Clinical Intervention Study Protocol Template

FULL PROTOCOL TITLE

Evaluating Specific and Non-Specific Mechanisms in Two Distinct Complementary/Integrative Interventions for Chronic Pain

Study Chairman or Principal Investigator:

John W Burns, PhD, Professor, Rush University Medical Center

Stephen Bruehl, PhD, Professor, Vanderbilt University Medical Center

Supported by:
The National Center for Complementary and Integrative Health

R01 AT009680-01A1

Study Intervention Provided by:

NA

Sponsor of IND (IDE):

NA

Tool Revision History

Version Number: 2
Version Date: 10/8/18
Summary of Revisions Made: Changes made to address NCCIH staff comments/questions

Version Number: 3
Version Date: 5/9/19
Summary of Revisions Made: Changes made to address recommendations from initiation site visit

Version Number: 4
Version Date: 6/13/19
Summary of Revisions Made: Clarification was added surrounded the reporting of protocol deviations and the discontinuation of participants and the study as a whole

Version Number: 5
Version Date: 10/31/2019
Summary of Revisions Made: Formatting changes, change in participant compensation rate, minor changes in surveys/assessments and exclusion criteria, and staff change

Version Number: 6
Version Date: 12/3/2019
Summary of Revisions Made: Corrected page numbers in the Table of Contents, added bone demineralization, osteoporosis, and suicidal ideation to the exclusion criteria, corrected errors related to laboratory and therapy session procedures, formatting changes, and added the names of RUMC's physical therapists

Version Number: 7
Version Date: 2/28/20
Summary of Revisions Made: Added opioid-dependency to the exclusion criteria, clarified that participants who experience withdrawal symptoms from the initial naloxone administration will be excluded, and edited staff information. In the assessment of spinal stiffness section added that the VerteTrack device has not been approved by the FDA at the request of the VUMC IRB.

Version Number: 8
Version Date: 07/16/2020
Summary of Revisions Made: Edited VUMC therapist information, added RUMC research nurse and additional pharmacy staff, added exclusion criteria relevant to the VerteTrack device, and added COVID-19 related safety precautions.

Version Number: 9
Version Date: 08/07/2020
Summary of Revisions Made: Added exclusion criteria relevant to the VerteTrack device and added RUMC research staff.

Version Number: 10
Version Date: 09/15/2020
Summary of Revisions Made: Edited therapy session times from 1 hour to 1-1.5 hours, removed MT weekly process checks from MT therapy sessions, removed spinal stiffness measurements from 3 and 6 month follow up visits, minor grammar edits, and edited our phone screen's exclusion criteria to be consistent with previous exclusion criteria.

Version Number: 11
Version Date: 10/12/2020
Summary of Revisions Made: Added a BMI of ≥40 or a waist measurement of 8.5-9.5 inches or greater from abdomen to back to the exclusion criteria to ensure that all enrolled participants will fit the Vertetrack device.

Version Number: 12
Version Date: 12/11/2020
Summary of Revisions Made: Staff change at both sites, corrected errors/typos and minor punctuation edits, added an online option for participants to complete their weekly post-treatment surveys and follow-up surveys, and added COVID-19 related safety precautions for MT sessions.

Version Number: 13
Version Date: 12/31/2020
Summary of Revisions Made: We added in the contact information for the new physical therapists at RUMC.

Version Number: 14
Version Date: 3/17/21Summary of Revisions Made: VUMC/RUMC staff change, changes to exclusion criteria, clarified drug dosing information, clarified procedures for urine opioid and pregnancy screening tests.

Version Number: 15
Version Date: 9/2/2021
Summary of Revisions Made: Staff changes at RUMC.

Version Number: 16
Version Date: 2/8/2022
Summary of Revisions Made: Staff changes at VUMC, dropped mid-treatment lab visits.

Version Number: 17
Version Date: 8/5/2022
Summary of Revisions Made: Staff changes at RUMC/VUMC, updated exclusion criteria, revised training requirements for MT therapists.

Version Number: 18
Version Date: 3/30/2023
Summary of Revisions Made: Staff changes at VUMC

Version Number: 19
Version Date: 4/24/2024
Summary of Revisions Made: Staff changes at RUMC

Version Number: 20
Version Date: 6/12/2024
Summary of Revisions Made: Error in the grant name label and addition of data analyst to RUMC

TABLE OF CONTENTS

Page

STUDY TEAM ROSTER

Principal Investigators:

John W. Burns, PhD
Department of Behavioral Sciences
Rush University Medical Center
1645 West Jackson Blvd, Suite 400
Chicago IL 60612
Ph. 312-942-0379
Fax: 312-942-4990
Email: John_Burns@rush.edu

Stephen Bruehl, Ph.D.
Professor
Department of Anesthesiology
Vanderbilt University Medical Center
701 Medical Arts Building
211 21st Avenue South
Nashville, TN 37212
Phone: (615) 936-1821
Email: stephen.bruehl@vumc.org

Co-Investigators:

Joel Bialosky, PhD
Clinical Assistant Professor
University of Florida
PO Box 100154
Gainesville, FL, 32601
Phone: 352 273 8636
E-Mail: bialosky@phhp.ufl.edu

Greg Kawchuk, PhD
University of Alberta
2-55 Corbett Hall
8205 114 St NW City
Alberta, Canada
Phone: 780 492 6891
E-Mail: greg.kawchuk@ualberta.ca

Asokumar Buvanendran, MD
Professor
Department of Anesthesiology
Rush University Medical Center
1645 W Jackson Blvd
Chicago, IL 60612
Phone: 312 942 3685
E-Mail: asokumar@aol.com

James Carmody, PhD
Professor
Univ of Massachusetts Medical School
55 Lake Ave North
Worcester, MA 01655
Phone: 508 856 1205
E-Mail: james.carmody@umassmed.edu

Dan Larach, MD, MSTR, MA
Assistant Professor of Anesthesiology
Division of Pain Medicine
Vanderbilt University Medical Center
Medical Arts Building
1211 21st Ave S Ste 708
Nashville, TN 37212-2717
Phone: (615) 875-8795
Email: daniel.larach@vumc.org

PARTICIPATING STUDY SITES

John W. Burns, PhD
Center for Pain Studies
Department of Behavioral Sciences
Rush University Medical Center
1645 West Jackson Blvd, Suite 400
Chicago IL 60612
Ph. 312-942-0379
Fax: 312-942-4990
Email: John_Burns@rush.edu

Stephen Bruehl, Ph.D.
Professor
Department of Anesthesiology
Vanderbilt University Medical Center
701 Medical Arts Building
211 21st Avenue South
Nashville, TN 37212
Phone: (615) 936-1821
Email: stephen.bruehl@vumc.org

Joel Bialosky, PhD
Clinical Assistant Professor
University of Florida
PO Box 100154
Gainesville, FL, 32601
Phone: 352 273 8636
E-Mail: bialosky@phhp.ufl.edu

James Carmody, PhD
Professor
Univ of Massachusetts Medical School
55 Lake Ave North
Worcester, MA 01655
Phone: 508 856 1205
E-Mail: james.carmody@umassmed.edu

Study Staff

Melissa Chont
Clinical/Translational Research Coordinator III
Department of Anesthesiology
Vanderbilt University
324 Medical Arts Building
1211 21st Avenue South
Nashville, TN 37212
Office: (615) 936-5664
Email: melissa.chont@vumc.org

Nicole Heath, PhD
Licensed Clinical Psychologist
Assistant Professor
Department of Psychiatry and Behavioral Sciences
Rush University Medical Center
1645 W. Jackson, Suite 400
Chicago, IL 60612-2344
Phone: (312) 942-0763
Email: Nicole_heath@rush.edu

Laurie Gold Carroll, PT, DPT
Department of Physical Therapy
1725 W Harrison St., Suite 440
Chicago, IL 60612
Phone: (312) 942-5847
Email: laurie_carroll@rush.edu

Rogelio A. Coronado, PT, PhD
Research Assistant Professor
Department of Orthopedic Surgery
Vanderbilt University Medical Center
1215 21st Avenue South, MCE-South, Suite 4200

Nashville, TN 37232
Phone: (615) 936-4348
Email: rogelio.coronado@vumc.org

Carrie E. Brintz, PhD
Assistant Professor of Anesthesiology
Division of Pain Medicine
Osher Center for Integrative Medicine
Vanderbilt University Medical Center
3401 West End Ave., Suite 380
Nashville TN 37203
Phone: (615) 322-6033
Email: carrie.brintz@vumc.org

Mandi Mizner, MSN, MSSW, APRN, LMSW
Nurse Practitioner
Osher Center for Integrative Medicine at Vanderbilt
3401 West End Ave., Suite 380
Nashville TN 37203
Phone: 615-343-1554
Email: mandi.mizner@vumc.org

Dana Mikrut, PharmD, BCPS
Investigational Drug Service
Department of Pharmacy
Rush University Medical Center
1653 W Congress Pkwy
Chicago IL, 60612
Phone: (312) 942-3018
Email: dana_mikrut@rush.edu

My G Ly, PharmD, BCOP
Investigational Drug Service
Department of Pharmacy
Rush University Medical Center
1653 W Congress Pkwy
Chicago IL, 60612
Phone: (312) 563-1246
Email: my_g_ly@rush.edu

Stacey Kuboske, PharmD MS
Clinical Pharmacist, Investigational Drug Service (IDS)
Vanderbilt University Hospital Pharmacy
1211 Medical Center Drive, VUH Room B-127
Nashville, TN 37232-7610
Phone: 615-343-1641
Email : stacey.l.kuboske@vumc.org

Wendy Kreider, RN, BSN, MS
Clinical Research Nurse III
Department of Anesthesiology

Rush University Medical Center
1750 W Harrison St.
Chicago, IL 60612
Phone: 312-942-1982
Email: Wendy_Kreider@rush.edu

Latrice Yates
Epi Research Assistant
Department of Psychiatry and Behavioral Sciences
1645 West Jackson Blvd, Suite 400
Chicago, IL 60612
Rush University Medical Center
Phone: 312-942-5932
Email: Latrice_Yates@rush.edu

Elias Mihan
Research Assistant I
Department of Anesthesiology
Vanderbilt University Medical Center
324 Medical Arts Building
1211 21st Avenue South
Nashville, TN 37212
Phone: 615-875-6530
Email: elias.mihan@vumc.org

Taylor Sorrells PT, DPT
Department of Physical Therapy
1725 W Harrison St., Suite 440
Chicago, IL 60612
Phone: (312) 942-5847
Email : Taylor_Sorrells@rush.edu

Sumihiro Suzuki, PhD
Data Analyst/Statistician
Department of Family and Preventative Medicine
Rush University Medical Center
1700 W VanBuren St., Suite 470
Chicago, IL 60612
Phone: (312)563-3718

The PIs (Bruehl & Burns) should be notified regarding protocol requirement questions, adverse events, unblinding a participant, questions surrounding eligibility or any other study logistical question. Dr. Buvanendran and Dr. Larach will be notified regarding medical questions. The Investigation Pharmacy will be contacted for all questions related to medication and lab drug condition. Co-Investigators Drs. Carmody and Bialosky will be unblinded to participant intervention and will be consulted about any questions related to intervention adherence or delivery. Requests for additional supplies will be made to the study coordinators and approved by the PIs.

PRÉCIS

Study Title

Evaluating Specific and Non-Specific Mechanisms in Two Distinct Complementary/Integrative Interventions for Chronic Pain

Objectives

Aim 1: Test effects of 2 treatments on non-specific mechanisms. We will test to what degree Mindfulness Therapy (MT) and Spinal Manipulation Therapy (SMT) produce changes in the 3 categories of non-specific mechanisms. We hypothesize that MT and SMT will produce changes in these non-specific mechanisms to approximately the same degree.

Aim 2: Test effects of 2 treatments on specific mechanisms. We will test to what degree MT and SMT produce changes in treatment-specific mechanisms (MT: changes in how patients think about pain; SMT: spinal stiffness). We expect that MT and SMT will each affect their own treatment-specific mechanism more than will the other treatment (e.g., MT will produce larger changes in mindfulness than SMT; SMT will produce larger changes in spinal stiffness than MT).

Aim 3: Test relative predictive validity of non-specific and specific mechanisms. We will test to what degree changes in non-specific and specific mechanisms predict changes in pain, mood and function, and whether these relationships depend on the treatment received. We will first test Mechanism Change x Treatment interactions to determine whether changes in any candidate mechanisms predict outcomes to a greater degree in one treatment than the other. In the absence of interactions, we will test the degree to which changes in non-specific and specific mechanisms account for unique and shared variance in predicting outcomes.

Aim 4: To address competing causation paths, we will test lagged and cross-lagged effects of early-treatment changes in non-specific and specific mechanisms predicting late-treatment changes in outcomes.

Design and Outcomes

In the proposed study, individuals with chronic low back pain (CLBP; n=286) will be assigned randomly to MT or SMT. For both MT and SMT, treatment will consist of 8 weekly, 60-90 min individual sessions. Self-report mechanism and outcome variables will be assessed at baseline, 1-day after each weekly session (via phone by research staff blind to condition or online by the patient), and at 3- and 6-mo follow-up. Spinal stiffness will be assessed for both conditions prior to and after each session. Endogenous opioid (EO) function and conditioned pain modulation (CPM) will be assessed for both conditions at each laboratory session. Specific mechanism factors were chosen to match the theoretical bases of each treatment. Mindfulness will be the specific mechanism for MT because (a) it is a key psychological factor targeted by MT and (b) preliminary research points to mindfulness as a viable mediator of psychological treatments. Spinal stiffness will be the specific mechanism for SMT because (a) it is a mechanical marker that can be measured and (b) changes in spinal stiffness have been shown to mediate treatment effects. Non-specific mechanisms will include changes in (a) CPM assessed via quantitative sensory testing (QST) methods; (b) EO function; (c) pain self-efficacy and catastrophizing; (d) patient expectations of benefit and quality of the therapeutic relationship. We will assess outcomes following published Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations. Pain interference (i.e., reported degree of interference in daily activities that is attributed to chronic pain) will be the primary outcome as it is equally relevant to both treatments, and given findings that reduction in pain intensity is not a primary focus of MT. Secondary outcomes will be pain intensity, mood, pain medication use, and use of pain-related healthcare.

Interventions and Duration

Mindfulness Training (MT)

Patients will receive training in mindfulness through (a) body scan meditation, a gradual moving of attention through the body, accompanied by awareness of breathing and other bodily sensations while in a lying position, (b) sitting meditation, focusing on awareness of breathing, bodily sensations, thoughts, and emotions, practiced sitting on a chair or cushion, (c) gentle movement exercises intended to develop awareness (mindfulness) during movement. Each session includes practice of these mindfulness techniques. In-session didactic material, interactions and discussion on subjects' experiences of developing and applying mindfulness in everyday life are also part of each session. In-session activities include suggestions for application of mindfulness as a method for responding positively to stress; dealing with the challenges of pain; and exercises focusing on the challenges and achievements patients experience in integrating mindfulness into their lives and the stressful situations they encounter. Additional discussion will focus on stress reactivity. To help patients deal with obstacles to increasing mindfulness, they will be taught problem-solving skills to develop solutions to meet MT goals. Finally, patients will develop a written maintenance plan that includes a list of short- and long-term goals for applying mindfulness methods and a plan for dealing with possible setbacks.

Spinal Manipulation Therapy (SMT)

SMT sessions will reflect a similar visit pattern and duration as MT sessions. Recent work showed small differences lacking clinical meaningfulness when comparing SMT provided 1, 2, or 3 times per week.(116) Furthermore, our visit pattern is consistent with professional guidelines. We will administer 2 SMT techniques each session, both of which have demonstrated effectiveness and are common for conservative management of individuals with CLBP. We will use scripted interactions between the physical therapist (PT) providing the SMT and subjects to stimulate therapist/subject relationships more consistent with the relationships that will develop in MT. Each SMT session will be organized as follows: 1) Participants will lie on the SMT table for 20 mins, while the PT sits approximately 6 ft away. As part of the script, the PT will review with subjects the inclusion/exclusion criteria ostensibly to ensure that nothing has changed. 2) The PT will perform the 2 SMT techniques during the next 20 mins. 3) Subjects will lie on the SMT table for the remaining 20 mins, while the PT sits approximately 6 feet away. As part of the script, the PT will ask subjects to perform a posterior pelvic tilt exercise. Subjects attempting to enter into discussion of issues beyond the scripted plan will be told, ''I'm sorry but because this is a research study I am not allowed to discuss this with you."

Each individual participant will be on study for 38 weeks. This includes baseline assessments, pre-treatment assessments, 8 therapy sessions, post-treatment assessments, and 3- and 6-month follow-up assessments.

Sample Size and Population

Participants will be 286 individuals experiencing CLBP recruited through referrals from staff at the University Pain Center, Midwest Orthopedic Clinic and Neurosurgery Clinic at Rush University, and at the Vanderbilt University Medical Center Interventional Pain Clinic. Flyers posted in community physician waiting rooms, local newspaper ads, and online patient recruitment systems will also be used. Based on our experience with randomized controlled trials (RCTs) involving CLBP

patients, we expect 16% drop out, and therefore plan to enroll 286 people to increase chances of 240 subjects completing follow-up.

Inclusion criteria are: 1) significant daily chronic pain intensity (≥4 on a 10-point scale) and interference in performing daily activities due to pain (≥3 on a 10-point scale) for at least 3 months; 2) age 18-75 years, and 3) not using opioid analgesics or Kratom on a daily basis or within 3 days of each laboratory session (confirmed via urine drug screen).

Exclusion criteria are: 1) meet criteria for past or present psychotic or bipolar disorders; 2) inability to understand English well enough to complete questionnaires or participate in therapy; 3) pain due to malignant conditions, rheumatoid arthritis, frequent migraines or tension headaches, complex regional pain syndrome, or fibromyalgia syndrome; 4) lumbar surgery within past 6 months; 5) pregnant; 6) signs of nerve root compression (ie, positive straight-leg raise <45°); 7) liver disease such as hepatitis or cirrhosis; 8)osteoporosis; 9) active suicidal ideation with intent; 10) opioid-dependency or daily use of Kratom; 11) inability to hold breath for 15 seconds; 12) acute trauma to spine; 13) long term use of corticosteroids; 14) have a spinal cord stimulator, an IT pump, or a similar device; 15) history of spinal fusion surgery; 16) arthritis of the hand, carpal tunnel syndrome, or any neuropathic pain diagnoses affecting the upper limbs; or 17) a BMI of ≥40.

1. STUDY OBJECTIVES

1.1 Primary Objective

The primary objective is to examine the degree to which MT and SMT exert effects on the non-specific mechanism, EO function. We will test to what degree MT and SMT produce pre- to mid- to post-treatment changes in EO function. Hypothesis 1: MT and SMT will produce near equivalent effects on EO function.

1.2 Secondary Objectives

A secondary objective is to examine the degree to which MT and SMT exert effects on the other non-specific mechanisms: CPM, pain-related cognitions, the working alliance and patient expectations. Hypothesis 2: MT and SMT will produce near equivalent effects on these non-specific mechanisms.

Another secondary objective is to test the effects of MT and SMT on specific mechanisms. We will test to what degree MT and SMT produce changes in treatment-specific mechanisms (MT: changes in how patients think about pain; SMT: spinal stiffness). Hypothesis 2: MT and SMT will each affect their own treatment-specific mechanism more than will the other treatment (e.g., MT will produce larger changes in mindfulness than SMT; SMT will produce larger changes in spinal stiffness than MT).

A third secondary objective is to test the relative predictive validity of non-specific and specific mechanisms. We will test to what degree changes in non-specific and

specific mechanisms predict changes in pain, mood and function, and whether these relationships depend on the treatment received. We will first test Mechanism Change x Treatment interactions to determine whether changes in any candidate mechanisms predict outcomes to a greater degree in one treatment than the other. In the absence of interactions, we will test the degree to which changes in non-specific and specific mechanisms account for unique and shared variance in predicting outcomes.

A final secondary objective is to examine competing causation paths. We will test lagged effects of early-treatment changes in specific and non-specific mechanisms on predicting late-treatment changes in outcomes, and vice versa.

2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

Chronic pain affects as many as 100 million individuals in the US alone (1), with management of chronic pain in recent years increasingly employing long-term opioid analgesic therapy (2-5). Such treatments carry the risk of serious side effects, misuse and addiction. In parallel, Complementary/Integrative (C/I) chronic pain interventions have also proliferated in recent years (e.g., Mindfulness Training [MT], spinal manipulation therapy [SMT]). Many of these approaches have support for efficacy, and pose low risk of side effects (6). The hope that interventions other than pharmacological ones can reduce pain and increase function has been partly realized. Thus, the popularity of C/I treatments for chronic pain has grown (7).

Most research regarding C/I interventions has focused on questions regarding overall treatment efficacy. That is, questions regarding "Does it work to improve pain and function?" have been in the forefront. Although establishing efficacy is vital, the bias in RCT research toward investigating only efficacy has left equally important questions about treatment mechanisms unanswered. Little attention has been devoted to explicitly testing how C/I pain treatments work, let alone whether they do so because of mechanisms specified by theory. Questions regarding "How does it work to improve pain and function?" have been relatively neglected.

2.2 Study Rationale

On one level are questions about mechanisms specified by theory ("specific mechanisms"). C/I treatments are each based on distinct theories of behavior, cognition, emotion, physical function and physiological pathways. From these principles, investigators derive putative therapeutic mechanisms. For example, MT is based on the premise that excessive attention to the "threat" aspect of pain generates negative affective responses thereby increasing pain and suffering. MT may work to improve patient function by altering cognitive processes or how a patient thinks about pain. This would include decreasing attentional fixation on pain-related sensations, cognitions and affect states, thereby reducing reactivity and developing the facility to redirect attention to sensations that do not cause emotional arousal. A tendency in evaluating MT outcomes research is to assume that if pre- to post-treatment gains are

observed, then changes in mindfulness are the primary agents bringing about those improvements. This remains an assumption that has not yet been subjected to rigorous empirical tests. In short, because many RCTs have not evaluated whether theoretically-specified mechanisms are valid, we do not yet know whether or to what degree the thought, emotion and behavior patterns we encourage patients to change are the actual vehicles by which they improve.

On a second level are questions about therapeutic mechanisms that are not specifically linked to any particular treatment approach in affecting outcomes, but have well-documented effects. These variables may be shared across C/I interventions, and may be responsible to some extent for their efficacy. These "non-specific mechanisms" include factors falling into at least 3 categories: changes in endogenous pain inhibitory systems (e.g., endogenous opioid [EO] function; conditioned pain modulation), changes in pain-related cognition (e.g., pain catastrophizing; self-efficacy), and therapy factors (therapeutic relationship, patient expectations). Non-specific mechanism factors have rarely been studied directly in RCTs of C/I interventions. However, the contribution of these mechanisms has been studied indirectly in research comparing active C/I interventions to sham control treatments (e.g., acupuncture vs sham acupuncture). Results have tended to reveal similar improvements on primary outcomes (i.e., pain, mood, function) between active and sham treatments (8,9). Findings where the target intervention allegedly driven by a specific mechanism produces similar effects to a sham intervention free of the specific mechanism suggests that mechanisms shared across the target and sham procedures were at work. Without explicit tests of the effects of these non-specific, shared mechanisms, it is not clear to what extent effects attributed to putative specific mechanisms may simply be proxies for the effects of non-specific mechanisms. Therefore, we do not yet have firm empirical bases for determining whether C/I pain treatments work for the reasons specified by theory, through non-specific shared mechanisms, or through some combination of these factors.

Addressing this knowledge gap is critical to the science and practice of C/I pain interventions because it: 1) tests theory validity, 2) provides an empirically-supported rationale for asking people with pain to devote time, energy and resources to common C/I techniques, 3) identifies the effective mechanisms of these pain treatments and reveals those that may be redundant or inert, 4) would highlight what exactly must be preserved in C/I pain treatments as they move from well-controlled RCTs to real-world clinical practice settings (92), and 5) provides theoretical and empirical principles by which to enhance the C/I techniques that are most closely linked to the largest benefits and potentially combine C/I interventions having complementary mechanistic effects. Addressing this knowledge gap requires that we shift attention in C/I pain research away from evaluating only treatment efficacy toward research that uncovers core treatment mechanisms.

The proposed comparative mechanism study will compare the degree to which MT and SMT activate both specific and non-specific mechanisms among individuals with chronic low back pain (CLBP), and the degree to which these mechanisms in turn affect key pain-related outcomes (e.g., pain interference, pain intensity). MT and SMT were chosen because: 1) data supports their efficacy; 2) their hypothesized

specific mechanisms of action are quite distinct; 3) they vary with regard to the degree of active vs passive participation required of patients; and 4) their use is widespread and growing.

Although there is mounting evidence that C/I interventions, such as MT and SMT, reduce pain and improve function in individuals with CLBP, evidence supporting how they work to bring about favorable outcomes is incomplete. Only a handful of studies have directly addressed whether MT works via its theoretically specific mechanism, increased mindfulness, and whether SMT works via its theoretically specific biomechanical mechanism (decreased spinal stiffness). Given that attention control or sham procedures produce a large measure of the effects shown by the active treatments, an alternative hypothesis is that C/I interventions work largely via non-specific mechanisms that many treatment approaches have in common. Much support for this inference comes from attention control and sham procedures wherein the suspected nonspecific mechanisms were not directly measured. Other disparate studies have assessed the role of factors such as evoked pain responsiveness, EO function, therapeutic relationship, etc., but not in a programmatic way, nor have they done so in concert with testing the effects of specific mechanisms.

Despite preliminary work in this area, definitive support for any putative mechanism for any C/I intervention is not yet available. We can glean only imprecise outlines about how C/I treatments work from a few studies, most of which were not designed to test mechanisms. Thus, we need comprehensive and well-powered studies that incorporate multiple treatments and multiple mechanism candidates to compare and contrast mechanism effects. If we are to advocate for the use of C/I interventions to treat chronic pain, we must know whether they are working at least in part via their specific mechanisms; putative mechanisms which in turn guide the development and use of specific therapeutic techniques. For example, to recommend use of SMT instead of an alternative, we should know that it produces improvements in pain and function via measurable mechanical changes wrought with spinal manipulation techniques. At the same time, nonspecific mechanisms are clearly at work in C/I interventions. Rather than characterize them as placebo or nuisance factors in our attempts to reveal specific mechanisms, we submit that we should instead define them and measure the magnitude of their effects, particularly in concert with specific mechanisms. For example, rather than seeing the therapeutic relationship as adding noise to the specific mechanism signal, we believe it may be more useful to quantify the precise effect of this treatment mechanism (114). If the therapeutic relationship accounts for 20% of a given treatment's effects, then perhaps training therapists to be more interpersonally adept would become a critical mission (see Kaptchuk et al (43) regarding effects of an augmented therapeutic relationship).

3. STUDY DESIGN

To break new ground in the study of C/I chronic pain mechanisms, and to lay groundwork for a new research strategy that focuses on principles of change and mechanisms, we propose a comparative mechanisms study that integrates RCT methods with methods developed in the psychotherapy process literature to better address questions of mechanism. As per Kazdin (92), frequent assessments of

mechanisms and outcomes during treatment are needed to examine patterns of change from early-late treatment and to examine lagged effects.

In the proposed study, individuals with CLBP (N=286) will be assigned randomly to MT or SMT. For both MT and SMT, treatment will consist of 8 weekly, 60-min individual sessions. Self-report mechanism and outcome variables will be assessed at baseline, 1-day after each weekly session (via phone by an RA blind to condition or online by the patient), and at 3- and 6-mo follow-up. Spinal stiffness will be assessed for both conditions prior to and after each therapy session. EO function and CPM will be assessed for both conditions at each laboratory session due to the complexity of this assessment. Specific mechanism factors were chosen to match the theoretical bases of each treatment. Mindfulness will be the specific mechanism for MT because (a) it is a key psychological factor targeted by MT (10) and (b) preliminary research points to mindfulness as a viable mediator of psychological treatments (16). Spinal stiffness will be the specific mechanism for SMT because (a) it is a mechanical marker that can be measured and (b) changes in spinal stiffness have been shown to mediate treatment effects (39). Non-specific mechanisms will include changes in (a) CPM assessed via QST methods; (b) EO function; (c) pain self-efficacy and catastrophizing; (d) patient expectations of benefit and quality of the therapeutic relationship. We will assess outcomes following IMMPACT recommendations. Pain interference will be the primary clinical outcome as it is equally relevant to both treatments, and given findings (97) that reduction in pain intensity is not a primary focus of MT. Secondary outcomes will be pain intensity, mood, pain medication use, and use of pain-related healthcare.

Given existing RCTs,(117-123), we expect MT and SMT to produce similar overall outcomes. As a comparative mechanisms study, analyses will focus primarily on documenting and characterizing mechanism effects. Note that all mechanism and outcome measures will be completed by all participants in both treatments at each assessment point, thus allowing us to test the degree to which mechanisms not specific to a treatment change and account for outcomes. To support the existence of a specific mechanism, analyses would reveal that: 1) putative specific mechanisms (i.e., mindfulness in MT, spinal stiffness in SMT) will show the largest pre-post changes in the relevant treatment condition (e.g., MT mindfulness changes > SMT mindfulness changes); 2) substantial changes in the mechanism will precede and predict substantial subsequent changes in outcomes only in the relevant treatment (e.g., mindfulness changes predict pain interference changes only in MT).

We will also take full advantage of this design and evaluate effects of mechanisms beyond pre- to post-treatment changes in outcomes. To our knowledge, no methodologically rigorous published study has yet examined effects of mechanisms on pre-post changes in concert with effects of mechanisms on maintenance or expansion of gains during follow-up. It may be that the true value of a mechanism may only be revealed through its effects on sustained gains out to 6-mos after treatment. Thus, mechanisms that do not show strong links with pre-post outcome changes may emerge as delayed predictors of 3- and 6-mos outcomes. Only by separating immediate pre-post mechanism effects from longer-term post-treatment mechanism effects can we build on current knowledge regarding the extended value

of C/I interventions for chronic pain.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

Participants will be recruited through referrals from staff at the University Pain Center, Midwest Orthopedic Clinic and Neurosurgery Clinic at Rush University, the Vanderbilt University Medical Center Interventional Pain Clinic, and the Osher Center for Integrative Medicine at Vanderbilt. Additionally, we will recruit in the community via flyers posted at community physician waiting rooms and other public sites, local newspaper ads, Facebook ads, and online patient recruitment systems (Vanderbilt e-mail recruitment system, My Research at Vanderbilt, Research Match). My Research at Vanderbilt is an informatics-based recruitment tool that uses Vanderbilt University Medical Center EMR data to match individuals expressing interest in research participation with studies which may be of interest to them. Research Match (ResearchMatch.org) is a national electronic, web-based recruitment tool that was created through the Clinical & Translational Science Awards Consortium in 2009 and is maintained at Vanderbilt University as an IRB-approved data repository. We have used all of these recruitment approaches in our prior work with a high degree of success. In addition, potentially qualifying individuals who have participated in past studies in our labs who have expressed an interest in writing to be contacted for future research may be contacted as well.

Participants will: 1) have significant daily chronic pain intensity (≥4 on a 10-point scale) and interference in performing daily activities due to pain (≥3 on a 10-point scale) for at least 3 months; and 2) be between age 18-75 years inclusive. Participants will not be using opioid analgesics or Kratom on a daily basis or within 3 days of each laboratory session (confirmed via urine drug screen).

Participants will not: 1) meet criteria for past or present psychotic or bipolar disorders; 2) be unable to understand English well enough to complete questionnaires or participate in therapy; 3) have pain due to malignant conditions, rheumatoid arthritis, frequent migraines or tension headaches, complex regional pain syndrome, or fibromyalgia syndrome; 4) have had lumbar surgery within past 6 months; 5) be pregnant; 6) have signs of nerve root compression (i.e., positive straight-leg raise <45○); 7) have liver disease such as hepatitis or cirrhosis; 8) have osteoporosis; 9) an active suicidal ideation with intent; 10) have opioid-dependency or daily use of Kratom; 11) have trouble holding their breath for 15 seconds; 12) have acute trauma to spine; 13) have long term use of corticosteroids; 14) have a spinal cord stimulator, an IT pump, or a similar device; 15) history of spinal fusion surgery; 16) arthritis of the hand, carpal tunnel syndrome, or any neuropathic pain diagnoses affecting the upper limbs; or 17) a BMI of ≥40.

4.1 Inclusion Criteria

Inclusion criteria are: 1) musculoskeletal pain of the lower back and/or leg pain stemming from degenerative disk disease, spinal stenosis, or disk herniation (radiculopathy subcategory), or muscular or ligamentous strain (chronic myofascial pain subcategory); 2) able to verify chronic pain diagnosis via written confirmation

from a physician; 3) significant daily chronic pain intensity (≥4 on a 10-point scale) and interference in performing daily activities due to pain (≥3 on a 10-point scale) for at least 3 months; 4) age 18-75 years, and 5) not using opioid analgesics or Kratom on a daily basis or within 3 days of each laboratory session (confirmed via urine drug screen).

Eligibility will be determined by MD review of medical records and RA administration of relevant items from the Mood Disorder, Psychotic Screening and Substance Use Disorders Modules of the Structured Clinical Interview for DSM-V Axis I Disorders - Non-Patient Edition (SCID-V/NP;77). General health will be assessed as will circumstances of the onset of low back pain, the sequence of events in terms of medical intervention to date, exacerbating/ameliorating factors, medications used currently and in the past, previous diagnostic modalities employed, and previous medical interventions and their impact.

4.2 Exclusion Criteria

Exclusion criteria are: 1) meet criteria for past or present psychotic or bipolar disorders; 2) inability to understand English well enough to complete questionnaires or participate in therapy; 3) pain due to malignant conditions, rheumatoid arthritis, frequent migraines or tension headaches, complex regional pain syndrome, or fibromyalgia syndrome; 4) lumbar surgery within past 6 mos; 5) pregnant; 6) signs of nerve root compression (i.e., positive straight-leg raise <45°); 7) have liver disease such as hepatitis or cirrhosis; 8) have osteoporosis; 9) have an active suicidal ideation with intent; 10) opioid-dependency or daily use of Kratom; 11) inability to hold breath for 15 seconds; 12) acute trauma to spine; 13) long term use of corticosteroids; 14) have a spinal cord stimulator, an IT pump, or a similar device; 15) history of spinal fusion surgery; 16) arthritis of the hand, carpal tunnel syndrome, or any neuropathic pain diagnoses affecting the upper limbs; or 17) a BMI of ≥40.

4.3 Study Enrollment Procedures

Participants will be recruited through referrals from staff at the University Pain Center, Midwest Orthopedic Clinic and Neurosurgery Clinic at Rush University, the Vanderbilt University Medical Center Interventional Pain Clinic, and the Osher Center for Integrative Medicine at Vanderbilt. Additionally, we will recruit in the community via flyers posted at community physician waiting rooms and other public sites, local newspaper ads, Facebook ads, and online patient recruitment systems (Vanderbilt e-mail recruitment system, My Research at Vanderbilt, Research Match). My Research at Vanderbilt is an informatics-based recruitment tool that uses Vanderbilt University Medical Center EMR data to match individuals expressing interest in research participation with studies which may be of interest to them. Research Match (ResearchMatch.org) is a national electronic, web-based recruitment tool that was created through the Clinical & Translational Science Awards Consortium in 2009 and is maintained at Vanderbilt University as an IRB-approved data repository. We have used all of these recruitment approaches in our prior work with a high degree of success. In addition, potentially qualifying individuals who

have participated in past studies in our labs who have expressed an interest in writing to be contacted for future research may be contacted as well.

Interested individuals will be able to contact the designated study research assistant by phone or email. Individuals expressing an interest will first be provided verbally with information on the study procedures, risks, and benefits, and if interested, will be given the opportunity to read the IRB-approved informed consent form. All questions from potential subjects will be answered by the study representative as accurately as possible. All individuals agreeing to participate will provide written informed consent prior to beginning any study procedures. Subject recruitment and consent procedures will be carried out by individuals designated and trained by each site PI and the IRB to carry out these procedures (i.e., the proposed research assistants). Potential subjects will be told that they will be compensated $605 for their time and effort to participate in all of the assessment and therapy sessions. In the Consent Form, it will be emphasized that subjects may discontinue participating at any time and still receive prorated compensation. The recruiter will inform potential subjects that participation is completely voluntary, and they may withdraw at any time without penalty or running the risk of jeopardizing current and future treatment at the Rush or Vanderbilt medical centers.

Study patients (n=286) will be randomized to receive either MT or SMT. The order of drug administration for each laboratory session will also be separately randomized and counterbalanced (placebo vs. naloxone) for both of the assessment time points (in double-blinded fashion). All randomization will be carried out using the Proc Plan procedure in SAS version 9.2 (SAS Institute, Cary, NC). This SAS procedure will be used to generate a randomization schedule for each sequential study slot (MT vs. SMT and the order of naloxone/placebo administration in each set of lab visits). Study subjects will be assigned to these previously randomized study slots in the order that they are enrolled, and the previously determined randomization status associated with each slot will determine the intervention condition each subject is in and the order of drug administration for each session. This randomized order will be maintained even if study appointments are missed (applies only to drug order in laboratory sessions). In the event of a true study dropout, that slot is considered used and future subjects will not be assigned to that slot.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

Drug Manipulation

Although not actually an intervention, we will administer naloxone during half of the pain induction sessions in order to quantify endogenous opioid (EO) function. We will use a placebo-controlled opioid blockade procedure to assess treatment-induced changes in EO function, by comparing pain responses under placebo to pain responses after opioid blockade with naloxone at pre- and post-treatment. Naloxone is an opioid antagonist with a brief half-life (1.1 hours; 78). We will use a weight-

adjusted dose of 0.11 mg/kg with a maximum dose of 8mg (8mg dose for a 160 lb. individual, consistent with our past work 69-71). As in our past studies, naloxone in 20 ml normal saline will be infused over a 10-minute period through an intravenous cannula placed in the non-dominant arm. At this dosage, naloxone provides effective blockade of all three major opioid receptor subtypes (79). Naloxone is FDA approved, and appears to have no clinical effects in non-opiate dependent individuals. Thus, participants using opioid analgesics on a daily basis or within 3 days of each laboratory session (confirmed via urine drug screen) and/or experiences withdrawal symptoms with the initial naloxone administration, will be excluded. It has been used safely at similar dosages in previous studies, including our studies in CLBP samples (68-72). Peak naloxone activity will be achieved approximately 10 minutes following completion of the infusion. A second dose of naloxone (0.055 mg/kg with a maximum dose of 4mg; 4mg for a 160 lb. individual) will be infused following the thermal and ischemic tasks (before CPM procedures). This dose will be used to maintain adequate opioid blockade across the duration of pain-induction procedures.

Study Interventions

Both study treatment interventions will consist of 8 weekly, 1-1.5 hr individual sessions. For MT and SMT, the content of each session will be based on a standardized treatment manual. Manuals will contain detailed session by session information, instructions and scripts for therapists, and patient handouts.

Mindfulness Training (MT)

Patients will receive training in mindfulness through (a) body scan meditation, a gradual moving of attention through the body, accompanied by awareness of breathing and other bodily sensations while in a lying position, (b) sitting meditation, focusing on awareness of breathing, bodily sensations, thoughts, and emotions, practiced sitting on a chair or cushion, (c) gentle movement exercises intended to develop awareness (mindfulness) during movement. Each session includes practice of these mindfulness techniques. In-session didactic material, interactions and discussion on subjects' experiences of developing and applying mindfulness in everyday life are also part of each session. In-session activities include suggestions for application of mindfulness as a method for responding positively to stress; dealing with the challenges of pain; and exercises focusing on the challenges and achievements patients experience in integrating mindfulness into their lives and the stressful situations they encounter. Additional discussion will focus on stress reactivity. To help patients deal with obstacles to increasing mindfulness, they will be taught problem-solving skills to develop solutions to meet MT goals. Finally, patients will develop a written maintenance plan that includes a list of short- and long-term goals for applying mindfulness methods and a plan for dealing with possible setbacks.

Spinal Manipulation Therapy (SMT)

SMT sessions will reflect a similar visit pattern and duration as MT sessions. Recent

work showed small differences lacking clinical meaningfulness when comparing SMT provided 1, 2, or 3 times per week. (88) Furthermore, our visit pattern is consistent with professional guidelines (89,90). Thus, we believe our design is optimal in matching time required for MT sessions and also meeting effective SMT practice patterns. We will administer 2 SMT techniques each session, both of which have demonstrated effectiveness and are common for conservative management of individuals with CLBP. (37,38,91) See Appendix for description and illustrations. We will use scripted interactions between the physical therapist (PT) providing the SMT and subjects to stimulate therapist/subject relationships more consistent with the relationships that will develop in MT. Each SMT session will be organized as follows: 1) Participants will lie on the SMT table for 20 mins, while the PT sits approximately 6 ft away. As part of the script, the PT will review with subjects the inclusion/exclusion criteria ostensibly to ensure that nothing has changed. 2) The PT will perform the 2 SMT techniques during the next 20 mins. 3) Subjects will lie on the SMT table for the remaining 20 mins, while the PT sits approximately 6 feet away. As part of the script, the PT will ask subjects to perform a posterior pelvic tilt exercise. Subjects attempting to enter into discussion of issues beyond the scripted plan will be told, ‘‘I’m sorry but because this is a research study I am not allowed to discuss this with you.”

Each individual participant will be in the study for approximately 38 weeks. This includes a baseline assessment, 2 pre-treatment laboratory assessments, 8 therapy sessions, 2 post-treatment assessments, and 3- and 6-month follow-up visits.

Therapist Training, Adherence, Participant Engagement

Therapist training. Therapists for MT will be post-doctoral level clinical psychologists or other licensed healthcare providers (e.g., nurse practitioner) with prior experience delivering MT for chronic pain. Therapists for SMT will be licensed PTs. Therapists at Rush and Vanderbilt sites will receive training prior to conducting treatment sessions with study subjects. Initial training will consist of a 2-day didactic and experiential course conducted by Burns and Carmody for MT and Bialosky for SMT. Therapists will be provided detailed manuals and outlines of treatment protocols, and the treatment strategies will be taught via direct instruction, recorded illustrations of techniques, and role-play of common scenarios. All instruction sessions will be digitally videotaped for reference and/or education of new therapists. Therapists will be certified to deliver each treatment by having supervisors (i.e., Drs. Burns, Carmody and Bialosky) rate tapes of practice role-play sessions prior to their working with study subjects. Mastery of each protocol will be required for therapists to deliver treatment in the research protocol.

Procedures to ensure consistency of treatment. To ensure that the therapists consistently follow the appropriate treatment protocol, four steps will be taken: (a) use of a detailed treatment manual; (b) weekly supervision sessions; (c) audio or video recording of sessions for treatment adherence ratings (see below), with these recordings and feedback from the adherence raters reviewed during the weekly supervision meetings conducted by Burns, Carmody and Bialosky; and (d) provision

of therapist feedback on treatment consistency and further didactics and role plays to correct "drift" if needed.

Treatment adherence, and therapist competence. Adherence refers to the extent to which a therapist uses interventions prescribed by a protocol. Ratings of adherence to the treatments will be conducted by Burns, Carmody, Bialosky and an RA. Protocol adherence criteria will be developed for each session with satisfactory adherence defined as 90% or more of the maximum possible score on the adherence rating scale. Ratings of therapists' competence in delivering the interventions will be used to evaluate 20% of the sessions for each of the treatment conditions. Sessions to be evaluated will be randomly selected.

Participant engagement in treatment. Receipt of the intervention by the participant, as well as participant perceived difficulty in understanding session content, will be assessed via weekly patient engagement checklists after each session. Under supervision of Dr. Burns and Bruehl, site RAs will evaluate the checklists for consistency.

5.2 Handling of Study Interventions

This is not a study about drug efficacy. However, we will administer naloxone during half of the pain induction sessions in order to determine endogenous opioid (EO) function. We will use a placebo-controlled opioid blockade procedure to assess treatment-induced changes in EO function, by comparing pain responses under placebo to pain responses after opioid blockade with naloxone at pre- and post-treatment. Naloxone is an opioid antagonist with a brief half-life (1.1 hours; 78). We will use a weight-adjusted dose of 0.11 mg/kg with a maximum dose of 8mg (8mg dose for a 160 lb. individual, consistent with our past work 69-71). As in our past studies, naloxone in 20 ml normal saline will be infused over a 10-minute period through an intravenous cannula placed in the non-dominant arm. At this dosage, naloxone provides effective blockade of all three major opioid receptor subtypes (79). Naloxone is FDA approved, and appears to have no clinical effects in non-opiate dependent individuals. It has been used safely at similar dosages in previous studies, including our studies in CLBP samples (68-72). Peak naloxone activity will be achieved approximately 10 minutes following completion of the infusion. A second dose of naloxone (0.055 mg/kg with a maximum dose of 4mg; 4mg for a 160 lb. individual) will be infused following the thermal and ischemic tasks (before CPM procedures). This dose will be used to maintain adequate opioid blockade across the duration of pain-induction procedures.

MT and SMT treatments will consist of 8 weekly, 1-1.5 hr individual sessions delivered by a therapist. For MT and SMT, the content of each session will be based on a standardized treatment manual. Manuals will contain detailed session by session information, instructions and scripts for therapists, and patient handouts.

5.3 Concomitant Interventions

5.3.1 Allowed Interventions

Psychotropic medications and non-opioid analgesic medications are allowed.

5.3.2 Required Interventions

NA

5.3.3 Prohibited Interventions

Subjects taking daily opiates, even if not dependent, will be excluded from the study to avoid precipitating minor withdrawal symptoms.

Concomitant psychosocial treatments (e.g., cognitive behavioral therapy) and physical or manipulation therapies (e.g., PT, chiropractic) are prohibited for this study.

5.4 Adherence Assessment

The primary adherence index will be participant attendance of 6 out of the possible 8 sessions. A secondary adherence index for MT and SMT will be completion of inter-session homework assignments.

6. STUDY PROCEDURES

6.1 Schedule of Evaluations (see table)

	Pre-Treatment			Intervention										Post		Follow-up	
Session	**Baseline**	**Lab 1**	**Lab 2**	**1**	**2**	**3**	**4**			**5**	**6**	**7**	**8**	**9**		**3m**	**6m**
Informed Consent	X																
Demographics (SR)	X													**Lab 1**	**Lab 2**		
AEI (SR)															X		
Bothersome Pain Item (SR)	X			X*	X*	X*	X*			X*	X*	X*	X*			X	X
Desirability of Control/Health Locus of Control (SR)															X		
Evoked Pain Intensity and Unpleasantness (SR)		X	X											X	X		
FFMQ-15/MAIA (SR)	X			X*	X*	X*	X*			X*	X*	X*	X*			X	X
Healthcare Utilization (SR)	X													X		X	X
Concomitant Medication	X	X	X											X	X	X	X
HOME Opioid Questionnaire (SR)	X																
McGill Pain Questionnaire (SR)		X	X											X	X		
MPQ (back pain- past week) (SR)	X													X		X	X
Oswestry Low Back Disability (SR)	X													X		X	X
Pain Catastrophizing Scale (SR)	X			X*	X*	X*	X*			X*	X*	X*	X*			X	X
Pain Self-Efficacy Questionnaire (SR)	X			X*	X*	X*	X*			X*	X*	X*	X*			X	X
PROMIS Anger/Anxiety/Depression/Pain Interference & Intensity/Sleep/Physical Function/Instrumental Support/Emotional Support (SR)	X			X*	X*	X*	X*			X*	X*	X*	X*			X	X
Working Alliance Inventory/Scale to Assess Therapeutic Relationship- Patient Version						X+					X+						
Reaction to Treatment Questionnaire (CEM)			X			X+					X+						
Pain Detect Questionnaire (SR)	X																
Pain Stages of Change Questionnaire (SR)	X			X*	X*	X*	X*			X*	X*	X*	X*			X	X
Naloxone Side Effects (SR)		X	X											X	X		
Patient Engagement Checklist (completed by therapist)				X	X	X	X			X	X	X	X				
Spinal Stiffness (before and after session- done via Vertetrack)				X	X	X	X			X	X	X	X				

Height & Weight (measured by scale)	X																
Blood Pressure (measured by Dinamap)	X																
Blood Draw (collected by RN)		X	X											X	X		
Urine Test (Opioid and Pregnancy-if female)		X	X											X	X		
Quantitative Sensory Testing		X	X											X	X		
If applicable: COVID-19 Safety Precautions (temperature check, travel history, signs/symptoms questionnaire)	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X

*Survey is done via phone call with research assistant and research assistant enters directly into REDCap or survey is entered directly into REDCap online by participant

+ Survey is done via pen and paper by participant and entered into REDCap by RAs (therapist-blinded)

SR = self –report. Will be directly entered into REDCap by participant

6.2 Description of Evaluations

COVID-19 PRECAUTIONS FOR STUDY VISITS

Due to the COVID-19 pandemic (also known as the coronavirus), participants are asked to wear a face mask when they come attend study visits. No exceptions are allowed. Participants will have their temperature taken upon arrival and will be asked to self-screen for signs/symptoms of COVID-19 **before** coming to their visit. Upon arrival, staff may ask these questions again and if the participant is showing any signs/symptoms, they will be asked to reschedule their study visit. Study staff reserves the right to reschedule appointments if they think participants may be showing signs/symptoms of COVID-19. Study staff may add additional screenings for participants based on new recommendations and policies from RUMC, VUMC, Chicago Public Health Department, Metro Public Health Department, or other government agencies. During the COVID-19 pandemic, MT sessions may be conducted via Zoom with therapists and participants in separate rooms, but face-to-face on an iPad to protect the safety of therapists and participants.

6.2.1 Phone Screening Evaluation

Potential participants responding to ads, flyers, etc., will be contacted by phone after indicating their desire to be contacted (via e-mail or phone call). They will be asked whether they agree to provide basic medical information in order to determine their study eligibility. If responding positively, they will be asked whether they have daily pain of at least 3 months duration, which is of an average intensity of at least 4/10 (with 0 being “no pain” and 10 “the worst pain possible”), and presents substantial interference in performance of social, work, and everyday activities (≥3/10 on a 10-point scale). They will be asked whether: 1) their pain is musculoskeletal pain of the lower back and/or leg; 2) they are aged between 18 and 75 years; 3) can understand English well enough to complete questionnaires or to participate in therapy; 4) their pain is due to malignant conditions, rheumatoid arthritis, complex regional pain syndrome, or fibromyalgia syndrome; 5) they have had lumbar surgery within the past 6 months or have ever had spinal fusion surgery; 6) they are pregnant; 7) they have had liver disease such as hepatitis or cirrhosis; 8) they have osteoporosis; 9) they have any active suicidal ideation with intent; 10) they have opioid-dependency or use Kratom daily; 11) they can hold their breath for 15 seconds; 12) they have acute trauma to spine; 13) they have long term use of corticosteroids; 14) they have a spinal cord stimulator, IT pump, or a similar device; 15) they have signs of nerve root compression (i.e., positive straight-leg raise <45○); 16) they meet criteria for past or present psychotic or bipolar disorders; 17) arthritis of the hand, carpal tunnel syndrome, or any neuropathic pain diagnoses affecting the upper limbs; and 18) they have a BMI of ≥40. If they meet eligibility criteria, they will be invited to an in-person interview.

6.2.2 Consent, Detailed Screening, Enrollment, Baseline, and/or Randomization

Consenting Procedure

All individuals agreeing to participate will provide written informed consent during Visit 1 (i.e., prior to beginning any study procedures). Subject consent procedures will be carried out by individuals designated and trained by each site PI and the IRB to carry out these procedures (i.e., the proposed research assistants). In the Consent Form, it will be emphasized that subjects may discontinue participating at any time and still receive prorated compensation. The recruiter will inform potential subjects that participation is completely voluntary, and they may withdraw at any time without penalty or running the risk of jeopardizing current and future treatment at the Rush or Vanderbilt medical centers. Consent forms with identifiable subject information will be maintained in a separate locked file from the actual study data files, which will be identified only by subject number. All subjects will be informed regarding how HIPAA requirements may impact on their study records, and will sign a notification regarding this issue. All published data will be reported in a manner in which individual data for specific subjects are not identifiable.

Screening

Screening can occur from 1 month prior to study enrollment to the day before study enrollment.

Screening evaluations will consist of:

- demographics
- confirmation of diagnosis of chronic low back pain
- pain duration and intensity ratings
- medical history
- list of current medications, prescribed dose and reported actual dose taken
- list of over the counter medications
- psychological screening: SCID-IV/NP

Please see sections 4.1 and 4.2 for inclusion/exclusion criteria. The criteria will be examined once all screening assessments are complete so as to not alert participants to our precise screening criteria.

Enrollment

The enrollment date is day the individual has met all the screening criteria and signs the informed consent form.

Baseline Assessment (Visit 1)

- Pain interference (primary outcome), pain intensity, negative affect (anger, anxiety, depression), physical function, sleep disturbance and social support will

be assessed via designated Patient-Reported Outcomes Measurement Information System (PROMIS) forms for each construct.

- Baseline demographics, neuropathy (painDETECT questionnaire), medication and healthcare use, opioid use (HOME Opioid Questionnaire), bothersome pain, back pain (McGill Pain Questionnaire) and disability (Oswestry Low Back Disability), and attitudes on changing pain (Pain Stages of Change Questionnaire) will also be assessed.
- Pain catastrophizing will be assessed with the Pain Catastrophizing Scale.
- Mindfulness will be assessed with the Five Facets of Mindfulness Questionnaire (short form), and the Multidimensional Assessment of Interoceptive Awareness (short form).
- Self-efficacy will be assessed with the Pain Self-Efficacy Questionnaire.
- Height and weight will be measured using a scale.
- Blood pressure will be measured using a Dinamap blood pressure monitor.

Pre-Treatment Lab Sessions (Visits 2 & 3)

- A urine sample will be collected and tested for opioids (using a rapid single panel opioid screening test) and pregnancy (females only – using an analog pregnancy test).
- Baseline assessment of opioid function and conditioned pain modulation will be assessed via the Quantitative Sensory Testing (QST) procedures described below.
- To enable potential future assessment of treatment-related changes in relevant biomarkers, a 4mL sample of whole blood will be drawn from the cannula placed for drug administration into a tube with EDTA prior to beginning laboratory pain or drug administration procedures in both laboratory sessions. Within 10 minutes of collection, samples will be centrifuged for 10 minutes at 3500rpm and 4○C. Plasma will then be pipetted into microcentrifuge tubes (0.5mL aliquots) and stored at -80○C until assayed.
- McGill Pain Questionnaire administered during the QST procedures in several versions to capture pain in back before and after each procedure.
- Evoked pain intensity and unpleasantness and naloxone side effects will be assessed.
- Assessment of any adverse events.

Endogenous Opioid (EO) Function

As in our previous work (68-72), we will use a placebo-controlled opioid blockade procedure to assess treatment-induced changes in EO function. Naloxone is an opioid antagonist with a brief half-life (1.1 hours; 78). We will use a weight-adjusted dose of 0.11 mg/kg with a maximum dose of 8mg (8mg dose for a 160 lb. individual,

consistent with our past work 69-71). As in our past studies, naloxone in 20 ml normal saline will be infused over a 10-minute period through an intravenous cannula placed in the non-dominant arm. At this dosage, naloxone provides effective blockade of all three major opioid receptor subtypes (79). Naloxone is FDA approved, and appears to have no clinical effects in non-opiate dependent individuals. Thus, participants using opioid analgesics on a daily basis or within 3 days of each laboratory session (confirmed via urine drug screen) and/or experiences withdrawal symptoms with the initial naloxone administration, will be excluded. It has been used safely at similar dosages in previous studies, including our studies in CLBP samples (68-72). Peak naloxone activity will be achieved approximately 10 minutes following completion of the infusion. A second dose of naloxone (0.055 mg/kg with a maximum dose of 4mg; 4mg for a 160 lb. individual) will be infused following the thermal and ischemic tasks (before CPM procedures). This dose will be used to maintain adequate opioid blockade across the duration of pain-induction procedures.

The QST protocol will use 2 laboratory pain tasks for evaluation of evoked pain responsiveness. An ischemic pain task will be used based on procedures described by Maurset et al. (80), similar to our past opioid blockade studies (68,72). Subjects will first engage in 2 mins of dominant forearm muscle exercise using a hand dynamometer at 50% of his or her maximal grip strength (as determined prior to beginning laboratory procedures), and then will be asked to raise the dominant forearm over their head for 15 secs. A blood pressure cuff will then be inflated on the participant's dominant biceps to 200 mmHg pressure, and the cuff will remain inflated until tolerance is reached, up to a maximum of 8 mins. As in our previous work (68,72), at 30-sec intervals throughout the ischemic task, participants will be asked to rate their current acute pain using a 0-100 verbal numeric rating scale (0 = "no pain" and 100 = "worst possible pain"). Pain threshold will be defined as time elapsed from task onset to when the sensation is first described as "painful." Pain tolerance will be defined as time elapsed between onset of the pain task and patients' expressed desire to terminate the task (8 min max). At tolerance, subjects will be asked to rate the overall ischemic task pain intensity using the McGill Pain Questionnaire (MPQ; see below).

A heat pain task using a Medoc TSAII NeuroSensory Analyzer (Medoc US., Minneapolis, MN) will then follow. This equipment will be used to assess heat pain threshold and tolerance using an ascending method of limits protocol as used in our prior work (68,71,72). The equipment to be used has a hardware temperature cutoff of 51○C in order to prevent tissue injury. Four trials each will be conducted for heat pain threshold and tolerance, with each trial conducted sequentially at 1 of 4 different non-overlapping sites on the non-dominant ventral forearm. An interval of 30 secs between successive stimuli will be employed. For threshold trials, the probe will start at an adaptation temp of 32○C, with the temp increasing at a ramp rate of 0.5○C/sec until the subject indicates that the stimulus has begun to feel "painful." For tolerance trials, the probe will start at an adaptation temperature of 40○C, with the temperature increasing at a ramp rate of 0.5○C/sec until the subject indicates maximum tolerance has been reached. Means of the 4 thermal pain threshold and tolerance trials will be derived for use in analyses. Immediately upon completion of the final heat pain tolerance trial, subjects will be asked to rate the overall pain experienced during this

trial using the MPQ. EO function will be operationalized as in our past work as changes in evoked pain responses between the placebo and naloxone conditions (68,71,72), with blockade effects on the visual analog scale (VAS) pain intensity measure of the MPQ considered primary.

Conditioned Pain Modulation (CPM)

Efficiency of descending inhibition of pain (i.e., CPM) will be assessed using a protocol adapted from Gehling et al. (81) which found that combining heat pain (test stimulus) with cold pressor pain (conditioning stimulus) demonstrated acceptable test-retest reliability over a 3 day test-retest interval. CPM is a centrally-mediated effect (107), and therefore is expected to be observed at sites throughout the body, e.g., CPM elicited with stimuli applied to the back vs. the forearm is similar (102). As is common in the CPM literature, and to avoid any local sensitization confounds with stimuli applied to the back in CLBP patients, the current project will apply both the test and conditioning stimuli in the periphery. A cold pressor task [circulating ice water bath; see our prior work (112,113)] applied to the nondominant upper extremity will be the tonic conditioning stimulus, and the same TSA-II heat pain stimulus used in thermal pain testing (applied to the dominant forearm) will be the test stimulus. At the beginning of lab session 1, we will determine the heat pain stimulus temperature corresponding with an intensity rating of 60/100 for that individual. This will be done using a series of brief (5 sec) thermal stimuli applied starting at 44○C, based on our prior work indicating a mean thermal pain threshold and tolerance of 44○C and 48○C respectively in chronic back pain patients. This stimulus intensity will be increased/decreased incrementally by 0.5○C until the targeted perceived pain intensity of 60/100 is reached. This temperature (referred to hereafter as P60) will be used as the stimulus intensity for the test stimulus in all CPM procedures. These CPM procedures will entail: (a) Three assessments of heat pain ratings (once every 10 sec) in response to 30 secs of a constant thermal stimulus applied at the predetermined P60 target temperature to the dominant arm ("Pre-Conditioning Phase"), (b) Initiation of the tonic cold pressor conditioning stimulus to the nondominant hand (immersion in an ice water bath) and after 30 sec of exposure to the conditioning stimulus, (c) Three assessments of heat pain ratings (once every 10 sec) in response to 30 secs of the P60 thermal test stimulus applied simultaneously with the conditioning stimulus ("Conditioning Phase"; the total cold pressor duration will be 60 seconds). Change in mean thermal stimulus pain ratings during the pre-conditioning minus conditioning phases will be used to index CPM.

Assessment of spinal stiffness

The VerteTrack device (VibeDx Diagnostic Corp) will be used to measure the lumbar posterior to anterior spinal stiffness, with L3 values considered primary per validation studies (40,103). The VerteTrack device has not been approved by the FDA. The device consists of a solid aluminum gantry (Width 108cm × Height 109cm × Length 151cm) on lockable casters that can be positioned over a participant lying in the prone position on a standard padded-plinth. Each assessment takes approximately 15 mins.

Two types of spinal stiffness values will be calculated from the force displacement data of each indentation: global stiffness and terminal stiffness. Global stiffness will be calculated from the slope of force displacement curve between 5 Newtons (N) and 60 N, representing the stiffness of underlying tissues throughout the indentation (39). Terminal stiffness is a ratio between the maximal applied force (60 N) and maximal resultant displacement, representing stiffness at the end of indentation (39). Spinal stiffness will be measured 3 times at each assessment. Averaging 3 measurements, within- and between-day reliability point estimates of both global and terminal stiffness were 0.99 and 0.98, respectively (40).

Randomization

Study subjects will be randomized to receive either MT or SMT. The order of drug administration for each laboratory session will also be randomized and counterbalanced (placebo vs. naloxone), and double-blinded. These randomizations will occur prior to the baseline screening visit (Visit 1). All randomization will be carried out using the Proc Plan procedure in SAS version 9.2 (SAS Institute, Cary, NC). This SAS procedure will be used to generate a randomization schedule for each sequential study slot (MT vs. SMT and the order of naloxone/placebo administration in each set of lab visits). Study subjects will be assigned to these previously randomized study slots in the order that they are enrolled, and the previously determined randomization status associated with each slot will determine the study condition each subject is in and the order of drug administration.

6.2.3 Blinding

Research staff at each site who will conduct weekly phone assessments (when applicable) and who will conduct the laboratory pain-induction sessions will be blind to subject treatment condition. The randomization scheme will be implemented by department administrative assistants who will have no other role in the study.

Given the nature of the interventions and that Co-Is Drs. Carmody and Bialosky will be providing intervention-specific oversight (e.g., review of MT and SMT audio- and video-recordings), neither of these Co-Is will be blinded as to intervention assignment. These individuals will not be engaged in review of individual level study data or analysis of study results. The PIs (Drs. Burns and Bruehl) will be blinded to intervention assignment. Moreover, during routine review of data, PIs and other research staff will also be blinded to participant intervention assignment by hiding from view the columns denoting subject ID and intervention status in the REDCap database.

Double blinding (patient and investigators) as to drug condition for all laboratory sessions will be maintained by the Investigational Pharmacy at each site. Drug blinding will be broken by the PIs for specific participants as needed in the event of possible safety or side effect issues.

Participants will not be blinded to treatment condition: the MT and SMT procedures will be obvious.

Stake Holder	Intervention Group Assignment	Lab Drug Condition	Primary Mechanistic Outcome Measure	Clinical/Functional Outcome Measure
Study Subjects/Patients	Unblinded	Blinded	Unblinded	Unblinded
Instructors/Practitioners	Unblinded	Blinded	Blinded	Blinded
Outcome Assessors	Blinded	Blinded	Unblinded	Unblinded
Statistician	Blinded	Blinded	Unblinded	Unblinded
Principal Investigators	Blinded	Blinded	Blinded	Blinded

6.2.4 Treatment Visits

Treatment Sessions 1-8 (Visits 4, 5, 6, 7, 8, 9, 10, 11)

- MT and SMT treatments (as assigned) will be conducted during these visits.
- Assessment of spinal stiffness pre- and post-session as described above.
- Patient engagement in session will be rated by therapist.
- Assessment of any adverse events.

Assessed via phone call by RA within 48 hours of session or online via REDCap by the patient:

- Pain interference (primary outcome), pain intensity, negative affect (anger, anxiety, depression), physical function, sleep disturbance and social support will be assessed via designated PROMIS measures.
- Pain catastrophizing will be assessed with the Pain Catastrophizing Scale.
- Mindfulness will be assessed with the Five Facets of Mindfulness Questionnaire (short form), and the Multidimensional Assessment of Interoceptive Awareness (short form).
- Self-efficacy will be assessed with the Pain Self-Efficacy Questionnaire.
- Bothersome pain and attitudes on changing pain (Pain Stages of Change Questionnaire) will also be assessed.

Treatment sessions 3 and 6

In addition to the measures above, the following measures will be given:

- The Working Alliance Inventory – short form, and the Scale to Assess Therapeutic Relationships – Patient Version will be administered in-person.
- The Reaction to Treatment Questionnaire will be administered in-person.

Post-Treatment Lab Sessions (Visits 12, 13)

- A urine sample will be collected and tested for opioids (using a rapid single panel opioid screening test) and pregnancy (females only – using an analog pregnancy test).
- Post-treatment endogenous opioid function and conditioned pain modulation will be assessed via the QST procedures described in Section 5.2.
- To enable potential future assessment of treatment-related changes in relevant biomarkers, a 4mL sample of whole blood will be drawn from the cannula placed for drug administration into a tube with EDTA prior to beginning laboratory pain or drug administration procedures in both laboratory sessions. Within 10 minutes of collection, samples will be centrifuged for 10 minutes at 3500rpm and 4○C. Plasma will then be pipetted into microcentrifuge tubes (0.5mL aliquots) and stored at -80○C until assayed.
- McGill Pain Questionnaire administered during the QST procedures.
- Evoked pain intensity and unpleasantness and naloxone side effects will be assessed.
- Assessment of any adverse events.

6.2.5 Follow-up Visits

Follow-ups 3-month & 6-month (Visits 14 & 15)

- Pain interference (primary outcome), pain intensity, negative affect (anger, anxiety, depression), physical function, sleep disturbance and social support will be assessed via PROMIS item banks.
- Pain catastrophizing will be assessed with the Pain Catastrophizing Scale.
- Mindfulness will be assessed with the Five Facets of Mindfulness Questionnaire (short form), and the Multidimensional Assessment of Interoceptive Awareness (short form).
- Self-efficacy will be assessed with the Pain Self-Efficacy Questionnaire.
- Bothersome pain and attitudes on changing pain (Pain Stages of Change Questionnaire) will also be assessed.
- Assessment of any adverse events**.**

6.2.6 Missed Evaluations

There is a 6-week window from baseline (visit 1) to the first lab session (visit 2). The first lab session (visit 2) must occur within this window and the second lab session (visit 3) must be within 2 weeks of the first. The first treatment visit (visit 4) is to

occur within one week from lab session 2 (visit 3).

If a participant misses an intervention session (MT or SMT) the staff will attempt to reschedule the visit for the following week, and the treatment schedule will be adjusted accordingly.

Treatment sessions 1-4 (visits 4-7) must all occur within 2 months of lab session 2 (visit 3). The first post-treatment lab session (visit 12) should occur within one month from treatment session 8 (visit 11).

The second post treatment lab session (visit 13) must occur within 2 weeks of the first post treatment lab session (visit 12).

The date of the follow-up assessments will be calculated from the date of the final post treatment lab session (visit 13). Participants will have a 2-week window around this date to complete the 3- and 6-month follow-ups (visits 14 & 15). Failure to complete these assessments within this window will result in the follow-ups being skipped.

All visits that fall outside of these allowable windows will be reported as protocol deviations.

7. SAFETY ASSESSMENTS

People with chronic pain who begin completing frequent assessments of current pain, mood and activity levels may report increased awareness of their pain and distress. Participants will be told that such phenomena associated with close self-monitoring are a part of the treatment approaches we are offering, and will be addressed as part of the interventions. However, participants will be closely monitored (by the study coordinator/RA who will report relevant observations to the site PIs) during the study for significant increases in pain intensity and negative mood, and if any are noted, participants will be contacted to discuss these issues with the site PI. As appropriate, they will be referred by the site PI to their physician for further evaluation should there be any unexpected or significant deleterious changes. Participants will also be monitored as above during the course of the study for evidence of significant emotional problems. Any participant judged to be deteriorating significantly in terms of psychological and pain condition as a result of their participation in this study will be withdrawn from the trial and referred for individual treatment.

Therefore, a standardized referral form is not considered adequate for this study. The site PI will personally monitor all such referrals and document them accordingly. Such documentation will be kept confidential in the locked data storage area.

7.1 Specification of Safety Parameters

During the assessment phase, and/or during the treatment phase, should any participant report significant physical or emotional distress or other adverse event, the site PI will be notified immediately. The site PI will contact the participant by telephone, assess the event, and determine whether referrals to other healthcare providers are appropriate. Any necessary referrals will be made through telephone contact by the site PI to the appropriate practitioner.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

Diligent study safety monitoring will be conducted by the PIs on an ongoing basis, in conjunction with the IMC, the IRB and NCCIH as appropriate (see above). Study progress and safety will be reviewed weekly by the PIs. Progress reports, including patient recruitment into the full study, and adverse events (AEs) will be provided to the Independent Monitoring Committee (IMC) each quarter. This quarterly IMC progress report will be submitted to the IMC on January 15, April 15, July 15, and October 15. The more detailed semi-annual report will be submitted to the IMC on January 15 and July 15. A separate report will be compiled every 6 months and will include a list and summary of AEs. In addition, the report will address (1) whether adverse event rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all subjects met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely. The IMC report prepared every 6 months will be signed by the members of the IMC and will be forwarded to the IRBs and NCCIH (reports will be provided more frequently on an ongoing basis if concerns are identified). The IRBs will review progress of this study on an annual basis.

Before the study begins, all subjects will be provided with contact phone numbers for research staff so that subjects can contact study staff at any time during the study. When in the laboratory, subjects will be supervised continuously. During the study, the PIs will monitor all adverse events, defined as any unfavorable or unintended symptom, sign or disease associated with a medical treatment or procedure that may or may not be related to the treatment or procedure. Part of this process will include monitoring of serial phone/online assessments by the research coordinator/RAs for worsening of physical or mental health during study participation. Adverse events can be related to participation in the study or to medical or psychiatric conditions being treated (e.g. depression), or they could be entirely unrelated to any of these (e.g., motor vehicle accident). In this study, we will use the FDA definition of serious adverse events (SAE; e.g., death, hospitalization, emergency room visits, suicide plans or attempts). SAEs will be systematically assessed at each lab visit. Any SAE, whether or not related to study intervention, will be immediately reported to the IRB and the NCCIH. Review by the IMC, IRB and NCCIH regarding the nature of the SAE will be used to decide whether the study should continue as is, whether changes to protocol are needed, or whether the study must be discontinued.

7.3 Adverse Events and Serious Adverse Events

To ensure the safety of trial participants, we will monitor all adverse events, defined as any unfavorable or unintended symptom, sign or disease associated with a medical treatment or procedure that may or may not be related to the treatment or procedure. Adverse events can be related to the treatment or to the disorder being treated (e.g. pain exacerbation), as well as to a concurrent disorder or treatment (e.g. diabetes or

its treatment), or they could be entirely unrelated to any of these (e.g., motor vehicle accident).

In this study, we will use the FDA definition of serious adverse events (SAE, e.g., death, hospitalization, emergency room visits, suicide plans or attempts).

A Serious Adverse Event (SAE) is any AE that results in one or more of the following outcomes:

- Death
- A life-threatening event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly or birth defect
- Important medical event based upon appropriate medical judgment

7.4 Reporting Procedures

SAEs will be systematically assessed at each treatment session. Any SAE, whether or not related to study intervention, will be reported to the IMC and the IRB, as well as NCCIH on an ongoing basis. In addition, the PIs will prepare a semi-annual report on data collection and occurrence of any SAE for review by the IMC and IRBs. The initial SAE report will be followed by submission of a completed resolution report to the IRBs and the IMC.

Solicited events will occur as part of the weekly phone calls/online assessments during the treatment epoch.

Unsolicited events will occur when a participant contacts study staff to report a worsening in their symptomatology, and when pain and mood data during the intervention is compared to baseline.

SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the IMC, IRB and NCCIH in accordance with requirements.

Unexpected fatal or life-threatening AEs related to the intervention will be reported to the NCCIH Program Officer within 7 days. Other serious and unexpected AEs related to the intervention will be reported to the NCCIH Program Official within 15 days.

Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the IMC, IRBs, NCCIH, and other oversight organizations in accordance with their requirements. In the annual AE summary, the IMC Report will state that they have reviewed all AE reports.

7.5 Follow-up for Adverse Events

In the event that a participant withdraws from the study or the investigator decides to discontinue a patient due to SAE, the patient will be monitored by the PIs via ongoing status assessment until (1) a resolution is reached (i.e., the problem has resolved or stabilized with no further changes expected), (2) the SAE is determined to be clearly

unrelated to the study intervention, or (3) the SAE results in death. Review by the IMC, IRB and NCCIH regarding the nature of any SAE will be used to decide whether the study should continue as is, whether changes to protocol are needed, or whether the study must be discontinued. In this case, the PI and Co-PI will discuss any proposed changes or study termination with the NCCIH Program Officer. We will also monitor safety alerts, defined as events that are relevant to the study populations and pose safety risks to study participants. Examples of safety alerts would include a sudden increase in pain symptoms or change in the type of pain experienced, or a clinically significant increase in patient depression or anxiety. Both SAEs and safety alerts will be tracked using a standardized form recording the date of the event, type of event, attribution of the event (e.g., judgment regarding whether it was intervention related), whether the event was resolved or controlled, and the resolution date. Any concerns identified will be reported to NCCIH and the IRB on an ongoing basis.

7.6 Safety Monitoring

Safety of participants will be ensured by the continued monitoring of their mental health and medical status. Subjects will all have access to treatment-as-usual services to address any study-induced adverse effects or other clinical concerns. We propose a Data Safety and Monitoring Committee (IMC) in which outside safety officers will oversee all implementation and data collection issues related to project safety in addition to careful IRB and PI monitoring. The IMC will be established external researchers who are experienced in the safe conduct of randomized controlled trials. They will monitor all data- and safety-related procedures and ensure participant safety during the study. The PIs will provide periodic updates (minimally, once per month) to the safety officers on study performance.

The proposed IMC is described in the DSMP document. All three monitors are not associated with this research project and thus work independently of the PIs, Dr. Bruehl and Dr. Burns. All three monitors are not part of the key personnel involved in this grant.

Study progress and safety will be reviewed quarterly (and more frequently if needed). Progress reports, including patient recruitment, retention/attrition, and AEs will be provided to the Independent Monitor(s) following each of the quarterly reviews. An Annual Report will be compiled and will include a list and summary of AEs. In addition, the Annual Report will address (1) whether AE rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely. The Annual Report will be sent to the IMC and will be forwarded to the IRB and NCCIH. The IRB and other applicable recipients will review progress of this study on an annual basis. The PIs will also send copies of signed recommendations and comments from the IMC to the NCCIH Program Officer within 1 month of each monitoring review.

8. INTERVENTION DISCONTINUATION

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial.

Other potential reasons for early termination may include individual participant gross noncompliance (e.g., not responding to phone calls from staff, several cancellations of treatment appointments, no-shows to treatment appointments). Participants will also be discontinued if study investigators see a >25% worsening of baseline pain and mood during the MT or SMT treatments.

Participants will be monitored during the course of the study for evidence of significant deleterious physical, pain-related or emotional changes. In the event that a participant is judged by the research assistants and/or PIs to be deteriorating significantly in terms of pain and emotional condition as a result of their participation in this study, the team may decide to withdraw the subject from the trial and refer them for appropriate treatment. Participants will also be informed that should any unexpected or significant deleterious changes in their condition occur, that they immediately call Dr. Burns or Dr. Bruehl (PhD licensed clinical psychologists). Subjects will be given the office phone numbers of Drs Burns and Bruehl to ensure access to study staff. Drs. Burns and Bruehl will determine whether referrals to other healthcare providers are appropriate. Any necessary referrals will be made through telephone contact by the PIs to the appropriate practitioner. Therefore, a standardized referral form is not considered adequate for this study. The PIs will personally monitor all such referrals and document them accordingly. Such documentation will be kept confidential in the locked data storage area in Drs. Burns' or Bruehl's office.

If a participant experiences a SAE, he/she will be discontinued in the study.

For the purposes of intent-to-treat analyses, we will make every effort to obtain scheduled follow-up assessments for all individuals failing to complete the study for any reason.

If NCCIH asks us to discontinue the study, we will discontinue all participants. If the study intervention is discontinued we will continue to follow participants for 1-month post intervention, with their permission. As planned for the follow up period, participants will be asked to rate their pain, function and mood.

There will be no cases of temporary discontinuation of treatment.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

This comparative mechanism study will compare the degree to which 2 distinct C/I interventions, MT vs. SMT, activate specific and non-specific mechanisms, and the degree to which these mechanisms affect pain-related outcomes. Comparing the role of diverse mechanisms in outcomes of these 2 interventions in a single RCT will permit testing the extent to which various mechanistic effects are shared across treatments vs. unique to a given treatment. Two hundred eighty-six people (to achieve 240 completed participants assuming 16% dropout) with CLBP will be randomly assigned to MT or SMT. These interventions were chosen because: a) RCT data already support their efficacy; b) their hypothesized specific mechanisms of action are quite distinct; c) they vary regarding the degree of active vs passive patient participation required; d) their use is widespread and growing. All mechanisms and outcomes will be assessed frequently across all treatments. We expect both treatments to produce significant changes in pain, mood and function.

Aim 1: Test effects of 2 treatments on non-specific mechanisms. We will test to what degree MT and SMT produce changes in the 3 categories of non-specific mechanisms: endogenous pain inhibitory systems (endogenous opioid function; conditioned pain modulation), pain-related cognition (pain catastrophizing; self-efficacy), and therapy factors (therapeutic relationship, patient expectations). We hypothesize that MT and SMT will produce changes in these non-specific mechanisms to approximately the same degree.

Aim 2: Test effects of 2 treatments on specific mechanisms. We will test to what degree MT and SMT produce changes in treatment-specific mechanisms (MT: changes in how patients think about pain; SMT: spinal stiffness). We expect that MT and SMT will each affect their own treatment-specific mechanism more than will the other treatment (e.g., MT will produce larger changes in mindfulness than SMT; SMT will produce larger changes in spinal stiffness than MT).

Aim 3: Test relative predictive validity of non-specific and specific mechanisms. We will test to what degree changes in non-specific and specific mechanisms predict changes in pain, mood and function, and whether these relationships depend on the treatment received. We will first test Mechanism Change x Treatment interactions to determine whether changes in any candidate mechanisms predict outcomes to a greater degree in one treatment than the other. In the absence of interactions, we will test the degree to which changes in non-specific and specific mechanisms account for unique and shared variance in predicting outcomes.

Aim 4: To address competing causation paths, we will test lagged and cross-lagged effects of early-treatment changes in non-specific and specific mechanisms predicting late-treatment changes in outcomes.

9.2 Sample Size and Randomization

Power consideration for Aim 1:

Based on past findings, we expect that Mindfulness Training (MT) and Spinal Manipulation Therapy (SMT) will have near-equivalent effects on the primary outcome, changes in EO function. We ran power calculations assuming a true difference of 0 between MT and SMT. Please note that we plan to enroll 286 participants to achieve a sample size of 240 completed participants. See below:

Power Analysis of Two-Sample T-Test for Testing Equivalence Using Differences

Power	MT Group Sample Size (N1)	SMT Group Sample Size (N2)	Lower Equiv. Limit	Upper Equiv. Limit	True Difference	Standard Deviation	Alpha	Beta
0.851	120	120	-3.0	3.0	0.0	7.5	0.050	0.149
0.950	120	120	-3.5	3.5	0.0	7.5	0.050	0.050
0.987	120	120	-4.0	4.0	0.0	7.5	0.050	0.013

An equivalence test of means using two one-sided tests on data from a parallel-group design with sample sizes of 120 in the reference group and 120 in the treatment group achieves 85% power at a 5% significance level when the true difference between the means is 0.0, the standard deviation is 7.5, and the equivalence limits are -3.0 and 3.

Power considerations for Aim 2:

We will test effects of MT and SMT on the treatment-specific mechanisms, pre-post treatment changes in mindfulness and spinal stiffness. Per reviewer suggestions and input from our co-I, Dr. Carmody, we expanded the assessment of "mindfulness" to include pain unpleasantness/bothersome ratings and the Multidimensional Assessment of Interoceptive Awareness (MAIA) scale as well as the Five Facets of Mindfulness Questionnaire (FFMQ). We expect MT to produce larger changes in the mindfulness measures than SMT, and for SMT to produce larger changes in spinal stiffness than MT.

Null Hypothesis: Mean1=Mean2. Alternative Hypothesis: Mean1<>Mean2

			Allocation						
Power	**N1**	**N2**	**Ratio**	**Alpha**	**Beta**	**Mean1**	**Mean2**	**S1**	**S2**
0.800	120	120	1.0	0.050	0.200	0.36	0.00	1.00	1.00
0.983	120	120	1.0	0.050	0.017	0.53	0.00	1.00	1.00

Treatment group sample sizes of 120 and 120 will achieve 80% power to detect a difference of Cohen's d = 0.36. With a larger effect – d = .53 -- at α=0.05 we will have 98.3% power to detect a treatment difference.

Power considerations for Aim 3:

The first focus is to determine whether pre-post changes in specific and non-specific mechanisms (e.g., specific: spinal stiffness changes; non-specific: self-efficacy changes) interact with Treatment Condition to predict pre-post changes in DVs (e.g. pain intensity changes). A significant interaction would suggest that pre-post changes in a mechanism factor predicted pre-post changes in a DV **differently** depending on Treatment Condition. In the case of a significant interaction, we will test simple slopes of pre-post mechanism changes for DV changes for each Treatment Condition separately. We do not expect many significant interactions. Thus, we focus our power analyses on detecting increments in R^2 when adding pre-post mechanism change scores into regressions to predict pre-post changes in outcomes.

Multiple Regression Power Analysis

Power	**N of independent variables teste**	**R^2 for Independent Variable(s) tested**	**R^2 for Variables controlled**
0.74152	1	0.025	0.1
0.81731	1	0.030	0.1
0.79137	1	0.025	0.2
0.86115	1	0.030	0.2
0.84360	1	0.025	0.3
0.90403	1	0.030	0.3

All calculations assume N=240 and α=0.05. Again note that we expect to recruit 286 subjects to achieve an analyzable sample of 240 completed subjects.

With 10% of variance in pre-post outcome changes accounted by mechanism variables already in the equation, we have 74% power to detect a 2.5% increment in R^2 with the addition of another mechanism variable. This increases to 90% power to detect a 3% increment in R^2 when mechanism variables already in the equation account for 30% of the outcome changes. Note that these power analyses for Aim 3 were based on testing the association between changes in EO function and changes in pain interference.

Treatment Assignment Procedures

Study patients will be randomized to receive either MT or SMT. The order of drug administration for each laboratory session will also be randomized and counterbalanced (placebo vs. naloxone), and double-blinded. All randomization will be carried out using the Proc Plan procedure in SAS version 9.2 (SAS Institute, Cary, NC). This SAS procedure will be used to generate a randomization schedule for each sequential study slot (MT vs. SMT and the order of naloxone/placebo administration in each set of lab visits). Study subjects will be assigned to these previously randomized study slots in the order that they are enrolled, and the previously determined randomization status associated with each slot will determine the study condition each subject is in and the order of drug administration.

The research assistants (RA) at each site who will conduct weekly phone assessments (when applicable) and who will conduct the laboratory pain-induction sessions will be blind to subject treatment condition. The randomization scheme will be implemented by department administrative assistants who will have no other role in the study.

Given the nature of the interventions and that Co-Is Drs. Carmody and Bialosky will be providing intervention-specific oversight (e.g., review of MT and SMT audio- and video-recordings), neither of these Co-Is will be blinded as to intervention assignment. These individuals will not be engaged in review of individual level study data or analysis of study results. The PIs (Drs. Burns and Bruehl) will be blinded to intervention assignment. Moreover, during routine review of data, PIs and other research staff will also be blinded to participant intervention assignment by hiding from view the columns denoting subject ID and intervention status in the REDCap database.

Double blinding (patient and investigators) as to drug condition for all laboratory sessions will be maintained by the Investigational Pharmacy at each site. Drug blinding will be broken for specific participants as needed in the event of possible safety or side effect issues. This unblinding will be done by the site PIs in conjunction with investigational pharmacists.

Participants will not be blinded to treatment condition: the MT and SMT procedures will be obvious.

Stake Holder	Intervention Group Assignment	Lab Drug Condition	Primary Mechanistic Outcome Measure	Clinical/Functional Outcome Measure
Study Subjects/Patients	Unblinded	Blinded	Unblinded	Unblinded
Instructors/Practitioners	Unblinded	Blinded	Blinded	Blinded
Outcome Assessors	Blinded	Blinded	Unblinded	Unblinded
Statistician	Blinded	Blinded	Unblinded	Unblinded

Principal Investigators	Blinded	Blinded	Blinded	Blinded

9.3 Definition of Populations

The ITT (intent to treat) sample will be all subjects who complete baseline measures. The "per protocol" sample (i.e., "treatment completers") will be those subjects who complete at least 6 of the 8 treatment sessions.

9.4 Interim Analyses and Stopping Rules

We do not plan to conduct interim analyses.

Findings that would trigger a safety review are two or more occurrences of a particular type of SAE, severe AEs/reactions, or increased frequency of events. The site PIs would present them to the IMC statistician to review the events by group to determine whether there are statistical as well as clinical concerns. The statistician reports his findings to a closed session of the IMC and/or NCCIH. The findings are used to determine what steps will be taken.

9.5 Outcomes

In Aims 1 and 2, our goal is to test the degree to which MT and SMT change specific and non-specific mechanisms. Thus, we will assess pre-post treatment changes in mindfulness and spinal stiffness (specific mechanisms), and in endogenous opioid (EO) function, CPM, pain-related cognition and therapy factors (non-specific mechanisms). For the sake of analyses for Aims 1 and 2, changes in these variables are "outcomes." The primary mechanism outcome is change in EO function.

In Aim 3, our goal is to determine the degree to which treatment-induced changes in mechanisms are related to treatment-induced changes in the pain, mood and function dependent variables. Prior to the multiple variate analyses, we will determine the degree to which MT and SMT affect pre-post changes in the primary dependent variable, "pain interference" and in secondary dependent variables (mood and function). Our primary goal in this project is to ascertain the degree to which MT and SMT alter putative mechanisms of action. Change in pain interference is the primary dependent variable, reflecting treatment effects, which will be predicted by change in mechanism factors.

Aim 1: Test effects of 2 treatments on non-specific mechanisms. The primary objective is to test to what degree MT and SMT produce changes in the 3 categories of non-specific mechanisms. The primary endpoints depend on the particular mechanism being examined: endogenous opioid function, conditioned pain modulation, pain-related cognition, and therapy factors. Analyses are described in detail below.

Aim 2: Test effects of 2 treatments on specific mechanisms. The primary objective is to test to what degree MT and SMT produce changes in treatment-specific mechanisms. The primary endpoints depend on the particular mechanism being examined: changes in mindfulness and spinal stiffness. Analyses are described in detail below.

Aim 3: Test relative predictive validity of non-specific and specific mechanisms. The primary objective is to test to what degree changes in non-specific and specific mechanisms predict changes in pain, mood and function, and whether these relationships depend on the treatment received. We will first test Mechanism Change x Treatment interactions to determine whether changes in any candidate mechanisms predict outcomes to a greater degree in one treatment than the other. In the absence of interactions, which we expect to be largely the case, we will test the degree to which changes in non-specific and specific mechanisms account for unique and shared variance in predicting outcomes.

Aim 4: To address competing causation paths. The primary objective is to test lagged and cross-lagged effects of early-treatment changes in non-specific and specific mechanisms predicting late-treatment changes in outcomes. Analyses are described in detail above.

9.5.1 Primary Outcome

Our primary mechanism outcome is pre- to post treatment changes in EO function.

9.5.2 Secondary Outcomes

Secondary outcomes are pre-post treatment changes in mindfulness and spinal stiffness (specific mechanisms), and in CPM, pain-related cognition and therapy factors (non-specific mechanisms). Other secondary outcomes refer to pre-post changes in patient reported clinical status. These are pain intensity, negative affect (anger, anxiety, depression), physical function, sleep disturbance and social support assessed via PROMIS item banks.

9.6 Data Analyses

Primary analyses will be conducted on an ITT basis.

Aim 1: To determine the degree to which MT and SMT produce effects in nonspecific mechanisms.

The primary analyses will employ the two-sample t-test to compare mean change in each nonspecific mechanism within a noninferiority test construct to compare mean change in outcome from pre to post treatment between the two treatment arms. An overall, 2-sided, significance level of 0.05 will be used. Linear mixed models will be used as a supplemental analysis, allowing us to utilize all data collected, account for within subject variation, and model changes over time. The fixed effect part of the model will be

$Mechanism_{ij} = \beta_0 + \beta_1 Time_{ij} + \beta_2 Tx_i + \beta_3 (Tx_i * Time_{ij}) + \varepsilon_{ij}$ for subject i at visit j.

If β_3 is significantly negative ($p < .05$), this would indicate that the mechanism variable decreased more in SMT than in MT (Fitzmaurice, Laird, & Ware, 2011). In case of a significant interaction, we will test simple slopes of Time for each Treatment Condition separately AND by testing post treatment differences between MT and SMT controlling for pre-treatment values.

Candidate covariance structures will be assessed using the data's correlation structure and Akaike's Information Criterion (AIC). Random coefficients (e.g. random intercept and/or random slope) will be included in the model if they significantly improve the model fit as determined by the likelihood ratio test. Standardized residuals and Cook's distance will be used to assess the influence of outliers and individual observations. Residual plots will be used to check the multivariate normal distribution assumption. The pattern of missing data will be examined to determine its missing mechanism and the amount. If data are missing not at random (MNAR), data imputations may be used. If other deviations from the model assumptions are detected, appropriate measures will be taken to prevent inferential bias, e.g. data transformations and use of bootstrap techniques to compute standard errors.

Potential covariates (site, age, and any baseline variables found to be significantly different ($p < .20$) between treatment groups) will be considered for model inclusion using a model selection method called least absolute shrinkage and selection operator (LASSO) (Tibshirani, 2011). This method identifies groups of covariates to form a parsimonious model; it avoids problems in stepwise procedures such as collinearity, bias, and variance deflation (Flom & Cassell, 2007); the method has recently been extended to mixed effects models (Bondell, Krishna, & Ghosh, 2010; Fan & Li, 2012; Fernandez, 2007).

Aim 2: To determine whether MT will produce greater improvements in mindfulness-related factors than SMT, and whether SMT will produce greater improvements in spinal stiffness than MT.

The primary analyses will employ the two-sample t-test to compare mean change in each specific mechanism to compare mean change in outcome from pre to post treatment between the two treatment arms. An overall, 2-sided, significance level of 0.05 will be used. Linear mixed models will be used as a supplemental analysis, allowing us to utilize all data collected, account for within subject variation, and model changes over time. The fixed effect part of the model will be

$Mechanism_{ij} = \beta_0 + \beta_1 Time_{ij} + \beta_2 Tx_i + \beta_3 (Tx_i * Time_{ij}) + \varepsilon_{ij}$ for subject i at visit j.

If β_3 is significantly negative ($p < .05$), this would indicate that the mechanism variable decreased more in SMT than in MT (Fitzmaurice, Laird, & Ware, 2011). In case of a significant interaction, we will test simple slopes of Time for each Treatment Condition separately AND by testing post treatment differences between MT and SMT controlling for pre-treatment values. As in Aim 1, we will follow this analysis with generalized linear mixed effects modeling (GLMM) with subject-specific intercepts and subject-specific slopes.

Candidate covariance structures will be assessed using the data's correlation structure and Akaike's Information Criterion (AIC). Random coefficients (e.g. random intercept and/or random slope) will be included in the model if they significantly improve the model fit as determined by the likelihood ratio test. Standardized residuals and Cook's distance will be used to assess the influence of outliers and individual observations. Residual plots will be used to check the multivariate normal distribution assumption. The pattern of missing data will be examined to determine its

missing mechanism and the amount. If data are missing not at random (MNAR), data imputations may be used. If other deviations from the model assumptions are detected, appropriate measures will be taken to prevent inferential bias, e.g. data transformations and use of bootstrap techniques to compute standard errors.

Potential covariates (site, age, and any baseline variables found to be significantly different ($p < .20$) between treatment groups) will be considered for model inclusion using a model selection method called least absolute shrinkage and selection operator (LASSO) (Tibshirani, 2011). This method identifies groups of covariates to form a parsimonious model; it avoids problems in stepwise procedures such as collinearity, bias, and variance deflation (Flom & Cassell, 2007); the method has recently been extended to mixed effects models (Bondell, Krishna, & Ghosh, 2010; Fan & Li, 2012; Fernandez, 2007).

Aim 3: To test the relative predictive validity of non-specific and specific mechanisms.

To test to what degree changes in non-specific and specific mechanisms predict changes in pain, mood and function, and whether these relationships depend on the treatment received, we will first test Mechanism x Treatment interactions to determine whether changes in any of the candidate mechanisms predict outcomes to a greater degree in one treatment over the other. Linear mixed effects regression models will be conducted to test, for example, a non-specific mechanism change score x Treatment interaction for each outcome change. If significant differences are observed, then the interaction effects will be interpreted to provide the unique effect of mechanism change for each treatment group.

In the absence of interactions, we will use linear mixed effects regression models to test the degree to which changes in non-specific and specific mechanisms account for unique and shared variance in pre-post outcome changes. More specifically, 0-order correlations among mechanism and outcome pre-post change scores will reveal "candidate" mechanisms (i.e., those with significant associations with pre-post outcome changes). We will use a series of hierarchical regressions to examine the degree to which ostensibly different mechanisms account for shared or unique variance in outcome changes. Such analyses will allow us to identify common areas of mechanism overlap (e.g., changes in self-efficacy and pain catastrophizing accounting for much shared variance in pain changes), and mechanism uniqueness (e.g., changes in spinal stiffness accounting for significant unique variance in pain changes even with other mechanism changes controlled).

Aim 4: Address competing causation pathways.

First, we will use an approach and techniques that we have used in previous publications [eg, Burns, J.W., Nielson, W.R., Jensen, M.P., Heapy, A., Czlapinski, R., & Kerns, R.D. (2015). Specific and general therapeutic mechanisms in cognitive-behavioral treatment of chronic pain. Journal of Consulting and Clinical Psychology.83, 1-11. PMID: 24979313]. Namely, we will test lagged and cross-

lagged effects using pre- to mid-treatment and mid- to post-treatment epochs. Given that endogenous opioid functioning will be assessed only at pre-and post-treatment, and given that the working alliance and subject expectations for benefit will be assessed only at 3- and 6-weeks, this approach will allow to examine comparable effects across all our specific and non-specific mechanisms. Residual change scores for all mechanism and outcome variables will be computed by regressing mid-treatment on pre-treatment values (i.e., a pre-mid residual change score), and regressing post-treatment on mid-treatment values (i.e., mid-post residual change score). For lagged relationships, regressions will be performed to identify the unique effect of pre-mid mechanism changes on mid-post outcome changes. This will require statistically controlling for the path from pre-mid mechanism change to mid-post mechanism change and pre-mid outcome change to mid-post outcome change. See Figure 1 and 2 below. The red line is the target lagged effect. The two blue lines are the paths to be controlled.

Figure 1

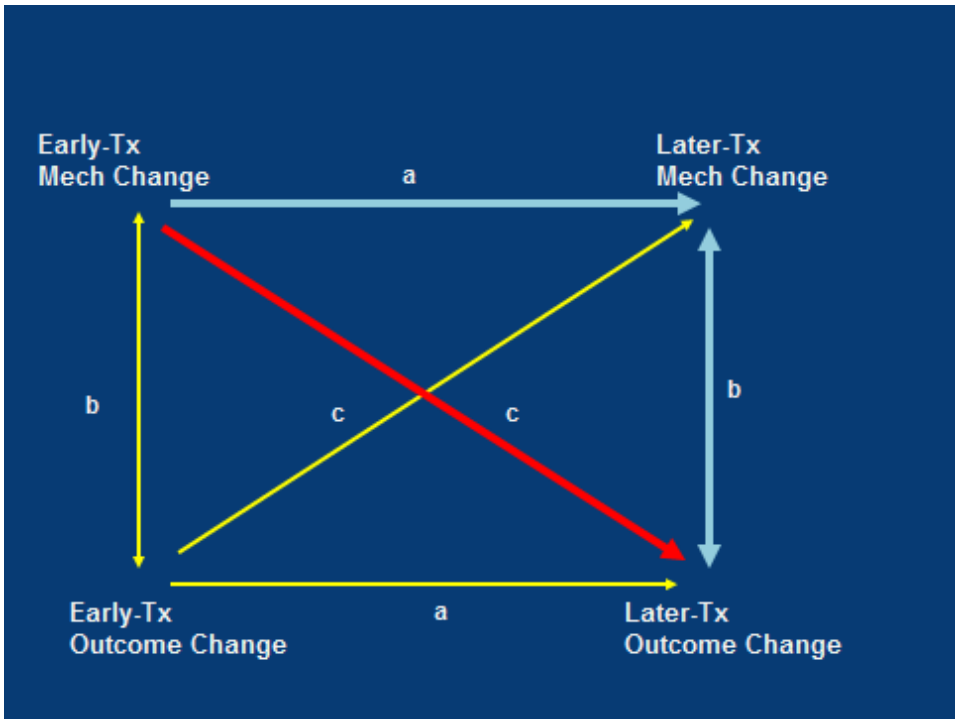
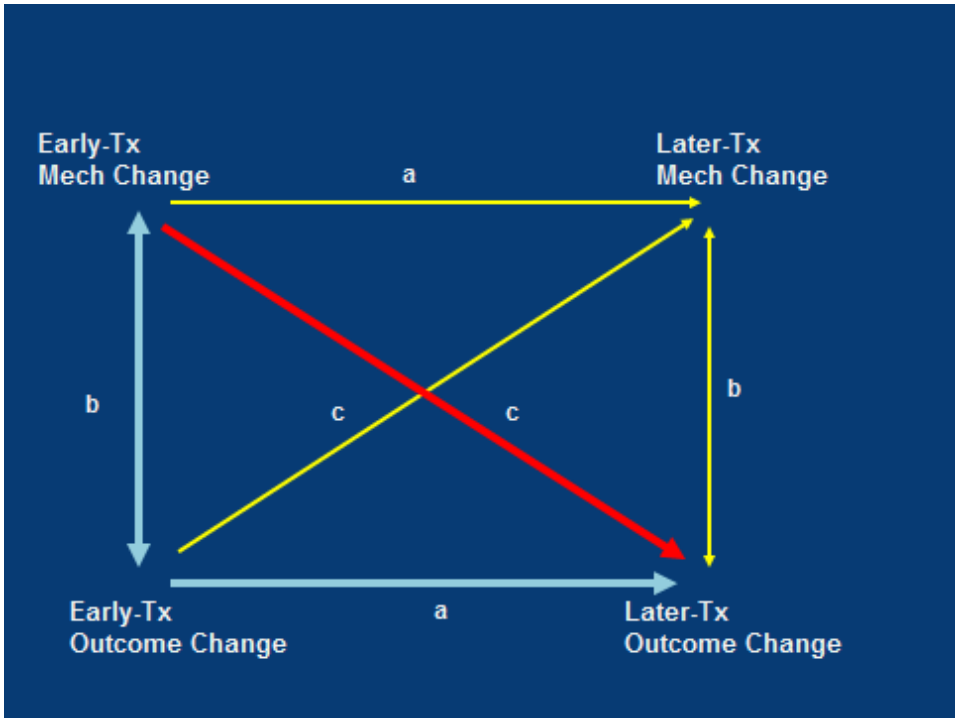


Figure 2



For cross-lagged effects, the procedure will be inverted. Namely, we will test whether pre-mid changes in outcomes predict mid-post changes in mechanisms. Significant lagged effects paired with non-significant cross-lagged effects will add support to the notion that early-treatment changes in putative mechanisms influenced later-treatment changes in outcomes. In general, we expect that pre-mid changes in mindfulness and spinal stiffness will predict mid-post changes in pain interference (and other outcomes), but the inverse will not be the case.

Second, we will take a more fine-grained HLM approach using the weekly data. We will test whether: a) previous week levels of specific (e.g., mindfulness, spinal stiffness) and nonspecific mechanisms (e.g. self-efficacy) predict previous week to next week changes in outcomes; b) these relationships depend on time in treatment (i.e. quadratic trends could emerge indicating that early- vs late-treatment effects are distinct); c) whether the inverse relationships (i.e. outcomes predicting mechanisms) are also significant; d) whether patterns of lagged effects are different between MT and SMT. In general, we expect that previous week levels in mechanisms will predict previous week to current week changes in outcomes, and that the strength of these relationships will be strongest from Week 3 to Week 6 (when specific mechanisms have improved sufficiently to best affect improvements in outcomes).

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

All data will be collected in REDCap; weekly surveys will be done over the phone with the RA reading items to subjects and entering their responses directly into REDCap or completed online in REDCap directly by the subject. As part of the end of the month data check RAs will review the REDCap to ensure that all forms that should be marked as completed are and also that no records were erroneously marked as completed.

Protocol compliance and data quality review will be ongoing with daily meetings between the PIs and research assistants. All data collection will be reviewed within days of collection so that the opportunity for feedback to research staff or the participants can occur. Additionally, all study materials and data are reviewed for accuracy and completeness by a trained research assistant within days of each subject completing the study to reduce the possibility of missing data.

The research assistants will be the primary collectors of data, and will refer questions to the PIs as they arise. All data entry will be double checked by the PIs, or a separate trained research assistant. Participants will complete weekly questionnaires via telephone calls with RAs or online via REDCap. Several aspects of the study procedures will be designed to minimize risks to confidentiality. Data will be coded and transferred to a computer database for later analysis. All paper and computer records, will be identified only by subject ID number rather than subject name to help ensure confidentiality. All subject records will be maintained in filing cabinets in the locked labs of the PIs, and will be accessible only to the PIs and research assistants. Hard copies of the data will be maintained for 6 years after the study, after which they will be destroyed. Computer data files (without subject IDs) will be maintained by the site PIs for future use. Consents and any other forms with identifiable subject information will be maintained in a separate locked file from the actual study data files, which will be identified only by subject number. All subjects will be informed regarding how HIPAA requirements may impact on their study records, and will sign a notification regarding this issue. All published data will be reported in a manner in which individual data for specific subjects are not identifiable.

No data will be directly recorded onto a case report form.

10.2 Data Management

We have extensive experience with studies of this type, and plan to employ the same types of strategies in the proposed project to address all of these issues. Our intention is to use REDCap (developed at Vanderbilt where Co-PI Dr. Bruehl is located) for data entry and data storage, a system that it is widely used, highly reliable, and secure. Data will be coded on paper and transferred to a computer database for later analysis. All paper and computer records, and digital video-recordings of sessions will be identified only by subject ID number rather than subject name to help insure confidentiality. All subject records will be maintained in filing cabinets in the locked offices of the PIs or designees, and will be accessible only to the PIs, co-I's and designees. Hard copies of the data will be maintained for 6 years after the study (including the audiotapes/videotapes), after which they will be destroyed. Computer data files (without subject IDs) will be maintained by the site PIs for future use. All

paper and computer data records will be identified by a subject number assigned solely for use in this study rather than by name to help insure confidentiality. The individual subjects associated with each subject number will be known only to the site PIs and designees. Consents and any other forms with identifiable subject information will be maintained in a separate locked file from the actual study data files, which will be identified only by subject number. All subjects will be informed regarding how HIPAA requirements may impact on their study records, and will sign a notification regarding this issue. All published data will be reported in a manner in which individual data for specific subjects are not identifiable.

The issue of "reproducible workflows and practices" is addressed in the originally submitted Multi-PI Plan (relevant text follows): "Dr. Burns and Dr. Bruehl will work closely to insure that the two study sites develop and implement identical procedures and training protocols, and that they acquire data in a coordinated and consistent fashion. Both Dr. Burns and Dr. Bruehl will be responsible for managing any potential missing data issues, to measure and correct for potential biases, and for administrative and fiscal oversight. Regular communication between the PIs via e-mail and telephone, as well as regularly scheduled in-person site visits will be used to coordinate the study sites. Similar coordination procedures have worked effectively in the PIs previous joint NIH-grant funded opioid blockade work (R01-MH071260, R01-DA031726, R01-DA037891)."

10.3 Quality Assurance

10.3.1 Training

The research assistants will be trained and daily supervised by the PIs. The PIs and RAs will meet at least weekly to review the week's activities, protocol violations, questions and answers to ensure continued standardized administration of study protocol.

10.3.2 Quality Control Committee

There is no quality control committee.

10.3.3 Metrics

One person enters data, a second checks the data entry and compares to paper record. As a double check we will also check frequency and means of data to check for out of bound data entry errors.

10.3.4 Protocol Deviations

All protocol deviations will be noted in the protocol deviation log and participant's chart. All protocol deviations (minor or major) will be reported to the corresponding site IRB through the PIs, and the deviation logs will be uploaded to the shared cloud-based document system. It is the policy of the IRB to be notified of any deviation from the protocol that results in an increase in risk or a decrease in potential benefit to participants. Consistent with IRB policies all minor deviations will be summarized and reported to the IRB at the continuing review. Major deviations will be

immediately reported to the IRB as specified by IRB procedures along with a corrective action plan to ensure that the deviation will not occur again. A "major deviation" is defined by the IRB as a deviation that impacts the safety of a subject or undermines the integrity of the study. In such a situation, the resulting IRB final response will be immediately forwarded to the NCCIH and IMC, along with the summary and corrective action plan submitted to the IRB.

A list of protocol deviations will be provided to the Independent Monitoring Committee (IMC) each quarter as part of the IMC progress report on January 15, April 15, July 15, and October 15. The more detailed semi-annual report will be submitted to the IMC on January 15 and July 15, and will include a list and summary of any major or minor deviations that occurred. As mentioned above, the IMC report prepared every 6 months will be signed by the members of the IMC and will be forwarded to the IRBs and NCCIH (reports will be provided more frequently on an ongoing basis if concerns are identified). All protocol deviations will be reported to NCCIH in the annual progress report and at site visits.

10.3.5 Monitoring

Protocol compliance and data quality review will be ongoing with daily meetings between the PIs and research assistants. All data collection will be reviewed within days of collection so that the opportunity for feedback to research staff or the participants can occur. Additionally, all study materials and data are reviewed for accuracy and completeness by the PI or trained research assistant within days of each subject completing the study to reduce the possibility of missing data.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by Rush University Medical Center and Vanderbilt University Medical Center IRBs.

11.2 Informed Consent Forms

All individuals agreeing to participate will provide written informed consent during Visit 1 (i.e., prior to beginning any study procedures). Subject consent procedures will be carried out by individuals designated and trained by each site PI and the IRB to carry out these procedures (i.e., the proposed research assistants). In the Consent Form, it will be emphasized that subjects may discontinue participating at any time and still receive prorated compensation. The recruiter will inform potential subjects that participation is completely voluntary, and they may withdraw at any time without penalty or running the risk of jeopardizing current and future treatment at the Rush or Vanderbilt medical centers. A signed consent form will be obtained from each participant. For participants who cannot consent for themselves, such as those with a legal guardian (e.g., person with power of attorney), this individual must sign the

consent form. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant or legal guardian and this fact will be documented in the participant's record.

11.3 Participant Confidentiality

Several aspects of the study procedures will be designed to minimize risks to confidentiality. Data will be coded on paper and transferred to a computer database for later analysis. All paper and computer records, and digital video-recordings of sessions will be identified only by subject ID number rather than subject name to help insure confidentiality. All subject records will be maintained in filing cabinets in the locked offices of the PIs or designees, and will be accessible only to the PIs, co-I's and designees. Hard copies of the data will be maintained for 6 years after the study (including the videotapes), after which they will be destroyed. Computer data files (without subject IDs) will be maintained by the site PIs for future use. All paper and computer data records will be identified by a subject number assigned solely for use in this study rather than by name to help insure confidentiality. The individual subjects associated with each subject number will be known only to the site PIs and designees. Consents and any other forms with identifiable subject information will be maintained in a separate locked file from the actual study data files, which will be identified only by subject number. All subjects will be informed regarding how HIPAA requirements may impact on their study records, and will sign a notification regarding this issue. All published data will be reported in a manner in which individual data for specific subjects are not identifiable.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NCCIH, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

If the study is discontinued, the PIs will email the IRB consultant assigned to the study, the NCCIH program officer, and the IMC to inform them of the discontinuation. In addition they will each email their study staff to ensure uniform information is disseminated to all.

12. COMMITTEES

The Independent Monitoring Committee (IMC) will review the following study parameters: recruitment status (targeted vs. actual), retention status, enrollment, demographics, subject status and adverse events.

13. PUBLICATION OF RESEARCH FINDINGS

Any presentation, abstract, or manuscript will be made available for review by the sponsor and the NCCIH prior to submission.

14. REFERENCES

References Cited

1. Institute of Medicine. Relieving pain in America: a blueprint for transforming prevention, care, education, and research. Washington, DC: The National Academies Press, 2011.

2. Boudreau D, Von Korff M, Rutter CM, Saunders K, Ray GT, Sullivan MD, Campbell CI, Merrill JO, Silverberg MJ, Banta-Green C, Weisner C. Trends in long-term opioid therapy for chronic non-cancer pain. Pharmacoepidemiol Drug Saf. 2009 Dec; 18(12): 1166-1175.

3. Kuehn BM. Opioid prescriptions soar: Increase in legitimate use as well as abuse. JAMA 17: 249-251, 2007.

4. Manchikanti L, Helm S 2nd, Fellows B, Janata JW, Pampati V, Grider JS, Boswell MV. Opioid epidemic in the United States. Pain Physician 2012; 15: ES9-38.

5. Sullivan MD, Edlund MJ, Fan MY, Devries A, Brennan Braden J, Martin BC. Trends in use of opioids for non-cancer pain conditions 2000-2005 in commercial and Medicaid insurance plans: the TROUP study. Pain 2008; 138: 440-449.

6. Rubinstein SM. Adverse events following chiropractic care for subjects with neck or low-back pain: do the benefits outweigh the risks? J Manipulative Physiol Ther. 2008 Jul-Aug;31(6):461-4. doi: 10.1016/j.jmpt.2008.06.001. PubMed PMID:18722202.

7. Chenot JF, Becker A, Leonhardt C, Keller S, Donner-Banzhoff N, Baum E, Pfingsten M, Hildebrandt J, Basler HD, Kochen MM. Use of complementary alternative medicine for low back pain consulting in general practice: a cohort study. BMC Complement Altern Med. 2007 Dec 18;7:42. PubMed PMID: 18088435; PubMed
Central PMCID: PMC2222227.

8. Ruddock, JK, Ost M, Sallis H, Ness A, Perry RE. Spinal Manipulation Vs Sham Manipulation for Nonspecific Low Back Pain: A Systematic Review and Meta-analysis Journal of Chiropractic Medicine, 167 Volume 15, Number 3 2016.

9. Yuan J, Purepong N, Kerr DP, Park J, Bradbury I, McDonough S. Effectiveness of acupuncture for low back pain: a systematic review. Spine (Phila Pa 1976). 2008 Nov 1;33(23):E887-900. doi: 10.1097/BRS.0b013e318186b276. Review. PubMed PMID: 18978583.

10. Cramer, H., Haller, H., Lauche, R., & Dobos, G. (2012). Mindfulness-based stress reduction for low back pain. A systematic review. *BMC Complementary and Alternative Medicine, 12*(1),162. http://dx.doi.org/10.1186/1472-6882-12-162.

11. Lauche R1, Cramer H, Dobos G, Langhorst J, Schmidt S. A systematic review and meta-analysis of mindfulness-based stress reduction for the fibromyalgia syndrome. J Psychosom Res. 2013 Dec;75(6):500-10. doi: 10.1016/j.jpsychores.2013.10.010.

12. Veehof MM, Trompetter, Bohlmeijer ET, Schreurs KM. Acceptance- and mindfulness-based interventions for the treatment of chronic pain: a meta-analytic review. Cogn Behav Ther. 2016;45(1):5-31. doi: 0.1080/16506073.2015.1098724.

13. Bawa FL, Mercer SW, Atherton RJ, Clague F, Keen A, Scott NW, Bond CM. Does mindfulness improve outcomes in patients with chronic pain? Systematic review and meta-analysis. Br J Gen Pract. 2015 Jun;65(635):e387-400. doi: 10.3399/bjgp15X685297.

14. Cherkin, D.C., Sherman, K.J., Balderson, B.H., Cook, A.J., Anderson, M.L., Hawkes, R.J., Hansen, K.E., Turner, J.A. (2016). Effects of mindfulness-based stress reduction vs cognitive behavioral therapy or usual care on back pain: A randomized clinical trial. Journal of American Medical Association, 315, 1240-1249.

15. Omidi A, Zargar F. Effect of mindfulness-based stress reduction on pain severity and mindful awareness in patients with tension headache: a randomized controlled clinical trial. Nurs Midwifery Stud. 2014 Sep;3(3):e21136.

16. Turner JA, Anderson ML, Balderson BH, Cook AJ, Sherman KJ, Cherkin DC. Mindfulness-based stress reduction and cognitive behavioral therapy for chronic low back pain: similar effects on mindfulness, catastrophizing, self-efficacy, and acceptance in a randomized controlled trial. Pain. 2016 Nov;157(11):2434-2444.

17. Day MA, Thorn BE, Ward LC, Rubin N, Hickman SD, Scogin F, Kilgo GR. Mindfulness-based cognitive therapy for the treatment of headache pain: a pilot study. Clin J Pain. 2014 Feb;30(2):152-61. doi: 10.1097/AJP.0b013e318287a1dc.

18. Schmidt, S., Grossman, P., Schwarzer, B., Jena, S., Naumann, J., & Walach, H. (2011). Treating fibromyalgia with mindfulness-based stress reduction: Results from a 3-armed randomized controlled trial. Pain, 152(2), 361-369. http://dx.doi.org/10.1016/j.pain.2010.10.043.

19. Baer, R.A., Carmody, J., Hunsinger, M. (2012). Weekly change in mindfulness and perceived stress in a mindfulness-based stress reduction program. Journal of Clinical Psychology, 68, 755-765.

20. UK BEAM Trial Team.. United Kingdom back pain exercise and manipulation (UK BEAM) randomised trial: effectiveness of physical treatments for back pain in primary care. BMJ. 2004 Dec 11;329(7479):1377. PubMed PMID: 15556955; PubMed Central PMCID: PMC535454.

21. Michaleff ZA, Lin CW, Maher CG, van Tulder MW. Spinal manipulation epidemiology: systematic review of cost effectiveness studies. J Electromyogr Kinesiol. 2012 Oct;22(5):655-62. doi: 10.1016/j.jelekin.2012.02.011. Review. PubMed PMID: 22429823.

22. Sherman KJ, Cherkin DC, Connelly MT, Erro J, Savetsky JB, Davis RB, Eisenberg DM. Complementary and alternative medical therapies for chronic low back pain: What treatments are patients willing to try? BMC Complement Altern Med. 2004 Jul 19;4:9. PubMed PMID: 15260884; PubMed Central PMCID: PMC503394.

23. Wolsko PM, Eisenberg DM, Davis RB, Kessler R, Phillips RS. Patterns and perceptions of care for treatment of back and neck pain: results of a national survey. Spine (Phila Pa 1976). 2003 Feb 1;28(3):292-7; discussion 298. PubMed PMID: 12567035.

24. Hurwitz EL. Epidemiology: spinal manipulation utilization. J Electromyogr Kinesiol. 2012 Oct;22(5):648-54. doi: 10.1016/j.jelekin.2012.01.006. Review.PubMed PMID: 22289432.

25. Dagenais S, Tricco AC, Haldeman S. Synthesis of recommendations for the assessment and management of low back pain from recent clinical practice guidelines. Spine J. 2010 Jun;10(6):514-29.

doi: 10.1016/j.spinee.2010.03.032.Review. PubMed PMID: 20494814.

26. Koes BW, van Tulder M, Lin CW, Macedo LG, McAuley J, Maher C. An updated overview of clinical guidelines for the management of non-specific low back pain in primary care. Eur Spine J. 2010 Dec;19(12):2075-94. doi: 10.1007/s00586-010-1502-y. Review. PubMed PMID: 20602122; PubMed Central PMCID: PMC2997201.

27.1: Franke H, Franke JD, Fryer G. Osteopathic manipulative treatment for nonspecific low back pain: a systematic review and meta-analysis. BMC Musculoskelet Disord. 2014 Aug 30;15:286. doi: 10.1186/1471-2474-15-286. Review. PubMed PMID: 25175885; PubMed Central PMCID: PMC4159549.

28. Rubinstein SM, van Middelkoop M, Assendelft WJ, de Boer MR, van Tulder MW. Spinal manipulative therapy for chronic low-back pain. Cochrane Database Syst Rev. 2011 Feb 16;(2):CD008112. doi: 10.1002/14651858.CD008112.pub2. Review.PubMed PMID: 21328304.

29. Chou R, Huffman LH; American Pain Society.; American College of Physicians. Nonpharmacologic therapies for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. Ann Intern Med. 2007 Oct 2;147(7):492-504. Review. Erratum
in: Ann Intern Med. 2008 Feb 5;148(3):247-8. PubMed PMID: 17909210.

30. Williams NH, Hendrya M, Lewis R, Russell I, Westmoreland A, Wilkinson C. Psychological response in spinal manipulation (PRISM): A systematic review of psychological outcomes in randomised controlled trials. Complementary Therapies in Medicine (2007) 15, 271—283.

31. Henderson CN. The basis for spinal manipulation: chiropractic perspective of indications and theory. J Electromyogr Kinesiol. 2012 Oct;22(5):632-42. doi:10.1016/j.jelekin.2012.03.008. Review. PubMed PMID: 22513367.

32. Bialosky JE, Simon CB, Bishop MD, George SZ. Basis for spinal manipulative therapy: a physical therapist perspective. J Electromyogr Kinesiol. 2012 Oct;22(5):643-7. doi: 10.1016/j.jelekin.2011.11.014. Review. PubMed PMID:22197083; PubMed Central PMCID: PMC3461123.

33. Triano JJ. Biomechanics of spinal manipulative therapy. Spine J. 2001 Mar-Apr;1(2):121-30. PubMed PMID: 14588392.

34. Evans DW. Mechanisms and effects of spinal high-velocity, low-amplitude thrust manipulation: previous theories. J Manipulative Physiol Ther. 2002 May;25(4):251-62. Review. PubMed PMID: 12021744.

35. Herzog W, Kats M, Symons B. The effective forces transmitted by high-speed,low-amplitude thoracic manipulation. Spine (Phila Pa 1976). 2001 Oct 1;26(19):2105-10; discussion 2110-1. PubMed PMID: 11698887.

36. Gál J, Herzog W, Kawchuk G, Conway PJ, Zhang YT. Movements of vertebrae during manipulative thrusts to unembalmed human cadavers. J Manipulative Physiol Ther. 1997 Jan;20(1):30-40. PubMed PMID: 9004120.

37. Flynn T, Fritz J, Whitman J, Wainner R, Magel J, Rendeiro D, Butler B, Garber M, Allison S. A clinical prediction rule for classifying patients with low back pain who demonstrate short-term

improvement with spinal manipulation. Spine (Phila Pa 1976). 2002 Dec 15;27(24):2835-43. PubMed PMID: 12486357.

38. Childs JD, Fritz JM, Flynn TW, Irrgang JJ, Johnson KK, Majkowski GR, Delitto A. A clinical prediction rule to identify patients with low back pain most likely to benefit from spinal manipulation: a validation study. Ann Intern Med. 2004 Dec 21;141(12):920-8. PubMed PMID: 15611489.

39. Fritz JM, Koppenhaver SL, Kawchuk GN, Teyhen DS, Hebert JJ, Childs JD. Preliminary investigation of the mechanisms underlying the effects of manipulation: exploration of a multivariate model including spinal stiffness, multifidus recruitment, and clinical findings. Spine (Phila Pa 1976). 2011 Oct 1;36(21):1772-81. doi: 10.1097/BRS.0b013e318216337d. PubMed PMID: 21358568; PubMed Central PMCID: PMC3150636.

40. Wong AY, Parent EC, Dhillon SS, Prasad N, Kawchuk GN. Do participants with low back pain who respond to spinal manipulative therapy differ biomechanically from nonresponders, untreated controls or asymptomatic controls? Spine (Phila Pa 1976). 2015 Sep 1;40(17):1329-37. doi: 10.1097/BRS.0000000000000981. PubMed PMID: 26020851.

41. White P, Bishop FL, Prescott P, Scott C, Little P, Lewith G. Practice, practitioner, or placebo? A multifactorial, mixed-methods randomized controlled trial of acupuncture. Pain. 2012 Feb;153(2):455-62. doi: 10.1016/j.pain.2011.11.007. PubMed PMID: 22169359.

42. Burns, J. W., Nielson, W. R., Jensen, M. P., Heapy, A., Czlapinski, R., Kerns, R. D. (2015a). Specific and general therapeutic mechanisms in cognitive behavioral treatment of chronic pain. Journal of Consulting and Clinical Psychology, 83(1), 1-11.

43. Kaptchuk TJ, Kelley JM, Conboy LA, Davis RB, Kerr CE, Jacobson EE, Kirsch I, Schyner RN, Nam BH, Nguyen LT, Park M, Rivers AL, McManus C, Kokkotou E, Drossman DA, Goldman P, Lembo AJ. Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. BMJ. 2008 May 3;336(7651):999-1003. doi: 10.1136/bmj.39524.439618.25. PubMed PMID: 18390493; PubMed Central PMCID: PMC2364862.

44. Bialosky JE, Bishop MD, Robinson ME, Zeppieri G Jr, George SZ. Spinal manipulative therapy has an immediate effect on thermal pain sensitivity in people with low back pain: a randomized controlled trial. Phys Ther. 2009 Dec;89(12):1292-303. doi: 10.2522/ptj.20090058. PubMed PMID: 19797305; PubMed
Central PMCID: PMC2794479.

45. Petersen SB, Cook C, Donaldson M, Hassen A, Ellis A, Learman K. The effect of manual therapy with augmentative exercises for neck pain: a randomised clinical trial. J Man Manip Ther. 2015 Dec;23(5):264-75. doi: 10.1179/2042618615Y.0000000011.

46. Courtney CA, Steffen AD, Fernández-de-las-Peñas C, Kim J, Chmell SJ Joint mobilization enhances mechanisms of conditioned pain modulation in individuals with osteoarthritis of the knee. Journal of Orthopaedic & Sports Physical Therapy® 2016.

47. Saral I, Sindel D, Esmaeilzadeh S, Sertel-Berk HO, Oral A. The effects of long- and short-term interdisciplinary treatment approaches in women with fibromyalgia: a randomized controlled trial. Rheumatol Int. 2016 Oct;36(10):1379-89. doi: 10.1007/s00296-016-3473-8.

48. Branstetter-Rost A1, Cushing C, Douleh T. Personal values and pain tolerance: does a values

intervention add to acceptance? J Pain. 2009 Aug;10(8):887-92. doi: 10.1016/j.jpain.2009.01.001.

49 Stolzman S, Bement MH. Does Exercise Decrease Pain via Conditioned Pain Modulation in Adolescents? Pediatr Phys Ther. 2016 Winter;28(4):470-3. PMCID: PMC5098832.

50 Vernon HT, Dhami MS, Howley TP, Annett R. Spinal manipulation and beta-endorphin: a controlled study of the effect of a spinal manipulation on plasma beta-endorphin levels in normal males. J Manipulative Physiol Ther. 1986 Jun;9(2):115-23. PubMed PMID: 2942618.

51. McCubbin JA, Wilson JF, Bruehl S, Ibarra P, Carlson CR, Norton JA, Colclough GW. Relaxation training and opioid inhibition of blood pressure response to stress. J Consult Clin Psychol. 1996 Jun;64(3):593-601. PubMed PMID: 8698954.

52 Harris RE, Zubieta JK, Scott DJ, Napadow V, Gracely RH, Clauw DJ. Traditional Chinese acupuncture and placebo (sham) acupuncture are differentiated by their effects on mu-opioid receptors (MORs). Neuroimage. 2009 Sep;47(3):1077-85. doi: 10.1016/j.neuroimage.2009.05.083. PubMed PMID: 19501658; PubMed Central PMCID: PMC2757074.

53. Eriksson SV, Lundeberg T, Lundeberg S. Interaction of diazepam and naloxone on acupuncture induced pain relief. Am J Chin Med. 1991;19: 1-7.

54. Ernst M, Lee MH. Influence of naloxone on electro-acupuncture analgesia using an experimental dental pain test. Review of possible mechanisms of action. Acupunct Electrother Res. 1987;12: 5-22.

55. Koltyn KF. Analgesia following exercise: a review. Sports Med. 2000; 29: 85-98.

56. Olausson B, Eriksson E, Ellmarker L, Rydenhag B, Shyu BC, Andersson SA. Effects of naloxone on dental pain threshold following muscle exercise and low frequency transcutaneous nerve stimulation: a comparative study in man. Acta Physiol Scand. 1986; 126: 299-305.

57. Paulev PE, Thorbøll JE, Nielsen U, Kruse P, Jordal R, Bach FW, Fenger M, Pokorski M. Opioid involvement in the perception of pain due to endurance exercise in trained man. Jpn J Physiol. 1989;39: 67-74.

58. Haier RJ, Quaid K, Mills JC. Naloxone alters pain perception after jogging. Psychiatry Res. 1981; 5: 231-232.

59. Burns, J.W., Kubilus, A., Bruehl, S., Harden, R.N., & Lofland, K. (2003). Do changes in cognitive factors influence outcome following multidisciplinary treatment for chronic pain? A cross-lagged panel analysis. Journal of Consulting & Clinical Psychology, 71, 81-91.

60. Burns, J.W., Glenn, B., Bruehl, S., Harden, R.N., & Lofland, K. (2003). Cognitive factors influence outcome following multidisciplinary chronic pain treatment: A replication and extension of a cross-lagged panel analysis. Behaviour Research & Therapy, 41, 1163-1182.

61. Thorn BE, Day MA, Burns JW, Kuhajda M, Gaskins SW, Sweeney K, McConley R, Ward CL, & Cabbil, C. (2011). Randomized trial of group cognitive-behavioral therapy compared to a pain education control for low literacy rural people with chronic pain. Pain, 152, 2710-2720.

62. Kerns RD, Burns JW, Shulman M, Jensen MP, Nielson WR, Czlapinski R, Dallas MI, Chatkoff D, Sellinger J, Heapy A, Rosenberger P. Can we improve cognitive-behavioral therapy for chronic back pain

treatment engagement and adherence? A controlled trial of tailored versus standard therapy. Health Psychol. 2014 Sep;33(9):938-47.

63. Bialosky JE, Bishop MD, Price DD, Robinson ME, George SZ. The mechanisms of manual therapy in the treatment of musculoskeletal pain: a comprehensive model. Man Ther. 2009 Oct;14(5):531-8. doi: 10.1016/j.math.2008.09.001. PubMed PMID: 19027342; PubMed Central PMCID: PMC2775050.

64. Bialosky JE, George SZ, Horn ME, Price DD, Staud R, Robinson ME. Spinal manipulative therapy-specific changes in pain sensitivity in individuals with low back pain (NCT01168999). J Pain. 2014 Feb;15(2):136-48. doi: 10.1016/j.jpain.2013.10.005. PubMed PMID: 24361109; PubMed Central PMCID: PMC3946602.

65. Bishop MD, Beneciuk JM, George SZ. Immediate reduction in temporal sensory summation after thoracic spinal manipulation. Spine J. 2011 May;11(5):440-6. doi: 10.1016/j.spinee.2011.03.001. PubMed PMID: 21463970; PubMed Central PMCID: PMC3092807.

66. George SZ, Bishop MD, Bialosky JE, Zeppieri G Jr, Robinson ME. Immediate effects of spinal manipulation on thermal pain sensitivity: an experimental study. BMC Musculoskelet Disord. 2006 Aug 15;7:68. PubMed PMID: 16911795; PubMed Central PMCID: PMC1578563.

68. Bruehl S, Burns JW, Chung OY, Chont M. Interacting effects of trait anger and acute anger arousal on pain: the role of endogenous opioids. Psychosom Med. 2011; 73: 612-619.

69. Bruehl S, Burns JW, Chung OY, Quartana P. Anger management style and emotional reactivity to noxious stimuli among chronic pain patients and healthy controls: the role of endogenous opioids. Health Psychol 2008; 27: 204-214.

70. Bruehl S, Burns JW, Chung OY, Ward P, Johnson B. Anger and pain sensitivity in chronic low back pain patients and pain-free controls: The role of endogenous opioids. Pain. 2002; 99: 223-233.

71. Bruehl S, Burns JW, Gupta R, Buvanendran A, Chont M, Kinner E, Schuster E, Passik S, France CR. Endogenous opioid function mediates the association between laboratory-evoked pain sensitivity and morphine analgesic responses. Pain 2013; 154:1856-1864.

72. Bruehl S, Burns JW, Gupta R, Buvanendran A, Chont M, Schuster E, France CR. Endogenous opioid inhibition of chronic low-back pain influences degree of back pain relief after morphine administration. Reg Anesth Pain Med 2014; 39: 120-125. PMCID: PMC3933525.

73. Bruehl S, Chung OY, Burns JW. Trait anger and blood pressure recovery following acute pain: evidence for opioid-mediated effects. International J Behav Med 2006; 13: 138-146.

74. Bruehl S, Chung OY, Burns JW, Biridepalli S. The association between anger expression and chronic pain intensity: evidence for partial mediation by endogenous opioid dysfunction. Pain. 2003; 106: 317-324.

75. Burns JW, Bruehl S, Chung OY, Magid E, Chont M, Goodlad JK, Gilliam W, Matsuura J, Somar K. Endogenous opioids may buffer effects of anger arousal on sensitivity to subsequent pain. Pain. 2009; 146: 276-282.

76. Bruehl S, Chung, OY. Parental history of chronic pain may be associated with impairments in endogenous opioid analgesic systems. Pain. 2006; 124: 287-294.

77. First, M.B., Spitzer, R.L., Gibbon, M., & Williams, J.B.W. (November 2002). Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-patient Edition. (SCID-I/NP).

78. Martin WR. Drugs five years later: naloxone. Ann Intern Med. 1976; 85: 765-768.

79. Lewis J, Mansour A, Khachaturian H, Watson SJ, Akil H. Opioids and pain regulation. Pain Headache. 1987; 9: 129-159.

80. Maurset A, Skoglung LA, Hustveit O, Klepstad P, Oye I. A new version of the ischemic tourniquet pain test. Meth Find Exp Clin Pharmacol. 1992; 13: 643-647.

81. Gehling J, Mainka T, Vollert J, Pogatzki-Zahn EM, Maier C, Enax-Krumova EK. Short-term test-retest-reliability of conditioned pain modulation using the cold-heat-pain method in healthy subjects and its correlation to parameters of standardized quantitative sensory testing. BMC Neurol. 2016 Aug 5;16:125. doi: 10.1186/s12883-016-0650-z. PubMed PMID: 27495743; PubMed Central PMCID: PMC4974731.

82. Sullivan, M.J.L., Bishop, S.R., & Pivik, J. (1995). The Pain Catastrophizing Scale: Development and validation. Psychological Assessment, 7, 524-532.

83. Nicholas, M.K. (2007). The pain self-efficacy questionnaire: Taking pain into account. European Journal of Pain, 11, 153-163.

84. Tracey, T.J., & Kokotovic, A.M. (1989). Factor structure of the Working Alliance Inventory. Psychological Assessment: A Journal of Consulting and Clinical Psychology, 1, 207-210.

85. Holt, C., & Heimberg, R. (1990). The Reaction to Treatment Questionnaire: Measuring treatment credibility and outcome expectancies. The Behavior Therapist, 13, 213-214.

86. Baer, R.A., Smith, G.T., Lykins, E., Button, D., Krietemeyer, J., Sauer, S., Williams, J.M. (2008). Construct validity of the Five Facet Mindfulness Questionnaire in meditating and nonmeditating samples. Assessment, 15, 329-342.

87. Melzack, R. The short form of the McGill Pain Questionnaire. Pain. 1987; 30: 191-197.

88. Haas M, Vavrek D, Peterson D, Polissar N, Neradilek MB. Dose-response and efficacy of spinal manipulation for care of chronic low back pain: a randomized controlled trial. Spine J. 2014 Jul 1;14(7):1106-16. doi: 10.1016/j.spinee.2013.07.468. PubMed PMID: 24139233; PubMed Central PMCID: PMC3989479.

89. Airaksinen O, Brox JI, Cedraschi C, Hildebrandt J, Klaber-Moffett J, Kovacs F, Mannion AF, Reis S, Staal JB, Ursin H, Zanoli G; COST B13 Working Group on Guidelines for Chronic Low Back Pain.. Chapter 4. European guidelines for the management of chronic nonspecific low back pain. Eur Spine J. 2006 Mar;15 Suppl 2:S192-300. PubMed PMID: 16550448; PubMed Central PMCID: PMC3454542.

90.: American Physical Therapy Association.. Guide to Physical Therapist Practice. Second Edition. American Physical Therapy Association. Phys Ther. 2001 Jan;81(1):9-746. PubMed PMID: 11175682.

91. Cleland JA, Fritz JM, Whitman JM, Childs JD, Palmer JA. The use of a lumbar spine manipulation technique by physical therapists in patients who satisfy a clinical prediction rule: a case series. J Orthop

Sports Phys Ther. 2006 Apr;36(4):209-14. PubMed PMID: 16676870.

92. Kazdin, A. E. (2007). Mediators and mechanisms of change in psychotherapy research. Annual Review of Clinical Psychology, 3, 1-27.

93. Burns JW, Day MA, Thorn BE (in press). Is reduction in pain catastrophizing a therapeutic mechanism specific to cognitive behavioral therapy for chronic pain? Translational Behavioral Medicine: Practice, Policy and Research.

94. Burns, J.W., Johnson, B.J., Mahoney, N., Devine, J., & Pawl, R. (1998). Cognitive and physical capacity process variables predict long-term outcome after treatment of chronic pain. Journal of Consulting & Clinical Psychology, 66, 434-439.

95. Lofland, K.R., Burns, J.W., Tsoutsouris, J., Laird, M.M., Blonsky, E.R., & Hejna, W.F. (1997). Predictors of outcome following multidisciplinary treatment of chronic pain: Effects of changes in perceived disability and depression. International Journal of Rehabilitation and Health, 3, 221-232.

96. Eccleston, C., Williams Amanda C de, C., & Morley, S. (2009). Psychological therapies for the management of chronic pain (excluding headache) in adults. Cochrane Database of Systematic Reviews.

97. Veehof, M.M., Oskam, M., Schreurs, K.M.G., & Bohlmeijer, E.T. (2011). Acceptance-based interventions for the treatment of chronic pain: A systematic review and meta-analysis. Pain, 152, 533-542.

98. Rubinstein SM. Adverse events following chiropractic care for subjects with neck or low-back pain: do the benefits outweigh the risks? Journal of manipulative and physiological therapeutics. 2008;31(6):461-4.

99. Team UBT. United Kingdom back pain exercise and manipulation (UK BEAM) randomised trial: effectiveness of physical treatments for back pain in primary care. BMJ (Clinical research ed). 2004;329:1377.

100. Leemann S, Peterson CK, Schmid C, Anklin B, Humphreys BK. Outcomes of acute and chronic patients with magnetic resonance imaging-confirmed symptomatic lumbar disc herniations receiving high-velocity, low-amplitude, spinal manipulative therapy: a prospective observational cohort study with one-year follow-up. Journal of manipulative and physiological therapeutics. 2014;37(3):155-63.

101. Carmody J. Re-Conceptualizing Mindfulness: The Psychological Principles of Attending in Mindfulness Practice and Their Role in Well-being. In Handbook of Mindfulness: Theory and Research. Brown K, Creswell D and Ryan R (Eds) Guilford. 2015.

102. Klyne DM, Schmid AB, Moseley GL, Sterling M, Hodges PW. Effect of types and anatomic arrangement of painful stimuli on conditioned pain modulation. J Pain. 2015 Feb;16(2):176-85.

103. Wong AY, Kawchuk G, Parent E, Prasad N. Within- and between-day reliability of spinal stiffness measurements obtained using a computer controlled mechanical indenter in individuals with and without low back pain. Man Ther. 2013 Oct;18(5):395-402

104. Zeidan F, Adler-Neal AL, Wells RE, Stagnaro E, May LM, Eisenach JC, McHaffie JG, Coghill RC. Mindfulness-Meditation-Based Pain Relief Is Not Mediated by Endogenous Opioids. J Neurosci. 2016 Mar 16;36(11):3391-7.

105. Sharon H, Maron-Katz A, Ben Simon E, Flusser Y, Hendler T, Tarrasch R, Brill S. Mindfulness Meditation Modulates Pain Through Endogenous Opioids. Am J Med. 2016 Jul;129(7):755-8.

106. Zeidan F, Martucci KT, Kraft RA, Gordon NS, McHaffie JG, Coghill RC. Brain mechanisms supporting the modulation of pain by mindfulness meditation. J Neurosci. 2011 Apr 6;31(14):5540-8.

107. Youssef AM, Macefield VG, Henderson LA. Pain inhibits pain; human brainstem mechanisms. Neuroimage. 2016 Jan 1;124(Pt A):54-62.

108. Valet M, Sprenger T, Boecker H, Willoch F, Rummeny E, Conrad B, Erhard P, Tolle TR. Distraction modulates connectivity of the cingulo-frontal cortex and the midbrain during pain--an fMRI analysis. Pain 2004; 109: 399-408.

109. Hadjipavlou et al., 2006 is: Hadjipavlou G, Dunckley P, Behrens TE, Tracey I. Determining anatomical connectivities between cortical and brainstem pain processing regions in humans: a diffusion tensor imaging study in healthy controls. Pain 2006; 123: 169-178.

110. Wager TD, Scott DJ, Zubieta JK. Placebo effects on human mu-opioid activity during pain. Proc Natl Acad Sci U S A 2007; 104): 11056-11061.

111. Wagner KJ, Sprenger T, Kochs EF, Tölle TR, Valet M, Willoch F. Imaging human cerebral pain modulation by dose-dependent opioid analgesia: a positron emission tomography activation study using remifentanil. Anesthesiology 2007; 106: 548-556.

112. Burns JW1, Quartana PJ, Bruehl S. Anger management style moderates effects of attention strategy during acute pain induction on physiological responses to subsequent mental stress and recovery: a comparison of chronic pain patients and healthy nonpatients. Psychosom Med. 2009 May;71(4):454-62.

113. Burns JW1, Bruehl S, Caceres C. Anger management style, blood pressure reactivity, and acute pain sensitivity: evidence for "Trait x Situation" models. Ann Behav Med. 2004 Jun;27(3):195-204.

114. Laska KM, Gurman AS, Wampold BE. Expanding the lens of evidence-based practice in psychotherapy: a common factors perspective. Psychotherapy (Chic). 2014 Dec;51(4):467-81.

115. Burns JW, Bruehl S, France CR, Schuster E, Orlowska D, Buvanendran A, Chont M, Gupta RK. Psychosocial factors predict opioid analgesia through endogenous opioid function. Pain. 2017 Mar;158(3):391-399.

116. Haas M, Vavrek D, Peterson D, Polissar N, Neradilek MB. Dose-response and efficacy of spinal manipulation for care of chronic low back pain: a randomized controlled trial. Spine J. 2014 Jul 1;14(7):1106-16.

117. Cramer, H., Haller, H., Lauche, R., & Dobos, G. (2012). Mindfulness-based stress reduction for low back pain. A systematic review. BMC Complementary and Alternative Medicine, 12(1),162.

118. Lauche R1, Cramer H, Dobos G, Langhorst J, Schmidt S. A systematic review and meta-analysis of mindfulness-based stress reduction for the fibromyalgia syndrome. J Psychosom Res. 2013 Dec;75(6):500-10.

119. Veehof MM, Trompetter, Bohlmeijer ET, Schreurs KM. Acceptance- and mindfulness-based interventions for the treatment of chronic pain: a meta-analytic review. Cogn Behav Ther. 2016;45(1):5-31.

120. Bawa FL, Mercer SW, Atherton RJ, Clague F, Keen A, Scott NW, Bond CM. Does mindfulness improve outcomes in patients with chronic pain? Systematic review and meta-analysis. Br J Gen Pract. 2015 Jun;65(635):e387-400.

121. Franke H, Franke JD, Fryer G. Osteopathic manipulative treatment for nonspecific low back pain: a systematic review and meta-analysis. BMC Musculoskelet Disord. 2014 Aug 30;15:8.

122. Rubinstein SM, van Middelkoop M, Assendelft WJ, de Boer MR, van Tulder MW. Spinal manipulative therapy for chronic low-back pain. Cochrane Database Syst Rev. 2011 Feb 16;(2):CD008112.

123. Chou R, Huffman LH; American Pain Society.; American College of Physicians. Nonpharmacologic therapies for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. Ann Intern Med. 2007 Oct 2;147(7):492-504.

124. Xia T, Long CR, Vining RD, Gudavalli MR, DeVocht JW, Kawchuk GN, Wilder DG, Goertz CM. Association of lumbar spine stiffness and flexion-relaxation phenomenon with patient-reported outcomes in adults with chronic low back pain - a single-arm clinical trial investigating the effects of thrust spinal manipulation. BMC Complement Altern Med. 2017 Jun 9;17(1):303.

15. SUPPLEMENTS/APPENDICES

Appendix I. Side effects from Naloxone compared to Placebo (N = 144)

Descriptives - Side Effects on 0-10 Scale (0 = None, 10 = The Most Possible)

Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
nxnausea	146	.00	7.00	.2808	.91533
nxvomit	144	.00	1.00	.0139	.11744
nxdiarrh	146	.00	1.00	.0137	.11664
nxhead	143	.00	5.00	.3986	.95046
nxrestles	145	.00	10.00	.8207	1.66111
nxtrem	145	.00	3.00	.0828	.39971
nxheart	144	.00	3.00	.1250	.47120
nxsweat	146	.00	8.00	.2671	1.09097
nxweak	143	.00	7.00	.4126	1.07027

nxdrow	146	.00	9.00	1.6918	2.09536
Valid N (listwise)	143				

Note. Prefix nx – naloxone. Side effects means are low.

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	nxnausea	.2778	144	.91944	.07662
	plnausea	.1667	144	.52889	.04407
Pair 2	nxvomit	.0141	142	.11826	.00992
	plvomit	.0141	142	.11826	.00992
Pair 3	nxdiarrh	.0139	144	.11744	.00979
	pldiarrh	.0139	144	.11744	.00979
Pair 4	nxhead	.4043	141	.95602	.08051
	plhead	.3333	141	1.05334	.08871
Pair 5	nxrestles	.8322	143	1.66989	.13964
	plrestles	.4615	143	1.36232	.11392
Pair 6	nxtrem	.0839	143	.40240	.03365
	pltrem	.0070	143	.08362	.00699
Pair 7	nxheart	.1268	142	.47429	.03980
	plheart	.0986	142	.45053	.03781
Pair 8	nxsweat	.2517	143	1.07774	.09013
	plsweat	.0210	143	.14382	.01203
Pair 9	nxweak	.4113	141	1.07618	.09063
	plweak	.3050	141	1.08195	.09112
Pair 10	nxdrow	1.7153	144	2.10033	.17503
	pldrow	1.4236	144	2.15997	.18000

Note. Prefix nx = naloxone. Prefix pl = placebo.

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
					95% Confidence Interval of the Difference				
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper			
Pair 1	nxnausea - plnausea	.11111	.80306	.06692	-.02117	.24340	1.660	143	.099
Pair 2	nxvomit - plvomit	.00000	.16843	.01413	-.02794	.02794	.000	141	1.000
Pair 3	nxdiarrh - pldiarrh	.00000	.11826	.00986	-.01948	.01948	.000	143	1.000
Pair 4	nxhead - plhead	.07092	1.24008	.10443	-.13555	.27739	.679	140	.498
Pair 5	nxrestles - plrestles	.37063	1.46161	.12223	.12901	.61225	3.032	142	.003
Pair 6	nxtrem - pltrem	.07692	.41243	.03449	.00874	.14510	2.230	142	.027
Pair 7	nxheart - plheart	.02817	.61821	.05188	-.07439	.13073	.543	141	.588
Pair 8	nxsweat - plsweat	.23077	1.08571	.09079	.05129	.41025	2.542	142	.012
Pair 9	nxweak - plweak	.10638	1.01209	.08523	-.06213	.27489	1.248	140	.214
Pair 10	nxdrow - pldrow	.29167	2.14875	.17906	-.06229	.64562	1.629	143	.106

Note. Prefix nx = naloxone. Prefix pl = placebo. Side effect ratings are similar between naloxone and placebo across 7 of 10 comparisons.