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A randomized trial to examine the mechanisms of cognitive, behavioral and mindfulness-based psychosocial treatments for chronic pain: Study protocol

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ABSTRACT

This randomized trial will evaluate the mechanisms of three chronic pain treatments: cognitive therapy (CT), mindfulness meditation (MM), and activation skills (AS). We will determine the extent to which late-treatment improvement in primary outcome (pain interference) is predicted by early-treatment changes in cognitive content, cognitive process, and/or activity level. The shared versus specific role of these mechanisms across the three treatments will be evaluated during treatment (Primary Aim), and immediately post-treatment to examine relapse mechanisms (Secondary Aim).

We will enroll 300 individuals with chronic pain (with low back pain as a primary or secondary condition), with 240 projected to complete the study. Participants will be randomly assigned to eight, 1.5 h telehealth group sessions of CT, MM, or AS. Mechanisms and outcomes will be assessed twice daily during 2-week baseline, 4-week treatment period, and 4-week post-treatment epoch via random cue-elicited ecological momentary assessment (EMA); activity level will be monitored during these time epochs via daily monitoring with ActiGraph technology. The primary outcome will be measured by the PROMIS 5-item Pain Interference scale. Structural equation modeling (SEM) will be used to test the primary aims. This study is pre-registered on clinicaltrials.gov (Identifier: NCT03687762).

This study will determine the temporal sequence of lagged mediation effects to evaluate rates of change in outcome as a function of change in mediators. The findings will provide an empirical basis for enhancing and streamlining psychosocial chronic pain interventions. Further, results will guide future efforts towards optimizing maintenance of gains to effectively reduce relapse risk.

1. Introduction

Chronic pain is debilitating, pervasive, and costly [1,2]. A number of interventions have demonstrated efficacy [3–5] for chronic pain management, including chronic low back pain (CLBP): (1) Cognitive Therapy (CT); (2) Mindfulness Meditation (MM); and (3) Activation Skills (AS) [6,7]. Each of these approaches has a unique theoretical rationale underpinning its application.

CT teaches patients to notice maladaptive thoughts and their influence on pain, and targets these for change. Thus, changing *what people think* (i.e., cognitive content) to more adaptive thoughts is a focus of CT [6]. MM encourages patients to disengage from automatic thinking and to mindfully place attention on different perceptive experiences [8]. MM therefore targets *how people think* (i.e., cognitive process). AS targets reductions in maladaptive pain behaviors and uses reinforcement principles to increase well behaviors. Hence, *what people do* (i.e., behavior) is targeted in AS [9].

Understanding the mechanisms of psychosocial pain treatments has been identified as critical [10,11]. While equivalent efficacy is typically obtained *on average* when active treatments are compared, e.g., [12,13] the theories underlying specific treatments argue that effects of different treatments work through unique mechanisms. It is also possible that these unique mechanisms underlie post-treatment changes. However, minimal research has examined whether CT, MM, and AS engender benefit via their specific theorized pathways – the Specific Mechanism Model – or if benefit is obtained via a combination of shared pathways – the Shared Mechanism Model [14–16].

If a mechanism factor plays a causal role in outcome, change in that factor must precede change in outcome [17]. Actigraphy and ecological momentary assessment (EMA) are repeated measures methodologies ideally suited to assess such mechanism relations in real-time [18]. EMA technology affords the capacity to disentangle temporal

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precedence of mechanism-outcome changes. These data will allow us to determine, for the first time, the timing of changes in mechanism variables during treatment, the effects of these changes on subsequent changes in outcome variables, and the extent to which these changes and effects are specific to, versus shared across, the three treatment conditions.

The purpose of this randomized trial is to identify the mechanisms of CT, MM, and AS for chronic pain, with low back pain experienced as a primary or secondary condition. Given past research showing equivalent efficacy for active treatments, we hypothesize no significant group level outcome differences.[e.g.,12,13] However, we do hypothesize *individual* variability in treatment response and maintenance of gains.[1]

1.1. Aim 1 (primary)

Identify the mechanisms of CT, MM, and AS. We will determine the extent to which late-treatment improvement in pain interference is predicted by early-treatment changes in three primary mechanism variables: cognitive content (i.e., catastrophizing), cognitive process (i.e., mindful non-judgment), and/or activity level (i.e., ActiGraph "activity counts").

Hypothesis 1a. Early treatment changes in mechanisms will be significantly associated with late treatment improvement in pain interference.

Hypothesis 1b. The Shared Mechanisms Model hypothesizes that if the mechanisms are shared, there would be small, non-significant between-treatment differences in early mechanism changes.

Hypothesis 1c. The Specific Mechanisms Model hypothesizes that if changes in mechanisms are *specific* to CT, MM, and AS, then treatment condition will have a significant effect on early changes in the mechanisms, which will then be associated with subsequent outcome change.

1.2. Aim 2 (secondary)

We will evaluate the post-treatment mechanisms that explain relapse (i.e., return to baseline levels – or worse – on pain interference), maintenance, and continued gains associated with these treatments. The Shared (Hypothesis 2a) and Specific (Hypothesis 2b) Mechanism models will be applied to test post-treatment mechanisms.

2. Methods

2.1. Design overview

In this study, we will use a 3-group parallel (1:1:1), single-blind design (see Fig. 1). We will recruit and enroll 300 individuals with chronic pain, with a low back pain problem experienced as a primary or secondary pain condition in the past 6-months. Participants will be randomly assigned to eight, 1.5 h, group Zoom videoconference sessions of CT, MM, or AS. Mechanism and outcome variables will be assessed twice daily during the 2-week baseline, 4-week treatment period, and 4-week post-treatment epoch via random cue-elicited EMA; physical activity level will be monitored during these time epochs via daily monitoring using ActiGraph technology. Follow-up assessments of mechanism and outcome variables will be conducted at 3- and 6-months post-treatment. The primary endpoint for the primary study aim (Aim 1) is the post-treatment pain interference score, operationalized as an average of pain interference ratings made on the twice-daily diaries during the first four days after treatment. The endpoint for the secondary study aim (Aim 2) is the post-treatment score at 28 days follow-up, as operationalized as the average of pain interference ratings on the diaries from the final four days of the immediate post-treatment follow-up period. All study procedures were piloted and developed in preliminary work by the investigative team. Specifically germane to this proposal, we have conducted numerous clinical trials examining psychological interventions based on the techniques investigated in this study for CLBP and other pain conditions [19–22], including telehealth assessment and treatment delivery [23–27]. We have also published multiple studies examining treatment mechanisms and have a great deal of experience in implementing EMA, with compliance rates exceeding 85% [14,15,21,28–48]. This study is pre-registered on clinicaltrials.gov (Identifier: NCT03687762). The trial protocol follows Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [49]. Informed consent will be obtained from all participants prior to enrollment.

3. Study sample and recruitment

Potential participants (N = 300 enrolled for N = 240 completers; see power analysis below) will be identified via diagnostic codes in the UW Medicine medical records. Recruitment will also occur via other strategies, including posting flyers in the relevant pain and rehabilitation clinics, clinician referrals, announcements on the hospitals-wide electronic reader boards and national recruitment strategies, including social media.

3.1. Participant inclusion and exclusion criteria

Study inclusion criteria include: (1) age ≥ 18 years; (2) endorse having low back pain as a primary or secondary pain problem in the past 6 months; (3) meet criteria for having a chronic pain problem (≥3 months, with pain experienced on ≥50% of days in the past 6 months) [1]; (4) average intensity of chronic pain ≥3 on a 10-point scale for most days of the previous 3 months; (5) chronic pain interference for general activities ≥3 on a 10-point scale for the past 3 months; (6) able to read, speak, and understand English to comprehend the worksheets, measures, and interventions implemented; (7) if currently taking analgesic or psychotropic medication, medications must have been stabilized for ≥4 weeks prior to this study; and (8) availability of a telephone, webcam, and microphone through computer or telephone, as well as daily internet access.

Exclusion criteria include: (1) primary pain condition is headache; (2) severe cognitive impairment; (3) current alcohol or substance dependence; (4) active malignancy (e.g., cancer not in remission), terminal illnesses, or serious medical conditions that may interfere with either study participation or with receiving potential treatment benefits (e.g., severe lupus); (5) inability to walk at least 50 yards, which would limit the ability of participants to benefit from the activation skills intervention; (6) significant pain from a recent surgery or injury; (7) pain condition for which surgery has been recommended and is planned; (8) any planned surgery, procedure, or hospitalization that may conflict with or otherwise influence participation in the study; (9) currently or recently receiving other psychosocial treatments for any pain condition (as this may influence these treatment results); (10) current or past participation in a UW Department of Rehabilitation Medicine research study with treatment components that may overlap those in the current study; (11) current or history of diagnosis of primary psychotic or major

[1] The exploratory aims of the study are not described in detail herein, due to space limitations. These exploratory tests will include: (1) evaluating the moderators of response per the Limit, Activate, and Enhance (LAE) moderation model from pre- to post-treatment (i.e., to test individual differences in treatment response), as well as moderators of change from pre-treatment to follow-up (i.e., to test individual differences related to maintenance of gains); (2) utilizing the ActiGraph and EMA data to explore the nature of the time course of micro-level changes in mechanisms and outcomes during and following treatment; (3) effects related to secondary outcomes (e.g., pain intensity) and non-specific mechanisms (e.g., therapeutic alliance), as well as changes at 3- and 6-month follow-up.

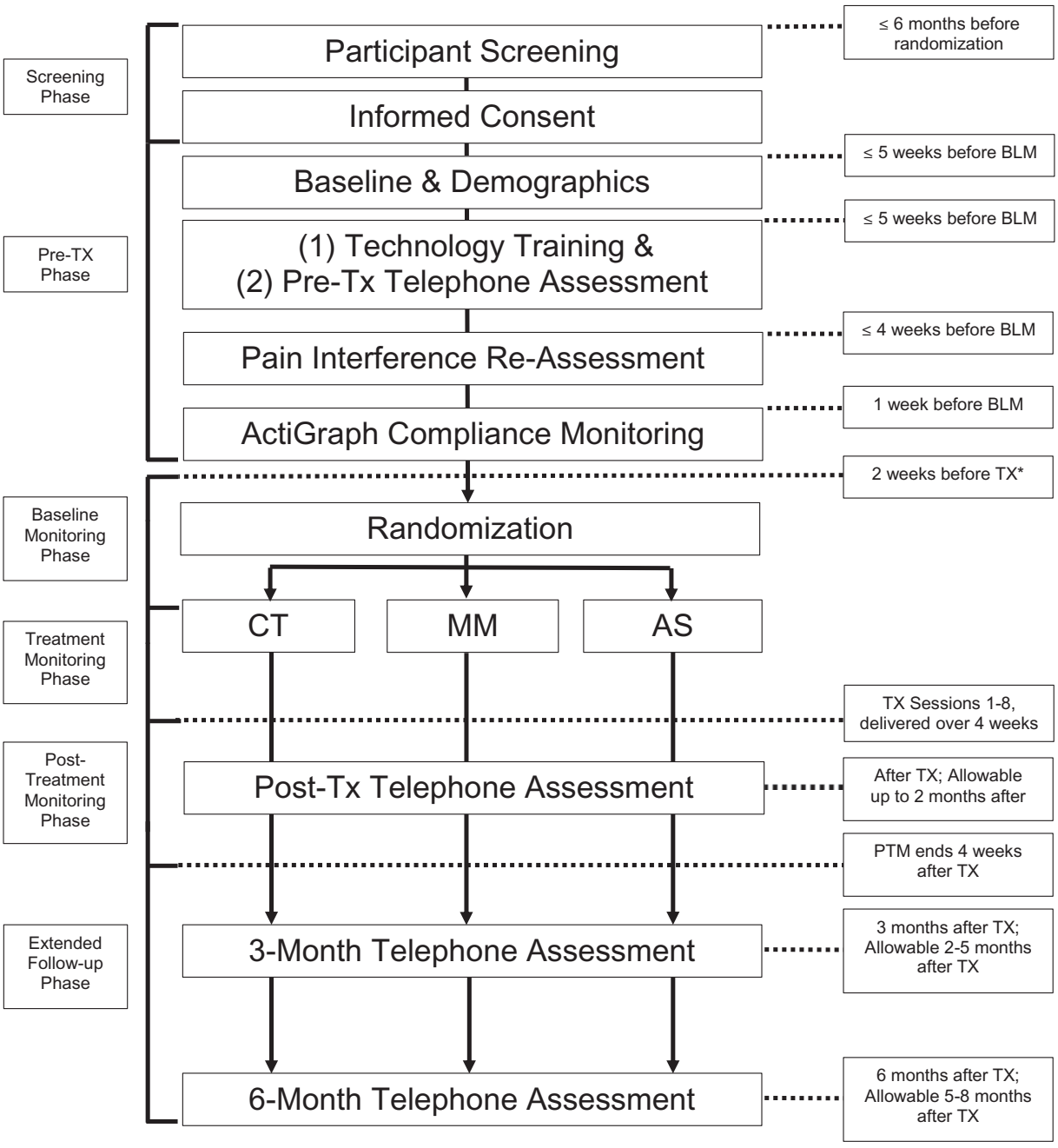

Fig. 1. Study design and trial flowchart. *Based on the Tx session 1 date of the earliest group.

thought disorder within the past 5 years; (12) psychiatric hospitalization within the past 6 months; (13) psychiatric or behavioral conditions in which symptoms were unstable or severe within the past 6 months; (14) any psychiatric or behavioral issues as noted in the medical record or disclosed/observed during self-report screening that would indicate participant may be inappropriate in a group setting; and (15) presenting symptoms at the time of screening that would interfere with participation, specifically active suicidal or homicidal ideation with intent to harm oneself or others, or active delusional or psychotic thinking.

3.2. Randomization

Assignment to one of the three groups will be accomplished using a covariate-adaptive randomization scheme. We will use a procedure proposed by Pocock and Simon, with the objective of balancing the covariate in the marginal distributions [50]. The covariates for the covariate-adaptive randomization will be sex, baseline pain interference score (mild/moderate or severe, as assessed via the 11-item Roland-Morris Disability Scale [51] with cutoff for severe being a score of ≥ 7), and low back pain type (primary or secondary pain).

3.3. Study interventions

3.3.1. Overview

Participants will be offered eight 1.5-h group treatment sessions scheduled twice per week for four weeks. This treatment format was

selected based on our successful application of these format specifications in prior clinical trials, which have evaluated eight session, group-delivered treatment programs, and programs with session duration length of 1.5 h (both in person and via telehealth). e.g., [19,23,25,52,53]. During their study participation, all participants will continue to receive their usual medical, psychiatric, and psychotherapeutic care. Clinicians will be expected to follow closely the treatment manuals to ensure all scheduled material is covered, and to ensure the consistency and replicability of treatment. In all three treatment conditions, group sessions will be conducted via the online, HIPAA-compliant Zoom videoconferencing platform (https://zoom.us/). Zoom videoconferences allow participants to see and hear each other, and also allow screen sharing, giving clinicians the opportunity to display visual information (e.g., PowerPoint slides) during sessions. All participants will receive a treatment workbook specific to their treatment allocation to refer to during the group sessions as well as additional content to read between sessions. In all conditions, home practice activities will be assigned to build skills in the coping techniques taught in sessions.

3.3.2. Cognitive Therapy (CT) condition

Cognitive-restructuring techniques will be used to help patients recognize the relationships between thoughts and the connection between thoughts with feelings, behaviors and pain [54]. These techniques will help patients: identify negative or unrealistic automatic thoughts; evaluate automatic thoughts for accuracy, identify sources of distorted thoughts, recognize the connection between automatic thoughts and emotional/physical shifts; challenge negative, distorted automatic thoughts via “weighing the evidence”; develop new realistic alternative cognitive appraisals; and practice applying new appraisals and beliefs.

3.3.3. Mindfulness Meditation (MM) condition

Participants will receive training in mindfulness meditation, specifically Vipassana, which is the form of meditation typically implemented in mindfulness research [55]. With this technique, the emphasis is placed upon developing focused attention on an object of awareness, e.g., the breath. This focus is then expanded to include a more open, non-judgmental monitoring of any sensory, emotional, or cognitive events. A standard script will be used by the clinician as a guide. The clinician will however lead the practice “from within,” in the sense that they will not simply just “read” the scripts, but will use their own language to guide the meditation taking into account his/her own experiences (for example, when describing sounds in the virtual room). Participants will be seated in a comfortable yet alert position. A guided inquiry of the participant's experiences will follow each in-person exercise, and will also be implemented in relation to discussing participant's at-home practice.

3.3.4. Activation Skills (AS) condition

Participants will be educated about the role of inactivity and behavioral avoidance in chronic pain and functioning [56]. They will learn how to be aware of the activities they avoid because of pain, and how to set effective goals so that, step by step, they can start being more active and resume some activities they enjoyed in the past but are currently avoiding. Explanation and practice of a set of specific skills – including appropriate pacing skills – to facilitate an increase in appropriate activity level will be provided.

3.4. Therapists and therapist training

The sessions will be conducted by a postdoctoral psychology fellow or licensed psychologist (the “clinician”) with at least two years of clinical experience, including experience working within the context of chronic pain treatment. The clinicians will be trained and supervised by the investigators who have considerable experience in the study treatments. During training, clinicians will be assigned reading materials [54–56] and will complete three, 6-h treatment workshops led by the investigators; all therapists will be trained in, and will deliver, all three treatments. MM therapists will be strongly encouraged to engage in their own personal practice of mindfulness, including discussions around how this personal practice is important for being able to respond genuinely and to have insight into the processes of meditation. Clinicians will also be trained in the use of Motivational Interviewing (MI) for enhancing motivation to engage in treatment, including reading Miller and Rollnick's text [57], and engaging in at least 3 h of MI instruction and practice. Clinicians will also receive training in group leadership techniques, including strategies for enhancing group cohesion. The clinicians will be provided with a detailed treatment manual and protocol, and will be provided with regularly scheduled supervision.

3.5. Fidelity monitoring

Adherence and fidelity will be monitored using session audio recordings. Masters-level or above clinicians supervised by the investigators will review a random selection of 25% of the recordings (2 randomly selected sessions per group) to ensure procedures are followed. Delivery quality and protocol adherence criteria will be developed for each session, adapted from the CT Adherence and Competence Scale [58] and the Mindfulness-Based CT-Adherence Appropriateness and Quality Scale [55]. Corrective feedback will be provided to the clinician during supervision; didactics and role plays to correct “drift” will be implemented if needed.

3.6. Participant retention and adherence to study procedures

We will implement a number of strategies to maximize participant retention. For example, across cohorts, sessions will be offered at different times on a recurrent basis (e.g., a morning session cohort will be offered, and then in the next cohort an evening session will be offered), giving participants scheduling flexibility; however, once a participant commences treatment, a participant cannot change groups/clinicians. We will track session attendance and reasons for missed sessions. Reasons for attrition will be assessed for participants who withdraw. Clinician-rated participant engagement will be assessed following each session for each participant [52]. Enactment of treatment-specific skills will be assessed by homework practice, assessed via EMA. To minimize possible missed extended surveys, EMA, and ActiGraph data, we will provide financial incentives.

3.7. Measures

The descriptive, primary and secondary outcome variables, covariates (variables to control for in planned analyses if needed), and mechanism (mediator and moderator) variables for this study are listed in Table 1. Specific measures by time point are provided in Table 2. Assessments will be undertaken via a combination of extended telephone assessments and EMA monitoring. Participants will have the option to complete the EMA surveys via smart phone, tablet, laptop, or desktop computer. The cue-elicited EMAs will be administered via software programmed to randomly alert participants daily within two pre-set 120-min blocks (via notifications for smart phone users and email messages for tablet, laptop, or desktop users) to complete the EMA surveys in the morning and evening. All participants will be given 3 predetermined options for the morning and evening blocks for receiving surveys: for example, 5–7 AM and PM, 6–8 AM and PM, or 7–9 AM and PM. Notification cues to complete the EMAs will be administered during a randomly selected time within these blocks. The number of items for each measure in the EMAs was selected on the basis of content validity, factor loadings established during initial measure development and validation studies, brevity, and pilot data. Building on this, the minimum number of items was then selected that achieved at least good

Table 1
Descriptive, Primary, Secondary, Co-Variate, and Mechanism Variables.

Variable type	Domain	Measure (# items EMA, # items Extended)
Descriptive/Demographics	Patient Characteristics	Purpose built demographics, patient characteristics, and pain history questionnaire [42–45]
Primary Outcome	Pain Interference	PROMIS Pain Interference (5, 5) [46,47]
Primary Mechanisms and Moderators	Cognitive Content	Pain Catastrophizing – Items from Pain Appraisal Scale (3, 5), Coping Strategy Questionnaire (2, Extended only) [48,49]
	Cognitive Process	Pain-Related Cognitive Process Questionnaire (PCPQ) Non-Judgment Scale (2, 6) [50]
	Activity Level	Actigraphy + Godin Leisure-Time Exercise Questionnaire (3, 3), hours spent sitting without exercising (EMA only) [51]
Secondary Outcomes	Average Pain Intensity	Numerical Rating Scale (NRS), 0–10 (1,1) [52]
	Mood	Positive and Negative Affect Schedule (PANAS) (2, 10) [53,54]
	Physical Function	PROMIS Physical Function (4, Extended only) [46,55]
	Sleep Quality	Actigraphy, PROMIS Sleep Disturbance (4, Extended only) [46,55]
	Depression	PROMIS Depression (4, Extended only) [46,55]
	Anxiety	PROMIS Anxiety (4, Extended only) [46,55]
	Medication Use	Purpose built Medication Use Questionnaire (Extended only)
	Medication Use Attitudes	Survey of Pain Attitudes (SOPA) Medication Beliefs Scale (6, Extended only) [56] and Pain Medication Questionnaire (PMQ) (26, Extended Baseline assessment only) [57]
	Post-Traumatic Stress Disorder	PTSD Checklist Civilian Version (PCL-C) (17, Extended only) [58]
Secondary Mechanisms	Pain Self-Efficacy	UW Pain-Related Self-Efficacy Scale (3, 6) [48]
	Patient Engagement	Clinician rated patient engagement (5, rated by clinician) [23]
	Therapeutic Alliance	Working Alliance Inventory (WAI) (12, EMA only) [59]
	Group Cohesion	Group Climate Questionnaire (GSQ-S) Engagement Scale (5, EMA only) [60]
	Skills Engagement	Purpose built duration and number of days/times practicing skills (EMA); number of days and duration of time practicing skills (Extended)
Tertiary Outcomes	Health Care Use	# visits to health care professional in last month (1, Extended only)
	Pleasurable Activity	Pleasant Events Schedule SF (10, Extended only) [61,62]
	Behavior Activation	Behavioral Activation for Depression Scale (BADS) (9, Extended only) [63]
	Quality of Life	Global quality of life (1, Extended only) [64]
	Employment Status	Employment question (1, Extended only)
	Weight Change	Weight question (1, Extended only)
	Patient Global Impressions of Change	Patient Global Impressions of Change (PGIC) (6, Extended post-treatment and follow-up assessment only); and Patient Global Assessment of Treatment Satisfaction (PGATS) (1, Extended post-treatment and follow-up assessment only)
Tertiary Mechanisms	Mindfulness	Mindful Attention Awareness Scale (MAAS) (15, Extended only) [65]
	Resilience	Pain Resilience Scale (14, Extended only) [66]
	Other Cognitive Processes	All other PCPQ items (47 additional, Extended only) [50]
	Pain Beliefs	Survey of Pain Attitudes (SOPA) Harm, Control and Disability Scales (18, Extended only) [56]
Exploratory Moderators	Cognitive Abilities	PROMIS Cognitive Function Abilities (6, Extended only) [46,55]
	Treatment Credibility	Treatment Credibility & Expectancies items [67] (5, EMA only)
	COVID-19	As of 2020: Investigator-developed items on COVID-19's effects (6 items ext. & 1 item Qualitative Interview)
Covariate	Primary Problem (LBP primary or secondary)	Purpose built screening, self-report
Optional Assessments	Responses to Pain	Positive & Negative Response to Pain Scales (85, Extended Optional only) [68]
	Future Self	Future Self Questionnaire (FSQ) (16, Extended Optional only)
	Values-Consistent Goals	Valued Living Scale (VLS) [69] (8, Extended Optional only)
Qualitative Outcomes	Experiences in group & program feedback	15″–30″ of investigator-developed qualitative items

internal consistency reliability ($\alpha \geq .80$) for the mechanism variables and excellent reliability ($\alpha \geq .90$) for the primary outcome variable of pain interference in our pilot data. The Actigraph will be worn throughout all EMA phases.[2] All outcome measures will be administered by staff blind to group allocation.

3.8. Statistical analyses

Due to space limitations, here we provide only a brief description of the planned analyses. Readers interested in more details can find them on clinicaltrials.gov (Identifier: NCT03687762). Only analyses planned to address the primary study aims are described here. Briefly, we plan to test the primary study hypotheses using a 3-wave structural equation modeling (SEM) approach.

We will first calculate slope coefficients representing the linear change in each outcome and mechanism variable during the first two weeks of treatment (early treatment) and second two weeks of treatment (late treatment), using regression. See Fig. 2 for the data time points included in these calculations. We will then enter these variables, along with control variables and variables representing treatment condition in a series of SEM models.

The model depicted in Fig. 3 represents the initial model we plan to test for the catastrophizing mechanism variable, providing that it evidences at least a small effect size for change over time for at least one treatment condition during the first two weeks of treatment. However, the model will be simplified (by removing treatment condition as a predictor, and the paths associated with treatment condition) if non-significant between treatment condition effects are found for change during the early treatment phase. Up to two additional SEM models will also be tested, with non-judgment and activity level as the mechanism variables.

In these models, the *a1* and *a2* coefficients represent the treatment

[2] The gold standard for assessment of movement (i.e., what people actually do) in the real world is Actigraph technology, which is why we elected to use this assessment approach in this trial. That this mechanism is not measured via self-report like the primary hypothesized mechanisms of the other two conditions is a potential methodological confound that was considered. Hence, to address this, we elected to also concurrently administer a self-report measure of what people do (i.e., GODIN, and self-reported amount of time spent sitting). This will allow us to test whether the findings differ as a function of form of assessment (i.e., self-report versus objective assessment).

Table 2
Study assessment schedule.

Measures	EMA	Baseline	Pre-TX	During Tx	Post-Tx	3-Month	6-Month
Demographic Information		X					
Pain and Treatment History		X					
Start Back Tool		X					
Pain Medication Questionnaire (PMQ)		X					
Roland Morris Disability Questionnaire SF (RMDQ)		X					
PROMIS Pain Interference	X		X		X	X	X
Pain Appraisal Scale (PAS)	X		X		X	X	X
2-item Catastrophizing Scale from the Coping Strategy Questionnaire (CSQ)			X		X	X	X
Non-Judgment Scale from the Pain-Related Cognitive Process Questionnaire (PCPQ)	X		X		X	X	X
Godin Leisure-Time Exercise Questionnaire	X		X		X	X	X
Hours Spent Sitting w/o Exercising	X						
Pain Intensity NRS	X	X	X		X	X	X
Positive and Negative Affect Schedule (PANAS)	X		X		X	X	X
PROMIS Sleep Disturbance			X		X	X	X
PROMIS Physical Function			X		X	X	X
PROMIS Depression			X		X	X	X
PROMIS Anxiety			X		X	X	X
PTSD Checklist (PCL-C)			X		X	X	X
Medication Use			X		X	X	X
UW Pain-Related Self-Efficacy Scale	X		X		X	X	X
Participant Engagement				X[a]			
Working Alliance Inventory (WAI)	X[b]						
Group Climate Questionnaire (GSQ-S)	X[b]						
Duration and Times Practicing Skills	X				X	X	X
Sleep/Wake Times	X						
Health Care Utilization			X		X	X	X
Pleasant Events Schedule SF			X		X	X	X
Behavioral Activation for Depression Scale (BADS)			X		X	X	X
Global Quality of Life			X		X	X	X
Employment Status			X		X	X	X
Weight			X		X	X	X
Mindful Awareness and Attention Scale (MAAS)			X		X	X	X
Pain Resilience Scale			X		X	X	X
Pain-Related Cognitive Process Questionnaire (PCPQ) – Full			X		X	X	X
Control, Harm, Disability and Medication scales from the Survey of Pain Attitudes (SOPA)			X		X	X	X
PROMIS Cognitive Function Abilities			X		X	X	X
COVID-19 Impact Questions (as of 2020)			X		X	X	X
Treatment Credibility and Expectancies	X[c]						
Patient Global Impression of Change (PGIC)					X	X	X
Patient Global Assessment of Treatment Satisfaction (PGATS)					X	X	X
Treatment Modality & Preferences					X		
Qualitative Outcomes					X		
Optional: Positive & Negative Response to Pain Scales, Future Self Questionnaire (FSQ), Valued Living Scale (VLS)			X		X	X	X

[a] Will be assessed for each participant and reported by the clinician following every treatment session.
[b] Will be assessed during the evening EMA following Sessions 4 & 8 only.
[c] Will be assessed once before Session 1 and once following Session 1 but before Session 2.

condition effect (two dummy IVs) on early change in the mechanism variable being examined. The *b* coefficient in this model represents the effect of early treatment change in the mechanism variable on subsequent late treatment change in outcome. A significant *b* coefficient would support Hypothesis 1a for that mechanism variable. Significant *a1* or *a2* coefficients, indicating between-treatment condition differences in early changes in mechanism variables, would support Hypothesis 1c (the Specific Mechanisms Model). Post-hoc analyses would then be performed to determine which treatment resulted in greater changes in the mechanism variable being examined. If both the *a1* and *a2* coefficients are not statistically significant, this would be consistent with Hypothesis 1b (i.e., the Shared Mechanisms Model) for that mechanism variable.

4. Power analysis

We will conduct *six primary* statistical tests (described above) to test the primary aim for three mechanism variables, in order to better understand the effects of the treatments on pain interference. Data from prior research – including means and standard deviations – supports the anticipated medium to large effects of (1) the causal effects of the treatments on the mechanism variables [52,59–61], (2) the association between the mechanism variables and pain interference [61–63], as well as (3) the mechanism paths that we propose to test [59,61,64], which form the basis of our assumptions for the power analyses. Although we were unable to identify any studies that examined the effect sizes associated with any of these treatments on behavioral activity, as a group these studies are consistent with our assumptions that CT, MM, and AS treatments have medium to strong effects on key mechanism variables.

Assuming at least medium effects (i.e., $rs \geq 0.30$ and/or $ds \geq 0.50$) [65] we then computed the sample sizes needed to detect significant effects for the planned primary analyses, using the Benjamini-Hochberg procedure to control for alpha inflation in these analyses [66]. The sample sizes needed to detect significant effects for each of these analyses is presented in Table 3, using the tests for the three direct mediation effects of the mechanism variables for three of these analyses, and a test for the three Treatment Condition X Mediation (representing moderated mediation) effects for the other three analyses, assuming at least medium effects for each of these effects. Sample size estimates needed to detect the primary mediation effects were conducted based on the joint significance method of testing mediated effects, using the

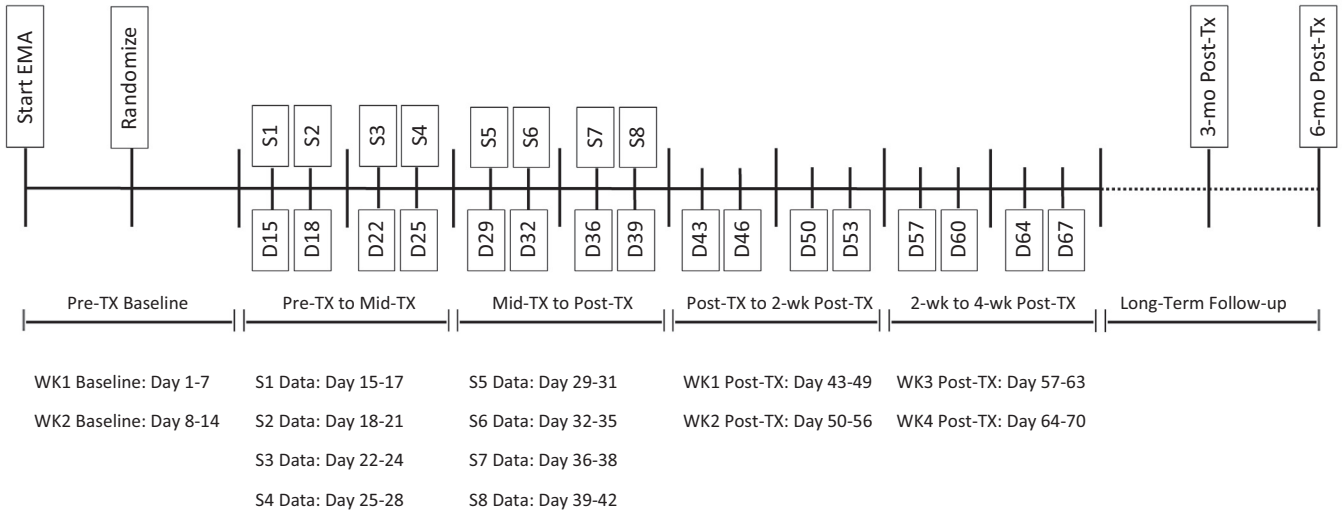

Fig. 2. EMA data collection and data time points used in statistical analyses. Note: The specific day counts are approximate and might slightly vary in the instance of extenuating circumstances for a given cohort.

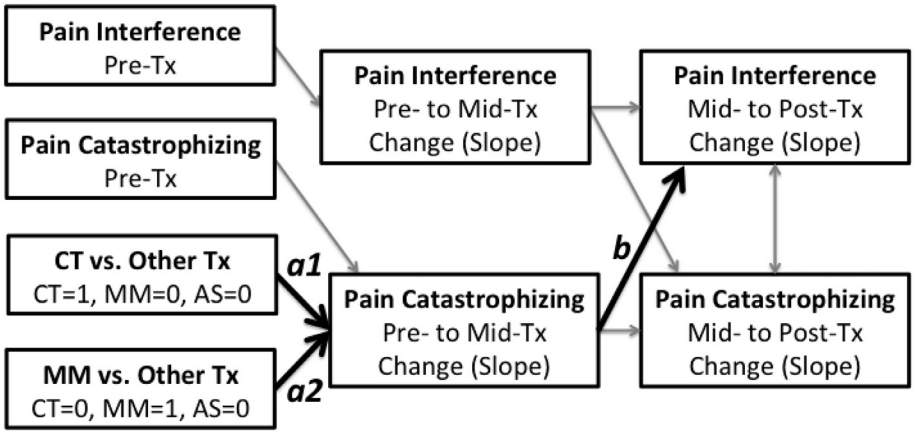

Fig. 3. Initial model testing the mechanism role of pain catastrophizing during treatment.

PowMedR program in R Version 3.0.2 statistical software with the following assumptions: (1) alpha levels consistent with the Benjamini-Hochberg procedure (see Table 3); (2) power of 0.80; and (3) at least medium effects. Power calculations for the interaction (mediated moderation) analyses were conducted using G*Power3 with the same assumptions.

Thus, by employing the analytic models experiment-wise, and by integrating treatment-condition into the model(s) as an interaction effect (rather than running separate analyses for each treatment condition), we will be able to take advantage of the power afforded by running the entire sample of participants (n = 240) through the planned tests. This, combined with the less stringent Benjamini-Hochberg type-I error adjustment, has left us well-powered to detect the hypothesized effects if they exist. That said, we plan to enroll 300 participants with a goal of obtaining complete data for 240 participants (n = 80 per condition).

5. Protection of human subjects: ethics

This study was reviewed and approved by the UW Human Subjects Division. An independent Data Safety Monitoring Committee (DSMC) comprised of an occupational therapist (Chair), biostatistician, and physical therapist with experience in treating CLBP has been appointed. The DSMC will monitor safety of participants throughout all phases of the trial. Per UW Human Subjects Division guidelines, we will monitor for and track possible adverse events (AEs) throughout the study.

Table 3
Sample size estimates for the six planned analyses, assuming medium effects for the causal paths (a and b) and at least a medium interaction effect (f2) for the three planned Treatment Condition X Mediation effects tests.

Alpha	Power	Effect size path a	Effect size path b	Interaction effects	n-required/n-planned
0.050	0.80	Medium (r = 0.30)	Medium (r = 0.30)		109/240
0.025	0.80	Medium (r = 0.30)	Medium (r = 0.30)		129/240
0.017	0.80	Medium (r = 0.30)	Medium (r = 0.30)		140/240
0.013	0.80			Medium (f^2 = 0.15)	93/240
0.010	0.80			Medium (f^2 = 0.15)	98/240
0.008	0.80			Medium (f^2 = 0.15)	102/240

Reviewing and reporting of AEs to the DSMC, the UW IRB, and NCCIH will be undertaken in accordance with requirements.

This study will be stopped prior to its completion if: (1) one of the interventions is associated with adverse effects that call into question the safety of the intervention; (2) any new information becomes available during the trial that necessitates stopping the trial; or (3) other situations occur that warrant stopping the trial.

6. Discussion

This study is designed to isolate the effects of coping skills typically taught in integrated, multi-modal treatments (i.e., CBT, MBIs) to determine their specific role in chronic pain management. Testing the mediators of these specific pain techniques – CT, MM, and AS – will identify if theorized mechanisms are unique to a specific treatment or are shared, trans-therapy mechanisms. Results of this study will determine the relative importance of targeting change in *what* people think, *how* people think, or what people *do* in relation to chronic pain management. Identification of treatment mediators will bring order and parsimony to psychotherapeutic theory [67,68].

Research has underscored the problem of patients relapsing back to baseline levels of pain/function following psychosocial pain interventions, with relapses found in as little as one month following treatment [69,70]. Thus, the time period immediately post-treatment might be critical. This study will examine the mechanisms that possibly precede continued improvement, maintenance, and relapse in the one month immediately post-treatment, and will investigate how these factors may relate to longer-term (i.e., 3- and 6-month) outcomes.

Although some prior research has used EMA or actigraphy to evaluate treatment outcomes,[e.g.,71,72] to the best of our knowledge, this study will be the first to utilize both actigraphy and EMA during pain treatment and during the critical month following administration of treatment to evaluate mechanisms. In planned secondary analyses, this methodological advancement of the inclusion of actigraphy and EMA will afford the capacity to determine precisely (1) when and how sudden gains might occur, (2) how long it takes for “slow and steady” gains to become meaningful and what processes underlie these gains, (3) the earliest point at which it is possible to conclusively determine that the treatment is not well suited to a given individual and that an alternative approach should be offered, and (4) the processes and temporal sequence underlying post-treatment relapse, maintenance, and continued gain. These findings could lead to streamlined interventions and informed relapse-prevention approaches that distill the most critical change factors into an efficient and cost-effective treatment package.

Trial status

Recruitment started in August 2018. The trial is underway; it is expected to be completed May 2022.

Conflicts of interest and sources of funding

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