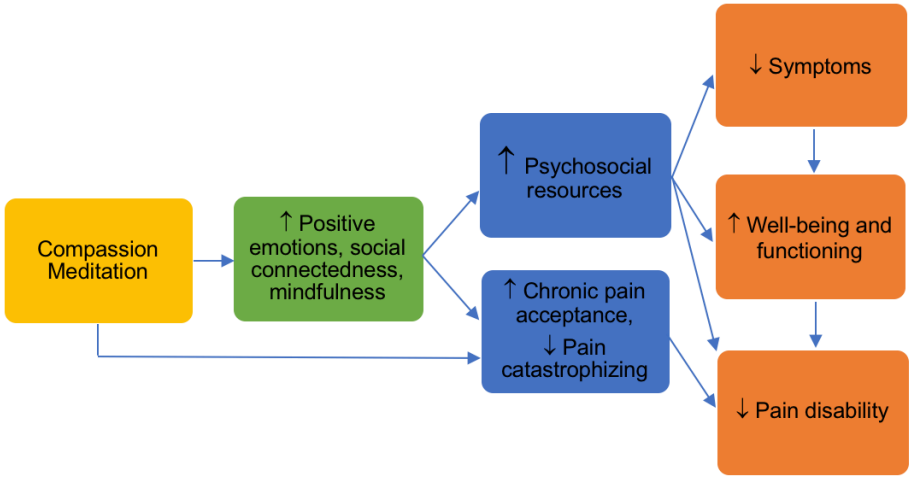


Figure 1. Theoretical model of recovery associated with CM.

Positive emotion. Contemporary viewpoints posit that positive

emotions are partially independent from negative emotions and can counteract the deleterious cognitive and physiological effects of negative emotions. The broaden-and-build theory describes the function of a variety of positive emotions, such as joy, contentment interest, and love (Fredrickson, 1998, 2001). This theory proposes that positive emotions broaden an individual's action tendencies (e.g., interest creates inspiration to explore), which is contrasted by the narrowed action tendencies associated with negative emotions (e.g., anger elicits the urge to attack). Although a narrowed thought-action repertoire may be adaptive in the face of threatening situations, the broadened mindset associated with positive emotions is beneficial in other ways. Namely, positive emotions spark creative and novel actions and foster social bonds, which thereby build up the individual's personal resources. Positive emotions have been associated with a) broadened cognitive and behavioral repertoires that can lead to openness to new ideas and greater psychological flexibility (Fredrickson et al., 2001); b) modifications in negative attentional biases (Smith et al., 2006); c) reductions in neuroendocrine, inflammatory, and cardiovascular activity (Steptoe et al., 2005); and d) enhancements in coping and resilience in the face of negative life events (Fredrickson, 2001; Moskowitz et al., 2012). For these reasons, the development of interventions promoting positive emotions is an important clinical need (Moskowitz et al., 2012).

It is well-established that CP is associated with persistent negative emotions, which can engender vulnerability to depression and other psychological comorbidities (Geisser et al., 2000), and diminished positive affect (Zautra et al., 2005). The broaden-and-build theory has been applied to contextualizing the potential role of positive emotion in CP (Finan et al., 2015). With a more flexible array of responses to challenging situations (including those presented by chronic pain), personal resources, including psychological resilience, social connectedness, and physical health, are enhanced. Among individuals with CP, positive emotions mediated the relationship between pain efficacy and pain interference (Park et al., 2010), and positive emotions mediated the relationship between psychological resilience and pain catastrophizing (Ong et al., 2006). Positive emotions may also buffer the impact of negative emotions on pain in part by downregulating the sympathetic nervous system (Strand et al., 2006). In addition, positive emotion may have important social impacts among individuals with chronic pain by increasing prosocial behavior (Smith et al., 2008).

There is some evidence that meditation practice, including compassion meditation, is associated with increases in positive emotion. For example, loving-kindness meditation, a meditative practice similar to compassion meditation, is associated with increased positive emotions and decreased negative emotions (Fredrickson et al., 2008; Hutcherson et al., 2008). Furthermore, in a neuroimaging study of individuals experienced in compassion meditation, the use of compassion meditation while viewing film clips depicting others in distress led to an increase in positive emotions, and was associated with activation of brain areas related to positive affect, affiliation, and reward processing (Engen et al., 2015). Our preliminary work similarly suggests increases in positive emotion with practice of compassion meditation among Veterans with PTSD (see **Preliminary Studies**).

Social Connectedness. Social connectedness, or belongingness, is associated with better psychosocial functioning, including reduced anxiety and greater self-esteem (Lee et al., 1998) and reduced pain perceptions among individuals with chronic pain (Holtzman et al., 2004). There is some evidence that social connectedness may be protective against stress and psychopathology (Cacioppo et al., 2006). Furthermore, a lack of social connectedness has been found to be an independent predictor of suicidal ideation among individuals with CP, while conversely, perceived social support mitigates risk (Shim et al., 2017). Compassion meditation may offer an avenue for increasing social connectedness. For example, loving-kindness meditation was associated with more positive reactions to others (Hutcherson et al., 2008). Similarly, in an RCT of CBCT vs. health discussion control group, compassion meditation practice was linked to increased empathic accuracy and the activation of related brain circuitry (Mascaro et al., 2013). Consistent with this, data from our pilot study showed a meaningful increase in social connectedness and empathy associated with practice of compassion meditation but not a relaxation control (see **Preliminary Studies**).

Mindfulness. Mindfulness, which has been defined as "paying attention in a particular way: on purpose, in the present moment, and non-judgmentally" (Kabat-Zinn, 1994), is a cornerstone of meditation practice. Mindfulness has been associated with diminished physiological arousal, increased attentional control, and increased acceptance of difficult experiences (Lang et al., 2012). One study found that mindfulness meditation led to modest improvements in PTSD (small ES) and depressive symptoms among Veterans with PTSD (Polusny et al., 2015). However, meta-analyses suggest overall small treatment effects (Bawa et al., 2015; Hilton et al., 2017). There is some evidence that formal mindfulness meditation confers benefits for CP

conditions (la Cour et al., 2015), while other studies have found no improvement in pain-related functioning (Serpa et al., 2014). At this time, there is mixed evidence for the efficacy of mindfulness-based interventions for reducing anxiety, depressive, and PTSD symptoms, and there is general agreement that formal mindfulness meditation holds promise as a CP intervention, but there is insufficient evidence and a dearth of high-quality studies to support its efficacy (Bawa et al., 2015). Furthermore, there is some indication that different types of meditation (e.g., mindfulness, compassion meditation) may confer different benefits (Lang et al., 2012).

Pain catastrophizing and pain acceptance. Pain catastrophizing has been described as "the tendency to increase attentional focus on pain-related thoughts, to exaggerate the threat value of pain stimuli, and to adopt a helpless orientation to coping with pain situations" (Edwards et al., 2011). There is considerable evidence of the association between pain catastrophizing and pain severity and disability (McCracken et al., 2004). Compassion meditation may provide opportunities for reducing pain catastrophizing. For example, self-compassion has been associated with reduced pain catastrophizing and pain disability among individuals with CP (Wren et al., 2012). Chronic pain acceptance includes the reduction of unhelpful attempts to resist, avoid, or control pain and focus on the pursuit of personally relevant goals (McCracken et al., 2003). Pain acceptance is predictive of pain severity and disability as well as pain-related anxiety and depression (McCracken et al., 2003). There is some evidence that compassion meditation may promote pain acceptance (Chapin et al., 2014), particularly through its emphasis on non-judgmental awareness and self-compassion.

Significance and Relevance to VA and Improving Veteran Health

Psychological comorbidities among Veterans with CP are prevalent, and yet treatment of these problems is often fragmented, and current treatment approaches fail to result in meaningful improvements in both domains. This application challenges and seeks to shift current VA clinical practice paradigms from extant disorder-specific treatments to integrative interventions that target both psychological comorbidities and chronic pain functioning. Accordingly, the aims of this project are to test the efficacy of a novel intervention for psychological comorbidities in CP, which are common and costly problems among Veterans presenting for care at the VA. Development of new treatments and best practices for Veterans with CP with psychological comorbidities is critical because not all Veterans receive or benefit from current psychotherapeutic or pharmacological interventions. If effective, the compassion meditation for CP with psychological comorbidities protocol described in this proposal would offer an alternative treatment approach for Veterans, which is well-aligned with the VHA's strategic goal of implementing complementary and integrative health approaches to improve mental health and manage chronic pain (DVA, 2014). Compassion meditation could ultimately be applied in a number of ways. The skills developed in compassion meditation may help to build the resources necessary to fully engage in other evidence-based, disorder-specific treatments, such as trauma-focused therapy, which can be emotionally challenging. Compassion meditation may be a good way to enhance functioning following treatment, e.g., helping to rebuild one's social network or engage in reinforcing activities, which support improvements in quality of life and well-being. Compassion meditation could also be an alternative to other interventions for individuals who respond very favorably. The proposed research project represents a unique opportunity to improve treatment and lead to reduced psychological symptomology, improved functioning, and increased well-being among Veterans, furthering the VA's commitment to improving the mental health, well-being, and quality of life of Veterans detailed in the 2018-2024 VHA Strategic Plan (DVA, 2014). An improvement in mental health functioning and a reduction in CP disability promises to reduce the healthcare and societal costs associated with CP, which have an economic burden of $600 billion annually in the U.S. alone. In sum, empirically evaluating this program through the support of this award will provide data that could greatly enhance Veteran mental health care, reduce associated costs, and provide the essential foundation for later VA grants examining multi-site efficacy.

Novelty and Significance of a Complementary and Integrative Health Approach to Psychological Comorbidities in CP

The proposed research plan aims to directly address three notable limitations within the current state of CP with psychological comorbidity treatment research. These include: 1) the need to identify methods to improve concerningly high partial and non-response rates of even the most effective CP and disorder-specific psychological treatments; 2) limited availability of integrative treatments addressing both psychological comorbidities and chronic pain disability, which often do not improve with disorder-specific treatment; and 3) paucity of adequately-powered, well-designed, controlled trials of meditation approaches, particularly among Veterans.

Among Veterans with both psychiatric condition(s) and CP, addressing these inter-related problems with a complementary and integrative health approach (compassion meditation), represents a logical, integrative, innovative, and empirically-informed method for augmenting existing treatments and optimizing symptom reduction and functional outcomes. Integrative treatment for CP with psychological comorbidities has the potential to benefit Veterans by: 1) allowing patients to address both psychiatric condition(s) and chronic pain disability within a shortened timeframe, 10 weeks, versus ~24 weeks if disorder-specific treatments were offered sequentially; 2) increasing continuity by allowing patients to work with a single provider; 3) simultaneously addressing psychiatric condition(s) and CP, which influence each other, reducing the likelihood that the untreated disorder can worsen the treated disorder (Outcalt et al., 2015; Turner et al., 2007); and 4) decreasing the risk of attrition between referral clinics and waitlists. An integrative treatment for psychiatric condition(s) and CP disability could thereby diminish clinicians' frustrations due to low engagement and poor outcomes in disorder-specific treatments while increasing treatment efficiency and Veterans' satisfaction with their care.

Diverse meditation techniques are currently being applied to ameliorate mental and physical health problems, but these techniques may not be interchangeable; different meditation practices may impact different psychological processes (Lang et al., 2012). The proposed project aims to improve both pain-related impairment and psychological comorbidities among Veterans with chronic pain, a goal that has largely remained elusive with existing treatment approaches. This proposal focuses on compassion meditation based on a clear theoretical model and empirical evidence of its relevance to this commonly comorbid set of symptoms. We suggest that CBCT-CP+ may be particularly useful in recovery from psychological comorbidities and chronic pain because it is believed to affect psychological processes, namely positive emotion, social connectedness and mindfulness, which are highly relevant to chronic pain and its common comorbidities (e.g., depression and PTSD) and are not the primary target of current empirically-supported approaches. Furthermore, unlike extant psychotherapies (e.g., CBT), which generally focus on symptom reduction, our compassion meditation for psychological comorbidities and CP may also facilitate improvements in life satisfaction and overall well-being.

PRELIMINARY STUDIES

Study 1a: Compassion Meditation Development and Refinement

We recently published our findings from a completed NCCIH R34 "A Proof of Concept and Feasibility Trial of Compassion Meditation for PTSD" (PI: Lang, primary mentor for this proposal; Lang et al., 2017, 2019). Thirty Veterans enrolled in the first phase of the study in which we iteratively refined CBCT© (see **Treatment Overview**) to meet the needs of Veterans with PTSD, thus creating CBCT-Vet (Lang et al., 2017). Study enrollment, treatment initiation, and treatment completion demonstrated feasibility of recruitment. A majority of the Veterans referred to the study were eligible and consented to treatment (82% enrollment rate); however, five of the enrolled Veterans did not begin the intervention (31/36 or 86% initiation rate). Twelve Veterans did not complete treatment (<7 sessions; 19/31 completed treatment or 61% per protocol initiation rate). Participants generally cited logistical reasons for not completing the group (i.e., surgery, moving, untenable commute, family emergency), although two stated that the group did not meet their expectations. Treatment credibility and satisfaction ratings indicated acceptability of the treatment among Veterans. Credibility questions were rated on an 8-point scale, with higher numbers indicating greater credibility; average credibility ratings among treatment completers ranged from 6.14–6.29. The average Client Satisfaction Questionnaire (CSQ-8) score was 25.5 (SD = 4.0, range 12–29, instrument range 8–32). Finally, Veterans reported moderate to high adherence with assigned meditation practice, ranging from 53-89% of assigned practice.

Study 1b: Phase 2 Compassion Meditation Proof of Concept and Feasibility

In the second phase of this project, we conducted a randomized controlled pilot study[69] with 37 Veterans. This study further demonstrates the feasibility, safety, and clinical promise of our compassion meditation intervention (CBCT-Vet). A majority of the Veterans referred to the study were eligible and consented to treatment (37/45 or 82% enrollment rate); however, nine of the randomized individuals did not begin the intervention (28/37 or 76% initiation rate). Seven additional Veterans dropped out within the first half of the intervention, which is prior to what we defined a priori as a meaningful treatment dose (21/28 or 75% per protocol initiation rate, or a 21/37 or 57% completion rate among the intent-to-treat (ITT) group). Credibility, attendance, homework compliance, and satisfaction demonstrate feasibility of both CBCT-Vet, and the relaxation-based comparison group, Veteran.calm (VC). Specifically, the average attendance rate was 70%;

attendance did not differ by group (73% in CBCT-Vet and 67% in VC, F(1,26) = 0.2, ns). Participants in both groups demonstrated adherence to daily at-home practice; CBCT-Vet participants completed an average of 75.5% of assigned meditation practice (SD = 53.0%; M = 634.1 minutes, SD = 444.9), while VC participants completed an average of 49.6% of assigned relaxation practice (SD = 36.8%; M = 416.5, SD = 309.1, F(1, 26) = 2.26, p = 0.15). Finally, client satisfaction was measured with the CSQ-8; CSQ-8 scores range from 8 to 32, with higher scores indicating greater satisfaction. Satisfaction among Veterans was highly similar across groups, with an average CSQ-8 score of 24.6 (SD = 3.7) in CBCT-Vet and 26.4 (SD = 3.0) in VC, F(1,22) = 0.21, ns.

Figure 2. Change in CAPS-5 from baseline to posttreatment

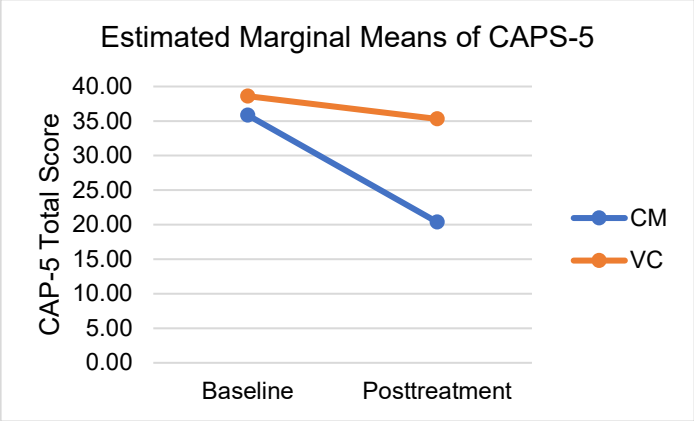
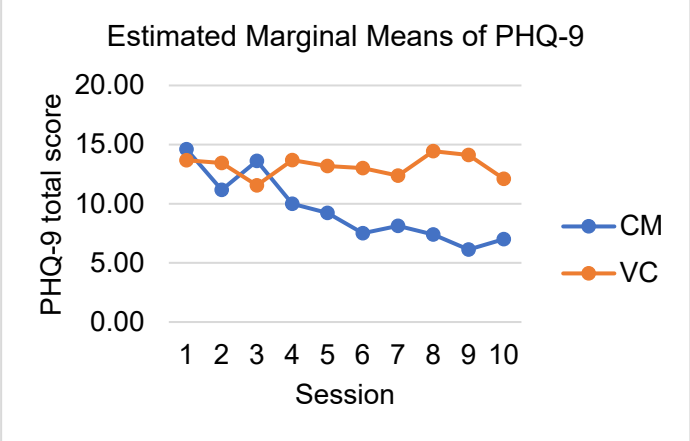


Figure 3. Weekly changes in PHQ-9



Although there are limitations to interpreting effect sizes (ES) based on a pilot study of this size, we find them to be a useful in understanding the potential clinical impact of the interventions; selected within group Cohen's d effect sizes are presented. Figure 2 shows a clinically meaningful reduction in the CBCT-Vet group in average PTSD symptom severity as measured by the CAPS-5 (~15 points; d = 1.10, large ES), whereas such change was not observed in the VC group (~2 points, d = 0.27, small ES). Similarly, the CBCT-Vet group appears to have a steeper downward trajectory in the weekly clinical measure, the Patient Health Questionnaire (PHQ-9; see Figure 3).

In addition, there was a modest improvement in psychosocial functioning in both groups as measured by the item average on the Sheehan Disability Scale (CBCT-Vet mean change of 1.7 points, d = 0.56, medium ES; VC mean change of 1.4, d = 0.53, medium ES). Based on this set of initial findings, we concluded that CBCT-Vet shows sufficient clinical promise to merit further examination. Consistent with predictions based on the Broaden-and-Build model, CBCT-Vet appears to have led to modest increases in positive emotion; however, these increases were no larger than those seen in relaxation condition. Also consistent with our expectations, CBCT-Vet appears to have led to substantial increases in social connectedness (large ES) and empathy (medium ES); these changes were not observed in VC group. Likewise, in the CBCT-Vet group alone, mindfulness increased (medium ES). Finally, self-compassion notably remained relatively unchanged in both groups (See Table 1). These findings suggest the clinical promise of CBCT as the intervention appears to be impacting Veterans in the theorized manner.

Table 1. *Mean (SD) Scores from Baseline to Posttreatment*

Measure	Baseline		Posttreatment		Within group Cohen's d	
	CM	VC	CM	VC	CM	VC
Positive Emotion (mDES)	16.5 (9.5)	17.8 (6.8)	19.8 (11.1)	22.8 (10.7)	**-0.32**	**-0.56**
Social Connectedness (SCS-R)	55.1 (14.0)	63.5 (14.2)	72.6 (17.9)	63.1 (15.6)	**1.09**	-0.03
Empathy (TEQ)	38.1 (10.8)	42.7 (6.2)	43.6 (10.1)	42.7 (10.2)	**0.53**	0.00
Self-compassion (SCS-SF)	37.1 (6.2)	39.1 (5.1)	37.3 (3.0)	37.6 (3.8)	0.04	**-0.33**
Mindful Awareness (PHMS)	35.1 (6.0)	34.4 (5.3)	38.4 (6.3)	33.4 (3.6)	**0.53**	-0.20
Mindful Acceptance (PHMS)	25.7 (7.4)	24.2 (8.1)	27.7 (8.3)	23.7 (8.2)	0.25	0.06

In studies 1a and 1b, we delivered CBCT-Vet to 50 Veterans with PTSD. In these phases, there were three adverse events, two of which were unrelated to the protocol (back injuries) and one that was probably related

(uncomfortable internal sensations during group 1). Together, we believe these studies provide evidence of the safety and feasibility of a randomized controlled trial evaluating the efficacy *of* CBCT-Vet , and they are promising in terms of the ultimate clinical impact.

Study 1c: Secondary Analyses of Pain Data from Compassion Meditation Pilot Study

We conducted a secondary analysis of pain data from Study 1b. Participants completed pre- and posttreatment evaluation of PTSD, depression, pain severity and interference. Although CBCT participants experienced a significantly greater reduction of PTSD and depressive symptoms than control participants, there were no group differences in changes in pain severity or interference. It is important to note that this particular sample was not selected for chronic pain. In fact, only one-third of participants had pain severity and interference levels consistent with chronic pain populations, and the duration of reported pain is unknown. This work was the basis for the iterative pain-specific augmentations of CBCT-Vet for this project.

Study 2: CBCT-CP+ Protocol Refinement and Open-Label Pilot Study

We further refined the CBCT-Vet protocol described in Study 1. We developed CBCT for chronic pain and psychological comorbidity (CBCT-CP+). While maintaining the core interventions from our initial feasibility and pilot study, we added CP-related didactics, including the rationale for compassion, pain-specific instructions for meditation, applications of non-judgmental awareness and self-compassion to managing chronic pain, simplified language, and streamlined materials to allow Veterans with both psychological comorbidities and CP to better engage with the active ingredients (see **Treatment Overview**). We conducted an initial pilot study to explore our novel intervention, inform feasibility, and identify additional modifications needed for a subsequent larger, adequately-powered efficacy study; we are unable to provide meaningful estimates of effect size from this small pilot sample (Leon et al., 2011).

We completed one CBCT-CP+ pilot group, consisting of 10 weekly, 90-minute group sessions. The attrition, attendance, credibility, and satisfaction of CBCT-CP+ in this initial nonrandomized pilot were similar to those seen in the CBCT-Vet randomized pilot study. Of the 5 Veterans who were enrolled in our CBCT-CP+ pilot study, 4 completed treatment (20% attrition rate) with an average attendance of 7.5 out of 10 sessions among treatment completers (75% attendance rate). Satisfaction in the pilot group was high (CSQ-8 M = 23, SD = 3.2) and similar to the treatment satisfaction observed in the CBCT-Vet randomized pilot study (CSQ-8 M = 24.6, SD = 3.7). In terms of credibility, which was completed after session 1, Veterans found CBCT-CP+ to be credible, and credibility of CBCT-CP+ was similar to that of CBCT-Vet (item 1, “How logical does this approach seem to you for helping people to manage chronic pain with mental health symptoms?” M= 5.8, SD =1.30 vs. M = 5.9, SD = 1.6 in CBCT-Vet; item 2, “How confident are you that this approach will help you function better?” M= 4.4, SD = 2.3, vs. M = 6.2, SD = 1.2 in CBCT-Vet; item 3, “How successful do you feel this approach will be in helping you to deal with your chronic pain with mental health symptoms?” M = 5.0, SD = 1.6 vs. CBCT-Vet, M = 5.8, SD = 1.8; and item 4, “How confident would you be in recommending this approach to a friend with similar problems?” M = 4.6, SD = 2.3 vs. CBCT-Vet, M = 6.4, SD = 1.5).

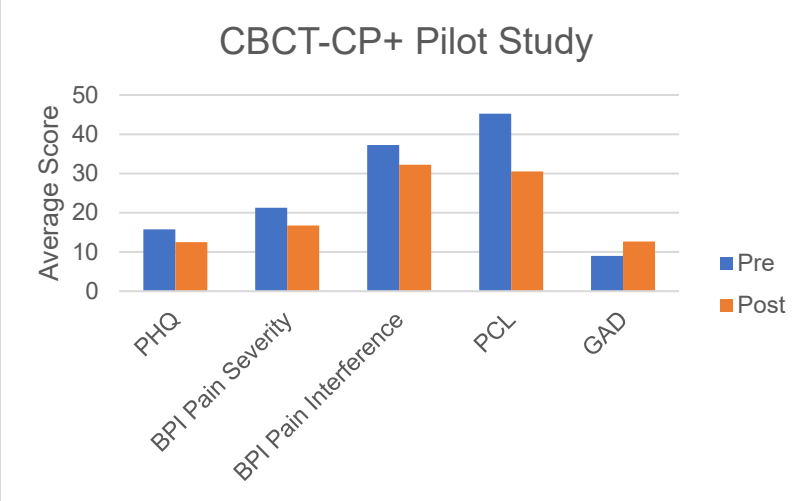


Figure 4. Pre- to posttreatment changes in CBCT-CP+ pilot

As shown in Figure 4, Veterans completing CBCT-CP+ evidenced pre- to posttreatment improvements in depressive symptoms (PHQ-9), pain severity (BPI), pain interference (BPI), and PTSD symptoms (PCL). Given the small sample size of this initial open-label pilot study, we are unable to compute inferential statistics. However, these initial findings are in line with our expectations, and similar to the results seen in CBCT-Vet randomized pilot study. We enrolled a second pilot group in March of 2019 (N = 7). However, this group had to be discontinued due to staffing issues. Our ability to continue enrolling Veterans to our CBCT-CP+ pilot study further demonstrates the feasibility of our recruitment and enrollment strategies.

Veterans were consulted regarding the design of the assessment procedures and interventions using formal (e.g., survey feedback; open-ended qualitative feedback) and informal strategies (e.g., verbal feedback shared with instructors and research assessors; spontaneous comments from homework journals) throughout Studies 1A, 1B, and 2. Input from Veterans as well as other VHA stakeholders (CBCT-CP+ instructors, other VHA healthcare providers) and subject experts (mentors and consultants) has been incorporated into ongoing refinements to the CBCT-CP+ manual (see **Description of Interventions**).

Other Randomized Controlled Trials at the VASDHS

Several chronic pain outcome studies have been completed at the VA San Diego Healthcare System (VASDHS). Specifically, an RCT comparing Acceptance and Commitment Therapy to CBT for chronic pain in a group format, and a non-inferiority trial comparing in-person to video-teleconferencing delivery of Acceptance and Commitment Therapy for CP, involved my primary mentor (Dr. Lang) and co-mentor (Dr. Afari) and share some similarities with the current application. Recruitment, retention, and sample characteristics for these studies (see Table 2) provide confidence that recruitment targets will be met in the present application.

Table 2. *Recruitment, retention, and sample characteristics of two RCTs completed at the VASDHS*

Study	Recruitment Dates	Total # assessed	Total # eligible	Total # randomized	Age M(SD)	Sex (% male)	Total # attrition	*Psychological Comorbidities*
ACT vs. CBT	Jan. 2007-Dec. 2008	N = 336	N = 129	N = 114	54.9(12.5)	49.0%*	N = 29	N = 61
IP vs. VTC ACT	April 2010-April 2013	N = 319	N =149	N = 129	52.0(13.3)	82.2%	N = 44**	N = 34***

Note: ACT= Acceptance and Commitment Therapy; CBT= CBT for Chronic Pain; IP= in-person; VTC= video teleconferencing; *Study included Veterans and civilians; **Majority of attrition was in VTC group (n = 29); ***Only assessed for PTSD.

Conclusions and considerations from preliminary studies

Several conclusions can be drawn from our preliminary work that supports the proposed application. First, Studies 1a and 1b demonstrate feasibility and acceptability of CBCT-Vet for Veterans with PTSD and indicate initial promise of the clinical benefit of CBCT for reducing psychological symptom severity among Veterans. Data from Study 1b provides preliminary support for the proposed theoretical model; namely, CBCT increases mindfulness, social connectedness, and positive emotion. Although the original CBCT-Vet did not meaningfully impact pain (Study 1c), our initial pilot study of our refined protocol, CBCT-CP+, suggests that we are now engaging this target following modification for this sample (Study 2); our initial findings are bolstered by the evidence from other trials supporting the efficacy of compassion-based interventions for reducing pain disability (Carson et al., 2005; Montero-Marín et al., 2018). Our study recruitment and retention rates (Studies 1a, 1B, and 2) were similar to other studies of meditation (Montero-Marín et al., 2018) interventions in chronic pain samples (~20-30% attrition). Our experiences from other RCTs of CP interventions at the VASDHS provide further support the feasibility of recruitment and retention in the proposed study and suggest that many Veterans seeking CP treatment present with distress associated with psychological comorbidities, especially depressive disorders and/or PTSD. A logical next step is to test the efficacy of CBCT-CP+ compared to an attention-matched, psychoeducation condition, Health Education while Living with Pain (H.E.L.P.), among Veterans living with chronic pain and psychological comorbidities.

RESEARCH DESIGN AND METHODS

This proposed project consists of a Phase II randomized controlled trial comparing CBCT-CP+ to H.E.L.P., which will set the stage for a multi-site efficacy trial. As depicted in Figure 1, there is a compelling theoretical model for application of compassion meditation to psychological comorbidities in chronic pain patients, and our initial trial results (see **Preliminary Studies)** suggest its feasibility and acceptability and show promise in terms of clinical impact. Thus, this project is designed to examine the clinical efficacy of our refined treatment protocol and to provide data to support an application for a VA Merit Award to execute a large-scale, multi-site efficacy trial. The execution of this trial relates directly to my overarching career goal of becoming an

applied intervention researcher in the management of CP and psychological comorbidities, especially PTSD and depression.

Study Setting. This project will be executed at the VASDHS.

Recruitment. Potential participants will be recruited using standardized strategies that were successful in previous trials of Drs. Lang and Afari, particularly referral by VA mental health and behavioral medicine clinicians and advertisement in the VA and surrounding community. Potential participants will be recruited primarily from the Behavioral Health Interdisciplinary Program (BHIP), Behavioral Medicine (BMed), Primary Care Mental Health Integration (PCMHI), and PTSD clinics at the VASDHS. Based on communication with these clinics and our previous studies, we anticipate approximately 10-15 study referrals per month. If need be, we may also recruit from the Pain Clinic/ Anesthesiology, Physical Medicine and Rehabilitation, Spinal Cord Injury Unit, and other studies. Veterans referred to our study will be informed about the study; study personnel will describe eligibility criteria via telephone (see **Inclusion and Exclusion Criteria**), and Veterans will be given an overview of the study. Veterans who express interest in participating in the study will be invited to the VASDHS for evaluation of eligibility and pre-treatment assessment.

Participants. The study population is US Veterans with chronic pain conditions with psychological comorbidities (depressive disorder and/or PTSD). One-hundred and sixty-eight such Veterans will be recruited from the VASDHS with the goal of randomizing 126 participants to one of two treatments. We have accounted for ineligibility/non-initiation rate of 33% (n = 42), which is a conservative estimate based on other clinical trials at the VASDHS with similar inclusion/exclusion criteria (11-12% ineligibility/non-initiation rate after in-person eligibility assessment; Herbert et al., 2017; Wetherell et al., 2011).

Sample size: The power analysis was performed using G*power statistical software. The target N was chosen based on the power estimations for an intent-to-treat design, which suggest that n = 63 per group (N = 126) are needed to ensure adequate power (80%) to test significant between-group effects on co-primary outcomes (α_1 = .025; α_2 = .025) 1) pain disability and 2) severity of comorbid mental health symptoms, (d = .8) accounting for a 25% post-randomization attrition rate by 3-month follow-up assessment and accounting for nested data (Moerbeek et al., 2003; van Breukelen et al., 2012). An effect size of d = .8 for changes in pain disability is a conservative estimate based on a previous study of a compassion-based intervention vs. relaxation control in a CP sample, which yielded large between groups effect sizes on pain disability (pre- to posttreatment change d = .1.13 and pre-treatment to follow-up changes d = 1.18). An effect size of d = .8 for changes in psychological symptom severity is a conservative estimate based on 1) a previous study of a compassion-based intervention vs. relaxation control in a CP sample, which yielded large between groups effect sizes [pre- to posttreatment change in severity of psychopathology (CGI-S, d = .96; HAM-D, d = .94) and pre-treatment to follow-up changes in severity of psychopathology (CGI-S, d = 1.14; HAM-D, d = 1.01)] (Montero-Marín et al., 2018); and 2) our previous study of compassion meditation vs. VC (relaxation control) for Veterans, which yielded large between groups effect size (CAPS-5 PTSD symptoms severity, d = .85; Lang et al., 2017). We do not have a good estimate for the correlation coefficients of pre- and posttreatment outcome measures, so we have conducted a conservative estimate of power without adjusting for correlation coefficients. We do not have a good estimate of the intra-class correlation (ICC) in order to calculate the Variance Inflation Factor (VIF; the number that indicates how much the sample size should be adjusted due to clustering; Moerbeek et al., 2003). Although our previous study yielded non-significant group level treatment effects (Lang et al., 2019), we have still accounted for the nesting within our data; we estimated our effective sample size using a small ICC. We will conduct 16 groups (8 CBCP-CP+ and 8 H.E.L.P.) with 6 - 10 Veterans in each group (year 1 = 1 group, year 2 = 5 groups, year 3 = 5 groups, year 4 = 5 groups). Anticipating up to a 33% rate of non-eligibility and a 25% attrition rate post-randomization, 168 participants will be recruited. We will conduct exploratory analyses on changes in primary and secondary outcome measures at 6-month follow-up assessment; although these analyses will likely be underpowered, these analyses will provide preliminary data for subsequent longer-term efficacy trial(s).

Inclusion and Exclusion Criteria. Criteria for inclusion include (1) Veteran status, (2) age 18 or greater, (3) able to consent, and (4) diagnosis of a chronic, non-terminal pain condition (per medical chart and/or self-report), (5) pain most days (> 3 days/week) for at least 6 months (per self-report), (6) average pain severity and interference with enjoyment of life and/or general activity rated ≥ 4/10 over the past week (as measured by the PEG; Krebs et al., 2009), and (7) probable diagnosis of depression and/or PTSD based on

the Mini International Neuropsychiatric Interview (MINI 7.0; Sheehan et al., 1998). The following are criteria for exclusion: (1) serious suicidality or homicidality that has required urgent or emergent evaluation or treatment within the past three months or a suicide attempt within the past year, (2) a known, untreated substance abuse or dependence problem (inclusion is possible if there is evidence that the individual has been afforded and is complying with treatment for the substance problem), (3) untreated/unstable serious mental disorders, such as psychotic disorders or bipolar disorder, or serious dissociative symptoms, (4) cognitive impairment that would interfere with treatment, and (5) concurrent enrollment in any other treatment specifically targeting chronic pain, anxiety, depression, or PTSD symptoms or social functioning (e.g., couples therapy) or any meditative or mind-body intervention (e.g., mindfulness, yoga). Participants can continue current pharmacological treatment provided they have stabilized on medication, i.e., no additional treatment response is expected, and no changes are anticipated during the study period. Concurrent supportive or nonspecific therapy is permitted as well provided that they have been attending for at least a month and expect to continue throughout the study. Inclusion/exclusion criteria were determined using procedures similar to those that Drs. Lang and Afari have implemented in their past studies and are based on IMMPACT consensus meeting recommendations and a review of empirical findings from chronic pain trials (Dworkin et al., 2010). A HIPAA waiver will be obtained so that the research assistant will be able to access potential participant's computerized medical records to check eligibility for the study, particularly for inclusion criteria and exclusion criteria documented in their chart.

Inclusion criteria 1 – 3 are standard inclusion criteria for clinical trials within the VASDHS. Inclusion criteria 4 – 6 are consistent with previous chronic pain trials at the VASDHS to include Veterans with a range of chronic pain conditions and etiologies in order to ensure maximum generalizability. Criterion 6 is included to ensure pain is significantly interfering in the lives of our sample and therefore are suitable for an intervention designed to improve pain-related functioning. Inclusion criterion 7 targets common psychological comorbidities. We also aim to develop an intervention that will give Veterans access to patient-centered, integrative, and comprehensive care that targets both mental health symptoms and CP functioning. Inclusion criteria 2, 4, 5, 6 are based on IMMPACT consensus meeting recommendations (Dworkin et al., 2010). Furthermore, the inclusion of individuals with psychological comorbidities (inclusion criteria 7) may make results more generalizable to chronic pain populations, where such comorbidities are prevalent (Dworkin et al., 2010).

The purpose of the exclusion criteria 1 – 4 is to ensure that participants are not affected by serious or uncontrolled factors that will hinder functional improvement and pose a potential barrier to their own or others' participation in a group format. In cases of ambiguity around exclusion or inclusion criteria (e.g., psychosis properly managed), the potential participant's primary care or mental health provider will be contacted, after consent is acquired, to determine appropriateness for study participation. Veterans who report serious suicidality or homicidality that has required urgent or emergent evaluation or treatment within the past three months or have a history of suicide attempt within the past year will be excluded. Suicidality will be assessed biweekly via self-report measures. Patients who require immediate treatment for suicidality or another mental health condition will be withdrawn from the study and referred for such care. Exclusion criterion 5 is required in order to assure that study results can be interpreted as due to the interventions provided in the study. Therefore, current participation in another group or individual psychotherapy will be exclusionary. In addition, participants who have recently started, stopped, or changed any professionally-delivered pain or psychotropic medication treatment will be ineligible to enroll until their treatment has been stable for one month. Unless medically necessary, patients will be requested to keep all treatments stable for the 10-week duration of the study. Chronic opioid users will be included in the proposed project; current opioid misuse will be assessed throughout the study (see **Measures)**. Exclusion criteria 1-4 and the inclusion of subjects using concurrent medications as based on IMMPACT consensus meeting recommendations to promote patient safety and increase generalizability of findings (Dworkin et al., 2010).

Participant retention. The proposed study's retention strategies have been informed by recommendations in the literature and by the mentorship team's own experience running similar RCTs.

Tracking, General Contact, Check-ins: Multiple strategies by the investigator, research assistant, and study therapists will be used to ensure high participant retention. During the initial screening assessment, a Locator Form will be completed for each participant that includes: (1) home address, (2) email address, (3) home/work/cell phone numbers, (4) employment or school information, and (5) contact information for two additional individuals to be used if contact with the participant is lost. Tracking information will be collected and updated at all follow-up interview points.

We will implement the following strategies to promote retention: 1) session 0 will help assess a participant's expectations of treatment, goals for treatment/reasons for engaging in treatment now, and

motivation for treatment. This session will also help to anticipate any barriers to session attendance and treatment engagement; 2) Study personnel will provide a reminder call and/or text message for each group session; 3) Participants will be assisted with applying for transportation reimbursement, if desired; 4) Participants will be offered treatment in the clinic location based on demand and preferences; 5) Prior to session 1, study staff will assist participants in setting up calendar reminders or planner appointments; 6) We will facilitate bonding among each cohort by encouraging participants to relate to one another regarding the challenges of learning new mind-body approaches; 7) Therapists will be trained to discuss missed sessions and incomplete homework with participants by phone and in-person to increase protocol adherence; 8) A reminder call will be placed the day prior to participants' scheduled in-lab assessments; 9) Research staff will mail a reminder to participants one week prior to their follow-up appointment. 10) To increase chances of completing assessments, we will offer Veterans the opportunity to schedule for a time they are already coming to the VA for an appointment.

Financial Incentives: Participants will receive a payment for the pre-treatment assessment, mid-treatment assessment, posttreatment assessment, 3-month follow-up, and 6-month follow-up, receiving $50 on each occasion. Participants will receive a one-time bonus payment of $50 for completing all five assessments.

Data Collection Procedures. Data will be collected at baseline, mid-treatment (before session 6), weekly throughout active treatment, posttreatment (1 week after session 10), 3-month follow-up, and 6-month follow-up assessments (See Figure 5, Study Flow Diagram). The research assistant will administer self-report questionnaires and will oversee all assessment visits. The study assessor will administer clinical interviews/ratings at pre-treatment, posttreatment, and 3- and 6-month follow-up visits and may assist with other baseline data collection. Both the research assistant and the study assessor will be blind to treatment condition during baseline assessment visit (randomization will not yet have occurred), and the study assessor will remain blind.

Consenting Protocol: Interested participants will be offered participation in an IRB-approved research protocol for the treatment of CP with psychological comorbidity. The voluntary nature of the study will be emphasized. Veterans will first provide written informed consent and HIPAA authorization. If participants choose not to participate in the study, referrals will be provided.

Baseline Assessment (2-3 hours): After consenting, participants will undergo in-person screening to confirm eligibility and complete baseline measures (see **Measures**).

Therapy Expectations Session. Prior to randomization, all participants will attend the Therapy Expectations Session. The goals of this session are to 1) identify reasons for coming into treatment at this time, 2) identify goals of engaging in treatment, 3) learn about expectations of the treatment and overview of the treatment process, 4) identify and discuss any barriers to treatment, and 5) assess for appropriateness of moving forward within the study.

Randomization. Following therapy expectations session, eligible participants will be randomized to one of two conditions by Dr. Lin Liu, biostatistical consultant: compassion meditation (CBCT-CP+) or a health and wellness psychoeducation control condition (H.E.L.P.; refer to **Description of Interventions**). We propose that group randomization be used in this trial, recognizing that there are significant advantages and disadvantages to this approach. The biggest advantage of group randomization is that it reduces wait times for study participants. In practice, individual randomization requires that 12 - 20 participants be enrolled within approximately a month, which is an aggressive target even in our busy facilities. In our previous experience, if participants are asked to wait longer than a month to begin, we observe rapidly increasing attrition. In addition, heavy recruitment for a month followed by no recruitment for 2 - 3 months hinders clinician referrals because the program is not a regular offering within the clinics. With group randomization, on the other hand, a new group can begin once 6 - 10 patients are enrolled. This practice supports a high initiation rate among those who enroll and more consistent referrals to the study. One disadvantage of group randomization is that staff will be aware of the condition of the final 1 - 2 groups. Anticipating this issue, we will take steps to ensure that the behavior of the recruitment staff remains constant even if the condition is apparent (e.g., providing scripts).

The target sample size is 126 (see **Participants**); participants will be assigned to 16 groups with 6-10 patients per group. A randomization list for 16 groups will be generated and groups will be randomly assigned to CBCT-CP+ or H.E.L.P. in a 1:1 ratio. The randomization list will be generated using a block randomization with block sizes of 4 such that the sample size will be balanced after every 4 groups are recruited.

Weekly Assessments (10 minutes): The participant will complete brief self-report assessments prior to the start of each group session (10 weeks). These assessments will measure changes in symptoms and suicidality, as is standard clinical practice in the VA (see **Measures**).

Mid-Treatment: Participants will complete self-report measures only before session 6 (0.5 hours).

Posttreatment and 3-month Follow-up Assessment (1.5-2 hours): At each time point, participants will return to the investigative clinic to complete the same battery of clinical assessments given during the baseline evaluation (other than eligibility measures).

6-month Follow-up Assessment (1.5 hours): Participants will complete assessment of primary and secondary outcomes only.

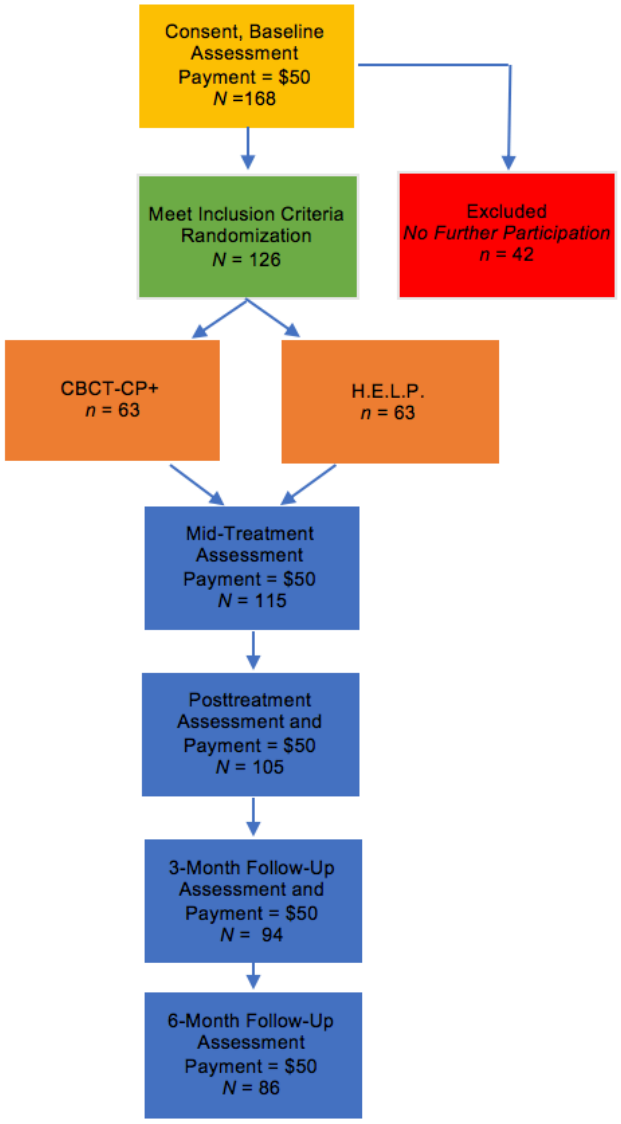


Figure 5. Study flow diagram

Treatment Overview, Training, and Fidelity

Treatment Overview.

CBCT-CP+. Our compassion meditation for CP with psychological comorbidity protocol (CBCT-CP+) is a modified version of Cognitively-Based Compassion Training (CBCT). CBCT is comprised of a set of meditative practices that aim to increase compassion. We developed a Veteran version (CBCT-Vet) in the first phase of Dr. Lang's R34 (Lang et al., 2017). CBCT-Vet consists of 10 weekly, 90-minute group sessions, which are reinforced by daily guided meditation recordings. Group-based meditation training can be informative and validating by providing opportunities for discussion and sharing similar experiences and frustrations. Each CBCT session begins with a review of homework and previous topics (15 – 30 minutes), includes experiential exercises and discussions of a treatment topic (30 – 45 minutes), and closes with a formal seated meditation practice (6 – 15 minutes). Meditation skills are taught in an iterative fashion across sessions, and are reinforced with in-session experiential exercises as well as at-home practice. Veterans are first taught to develop a "strengthening moment" by recalling a time or place in which they felt safe and cared for by another. This strengthening moment exercise allows Veterans to develop a sense of safety and to begin to recognize that value of compassion in their own lives. Next, Veterans engage in an attention-training practice by focusing on the breath and simply observing the breath, without judgment. The focus is then expanded to a present-moment awareness, where Veterans learn to observe their mental experiences. A greater appreciation of the habits of one's mind then sets the stage for the contemplation of the nature of distress and dissatisfaction in one's life. The Veteran can then adopt a more realistic and constructive attitude towards difficult situations. The focus then shifts to examining attitudes and perspectives towards other people ("us" vs. "them", Veterans vs. civilians); Veterans begin to consider how all people, despite our differences, share a fundamental desire to be happy and free from suffering. By acknowledging our common humanity, Veterans are then prepared for a more empathic response and a more universal compassion towards others. Veterans are then encouraged to realize how much other people contribute to their well-being. Ultimately, this recognition of our interdependence facilitates the development of compassion towards others.

CBCT-CP+ was refined over the last two years based on clinical experience, Veteran feedback and input from other VHA stakeholders, and consultation with mentors and subject-expert consultants. The core intervention of CBCT (namely, compassion meditation) is a transdiagnostic concept based on ancient practices derived from the lojong (mind training) tradition of Tibetan Buddhism. The principal method in CBCT-CP+ is daily formal meditation. Group topics are aligned with the Broaden-and-Build Model, and formal meditation is explicitly linked with present-moment contact, non-judgmentalness, self-compassion, equanimity, interdependence, gratitude and engaged compassion, thus CBCT-CP+ holds promise to improve

psychological comorbidities while decreasing pain-related barriers to functional improvement. The refinements to the CBCT protocol focused on three main areas: 1) the addition of pain-related didactics, including the rationale for compassion, 2) improving the ability for Veterans to leverage an existing meditative practice by including pain-specific instructions for meditation, and 3) increasing the ease of use for Veterans with a high likelihood of cognitive impairment due to chronic pain, medication use, and psychological conditions by simplifying language of materials and streamlining meditations. Specific changes were made to the protocol as follows: in session 1 the rationale for compassion was expanded to address both psychological comorbidity (especially depression or PTSD) and CP. Additional instructions for how to meditate and how to set up a meditation space at home were added to address the unique concerns of individuals with pain. These instructions are also emphasized in meditation recordings throughout. In developing a stability of focus in session 2, Veterans are instructed how to cope with pain-related sensations, emotions, and thoughts. In sessions 3 - 4, Veterans are taught to observe pain-related experiences with an objective and accepting stance. Veterans learn that struggling with pain-related experiences only make them worse. In session 5, Veterans are encouraged to use activity pacing as a self-compassionate response. In sessions 6 - 7, Veterans learn that they can be grateful for their bodies, even when they are in pain, in addition to appreciating our interdependence, or the contributions that others make to our lives. In session 8, Veterans learn that empathy for one's self as well as other-oriented empathy can help to repair the social isolation and loneliness that often results from chronic pain and related mental health symptoms. Finally, in sessions 9 - 10, Veterans learn about the Broaden-and-Build model as it applies to CP; namely, many of the skills developed in CBCT-CP+, including feeling gratitude and cultivating mindful awareness, in turn increase positive emotions, which have numerous benefits for physical and mental health.

Based on our pilot studies (see **PRELIMINARY STUDIES**), our ongoing use of CBCT in clinical and other research settings, and Veteran feedback, we have continued to refine the CBCT-CP+ manual. Primarily, these changes focused on making the general strategies and concepts from CBCT more applicable and accessible for individuals with both CP and comorbid mental health symptoms. For example, in session 1, Veterans are given more specific instructions for various postures for meditation and how to accommodate specific physical limitations. Veterans are also given more detailed instructions for use and purpose of foundational practices (diaphragmatic/relaxed breathing, strengthening moment, focused attention/mindfulness of breathing) and how these practices can be used to cope with CP, PTSD, and depression. In session 2-3, Veterans are further guided in differentiating between focused attention vs. present-moment awareness using new metaphors and population-relevant examples. We've modified session 5 (self-compassion) to specifically target pain- depression- and trauma-related "habits of the mind" including self-criticism, exaggerated beliefs in control of external circumstances, and exaggerated expectations of being perfect or superhuman. We've added content to bring greater awareness to how much suffering these "habits" cause and provide a path forward by helping Veterans to recognize their innate worthiness of kindness and self-acceptance. Finally, in sessions 5-6, we have emphasized the recognition of common humanity as a way to feel less alone and isolated due to chronic pain, depression, and/or PTSD. We've also clarified the manual content more generally in order to address Veteran and instructor feedback with the following: 1) enhanced group rules to clarify expectations and responsibilities of group members, 2) refined daily homework questions to be clearer and more useful, 3) theoretical basis for process of skills acquisition in CBCT (Ash et al., 2019), 4) clarified instructions for mindful listening exercise in session 4.

Health Education while Living with Pain (H.E.L.P.) comparison group. Health Education while Living with Pain (H.E.L.P.) is a "mind-body" health and wellness psychoeducation group that matches CBCT-CP+ in length of group meetings, provider attention, social interaction with group members, psychoeducation, homework assignments and appeal of mind-body courses. H.E.L.P. consists of 10 weekly 90-minute sessions featuring didactics and group discussion of health and wellness topics relevant to the population (Veterans with chronic pain and psychological comorbidity) including nutrition/eating healthy, getting better sleep, relaxation, exercise/physical activity, tobacco/nicotine, alcohol, and other substance use, stress management and mood, communication and talking to medical providers, and social support. The group was designed to increase Veterans' understanding of health and wellness in the context of CP and psychological comorbidity; H.E.L.P. is informational only, and does not include any specific setting of behavioral goals or skills practice while controlling for important variables (described above) and allows for better delineation of meditation-specific effects. Our H.E.L.P. protocol was based on similar health-related psychoeducation control groups (Haddad et al., 2020; Williams et al., 2020), which have been utilized in numerous RCTs in similar populations (Haddad et al., 2020; Mascaro et al., 2013; Williams et al., 2020). H.E.L.P. controls for important confounding variables and is expected to have minimal impact on clinical outcomes measures (e.g., PTSD and depression severity;

pain disability) and mechanisms (e.g., mindfulness; Elbers et al., 2018; Haddad et al., 2020; Williams et al., 2020).

Training. CBCT instructor(s) will be trained in CBCT using the Emory Intensive Teacher Training Program. The training program is designed to help potential teachers explore effective contemplative pedagogy and understand and adapt to the needs of various populations. The first portion of the training involves an introduction to the key concepts, skills, and practices, including understanding the theory and practice of compassion meditation, learning how CBCT differs from other meditation-based programs and recognizing the rationale and significance of teaching secularized meditation programs. The second portion of the training, which is a retreat, affords teachers an opportunity to deepen their practice and experience with compassion meditation. The third training component involves supervised administration of the protocol. A supervisor from Emory University or Dr. Casmar will watch a video-recording of every class for one 10 session group and provide feedback to the instructor prior to the next class. To minimize bias, a separate H.E.L.P. instructor will be trained in Health Education while Living with Pain by Dr. Malaktaris. Training will involve intensive review of the treatment manual with demonstration of in-class didactics. For one 10 session group for each instructor, Dr. Malaktaris will watch a video-recording of every class and provide feedback to the instructors.

The research assistant will be trained through a minimum of two assessments for each measure and then be observed for a minimum of two assessments. Additionally, the research assistant will be tested for reliability (random selection of 5% of interviews), and participate in weekly staff meetings to address questions or concerns. Training will also be provided on common issues associated with self-report measures. Drs. Lang and Malaktaris will train study assessor through review of training materials, observation of CAPS-5 and HAM-D administration, and diagnostic matching on three interviews each. They will also provide ongoing supervision of the assessors' interviews throughout the study, and all interviews will be audio-recorded in case detailed review of an interview is needed. We will follow standard procedures for examining inter-rater reliability between assessors and over time. Each assessor's score will be compared to "gold standard" rating. Intra-class correlation coefficients (ICCs) of each assessor must be .90 or higher.

Treatment Fidelity. Treatment fidelity is essential to the reliability and validity of study findings as well as the eventual multi-site trial and dissemination of CBCT-CP+. In consultation with CBCT developers, we are currently developing a fidelity tool based on a previously used instrument (Lang et al., 2017). This measure will assess a) unique and essential elements of each approach, (b) essential features that are not unique (e.g., warmth), and (c) proscribed elements (e.g., features of the control or other common interventions), as well as a general appraisal of the session. A random sample of 10% of all treatment sessions, divided equally across type of intervention, will be audiotaped and reviewed by supervisors; recordings will be scored for percent compliance and therapist adequacy within element types and overall, based on the fidelity measures. CBCT-CP+ and H.E.L.P. courses will be taught be different instructors. Using different instructors for the CBCT-CP+ and H.E.L.P. interventions will maximize treatment adherence and minimize contamination or allegiance bias across groups.

Limitations to the proposed procedures and alternative approaches.

1. Given the findings from our secondary analyses of pain data from compassion meditation pilot study, one potential concern that reviewers may have regarding the proposed CDA-2 is the possibility of failure to impact pain outcomes. However, this study did not specifically recruit or assess for CP conditions; these participants may have had more transitory and/or less problematic pain. The proposed study differs from our pilot study (Lang et al., 2019) in several ways. We will specifically recruit individuals with CP conditions, and we have refined the treatment protocol to add components specifically targeting pain interference (see **Description of Interventions**). We have found consistent evidence of the potential clinical utility of CBCT in reducing mental health symptoms (see **Preliminary Studies)**; CBCT-CP+ could still be useful in this CP sample even if it does not ultimately address CP-related symptoms.
2. A primary design consideration concerned choice of comparison condition. Selection of comparison groups for psychosocial treatments in clinical trials is complex, as there is no clear-cut standard of choice; we have followed best-practice guidelines in selecting our control condition (Mohr et al., 2009). For the proposed project, H.E.L.P. was chosen as the comparison group for several reasons. H.E.L.P. controls for a number of important confounding variables (e.g., social interaction/interaction with instructor, psychoeducation, at home assignments; Mohr et al., 2009; Tang et al., 2015) while similar health education groups have had minimal impact on clinical outcomes in previous studies (Elbers et al., 2018; Haddad et al., 2020). We will

ensure that instructors across treatment conditions receive similar training, fidelity monitoring, and supervision. We considered several alternatives for a control condition:

a. Wait-list control, no treatment, or treatment as usual (TAU). Wait-list and no treatment controls are not recommended given the indication for and availability of treatment for this population (Dworkin et al., 2010; Mohr et al., 2009). Considering the heterogeneity and complexity of this sample, TAU may vary considerably across clinicians and settings (Mohr et al., 2009).
b. Relaxation-based control. We have previously validated a manualized relaxation-based control group (Veteran.Calm, VC) with a similar level of specificity to CBCT. While VC was similar to CBCT in terms of feasibility, acceptability, and treatment satisfaction, and had minimal impact on clinical outcomes in a PTSD sample (Lang et al., 2019), there may be some (albeit mixed) evidence that relaxation-based interventions could have modest impacts on chronic pain intensity, disability, and other pain-related variables (Lee et al., 2014).
c. Other active comparison conditions (e.g., CBT for Chronic Pain [CBT-CP], Acceptance and Commitment Therapy [ACT]). The current widely-used CBT protocols for mental health conditions are disorder-specific, which creates pragmatic issues when attempting to match treatment length with our integrative treatment. ACT and CBCT-CP+ include some overlapping methods; it may be difficult to clearly differentiate these two interventions from CBCT-CP+ within the scope of the proposed project.

3. A second design consideration concerned selection of inclusion and exclusion criteria. We considered the IMMPACT consensus meeting recommendations in selecting our criteria (Dworkin et al., 2010).
   a. Type and duration of CP condition. There are various alternatives with respect to the type and duration of CP conditions. For example, we chose to exclude individuals with malignant pain (such as the result of cancer, multiple sclerosis, or other terminal disease processes) because patients with malignant pain are often experiencing more significant difficulties that should be the focus of treatment and because these patients are more likely to be lost to follow-up over the course of participation in the study. While some definitions of chronic pain require a duration of three months, we are requiring participants to have experienced at least six months of pain in order to assure that our sample has chronic pain rather than an acute or intermittent condition. Both of these requirements may impose limitations on referrals and recruitment.
   b. Psychological comorbidities. We have chosen to eliminate narrow inclusion criteria related to specific mental health diagnoses given the high prevalence of comorbidities among Veterans with CP and their contribution to disability among chronic pain patients. We aim for an inclusive, representative sample of Veterans. Moreover, CBCT-CP+ aims to improve both chronic pain and comorbid mental health symptoms (e.g., depression, PTSD). However, participants with serious uncontrolled mental illness or substance use disorders will be excluded.
4. Substantial consideration was given to the acceptable use of medications and other medical treatments in the study and the potential impact these treatments might have on primary outcome measures. Based on our previous experience, Veterans will continue receiving their usual health care, including treatment for pain, during participation in the study. These treatments may include traditional medical treatments (e.g., injections). We made this decision on the grounds that a) a high percentage of Veterans with CP and psychological comorbidities will receive one or more other treatments for pain and it would be difficult to recruit participants by excluding all those using other treatments, and b) if patients met eligibility for the study, then it is likely that the other treatments alone were not satisfactorily managing pain. Our general approach, therefore, will be to allow for prescription medication use provided that participants are on a stable medication regimen for at least one month prior to enrollment in the study and do not plan to start, stop, or change dosage during the study (changes during the study will be noted). We will request patients take no more than their lowest usual dose within 24 hours of baseline and post-intervention assessments.

Assessment Measures (see Table 3 below for schedule of assessments).

Demographics. We will collect demographic information (Dworkin et al., 2010): age, gender, race/ethnicity, relationship status, years of education, SES/income/living situation, occupation/work status, and branch of service/highest rank.

Eligibility Measures. We will administer the PEG (Krebs et al., 2009), a brief screening tool, to screen for chronic pain. The PEG has three items assessing pain intensity (P), interference with enjoyment of life (E), and interference with general activity (G). Veterans will be screened for the probable diagnosis of depression and/or PTSD with the MINI 7.0 (Sheehan et al., 1998), which has been validated against other established clinical interviews and updated for DSM-5. It takes 15-30 minutes. Diagnostic profile and suicide risk (exclusion

criteria 1-3) will also be established using the MINI 7.0 (Sheehan et al., 1998), which will be supplemented with questions to assess homicidality. Cognitive impairment will be evaluated with the Montreal Cognitive Assessment (MoCA 8.1; Nasreddine et al., 2005), a brief (~10 minutes) clinician-administered cognitive screening test. If the score is < 23, which has been established as an appropriate cut-off for psychiatric samples (Gierus et al., 2015), patients will be referred for additional evaluation and excluded (exclusion criteria 4) unless a qualified clinician provides clearance to participate. Participants who do not meet eligibility criteria based on PEG, MINI, and MoCA will be compensated for their participation and will not continue with the remainder of baseline assessment.

Primary Outcome Measures (Aim 1). For our primary and secondary outcome measures and other clinical measures, we have selected brief, well-established, reliable and valid measures based on IMMPACT consensus meeting recommendations (Dworkin et al., 2005). The co-primary clinical outcomes will be measured with

1. Brief Pain Inventory (BPI) Pain Interference subscale (Cleeland et al., 1994). We will assess pain-related functional interference with the BPI Pain Interference subscale, which is one of the most commonly used primary outcome measures in psychosocial intervention trials of chronic pain. The BPI Pain Interference subscale has 7 items measuring the degree to which pain interferes with various aspects of life, including mobility, social activities, and mood; and
2. Clinical Global Impression scale (CGI; Guy et al., 1976). The CGI consists of two one-item measures assessing 1) the severity of psychopathology from 1 (normal, not at all ill) to 7 (among the most extremely ill patients), CGI-S, and 2) the improvement in functioning since baseline assessment from 1 (very much improved since the initiation of treatment) to 7 (very much worse since the initiation of treatment), CGI-I. The CGI is a well-established measure of psychological symptom severity and is applicable across psychological conditions. The CGI-S has been used as a clinical outcome measure in previous randomized controlled trials in individuals with chronic pain (Montero-Marín et al., 2019), PTSD (Rasmusson et al., 2017), and mood and anxiety disorders (Mehl-Madrona et al., 2017; Meyer et al., 2010), and in previous RCTs using meditation-based interventions (Haddad et al., 2020; Montero-Marín et al., 2019). The CGI has been validated against gold-standard disorder-specific interviews (Bandelow et al., 2006; Stefanovis et al., 2018), and has good internal consistency and concurrent validity (Leon et al., 1993), which are further improved by the use of well-structured anchor points (Dunlop et al., 2017). The CGI will be utilized to assess severity of psychopathology regardless of comorbid condition (Dunlop et al., 2017). The assessor's severity and improvement ratings on the CGI will be primarily guided by transdiagnostic scoring anchors, which will be informed by participant responses to disorder-specific clinician-administered interviews (see below).
    a. Clinician Administered PTSD Scale (CAPS-5; Weathers et al., 2013). The CAPS-5 is the gold-standard clinician-administered measure to establish PTSD diagnosis and quantify severity. The CAPS-5 has good internal consistency and validity.
    b. Hamilton Rating Scale for Depression (HAM-D) is the gold-standard rating clinician-administered measure of depression with adequate reliability and validity (Cusin et al., 2009). The HAM-D will be administered using a structured interview guide to improve inter-rater reliability (Rohan et al., 2016).

   The CAPS-5 and HAM-D will be used to inform the CGI ratings, describe the sample, and perform disorder-specific sub-group analyses (see **Data Analysis).**

Secondary Outcome Measures (Aim 2). The secondary clinical outcomes, life satisfaction and health-related quality of life will be measured with the Satisfaction with Life Scale (SWLS; Diener et al., 1998) and the Veterans SF-36 (Kazis et al., 2000), respectively.

1. We will assess life satisfaction with the SWLS, a 5-item measure of global life satisfaction (Diener et al., 1998).
2. We will assess health-related quality of life with the Veterans SF-36, a widely-used, reliable, and valid self-report measure (Kazis et al., 2000, 2004); the SF-36 yields a physical component summary (PCS) and a mental component summary (MCS).

Exploratory mechanistic measures (*Exploratory Aim 3*). We are interested in exploring potential mediators of treatment response based on our theoretical model of recovery (Fredrickson, 1998, 2001) and previous empirical findings (Holtzman et al., 2004; la Cour et al., 2015; Ong et al., 2006; Park et al., 2010; Smith et al., 2008).

1. Pain acceptance will be measured with the Chronic Pain Acceptance Questionnaire (CPAQ; McCracken et al., 2003). The CPAQ consists of 20 items on a 7-point Likert scale comprising two subscales: activity engagement and pain willingness. The CPAQ has good psychometric properties (McCracken et al., 2004).
2. The Pain Catastrophizing Scale (PCS; Sullivan et al., 1995) contains 13 items that measure the degree to which people experience an aversive orientation towards pain. The PCS yields a stable three-factor structure including rumination, magnification, and helplessness, and good reliability and validity.
3. Positive and negative emotions will be measured with the Positive and Negative Affect Scale (PANAS; Watson et al., 1988). The PANAS includes two 10-item scales (positive and negative emotions).
4. Social connectedness will be measured with the 20-item self-report Social Connectedness Scale – Revised (SCS-R; Lee et al., 2001). The SCS-R has good psychometric properties including internal consistency, convergent and divergent validity.
5. Mindfulness will be measured with the Freiburg Mindfulness Inventory (FMI; Walach et al., 2006), a well-established 14-item self-report measure of mindfulness that has good reliability and validity in psychiatric populations.

Exploratory outcome measures (Exploratory Aim *4*). Suicidality, alcohol misuse, and opioid misuse are all potential concerns in the study population (Lee et al., 2018; Seal et al., 2012); IMMPACT consensus meeting guidelines suggest implementing comprehensive strategies for monitoring for such events (Dworkin et al., 2005). Although individuals with serious suicidality or homicidality and/or history of recent suicide attempt will be excluded, suicidal ideation is still likely to be present (Lee et al., 2018). We will monitor for changes in suicidal ideation with the Columbia–Suicide Severity Rating Scale (C–SSRS; Posner et al., 2008). The C–SSRS is a semi-structured interview that prospectively evaluates suicidal ideation and behavior; severity and intensity of ideation subscale scores will be examined. The C–SSRS has good convergent, divergent, and predictive validity and sensitivity to change (Posner et al., 2011). We will assess problematic alcohol with the Alcohol Use Disorders Identification Test (Saunders et al., 1993) consumption questions (AUDIT-C), a 3-item measure of problematic alcohol consumption. We will measure opioid misuse with the Current Opioid Misuse Measure (COMM; Butler et al., 2007), a 17-item self-report measure. The Patient Health Questionnaire 9-item (PHQ-9; Kroenke et al., 2001) will be used to measure depressive symptoms. The assessment of emotional functioning of individuals in chronic pain trials is recommended by IMMPACT consensus meeting due to the prevalence of psychological distress and psychiatric comorbidities (Dworkin et al., 2005). The PHQ-9 is based directly on the diagnostic criteria for major depressive disorder in the Diagnostic and Statistical Manual, 4th version. The PTSD Checklist for DSM-5 (PCL-5; Weathers et al., 2013) will be used to measure PTSD symptoms. The PCL-5 is a 20-item self-report measure of PTSD symptoms that maps directly onto the DSM-5 criteria. The Generalized Anxiety Disorder 7-item scale (GAD-7; Spitzer et al., 2006) will be used to measure anxiety symptoms. Pain severity will be measured with the a 4-item BPI Pain Severity subscale (Cleeland et al., 1994).

Other data. To assess compliance with treatment, average time spent per week in meditation practice (CBCT-CP+) or health and wellness education (H.E.L.P.) will be calculated from daily homework journals as has been done in prior trials (Lan et al., 2019). Daily homework journals for the previous week will be collected at the beginning of group sessions, and group instructors will encourage engagement with assignments. Medications will be recorded at the baseline, posttreatment, and follow-up assessments (Dworkin et al., 2005). At follow-up, Veterans will also be asked whether they are still using mind-body approaches (e.g., meditation or health and wellness education), and what approaches they are using.

Patient Safety. Since these groups focus on learning mind-body approaches in a group setting, we will administer brief measures (PHQ-9, BPI, PCL-5) biweekly to monitor fluctuations in symptoms. Veterans are asked to complete these types of questionnaires to briefly check-in on symptoms in routine clinical care. We will also administer the AUDIT-C at baseline, mid-treatment, posttreatment, and follow-up assessments to monitor for changes in problematic alcohol use. The participants' therapists will collect symptom measures during active psychotherapy and monitor for changes in health, possible adverse events, suicidal ideation, and clinically significant worsening of symptoms. Any exacerbation of symptoms will be reported and discussed with the PI so that appropriate action can be taken if necessary.

Table 3. *Timeline of Assessments*

Assessment Measure	Baseline	Mid-Treatment	Biweekly During Intervention	Posttreatment	3 mo. Follow-Up	*6 mo. Follow-Up*
Eligibility Measures						

PEG	X					
MINI	X					
MoCA	X					
Primary and Secondary Outcome Measures						
BPI	X		X	X	X	X
CGI	X			X	X	X
CAPS-5	X			X	X	X
HAM-D	X			X	X	X
SWLS	X	X		X	X	X
SF-36	X	X		X	X	X
Mechanistic Measures						
PCS	X	X		X	X	
CPAQ	X	X		X	X	
PANAS	X	X		X	X	
SCS-R	X	X		X	X	
FMI	X	X		X	X	
Other Outcome Measures						
C–SSRS	X	X		X	X	
AUDIT-C	X	X		X	X	
COMM	X	X		X	X	
PHQ-9	X		X	X	X	
PCL-5	X		X	X	X	
GAD-7	X	X		X	X	

Data Analysis

Dr. Liu (consultant) will oversee the development of the study database. Participant names will be held separate from data. Veterans will be assigned a unique ID number, and the single name-to-ID key will be kept in an encrypted electronic form as well as in locked filing cabinet physically. Preliminary analyses will examine: 1) descriptive statistics of the study sample, 2) variable distributions and outliers, 3) internal consistency and reliability of scales, and 4) between groups differences at baseline in age, gender, and concomitant medications. The preliminary analysis will be used to inform whether transformations of variables will be needed and which covariates should be entered in building models for testing the study hypotheses. Missing data will be minimized by checking questionnaires and clarifying answers while Veterans are on-site. Other data that are missing will be examined to assess randomness. The pattern of missing data will be examined according to the recommended procedures (Little et al., 2014), which includes comparing group differences in the primary outcomes of participants versus without missing data. We will test whether the drop-outs are random or systematic by comparing the drop-outs with the study completers on the baseline data.

Aim 1 (co-primary treatment outcomes): Hypothesis 1A: Veterans who receive CBCT-CP+, compared to H.E.L.P., will demonstrate improvements in pain disability. **Dependent variables:** BPI Pain Interference subscale scores. **Hypothesis 1B:** Veterans who receive CBCT-CP+, compared to H.E.L.P., will demonstrate reductions in severity of comorbid mental health symptoms. **Dependent variable:** CGI-S. **Analyses 1:** Analyses will be conducted using a random effects models (also known as hierarchical linear models [HLM], Linear Mixed Effects models [LMEs] or multilevel models), which have several advantages over more traditional analytic approaches such as a change score or repeated measures analysis of variance (Finch et al., 2016). This method allows the inclusion of subjects with missing data without relying on data imputation procedures. This method provides an estimate of the individual variability around the population trend, the variability of the individual intercepts (baseline values) and slopes (changes across time), and the correlation between them. The models for pain disability (BPI) and severity of comorbid mental health symptoms (CGI-S) will include a random intercept, a random effect for assessment time (baseline, posttreatment, 3-month follow-up), and fixed effects for comparison groups (CBCT-CP+, H.E.L.P.) and group-by-time interaction. We will first analyze global improvement or change in severity of comorbid mental health symptoms, and then we will conduct stratified secondary analyses of disorder-specific improvement or change in depression (HAM-D total severity) or PTSD (CAPS-5 total severity score). We will assess the significance of random effect of time; if it is not significant, then it will not be included. Covariance structure will be chosen based on Akaike's Information Criterion (AIC) and compared to each other using a likelihood ratio test. Since the intervention will be delivered

in groups, we will consider random group level treatment effects for importance based on the model AIC and will incorporate group level effects into the model if needed. Data will be analyzed from all randomized subjects using all available data. The between group pre- to posttreatment effect sizes will be calculated according to procedures described by Cohen (1988) and interpreted in the context of the 95% confidence interval (CI) that surrounds them. Analyses of primary outcome measures at 6-month follow-up assessment will be exploratory and will be conducted using the same analyses described above.

Aim 2 (secondary treatment outcomes): Hypothesis 2: Veterans who receive CBCT-CP+, compared to H.E.L.P., will demonstrate improvements in life satisfaction and health-related quality of life (secondary). **Dependent variables:** SWLS scores, Veterans SF-36 scores (PCS & MCS). Analyses of secondary outcome measures will be conducted using the same procedures as the primary outcome measures (described above).

Exploratory Aim 3 (mediation): Hypothesis 3A: Improved pain catastrophizing and pain acceptance will mediate the relationship between treatment group and improvements in pain disability. **Dependent variable:** BPI pain interference subscale scores. **Hypothesis 3B:** Increased positive emotions, social connectedness, and mindfulness will mediate the relationship between treatment group and reductions in severity of comorbid mental health symptoms. **Dependent variable:** CGI-S scores**. Analyses 3:** We define treatment mediators as mechanisms through which a treatment might achieve its effects, i.e., factors that explain how or why the treatment had worked. This mediator's effect is measured during the treatment and is correlated with treatment and may possibly be a result of treatment and have either a main or interactive effect on the outcome. Analyses will be conducted using the same random effects models as in Aim 1. For the model of pain disability (BPI interference subscale scores) at each time point (baseline, mid-point, posttreatment, 3-month follow-up), pain catastrophizing (PCS) and pain acceptance (CPAQ) will be added to the model as covariates. A significant main effect or significant interaction with treatment group (CBCT-CP+, H.E.L.P.) for pain catastrophizing or pain acceptance indicates that they account for the changes in pain disability seen between groups. Likewise, for the model of severity of comorbid mental health symptoms (CGI-S scores), at each time point, positive emotions (PANAS), social connectedness (SCS-R) and mindfulness (FMI) will be added to the model as covariates. A significant main effect or significant interaction with treatment group for positive emotions, social connectedness, or mindfulness indicates that they account for the changes in severity of comorbid mental health symptoms seen between groups (Lachowicz et al., 2015).

Exploratory Aim 4 (exploratory outcome measures and moderators): Dependent variables: C–SSRS severity and intensity of ideation subscale scores, COMM scores. **Moderator variables:** patient factors (PTSD severity, depression severity, anxiety severity) and other factors (sessions completed, length of daily homework completed). **Analyses 4:** Analyses for exploratory outcome measures will be conducted using the same analyses as Aim 1. We define treatment moderators as variables that identify on whom and under what circumstances treatments have different effects (Kraemer et al., 2002). The moderator's effect is measured during the treatment and is not correlated with treatment, but may suggest which individuals will be most responsive to treatment. Analyses of moderators will be conducted using the same analyses as Aim 1. An interaction between the moderators, patient factors (PTSD severity [PCL-5], depression severity [PHQ-9], anxiety severity [GAD-7]) and other factors (sessions completed, length of daily homework completed), and treatment that predicts the change in pain disability (BPI subscales) or severity of comorbid mental health symptoms (CGI-S, CAPS-5 severity, HAM-D severity) would indicate significant moderation (Preacher et al., 2016).

Future Directions

The proposed project is designed to execute an initial RCT of CBCT-CP+ vs. H.E.L.P. among Veterans with chronic pain and psychological comorbidity. This initial trial will set the stage for a future multi-site efficacy trial. In addition to exploring within-group effects on key relevant clinical measures and between-group effects on primary and secondary outcomes measures, we will consider other factors to help determine future steps, including exploration of potential mechanisms of treatment response. My mentor team and I will consider all available data to determine if a subsequent multi-site efficacy RCT of CBCT-CP+ is warranted. A future RCT would include training other therapists at multiple study sites to deliver CBCT-CP+ and control, use of more active control condition, formal inspection moderators and mediators, and examining the longer-term durability of treatment effects.

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