Title: Chronic Low Back Pain and Meditation

NCT Record #: NCT04034004
Date: June 2, 2023

PI: Fadel Zeidan

UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN
Instructions for completing the Research Plan are available on the HRPP website.
The headings on this set of instructions correspond to the headings of the Research Plan.
General Instructions: Enter a response for all topic headings.
Enter “Not Applicable” rather than leaving an item blank if the item does not apply to this project.
Version date: 6/02/2023

1. PROJECT TITLE

The role of endogenous opioids in mindfulness-based chronic pain relief.

2. PRINCIPAL INVESTIGATOR

Fadel Zeidan, Assistant Professor, Department of Anesthesiology

3. FACILITIES

* Altman Clinical and Translational Research Institute (ACTRI).
* UCSD Center for Mindfulness (CfM)

4. ESTIMATED DURATION OF THE STUDY

We estimate that the proposed study will take 5 years to complete. This includes completing data collection on 60 chronic low back pain patients, data analyses, and time for publication. Each participant will complete 7 study sessions, which includes review of medical records for confirmation of chronic low back pain, confirmation of study eligibility (i.e., positive response to the straight leg raise test, exclusion/inclusion criteria), baseline pain testing, four days of mental training (mindfulness/ non-mindfulness) and two clinical visits where participants will be administered the straight leg raise test during placebo-saline or naloxone infusion. After all of the data has been collected, the investigators of the study will be unblinded and statistical analyses will be performed to test the study hypotheses at which point we will prepare the manuscript for publication.

We do expect recruitment to go smoothly and anticipate that data collection will be completed after 16 months which would provide ample time for data analyses and manuscript preparation.

With respect to the subject focused study procedures, a 4-subject cohort strategy would produce a start to finish accrual process of 1-2 months or less. An extra 2-3 weeks will be added to the schedule after one cohort completes to allow for the required accrual of the next group of 8 subjects. The total outside accrual boundary of this study, taking into account increased stringency with recruitment towards the end of the study and accounting for a 20% retention loss, is at an estimate of 12 months.

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

Chronic pain affects over 100 million Americans and costs the United States an estimated $635 billion per year in medical expenses and lost work productivity (Institute of Medicine (US) Committee on Advancing Pain Research 2011, Steglitz 2012). Low back pain is the most common clinical pain condition (Hoy, Bain et al. 2012) with an average prevalence of 30%; it is the leading cause for disability (Andersson 1999). In spite of treatment advances, the pervasiveness and burden of chronic low back pain (cLBP) has dramatically increased Medicare expenditures for steroid injections (629%) and opioid treatments (423%) (Deyo, Mirza et al. 2009). The widespread use of opioids to alleviate chronic pain has led to the so-called “opioid epidemic” (Nelson, Juurlink et al. 2015) with an exponential rise in opioid misuse and addiction (Han, Compton et al. 2015, Saloner and Karthikeyan 2015). These staggering statistics signify the importance of developing fast-acting non-pharmacologic approaches, such as mindfulness meditation (Jacob 2016), to treat acute exacerbations of cLBP. The central aim of the proposed NIH sponsored study is to determine if mindfulness-based chronic pain relief, as compared to non-mindfulness, is associated with the release of endogenous opioids. This study will examine if mindfulness reduces acutely evoked radicular pain in cLBP through endogenous

opioids, as compared to a validated, non-mindfulness technique that we have characterized as non-mindfulness meditation (Zeidan, Johnson et al. 2010, Zeidan, Emerson et al. 2015). The knowledge gained from this study will provide novel mechanistic insight to better develop and tailor cognitive therapeutic interventions to target multiple chronic pain conditions.

6. SPECIFIC AIMS

Primary Objective

Determine if mindfulness-based chronic back pain relief is mediated by endogenous opioids.

7. BACKGROUND AND SIGNIFICANCE

Pain is a multidimensional experience that involves sensory, cognitive and affective factors. The constellation of interactions between these factors renders the treatment of chronic pain challenging and often a financial burden. In fact, chronic pain affects over 100 million Americans and costs the United States approximately $635 billion dollars a year. The widespread use of opioids to treat chronic pain has led to the so-called “opioid epidemic” due to the exponential growth in opioid misuse and addiction. These staggering statistics highlight the importance of developing, testing and validating fast-acting, non-pharmacological approaches to treat pain. Mindfulness meditation is a technique that has been found to significantly reduce pain in experimental and clinical settings. However, lack of mechanistic data and the assumption that extensive meditation training is required to experience analgesia has limited the clinical deployment of this cost-effective and narcotic-free treatment. Recent findings from our laboratory determined that mindfulness meditation reduces pain (mean pain intensity = 34%; mean pain unpleasantness = 51%), after only 4 training sessions, through multiple brain mechanisms (Zeidan, Martucci et al. 2011, Zeidan, Emerson et al. 2015). We have also found that a) mindfulness-based pain relief is more effective and mechanistically distinct from placebo-analgesia and b) surprisingly, mindfulness meditation does not engage endogenous opioidergic systems to reduce pain (Zeidan, Adler-Neal et al. 2016, May, Kosek et al. 2018). Yet, these findings are difficult to explicitly generalize to chronic pain patients because they were conducted in pain-free individuals using thermally induced pain. The experience of pain promotes endogenous opioid release in healthy individuals (Zubieta, Smith et al. 2001, Anderson, Sheth et al. 2002, Bencherif, Fuchs et al. 2002, Zubieta, Smith et al. 2002). In contrast, there is robust evidence that opioid receptor availability is significantly reduced in the brain across a wide spectrum of chronic pain conditions (Jones, Cunningham et al. 1994, Jones, Kitchen et al. 1999, Jones, Watabe et al. 2004, Harris, Clauw et al. 2007, Maarrawi, Peyron et al. 2007, Klega, Eberle et al. 2010, DosSantos, Martikainen et al. 2012, Brown, Matthews et al. 2015), including chronic low back pain (Bruehl, Chung et al. 2003, Bruehl and Chung 2006, Bruehl, Chung et al. 2007, Martikainen, Pecina et al. 2013, Bruehl, Burns et al. 2015, Burns, Bruehl et al. 2017), the cause postulated to be the development of chronic pain (Thompson, Pitcher et al. 2018). However, while we have repeatedly shown that mindfulness does not employ endogenous opioids to reduce pain in healthy subjects, it is also possible that the role of endogenous opioids in mindfulness-based analgesia is more pronounced in clinical pain populations. Thus, the central aim of the proposed study to determine if mindfulness-based cLBP relief, the most prevalent and financially burdensome chronic pain condition, is mediated by endogenous opioids.

The use of high dose naloxone is commonplace and routinely employed in mechanistically focused pain research for over 40 years now (citations selected out of > 1000 studies) (Goldstein and Grevert 1978, Skrabanek 1978, Gracely, Dubner et al. 1983, Posner and Burke 1985, Levine and Gordon 1986, Benedetti 1996, Amanzio and Benedetti 1999, Amanzio, Pollo et al. 2001, Bruehl, Chung et al. 2004, Bruehl, Burns et al. 2008, Burns, Bruehl et al. 2009, Bruehl, Burns et al. 2011, Taylor, Borckardt et al. 2012, Pereira, Werner et al. 2013, Schoell, Bingel et al. 2013, Dowell, Haegerich et al. 2016, Springborg, Jensen et al. 2016, Zeidan, Adler-Neal et al. 2016, Berna, Leknes et al. 2018, May, Kosek et al. 2018) (Grevert, Albert et al. 1983, Amanzio and Benedetti 1999, Benedetti, Arduino et al. 1999) (Adams 1976, Hosobuchi, Adams et al. 1977) (de Andrade, Mhalla et al. 2011, Taylor, Borckardt et al. 2013) (Mayer, Price et al. 1977) (Stephenson 1978). Naloxone at a high does provides complete blockade of opioid receptors which allows us to identify the role of endogenous

systems in the construction and modulation of pain. If we do not comprehensively block endogenous opioids, then we will not be able reliably inference our results to the recruitment (or lack thereof) of endogenous opioids in mindfulness-based pain relief (Grevert, Albert et al. 1983, Spiegel and Albert 1983). Fortunately, naloxone does not produce significant side effects in opioid independent participants(Mangold, McCaul et al. 2000) and thus we probe the role of endogenous opioids quite reliably.

This work could guide future clinical trial(s) development to better target outcomes and corresponding mechanisms supporting meditation-related cLBP relief. If meditation induced chronic pain relief were associated with non-opioidergic mechanisms, it would provide significant evidence that mindfulness relieves pain by altering the contextual evaluation of nociceptive information via unique top-down control processes (Zeidan, Grant et al. 2012). Since opioid and non-opioid mechanisms of analgesia interact in a synergistic manner, the present work could show that the combination of mindfulness and pharmacologic/non-pharmacologic analgesic strategies, that rely on opioid signaling, may be acutely effective in the treatment of clinical pain, a potentially critical finding for the millions of pain patients seeking a non-opioid therapy.

8. PROGRESS REPORT

Not applicable. This is a new study.

9. RESEARCH DESIGN AND METHODS

This proposed NIH-sponsored, randomized, and double-blinded psychophysical and pharmacologic study includes 7 separate study sessions. In this experiment, we are assessing if mindfulness reduces acutely evoked radicular pain in cLBP through endogenous opioids as compared to a validated (Zeidan, Johnson et al. 2010, Zeidan, Emerson et al. 2015), non-mindfulness meditation technique (non-mindfulness) by administering an opioid antagonist, naloxone, to determine if mindfulness based cLBP relief is mediated by endogenous opioidergic systems. Importantly, we are employing a well-validated, non-mindfulness meditation intervention as a placebo control. As previously (Zeidan, Johnson et al. 2010, Zeidan, Emerson et al. 2015), the non-mindfulness group will be instructed that they are in the “mindfulness meditation” intervention. Thus, we must blind non-mindfulness subjects to the nature of their respective intervention.

Each study session will be conducted on a separate day. All potential participants will be assessed for study eligibility at the pre-study screening and first study session. Participants will have 40 days to complete the study.

Exemption from 21 CFR 312.2(b)(iii): We and many other groups are exempt from key criterion outlined in 21 CFR 312.2(b)(iii) (The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product) because the dosage employed has been repeatedly demonstrated to be highly safe and effective at examining the study aims. This is demonstrated below and described in the attached IND Exempt supplement document (item 25).

Critically, the use of high dose naloxone is commonplace and routinely employed in mechanistically focused pain research for over 40 years now (citations selected out of > 1000 studies) (Goldstein and Grevert 1978, Skrabanek 1978, Gracely, Dubner et al. 1983, Posner and Burke 1985, Levine and Gordon 1986, Benedetti 1996, Amanzio and Benedetti 1999, Amanzio, Pollo et al. 2001, Bruehl, Chung et al. 2004, Bruehl, Burns et al. 2008, Burns, Bruehl et al. 2009, Bruehl, Burns et al. 2011, Taylor, Borckardt et al. 2012, Pereira, Werner et al. 2013, Schoell, Bingel et al. 2013, Dowell, Haegerich et al. 2016, Springborg, Jensen et al. 2016, Zeidan, Adler-Neal et al. 2016, Berna, Leknes et al. 2018, May, Kosek et al. 2018) (Grevert, Albert et al. 1983, Amanzio and Benedetti 1999, Benedetti, Arduino et al. 1999) (Adams 1976, Hosobuchi, Adams et al. 1977) (de Andrade, Mhalla et al. 2011, Taylor, Borckardt et al. 2013) (Mayer, Price et al. 1977) (Stephenson 1978).

In addition, our laboratory has now successfully completed three separate experiments combining noxious stimulation, mindfulness-based meditation (and sham-mindfulness), and IV naloxone/saline infusion employing the exact procedures that match this NIH sponsored project.

In our first two published studies (Zeidan, Adler-Neal et al. 2016, May, Kosek et al. 2018), we employed the exact naloxone dosages and procedures (very safely) as the ones for this study.

We have recently completed (data collection completed; writing manuscript now) a third study, where we employed what we (and the NIH) characterized as a cross-over design, naloxone infusion procedure in 60 individuals without any safety events. The four participants that exhibited side effects in our Journal of Neuroscience, 2016 study was related to these subjects' previous history of syncope, fear of needles, and blood and not directly related to naloxone. Thus, in our latest study (in preparation), we excluded individuals that have no prior history of syncope, fear of blood/needles, and report no side effects, safety and/or adverse events.

Further, the naloxone dosages employed in our laboratory studies corresponded to a 0.15 mg/kg bolus dose of naloxone (Naloxone HCI, Amphastar Pharmaceuticals, Inc., Rancho Cucamonga, California) or saline in 25ml normal saline was administered over 10 minutes via the intravenous (IV) line inserted into the antecubital vein of the non-dominant arm. To ensure that naloxone antagonizes opioid receptors for entirety of the experiment, we administered a supplementary IV infusion dose of 0.1mg/kg/hour naloxone or saline immediately after bolus infusion ceased till the end of the experiment. This large dose comprehensively antagonizes endogenous opioids (Levine and Gordon 1986) and reverses pain relief produced by placebo (Levine, Gordon et al. 1978, Grevert, Albert et al. 1983, Amanzio and Benedetti 1999, Benedetti, Arduino et al. 1999), electrical stimulation of periventricular gray matter (Adams 1976, Hosobuchi, Adams et al. 1977), transcranial magnetic stimulation (de Andrade, Mhalla et al. 2011, Taylor, Borckardt et al. 2013), acupuncture (Mayer, Price et al. 1977), and hypnosis (Stephenson 1978).

In our third study conducted at the University of Oregon, we used an even larger dosage of 0.15 mg/kg bolus dose of naloxone (Naloxone HCI, Amphastar Pharmaceuticals, Inc., Rancho Cucamonga, California) with a .20 mg/kg/hour infusion. There were no side effects exhibited in this study. Further, other groups (Mangold, McCaul et al. 2000, Eippert, Bingel et al. 2009, Schoell, Bingel et al. 2013, Berna, Leknes et al. 2018) have employed larger IV dosages of naloxone than our protocol without any side effects or adverse events. We have extensively piloted our procedures to ensure that no side effects arise, we do not unblind subjects and can comprehensively block endogenous opioids. We have run over 180 participants with only four minor side effects in a study where we did not exclude subjects with prior history of syncope, fear of blood and/or needles. We will employ this new exclusion criteria in the present study.

Duration of Human Involvement

Successful completion of the proposed study will include a total of 7 sessions. Prior to their enrollment potential subjects will first be screened over the phone to determine if they qualify for the proposed project. There may be up to 2 weeks between a patient's initial screening and their official enrollment of the study.

We will provide up to a 14-day gap between enrollment and the first experimental session to provide time to enroll cohorts, group randomization, and individualized scheduling. Once the schedules have been determined, the participants' baseline assessment and baseline testing session will be scheduled, and coordinator study team member will schedule intervention regimens. Study participants will be required to complete 4 respective training sessions over a 14-day period (including weekends; interventions will be offered over the weekend). This approach will increase study feasibility, compliance and adherence. The clinical pharmacologic testing sessions will be scheduled

individually during the respective interventions. After the first pharmacologic testing session, participants must wait no less than 2 days and no more than 6 days to complete the second clinical pharmacologic testing session.

Planned Data Collection

Data Collection:
The following information will be collected from all patients: name, date of birth, age, gender, ethnicity, telephone number email address, medical record number (will be deleted from study file once review of medical records is complete), diagnosis, condition, current/previous drug regimen, handedness and meditation experience. Also, in order to process subject compensation, address and social security number will be collected.

Experimental Sessions: All of the proposed procedures are characterized as “experimental”.

Session 1 Pre-Regimen Session: Subjects will first report to the Altman Clinical and Translational Research Institute (ACTRI).

This session will also be employed to determine participant eligibility based on our inclusion and exclusion criteria and will serve as the baseline behavioral control. After obtaining informed consent, subjects will complete study questionnaires (see Questionnaires) and will be trained to reliably use the visual analog scale (VAS) to rate their pain (Zeidan, Martucci et al. 2011, Zeidan, Emerson et al. 2015, Zeidan, Lobanov et al. 2015), in response to heat stimuli (32 stimuli of 5 second duration) ranging from 35-49°C in a fixed order, and the chronic low back pain exacerbation procedure. This psychophysical training will also maximize reproducibility of pain ratings (Rosier, Iadarola et al. 2002). These assessments will be based on self-report, review of medical history from the subject’s current/previous physician(s), and/or confirmation of chronic low back pain diagnosis by a study physician during Session 1 at the ACTRI. In the review of a subject’s medical history, a trained study staff member will review and record necessary data, in order to confirm eligibility criteria are met. Information will be reviewed from the EPIC medical records of subjects who are UCSD patients or from copies of the medical records provided by non-UCSD patient subjects. These outcomes include: the subject’s diagnosis (spinal pathology and date), condition, and current/previous drug regimen. Confirmation of chronic low back pain must also be determined through performance of the straight leg raise test. That is, a study physician (Krishnan Chakravarthy) or trained research technicians will confirm diagnosis by examining the medical history record. If a medical record is not available, then we will confirm low back pain by determining if the patient is “positive” on the straight leg raise test, which will serve as the primary method of low back pain confirmation. As described in Session 1, we will test to see if the straight leg raise test (SLR) produces an increase in subjective pain corresponding to the low back. Subjects that report an increase of pain when lifting their legs up from 15-60 degrees, or to a height in that range, will be characterized as “straight leg raise test positive.” This is an indicator of radicular pain stemming from the low back.

Psychophysical Testing

Thermal stimulation: As in all of our prior IRB approved experiments (Zeidan, Martucci et al. 2011, Lobanov, Zeidan et al. 2014, Zeidan, Emerson et al. 2015, Zeidan, Lobanov et al. 2015, Zeidan, Adler-Neal et al. 2016, Zeidan, Salomons et al. 2018, Adler-Neal, Emerson et al. 2019, Adler-Neal, Waugh et al. 2019), the MEDOC TSA-II will be used to deliver all thermal stimuli. All stimulus temperatures will be less than or equal to 50°C, and volunteers will be free to escape the stimulator at any time. No stimulus will produce tissue damage. This study will use a 16x16 mm surface area for the delivery of neutral and noxious stimuli. This modest stimulus area allows a relatively wide range of noxious stimuli to be delivered (up to 50°C for 30 seconds) without either tissue damage or significant subject withdrawals/drop-outs. Stimuli in this temperature range have been used extensively by the PI

and numerous laboratories around the world and do not produce tissue damage or burns. In order to facilitate escape from the stimulator, the stimulator will be attached to a custom-designed thermal stimulation probe holder. Participants will place their calf on top of the probe holder and will not be strapped in or otherwise restrained. Therefore, participants will be able to simply lift their legs at any time.

Chronic low-back pain exacerbation procedure: Co-investigators and/or trained study staff will conduct the cLBP exacerbating straight leg-raise test, which is commonly used to assess mobility and pain severity in those with low-back pain (Mens, Vleeming et al. 1999, Roussel, Nijs et al. 2007, Kwong, Virani et al. 2013, Bruno, Millar et al. 2014). This procedure significantly increases behavioral and neural pain responses for 10-15 minutes (Apkarian, Krauss et al. 2001, Sharma, Gupta et al. 2011, Wasan, Loggia et al. 2011, Loggia, Kim et al. 2013). Session 1 will determine if the straight leg raise test will reliably exacerbate cLBP and allow patients to decide if they are willing to perform subsequent straight leg raises. Co-investigators and/or trained staff will first instruct patients to lie in supine position for 15 seconds before collecting baseline pain ratings. For each patient, we will first measure the straight leg angle/height required to produce a 2-point VAS pain intensity increase using a goniometer [70]. With the aid of study staff, participants will again perform a straight leg-raise ranging from 15-60° (Rebain, Baxter et al. 2002, Summers, Malhan et al. 2005), depending on the angle/height required to produce the targeted pain increase and hold the position for 10 seconds. After lowering their legs, we will assess if the patient's pain ratings increased to the targeted pain increase compared to baseline pain ratings (Wasan, Loggia et al. 2011). This procedure will be repeated up to three times to ensure inter-maneuver reliability (Wasan, Loggia et al. 2011). Since this procedure can exacerbate pain for up to 15 minutes, we will wait at least 20 minutes between tests to confirm that pain returned to baseline. The leg-raise angle/height corresponding to a 2-point VAS pain increase will be targeted in each subsequent testing session. This session should take approximately 2.0 hours or less to complete.

Procedures

Pre Rest + Heat: A thermal probe will be placed on the back of the "unaffected" calf (i.e., non-responsive to SLR) while patients lie in the supine position. They will be instructed to "rest with your eyes closed" for 5 minutes. We will administer the so-called "Heat" series that includes 10 alternating, 12-second plateaus of noxious (49°C) and 35°C stimulation. VAS pain intensity, VAS unpleasantness, and numerical pain ratings will be collected after the series has completed. We will then remove the calf from the probe holder.

Pre Rest + SLR: After identifying the appropriate angle/height to induce a 2-point pain increase, patients will lie in the supine position and will be instructed to "rest with your eyes closed" for 5 minutes. VAS pain ratings will then be collected. With the aid of a technician, patients will then lift their legs to the angle/height calibrated to produce a 2-point VAS pain increase. After 5 minutes, we will collect pain ratings.

Post Rest + SLR: We will wait 10 minutes before continuing the study to control for the time spent administrating the drug/saline bolus take effect. VAS pain ratings will be collected after 10 minutes. We will then match the procedures employed in Pre-Rest + SLR.

Post Rest + Heat: A thermal probe will be placed on the back of the "unaffected" calf while patients lie in the supine position. They will be instructed to "rest with your eyes closed" for 8 minutes. We will then match the procedures employed in Pre Rest + Heat.

Patient Randomization:
After successful completion of session 1, participants will be randomized to their respective group. Randomization will be tracked in the Screening/Enrollment Log that is maintained by the clinical

coordinator. Randomization will be stratified so that each sex will have their respective list of randomization codes. Males and females will be randomized without replacement across a block of 60 codes using an Excel-based random number generator. Male and female participants will be randomized within three days of their respective scheduled psychophysical training session. The two treatment arms (mindfulness meditation = A; non-mindfulness meditation =B) will be permuted with respect to treatment assignment, in a double-blind fashion, respectively. We will employ a similar randomization procedure within each group to determine when (i.e., Session 6 or 7) each participant will receive naloxone and saline in a crossover manner.

Sessions 2-5: Regimen:
Procedures corresponding to the regimen sessions will parallel the mindfulness meditation and non-mindfulness meditation training regimens employed previously (Zeidan, Emerson et al. 2015). Interventions will be conducted in groups of one (1 = makeup sessions) to six (Zeidan, Gordon et al. 2010, Zeidan, Johnson et al. 2010, Zeidan, Johnson et al. 2010, Zeidan, Martucci et al. 2011, Zeidan, Martucci et al. 2014, Zeidan, Emerson et al. 2015) and taught by certified facilitators at the UCSD Center for Mindfulness (CfM). A research technician will greet patients as they arrive to the CfM and guide them to their respective classrooms. Both prior to and after completion of each intervention regimen, the research technician will issue and collect study assessment data (SAI both pre and post-intervention session; Perceived Intervention Effectiveness post-intervention session) to each participant. Each of these sessions will take no longer than 45 minutes to complete.

Mindfulness Meditation Training: We will use our well-validated mindfulness-based mental training regimen to teach participants to independently practice mindfulness meditation (Zeidan, Johnson et al. 2010, Zeidan, Johnson et al. 2010, Zeidan, Martucci et al. 2011, Zeidan, Emerson et al. 2015, Zeidan, Adler-Neal et al. 2016). In each of the four 20-minute sessions, participants will be asked to close their eyes, focus on the breath sensations, recognize distracting thoughts and feelings, and to “simply let go” of sensory events without judgment. They will be taught that perceived sensory and affective events are “momentary” and “fleeting” and do not require evaluation.

Non-mindfulness Meditation Training: The main purpose of the non-mindfulness meditation regimen is to serve as an active control for a crucial, essential element of mindfulness meditation (i.e., mindful attention to breath and non-reactivity to sensory events)(Zeidan, Johnson et al. 2010, Zeidan, Emerson et al. 2015). This regimen is designed so that the primary difference between the mindfulness and non-mindfulness meditation training is the mindfulness meditation group’s explicit mindfulness-based instructions (e.g., mindful attention to the breath). The non-mindfulness meditation group will be told that they are randomly assigned to the meditation group (Zeidan, Johnson et al. 2010, Zeidan, Emerson et al. 2015). In each of the four 20-minute training sessions, participants will be instructed to close their eyes, and to take a deep breath “as we sit here in meditation” every 2-3 minutes (Zeidan, Johnson et al. 2010, Zeidan, Emerson et al. 2015). All other aspects (training room, posture, facilitator, time providing instruction) of the non-mindfulness meditation intervention will be matched.

Sessions 6 & 7: Post-Regimen Session: We will employ a double-blinded crossover design to correspond to the administration of the opioid antagonist, naloxone and placebo-saline across two separate sessions at UCSD’s Altman Clinical and Translational Research Institute (ACTRI). A total of 30 subjects in each group will receive naloxone in Session 6 and saline in Session 7. Conversely, the other 30 subjects in each group will receive saline in Session 6 and naloxone in Session 7. After successful completion of their respective regimen, participants will report to the ACTRI. A research technician will greet patients as they arrive to the ACTRI and guide them to the clinic room. Next, the research technician will issue study assessments to the participant. ACTRI nurses will then administer an opiate-focused urine drug screening to confirm that no participants are using opioids to remove the risk of opioid withdrawal symptoms during naloxone administration, and a pregnancy test (if applicable). Weight will be subsequently measured to confirm the prescribed drug dosage. Next, the

research technician will issue study assessments to the subject. We will recalibrate each participant's leg raise height/angle required to elicit a 2-point pain increase employing the methods described in Session 1. An ACTRI nurse will then insert the IV catheter into
the non-dominant arm of each participant. As previously employed (Zeidan, Adler-Neal et al. 2016) for safety purposes, blood pressure, respiration, oxygen saturation, and heart rate will be systematically monitored/recorded. These sessions should take approximately 1.0 hour to complete.

Pre Rest + Heat: A thermal probe will be placed on the back of the "unaffected" calf while patients lie in the supine position. They will be instructed to "rest with your eyes closed" (~ 5 minutes). We will administer a "Heat" series that includes 10 alternating, 12-second plateaus of noxious (49°C) and 35°C stimulation. After completion, we will collect pain ratings.

Pre Rest + SLR: The procedures employed in Pre Rest + SLR will be matched to those employed in Session 1. Briefly, patients will lie in the supine position and be instructed to "rest with your eyes closed". VAS pain ratings will then be collected. With the aid of a technician, participants will then lift their legs to the angle/height calibrated to produce a 2-point VAS pain increase. After completion, we will collect pain ratings.

Bolus: An ACTRI nurse will then initiate the naloxone/saline bolus (based on weight) for approximately 8 minutes.

Pre Meditation + SLR: After completion of the bolus (~8 minutes), a study technician will aid participants to lift their legs to the height/angle calibrated to produce a 2-point VAS pain increase. Participants in the mindfulness and non-mindfulness meditation groups will then be instructed to "begin meditating until the end of the session" (Zeidan, Martucci et al. 2011, Zeidan, Emerson et al. 2015). An ACTRI nurse will then initiate the naloxone or placebo-saline infusion. After completion, we will collect pain ratings.

Post Meditation + Heat: A thermal probe will be placed on the back of the "unaffected" calf while patients lie in the supine position and during meditation. We will administer a "Heat" series that includes 10 alternating, 12-second plateaus of noxious (49°C) and 35°C stimulation. After completion, we will collect pain ratings.

Patients will return to the ACTRI to complete session 7 and will follow the same procedures (except for drug administration) as Session 6. Participants must wait 2 days to participate but no longer than 7 days to complete Session 7. Drug symptomology will be assessed after each session.

Primary Outcome Measure(s):

1. Visual Analog Scale (VAS) and numerical rating scales (NRS): Pain ratings (VAS pain intensity, VAS unpleasantness, and numerical pain ratings) will be assessed in response to the straight leg raise test.
2. exploratory outcomes include those corresponding to "heat induced pain ratings" (i.e. thermal stimulation), and lying supine. The minimum rating ("0") is designated as "no pain" whereas the maximum ("10") is labeled as "most intense imaginable" or "most unpleasant imaginable." Higher numbers correspond to higher pain.

a. We will collect naloxone and saline induced changes in pain intensity and pain unpleasantness ratings

Sample Size Determination: Our targeted sample size is 60 cLBP patients (30/group). To conduct group comparisons among the two primary outcomes (naloxone + saline induced changes in pain intensity + unpleasantness) and to ensure an overall type I error rate < 0.05, we used conservative Bonferroni corrections (p = .025) in all power calculations. Employing the pilot data corresponding to our previous work (Wells et al., 2020), we fit repeated measures ANOVA models that include indicator

variables for group (mindfulness vs. sham) and drug (naloxone vs. saline). The estimated square root of mean square errors is 0.23 (23%) and 0.30 (30%) for pain intensity and pain unpleasantness, respectively. Thirty subjects will provide 80% power to detect a pain rating difference of 22% between the naloxone and saline conditions in the non-mindfulness group with an estimated SD of 0.3 (30%). We expect no meaningful differences in pain reductions between naloxone and saline infusion during mindfulness meditation. Thus, we will have 80% power to detect a significant group X drug type interaction. Finally, 30 subjects/group will provide 80% power to detect a significant group difference of 19% for pain intensity and 24% for pain unpleasantness. Such effect sizes parallel those observed in our pilot data(Wells et al., 2020). Statistical power will be also greater when pre-regimen pain ratings are entered as covariates to reduce residual variance.

Questionnaires for Study Assessments:
All questionnaires will be delivered using Research Electronic Data Capture (REDCap) on iPad tablets administered and supervised by study personnel. After a number of pilot trials in our laboratory, the total amount of time to complete all assessments averaged 30 minutes with a range of 25-45 minutes. The questionnaires to be presented on the REDCap platform include the following:

2. Five Facet Mindfulness Questionnaire (FFMQ): This is a 39-item multidimensional measure of trait mindfulness and includes five subscales: non-reactivity, nonjudgement, describing, observing, and acting with awareness.
3. Profile of Mood States Questionnaire (POMS-short form): This is a 40-item measure of 6 mood states: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. This assessment is recommended by the IMMPACT group as a core measure of emotional functioning.
4. Subjects' Global Impression of Change (PGIC): This is a self-report assessment recommended to evaluate self-reported perception of improvement over trial/efficacy of treatment.
5. Pain Self Efficacy Questionnaire (PSEQ): This is a 10-item questionnaire that's designed to assess confidence in performing activities while in pain, for those with ongoing pain.
6. PROMIS 29-Item Profile: This is a 29-item generic health-related survey that assesses the following 7 domains: depression, anxiety, physical function, pain interference, fatigue, sleep disturbance, and ability to participant in social roles/activities.
7. PROMIS Pain Behavior Measure: This is a 5-item questionnaire that measures complaints of suffering, verbal or nonverbal (i.e. such as when I am in pain I squirm), from the past 7 days.
8. PROMIS Physical Function Measure: This is a 13-item self-report assessment that measures capability rather than actual performance of physical activities.
9. PROMIS Pain Quality Measure: This is a 5-item questionnaire that measures sensory quality of pain experience (throbbing, aching, etc).
10. Chronic Pain Acceptance Questionnaire (CPAQ-R): This is a 20-item assessment designed to measure acceptance of pain. The acceptance of chronic pain is thought to reduce attempts to avoid or control pain and thus focus on engaging in valued activities.

11. State Anxiety Inventory (SAI): The SAI is a prominent 20-item measure for anxiety, and will be utilized as a manipulation check for our behavioral interventions.
12. Brief Pain Inventory (BPI): This is an 8-item assessment widely used to measure clinical pain.
13. SF-12 Health Survey (SF-12): This is a 12-item version of the SF-36 item Health Survey designed to assess general mental and physical functioning, and overall health-related quality of life.
14. Pain Catastrophizing Scale (PCS): This is a 13-item assessment derived from definitions of catastrophizing. The PCS yields a total score and three subscale scores assessing rumination, magnification, and helplessness in subjects.
15. Beck Depression Inventory (BDI): This is a 21-item standard assessment widely used to measure clinical depression.
16. The Freiburg Mindfulness Inventory (FMI): This is a 14-item standard mindfulness scale to measure potential changes in mindfulness before and after intervention.

17. Roland-Morris Disability Questionnaire (RMDQ): This is a critical assessment for the chronic low back pain phenotype and was recommended for use by the NIH.
18. Pittsburgh Sleep Quality Index (PSQI): This is a 10-item assessment designed to measure quality of sleep.
19. Cohen Perceived Stress Scale (PSS): This assessment is critical for controlling stress in our analyses as well as a potential predictor in clinical pain improvements
20. Multidimensional Assessment of Interoceptive Awareness (MAIA): This is a 32-item multidimensional instrument that includes 8 scales ranging from 3 to 7 items each. The scales are noticing, not-distracting, not-worrying, attention regulation, emotional awareness, self-regulation, body listening, and trusting.
21. Nondual Awareness Dimensional Assessment (NADA): This is a 13-item standardized instrument capable of facilitating quantitative investigation of nondual awareness using two dimensions: bliss and self-transcendence.
22. Social Connectedness Scale (SCS): This is a 20-item assessment designed to measure social connectedness, an attribute of the self that reflects cognitions of enduring interpersonal closeness with the social world.

Drug Administration: All studies will be conducted with the supervision of ACTRI nurses in the ACTRI. As previously conducted (Zeidan, Adler-Neal et al. 2016), a 0.15mg/kg bolus dose of naloxone (Naloxone HCI, Amphastar Pharmaceuticals) or 25ml of normal saline will be administered over 10 minutes via the IV line of the antecubital vein of the non-dominant arm. Onset of naloxone-induced opioidergic antagonism occurs within 2 min of infusion and exhibits an average half-life of 64 min (Ngai, Berkowitz et al. 1976). To further ensure that naloxone will antagonize opioid receptors for the study entirety, we will administer a supplementary maintenance intravenous infusion dose of 0.15 mg/kg/h naloxone or saline immediately after bolus infusion ceases. The duration of the study from the onset of IV infusion to completion will be no more than 25 (average time of infusion = approx. 15 minutes). Only the study physicians, research pharmacist, and study coordinator will be aware of participant drug assignment.

Sample Size Determination & Power:
Assuming a conservative 20% dropout rate, we will recruit and randomize a total of 74 cLBP patients (n=37/group) to a mindfulness meditation or non-mindfulness meditation regimen. To conduct group comparisons among the two primary outcomes (naloxone + saline induced changes in pain intensity + unpleasantness) and to ensure an overall type I error rate < 0.05, we used conservative Bonferroni corrections (p= .025) in all power calculations. Employing the pilot data corresponding to preliminary findings and our previous work [22], we fit repeated measures ANOVA models that include indicator variables for group (mindfulness vs. non-mindfulness), drug (naloxone vs. saline), and session order. The estimated square root of mean square errors is 0.23 and 0.30 for pain intensity and pain unpleasantness, respectively. Thirty participants per group will provide 80% power to detect a group difference of 0.19 for pain intensity and 0.24 for pain unpleasantness. Such effect sizes are consistent with those observed from our pilot data. Statistical power will be also greater when pre-regimen pain ratings are entered as covariates to reduce residual variance.

Data Analyses and Interpretation:
Primary Outcome: Age and sex will be entered as covariates in all appropriate analyses if between group differences exist. To test study hypotheses, a 2 (group) X 2 (rest vs. manipulation) X 3 (naloxone vs. saline) repeated measures (RM) ANOVA will be employed. Post-hoc paired samples t-tests (in each group) will be conducted to test the hypotheses that non-mindfulness meditation but not mindfulness induced analgesia will be reversed by administration of naloxone but not saline.

Exploratory analyses may be conducted (in supplementary papers) on the psychological assessments (Questionnaires for Study Assessments) to better appreciate the relationship in dispositional pain and the potential changes in pain responses due to the respective interventions.

Inclusion of Women and Minorities: Participants will include all sexes and races. We plan to screen from over 2500 cLBP patients from the ACTRI's pain recruitment service, 11 separate providers, and the local community. Based on the latest San Diego-based demographic consensus, we plan to recruit 60% White, 16% Asian, 7% Black, 0.5% Native American, 0.5% Pacific Islander, 12% Other race, 5% two or more races (We expect that 29% of our participants will be Hispanic or Latino). If necessary to obtain minority representation, under-represented racial groups will be targeted specifically for recruitment.

General Considerations:
Data for all individual participants randomized or exposed to study drug will be presented in data listings. Continuous data will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, SD, SE, median, minimum value (min), and maximum value (max). Categorical data will be summarized using counts and percentages.

10. HUMAN SUBJECTS
Total number of subjects to be enrolled at UCSD
Our targeted sample size is 60 cLBP (30/group). We have exhibited a relatively low attrition rate on previous work, thus we request permission to enroll 74 participants with the goal of retaining 60 participants.

Age: Age will range between 18 and 65 years.

Sex: We will have equal males and females in each group. Groups will be matched by age and sex (15 males/15 females).

Ethnic background: We will include all ethnicities.

Health status: Participants must have a chronic low back pain diagnosis.

All study participants will be recruited from the ACTRI and the local community. We will employ our NIH-approved exclusion and inclusion criteria delineated in previous studies examining cLBP [27; 37; 42] as described below.

Eligibility Criteria: Patients will qualify for the study if medical evaluation demonstrates chronic low back pain that is evoked by lifting the legs. Existing medical records, per physician discretion and low back examinations will confirm diagnosis. Study physicians will confirm diagnosis (Fardon 2001, Wasan, Davar et al. 2005, Jamison, Ross et al. 2010, Wasan, Loggia et al. 2011, Fardon, Williams et al. 2014).

Inclusion criteria include those who:
a) are between 18-65 years old;
b) have ongoing chronic pain (pain intensity ≥ 3 on a 0-10 VAS);
c) have radicular pain for at least 3 months;
d) are not using other pain management procedures (i.e. CBD oil products) during the study period;
e) are not taking opioids;
f) if female and of a child bearing potential age, are not pregnant or nursing mothers;
g) have not had back surgery within a year of the study start date;
h) lack sensory/motor deficits that preclude participation in pain-inducing procedures;
i) have no meditation experience;
j) are straight leg raise test positive
k) do not have any known allergies to naloxone or similar drugs

l) do not have a history of syncope and/or fear of needles/blood.

11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH

Patients will be recruited through two primary streams: (1) from IRB approved flyers and recommendations by UCSD study physicians and 2) the ResearchMatch website. We will begin study recruitment after we have completed all NIH oversight requirements.

To be clear: we will post IRB approved flyers throughout the community and UCSD Pain Medicine physician offices. If a physician believes a patient is qualified for this study, they will refer the potential participant to the flyer at which point they can voluntarily call the coordinator to assess eligibility. We will not access medical records until after we have permission and the subject completes Visit 1's procedures.

Recruitment Stream 1:

The study will be advertised on ResearchMatch to gain interest for participation in the pilot to this cLBP study. This site will allow for members of the community to inquire as to their potential interests in the study's goals and requirements.

Recruitment Stream 2:

In addition, we will both advertise with flyers within these clinics that see thousands of patients each year. Hence, the sheer aggregate of potential community and clinical sources for this study would suggest more than adequate potential for our recruitment aims. The patient's treating physician will be requested to approach the participant and introduce the study. The treating physician will further discuss the research study with the potential participant and refer them to the coordinator's contact information at which point the patient has the discretion to contact the study coordinator. There will be no direct contact of the potential research participant by the study staff unless prompted by the potential participant. Their treating physicians can refer them to our study and they will call us, if they choose, on their volition.

If a potential participant is interested in the study. They will email and/or call the study coordinator to assess eligibility. This is strictly based on the patients' discretion and volition. A brief subset of preliminary eligibility criteria (such as age, gender, etc.), will be reviewed by study personnel to determine subjects' preliminary eligibility for the research study during the phone screening and Visit 1.

The phone screen script will be employed to identify preliminary study eligibility. The study team member screening potential participants, will obtain verbal consent before any participant information is collected, see item 12 below for request for waiver of documented consent for this screening. Subjects who fulfill the preliminary eligibility criteria will be offered further participation in this study.

Preliminary eligibility may be determined at the time of phone screening, but formal eligibility will only be determined after informed consent is obtained and a standard, stand-alone HIPAA authorization form is signed. The primary method of determining eligibility for the study is the straight leg raise test confirmation during Visit 1. Standard HIPAA authorization to collect research data from the patient's medical record will be obtained at the time of informed consent during Session 1. Only subjects who have consented and provided HIPAA authorization will have identifiers or linked information (e.g., subjects initials, study numbers, etc.) recorded on the Screening/Enrollment Log.

The study funder (NIH) will not have access to the subject's PHI. Only team members, as described in item 21, will have access to this information.

Strategies: Diversity and reflection of regional population. Geographically, the clinics at the ACTRI service a broad portion of the greater San Diego region. Moreover, we accept referrals from all over Southern California. As a result, our study team will recruit patients from a highly diverse patient population in terms of race, sex, and socioeconomic status. Subject populations in previous and

ongoing studies have reflected the diversity of the region and disease-specific demographics. If we are unable to obtain sufficient minority representation in our sample, under-represented racial groups will be specifically targeted for recruitment.

Contingency plans: Should the above streams of recruitment prove inadequate for us to meet our accrual timetable and keep our cohort schedule on track, we will reach out to social media and other local print and multi-media-based advertisement strategies prominent within the San Diego area. This approach has proved useful in past studies and should do so again. Participants will also be reimbursed ($400) for successful study completion. This approach has been useful in motivating participants to complete their study responsibilities in the past. If we find that the amount offered is inadequate for maintaining active participant engagement, we will consider increasing it. This lab has had a good track record with subject accrual and retention rates.

These recruitment plans have been very successful at attaining targeted sample sizes in previous studies and have been recognized by UCSD and the NIH as appropriate models for recruitment success. The Research Plan will be amended to include these recruitment strategies (and materials if appropriate) as they are added but prior to their use.

12. INFORMED CONSENT

Waiver of Documented Consent for Aiding in Determining Preliminary Eligibility during Research Recruitment:

We are asking for a waiver of documented consent while recruiting patients to appropriately identify potential participants with chronic low back pain during the phone screening procedure.

The phone screen is considered no more than low risk to the potential participants, since we will not perform any procedure, and the probability and magnitude of harm or discomfort anticipated in this research are not greater than those ordinarily encountered in daily life. In addition, our methods of recruitment do not allow the pre-screener to directly contact or call the patient unless the patient, themselves, contacts the study team first through contact information provided on study advertisements or the patient's treating physician refers them to the study.

The information inquired about and collected from the phone screen is necessary to ascertain the potential participant's suitability for entry into the study. While reviewing responses and information during the phone screen, the screener may determine that the potential participant qualifies for the study and then proceed to ask if they would be interested in participating. The screener will indicate to potential participants that review of their medical records will be involved in determining formal study eligibility.

Consenting Procedures:

Patients will be asked to provide written consent, using an IRB-approved consent form during their first study session at the ACTRI. The consent process will take place prior to performing any study related procedures and in a private room with the door closed. The study team member will describe the study, including detailed information about risks and benefits, to potential participants. The study team member will provide potential participants with an IRB-approved consent form. Potential participants will be given ample time to read this consent form at the same visit or may take it with them to read at another time. Potential study participants will be given the opportunity to ask and receive answers to all questions they may have about the study, its risks and benefits, or the consent form itself before signing the consent form. As this research is subject to HIPAA privacy rule provisions, patients will also be requested to sign a separate HIPAA authorization for the use of protected health information. The study team member will obtain informed consent in a language understood by the prospective subject or their legally authorized representative, using certified translations of study documents that will be uploaded for IRB review and approval upon the PI's receipt of IRB approval for the English version of the document. Certified translations of study documents and qualified translators will be provided, where applicable.

Potential participants who fulfill the eligibility criteria will be offered further participation in this study. Only participants who have consented and provided HIPAA authorization will have identifiers or linked information (e.g., subjects initials, study numbers, etc.) recorded on the Screening/Enrollment Log.

All signed consents will be maintained in marked binders, secured in locked filing cabinets within private administrative offices at Dr. Zeidan's Laboratory at the ACTRI. Documentation of this process will be in written form and placed in the research record. A copy of the informed consent document will be placed in the patient's medical record, and a copy has been uploaded for IRB review and approval.

The study consent form will include:
1. Who is conducting the study
2. Purpose of the study
3. Why he/she is being asked to participate
4. What will happen during the study
5. The duration of the study
6. Potential risks
7. Potential of unforeseeable risks
8. Alternatives to study participation
9. Benefits reasonably expected
10. Care if injured
11. Costs to participate
12. Payment for participation
13. Voluntary nature of participation
14. Extent confidentiality if maintained
15. clinicaltrials.gov registry
16. Provided time to ask and answer questions
17. HIPAA discussion

13. ALTERNATIVES TO STUDY PARTICIPATION

As this is not a treatment study, the only alternative to study participation is to not participate.

14. POTENTIAL RISKS

This study may involve some risk, although the risks are considered low risk.

Straight Leg Raise Test

The straight leg raise test may produce the feeling of pain. The goal is to produce a targeted 30% increase (2-point increase) in the feeling of pain for no more than 20 minutes. Although rare (less than 2% occurrence), participants may feel discomfort and/or pain for up to 24 hours. The study team will ensure participants' comfort and/or safety during this procedure. Importantly, participants will have complete control of how much they raise their leg.

Reproductive Risks

Due to unknown risks and potential harm to the unborn fetus, sexually active women of childbearing potential must use a reliable method of birth control while participating in this study.

Pregnant women are excluded from participation in this study. Because some methods of birth control are not 100% reliable, a urine pregnancy test will be required at least 10 days from subjects' last normal menstrual period, if they are a sexually active woman of childbearing potential and not using reliable birth control.

Randomization

Participants will be instructed in the consent form with the following “You will be assigned to a study group at random (by chance). Your assignment is based on chance rather than a medical decision made by the researchers. The study group you are assigned to might not be the group you would prefer to be in. Your assigned study group might also prove to be less effective or have more side effects than the other study groups(s), or other treatments available for your condition. You will also be randomly administered either naloxone or saline (or vice versa) in experimental sessions 6 and 7 which may influence some of their responses.”

Psychological Assessments
Participants may experience eye straining while completing psychological assessments. In this rare case, we will adjust/increase the font size of our assessments on our electronic devices. Although this has not occurred in our research studies, completing psychological assessments may increase emotional distress. If this is the case, we will ask our participants to “take a break” or excuse themselves from the study. We will also refer them to counseling services if need be. There may be a perception of possible invasion of privacy or probing of information that might be considered sensitive. To address this concern, all members of the research team will be sensitive to the needs of participants by reminding them that they do not need to answer any questions that they would prefer not to answer, complete any tasks that they would prefer not to complete, or follow through with any procedure that they would rather decline. Study staff will use their clinical judgment to discontinue assessment if a participant appears upset.

Respiratory Transducer and Pulse Oximeter
During the cLBP inducing procedure, the straight leg raise test, participants will be fitted with a respiratory transducer around the chest. We have not experienced any problems with this device however, participants may feel uncomfortable with the placing of this device. We will instruct participants to inform us if that is the case, and we will make adjustments (tightening or loosening the device’s placement).

Meditation Risks
Although extremely rare, long bouts of meditation practice (greater than 3-4 hours at a time), can potentially lead to feelings of confusion, light-headedness, anxiety, sleepiness, and agitation. Further, sitting for long periods of time could cause soreness in the body. Participants will be informed at the beginning of each session that simply opening their eyes and moving could address all of these rare risks.

Naloxone
The use of high naloxone is critically needed to comprehensively antagonize endogenous opioids. This procedure is well-validated, largely safe in opioid free individuals and has reliably testing in a number of studies. However, naloxone may also worsen or exacerbate feelings of nausea, vomiting, sweating, increased heart rate, tremors, rapid breathing, and changes in body temperature, agitation, and excitement. Although extremely rare, cardiac arrest may also occur as a function naloxone infusion. Most of these side effects are mild and short-lived if they occur at all. Withdrawal symptoms can arise if patients are taking opioids. Additional care will also be provided if any of these symptoms exist. In our most recent psychophysical and pharmacologic study, 60 participants were administered intravenous naloxone and there were 0 safety events or side effects reported.

In rare cases, naloxone may cause side effects such as: nausea or vomiting, sweating, increased heart rate, tremor, rapid breathing, changes in body temperature, light-headedness, clouding of vision, fainting, agitation and/or irritability, restlessness and/or excitement. Though they are highly unlikely to occur, most of these side effects are mild and short-lived, if they occur at all. Naloxone has rarely been associated with potentially fatal cardiac arrhythmias and even flagrant cardiac arrest. Additional care will also be provided if any of these symptoms exist. Further, individuals with a history of syncope and light headedness, fear of needles and blood are excluded from this study. The ACTRI nursing

staff and/or a physician will oversee all experimental procedures where naloxone is involved to ensure complete participant safety and comfort.

Thermal Stimuli
Thermal stimuli may elicit the feeling of pain and some temporary reddening of the skin. There is the exceptionally rare potential to burning of the skin, although this has not occurred. To address this, we never strap the probe to the limb (recommended use) and have customized a probe holder that will allow the participant to escape at any time.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES
The study was carefully designed to minimize or negate any potential risk/discomfort to participants.

An Independent Monitoring Committee (IMC) will monitor the activities of this study for purposes of evaluating subject safety and study integrity. The key elements of the IMC plan include protection of participant privacy, database protection, adverse event reporting, data quality and safety reports, participant compliance, and safety review plans. For the proposed study, the IMC will review the progress of and safety after 20, 40, 60 and 74 (if needed) study participants have completed all study procedures. There will be no fee for the independent monitoring of the proposed studies. Dr. Zeidan will oversee all experimental procedures of the proposed research activities. In the event of an adverse safety event, protocol deviations and adverse events will be promptly (less than 24 hours) reported to the IMC and the IRB.

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.

We do not anticipate any events that would cause a cessation of the study. We have repeatedly demonstrated the ability to reliably recruit, retain, and execute data collection in a fashion that ensures successful completion of our experiments.

However, in the unforeseeable case that the proposed study has to be stopped, the PI will include an assessment of futility in the annual progress report to NIH. We will consult with the IMC and NCCIH to assess the impact of significant data loss due to problems associated with stopping the study.

Straight Leg-Raise Test: The straight leg-raise test is a commonly employed maneuver to examine chronic low-back pain severity and patient mobility. In the rare case that pain exacerbation is increased by greater than 4 VAS points and does not return to baseline levels after 40 minutes, we will discontinue patient study participation with reimbursement and a physician will evaluate the participant.

Pregnancy: Due to unknown risks and potential harm to the unborn fetus, sexually active women of childbearing potential must use a reliable method of birth control while participating in this study. Pregnant women and nursing mothers are excluded from participation in this study. Because some methods of birth control are not 100% reliable, a pregnancy test may be required at least 10 days from a participant's last normal menstrual period, if they are a sexually active woman of childbearing potential.

Psychological Assessments: Although there are generally very low risks to completing psychological scales, we will instruct (verbally; consent form) participants that psychological assessments may produce emotional distress. A clinical psychologist may also be available to triage any concerns.

Respiratory transducer: In order to reduce any discomfort from the respiratory transducer, we will instruct participants to “let us know” when the belt is most comfortable and/or not comfortable.

Naloxone: Naloxone will be administered intravenously. Nausea or vomiting, sweating, increased heart rate, tremor, rapid breathing, changes in body temperature; agitation and/or irritability, restlessness and/or excitement are known side effects of taking naloxone. Most of these side effects are mild and short-lived if they occur at all. Withdrawal symptoms can arise if patients are taking opioids. Thus, before any naloxone/saline infusion testing session, we will administer an opiate focused urine screening.

Thermal Stimuli: Participants will experience painful stimuli produced by heating the skin to temperatures from 35°C to 49°C. Stimuli in this temperature range have been used extensively by the PI and numerous laboratories around the world and do not produce tissue damage or burns. In order to facilitate escape from the stimulator, the stimulator will be attached to a custom-designed thermal stimulation probe holder. Participants will place their calf on top of the probe holder and will not be strapped in or otherwise restrained. Therefore, participants will be able to simply lift their legs at any time. Furthermore, stimulus temperature will be monitored continuously with an external digital chart recorder that is independent of the microprocessor in the stimulator. Specifically, the unprocessed output of the temperature sensor in the head of the stimulus probe will be both monitored and recorded. In the event of a significant deviation from the target temperature, the TSA-II is designed to shut off automatically. If the device does not shut itself off, the operator will terminate stimulation. Furthermore, all volunteers will be conscious, lift their legs (respectively) from the probe, and will be free to terminate the stimulus. In the remote event that a burn does occur, the affected area will be gently rinsed with cold water and covered with a protective bandage. The participant will then be referred to the burn clinic for treatment.

All study participants will provide informed consent. They will be reminded that their behavioral data is confidential and that they can refuse to participate and/or withdraw from study participation without explanation and financial reimbursement and this would not affect their respective relationship with their physicians.

The proposed study will be conducted in a way that assures protection of the rights and welfare of subjects. The ACTRI has an established history of successfully and safely completing clinical studies. The proposed NIH sponsored 1-year project has plenty of time to ensure completion. The ACTRI is a world-renown facility known for employing the highest standards of clinical research excellence. We will conduct Sessions 1, 6, and 7 at this facility. All intervention sessions will be conducted at the UCSD Center for Mindfulness, an established leader in conducting behavioral interventions. All research staff will be trained to reliably conduct all activities. This project will include the study team members noted in item 21 below. Due to the low risk of the study, we do not anticipate emergency medical care services.

As in the naloxone studies previously conducted by this research lab, we are solely using an opiate-focused urine drug screening as a precautionary measure to avoid any conflict, withdrawal, or side effects that naloxone would elicit if a subject was presently using opiates/opioids. It is an eligibility requirement that participants are not taking opioids. We will inquire about this thoroughly with each participant through self-report and medical history confirmation, to ensure maximum safety.

Adverse Event: An AE is any problematic medical occurrence in a subject during participation in the study.

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to

subjects or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied.
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.
- Any unanticipated problems, serious/unexpected adverse events, deviations or protocol changes will be promptly reported to the IRB and IMC.

Serious Adverse Event (SAE)
A serious adverse event (SAE) is one that meets one or more of the following criteria:
- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect

An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Time Period and Frequency for Event Assessment and Follow-Up: Unanticipated problems will be recorded in the data collection system throughout the study. The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non- serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the PI will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

To assess relationship of an event to study intervention, the following guidelines are used:
1. Related (Possible, Probable, Definite)
1. The event is known to occur with the study intervention.
2. There is a temporal relationship between the intervention and event onset.
3. The event abates when the intervention is discontinued.
4. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)

There is no temporal relationship between the intervention and event onset. An alternate etiology has been established.

Expectedness of SAEs: The study PI and the IMC will be responsible for determining whether an SAE is expected or unexpected. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

Severity of Event: The following scale will be used to grade adverse events:
Mild: no intervention required; no impact on activities of daily living (ADL)
Moderate: minimal, local, or non-invasive intervention indicated; moderate impact on ADL

Severe: significant symptoms requiring invasive intervention; subject seeks medical attention, needs major assistance with ADL

Reporting Procedures: SAEs that are unanticipated, serious, and possibly related to the study intervention will be promptly reported by the principal investigator to the IRB and IMC. Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the IMC, UCSD IRB, 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.

Confidentiality During Adverse Event (AE) Reporting: All adverse event (AE) reports and annual summaries will not include subject or group-identifiable material. Each report will only include subjects' SIDs. Any unanticipated problems, serious and unexpected adverse events, deviation/protocol changes will be promptly reported by the PI to the IRB and IMC. AE reports and annual summaries will not include patient or group-identifiable material. Each report will only include subjects' SIDs.

Data and Safety Monitoring: The PI and the IMC will be responsible for the overall monitoring of the data and safety of study participants. The PI will be assisted by other members of the study staff.

Reporting of Unanticipated Problems, Adverse Events or Deviations: Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the PI or designated member of the research team to the IRB and NIH or appropriate government agency if appropriate.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

Study recruitment and enrollment will be monitored through a Screening/Enrollment Log, both created as password protected Microsoft Excel spreadsheets.

The Screening/Enrollment Log will include a participant's: name source of contact (community vs. clinic), age, diagnosis (spinal pathology and date), gender, ethnicity, current drug regimen (i.e. mostly focused on opiate usage), handedness and meditation experience. The Screening/Enrollment Log will provide dates corresponding to when informed consent was obtained, the identified 2-point VAS increase angle/height (from the straight leg raise test), height and weight on the day of the screening/session 1, confirmed eligibility, as well as a note section for miscellaneous notations. This information will be obtained from a phone screening and their responses will be logged into the spreadsheet, where a judgment will be made regarding their suitability for entry into the study according to study eligibility criteria.

The Screening/Enrollment Log will be analyzed in the interim between cohorts to determine which input stream (community vs. clinical) yields the highest percentage of input to the study. This analysis may prove useful for future tweaks of our recruiting strategies. We will also look at the stream sourcing with respect to cohort diversity. Whenever possible, we will seek to maximize ethnic and socioeconomic diversity in order to broaden the implications of the study's results.The

No identifying information will be used on any study documents after enrollment. Enrolled participants will be assigned a unique subject identification number (SID) that will be used on all CRFs and study related documents after enrollment. The SID will be linked to participant identifiable information (as described in item 9) in a separate Subject Identification Log, created and password protected in a Microsoft excel spreadsheet. This will be stored on the coordinator's password protected and encrypted computer on the 3rd floor of the ACTRI.

All completed case report forms (CRF), created for all study related visit requirements, will kept in a study binder at a central and secure location in our facility to better facilitate the tracking of each enrolled participant and cohort. All study related documents with corresponding SIDs will be stored in

a folder, in a larger cohort binder that's divided by each individual participant. Each participant's binder will be monitored periodically (monthly) to ensure subject's progress through the study as well as positive or negative progression of symptoms of interest. All study-related safety and adverse events will be reported to the UCSD Institutional Review Board (IRB) and IMC per appropriate reporting timeframes. All study-related records/information will be made available to the UCSD IRB and IMC at any time of their choosing.
All study data will be processed in a HIPPA-compliant fashion to ensure confidentiality and to protect the PHI collected from improper use and/or disclosure. Digital data will be stored on both physically and software protected computers and will only be accessed by study personnel from within the ACTRI building (coordinator computer). Any reference to individual subjects in reports of this work will utilize a study identification number (SID) to preserve confidentiality.
Following data collection participant identifying information will be destroyed when data collection and corresponding statistical analyses for the primary aims are completed, consistent with data validation and study design, producing an anonymous analytical data set. When these are complete, the study coordinator(s) or PI will shred any and all physical documents containing any identifiers/PHI on it. Our primary aim is to ensure participant safety and confidentiality; thus, we will take the highest measures and uphold the most stringent standards to ensure patient confidentiality.

17. POTENTIAL BENEFITS

This research is not expected to directly benefit individual participants, but is likely to yield generalizable knowledge. The basic understanding of how mind body approaches function to alleviate pain and improve wellbeing are unknown. The primary purpose of the proposed study is to determine if endogenous opioidergic systems are engaged by mindfulness meditation to reduce chronic low back pain. This work will also inform whether or not mind body approaches can be utilized in combination with more traditional pain therapies by combining two distinct pain modulatory processes/therapies. The knowledge gained from this study will provide novel mechanistic insight to better develop and tailor cognitive therapeutic interventions to target multiple chronic pain conditions.

18. RISK/BENEFIT RATIO

This study has a low risk, and the potential benefits of the proposed study outweigh the risks in terms of overall reward. The knowledge to be gained significantly outweigh the low risks associated with this study. In light of the ongoing opioid epidemic and the new prescribing guidelines by the Center for Disease Control to employ non-opiate based therapies, the identification of the endogenous and physiological mechanisms supporting such therapies is timely and of paramount importance. One promising behavioral therapy is mindfulness-based meditation training. However, we still do not fully appreciate how mindfulness reduces chronic pain. The primary purpose of this proposed study is to determine if endogenous opioidergic systems are engaged by mindfulness meditation to reduce chronic low back pain. Inquiry into this work may inform how mindfulness meditation can act as effectively as leading prescribed opiates, providing an alternative non-pharmacological pain treatment option. Importantly, if we replicate our findings in healthy individuals (i.e., mindfulness-based analgesia is not opioidergically mediated), then the treatment of chronic pain may be more effective with mindfulness and more conventional therapies due to a lack of cross-tolerance with opiate based medications. Thus, the benefits significantly outweigh the low risks of this study.

19. EXPENSE TO PARTICIPANT

Patients will have to pay $4 for parking for every visit to the ACTRI (3 visits to the ACTRI = $12), and will be responsible for their own method of transportation.

20. COMPENSATION FOR PARTICIPATION

Participants will not be compensated for parking but will receive $400.00 in pro-rated payments as compensation for participation in this research. Participants will be paid with Vanilla Visa Gift Cards after each attended study session. They will be paid $40 for each experimental session that pain evoking procedures are used (3 sessions = $120). For each mindfulness session, they will be

compensated $10 (4 sessions = $40). For each session where naloxone/saline is administered, they will be compensated $80 (2 sessions = $160). And upon study completion, they will also receive an additional $80 for successfully completing all study sessions.

We believe that the modest stipend of $400 is appropriate without invoking coercion.

To receive payment, participants must provide their social security number, name and address in compliance with IRS (Internal Revenue Service) reporting requirements. When payments are reported to the IRS, the study team will not let them know what the payment is for, only that participants have been paid. If participants do not wish to provide this information, they can still take part in this study but will not be paid.

22. BIBLIOGRAPHY

Adams, J. E. (1976). "Naloxone reversal of analgesia produced by brain stimulation in the human." Pain 2(2): 161-166.
Adler-Neal, A. L., N. M. Emerson, S. R. Farris, Y. Jung, R. C. Coghill and F. Zeidan (2019). "Brain moderators supporting the relationship between depressive mood and pain." Pain 160(9): 2028-2035.
Adler-Neal, A. L., C. E. Waugh, E. L. Garland, H. A. Shaltout, D. I. Diz and F. Zeidan (2019). "The role of heart rate variability in mindfulness-based pain relief." J Pain.
Amanzio, M. and F. Benedetti (1999). "Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems." J Neurosci 19(1): 484-494.
Amanzio, M., A. Pollo, G. Maggi and F. Benedetti (2001). "Response variability to analgesics: a role for non-specific activation of endogenous opioids." Pain 90(3): 205-215.
Anderson, W. S., R. N. Sheth, B. Bencherif, J. J. Frost and J. N. Campbell (2002). "Naloxone increases pain induced by topical capsaicin in healthy human volunteers." Pain 99(1-2): 207-216.
Andersson, G. B. (1999). "Epidemiological features of chronic low-back pain." Lancet 354(9178): 581-585.
Apkarian, A. V., B. R. Krauss, B. E. Fredrickson and N. M. Szeverenyi (2001). "Imaging the pain of low back pain: functional magnetic resonance imaging in combination with monitoring subjective pain perception allows the study of clinical pain states." Neurosci Lett 299(1-2): 57-60.
Bencherif, B., P. N. Fuchs, R. Sheth, R. F. Dannals, J. N. Campbell and J. J. Frost (2002). "Pain activation of human supraspinal opioid pathways as demonstrated by [11C]-carfentanil and positron emission tomography (PET)." Pain 99(3): 589-598.
Benedetti, F. (1996). "The opposite effects of the opiate antagonist naloxone and the cholecystokinin antagonist proglumide on placebo analgesia." Pain 64(3): 535-543.
Benedetti, F., C. Arduino and M. Amanzio (1999). "Somatotopic activation of opioid systems by target-directed expectations of analgesia." J Neurosci 19(9): 3639-3648.
Berna, C., S. Leknes, A. H. Ahmad, R. N. Mhuircheartaigh, G. M. Goodwin and I. Tracey (2018). "Opioid-Independent and Opioid-Mediated Modes of Pain Modulation." J Neurosci 38(42): 9047-9058.
Brown, C. A., J. Matthews, M. Fairclough, A. McMahon, E. Barnett, A. Al-Kaysi, W. El-Deredy and A. K. Jones (2015). "Striatal opioid receptor availability is related to acute and chronic pain perception in arthritis: does opioid adaptation increase resilience to chronic pain?" Pain 156(11): 2267-2275.
Bruehl, S., J. W. Burns, O. Y. Chung and M. Chont (2011). "Interacting effects of trait anger and acute anger arousal on pain: the role of endogenous opioids." Psychosom Med 73(7): 612-619.
Bruehl, S., J. W. Burns, O. Y. Chung and P. Quartana (2008). "Anger management style and emotional reactivity to noxious stimuli among chronic pain patients and healthy controls: the role of endogenous opioids." Health Psychol 27(2): 204-214.
Bruehl, S., J. W. Burns, S. D. Passik, R. Gupta, A. Buvanendran, M. Chont, E. Schuster, D. Orlowska and C. R. France (2015). "The Contribution of Differential Opioid Responsiveness to Identification of Opioid Risk in Chronic Pain Patients." J Pain 16(7): 666-675.
Bruehl, S. and O. Y. Chung (2006). "Parental history of chronic pain may be associated with impairments in endogenous opioid analgesic systems." Pain 124(3): 287-294.

Bruehl, S., O. Y. Chung, J. W. Burns and S. Biridepalli (2003). "The association between anger expression and chronic pain intensity: evidence for partial mediation by endogenous opioid dysfunction." Pain 106(3): 317-324.
Bruehl, S., O. Y. Chung, J. W. Burns and L. Diedrich (2007). "Trait anger expressiveness and pain-induced beta-endorphin release: support for the opioid dysfunction hypothesis." Pain 130(3): 208-215.
Bruehl, S., O. Y. Chung, P. Ward and B. Johnson (2004). "Endogenous opioids and chronic pain intensity: interactions with level of disability." Clin J Pain 20(5): 283-292.
Bruno, P. A., D. P. Millar and D. A. Goertzen (2014). "Inter-rater agreement, sensitivity, and specificity of the prone hip extension test and active straight leg raise test." Chiropr Man Therap 22: 23.
Burns, J. W., S. Bruehl, O. Y. Chung, E. Magid, M. Chont, J. K. Goodlad, W. Gilliam, J. Matsuura and K. Somar (2009). "Endogenous opioids may buffer effects of anger arousal on sensitivity to subsequent pain." Pain 146(3): 276-282.
Burns, J. W., S. Bruehl, C. R. France, E. Schuster, D. Orlowska, M. Chont, R. K. Gupta and A. Buvanendran (2017). "Endogenous Opioid Function and Responses to Morphine: The Moderating Effects of Anger Expressiveness." J Pain 18(8): 923-932.
de Andrade, D. C., A. Mhalla, F. Adam, M. J. Texeira and D. Bouhassira (2011). "Neuropharmacological basis of rTMS-induced analgesia: the role of endogenous opioids." Pain 152(2): 320-326.
Deyo, R. A., S. K. Mirza, J. A. Turner and B. I. Martin (2009). "Overtreating chronic back pain: time to back off?" J Am Board Fam Med 22(1): 62-68.
DosSantos, M. F., I. K. Martikainen, T. D. Nascimento, T. M. Love, M. D. Deboer, E. C. Maslowski, A. A. Monteiro, M. B. Vincent, J. K. Zubieta and A. F. DaSilva (2012). "Reduced basal ganglia mu-opioid receptor availability in trigeminal neuropathic pain: a pilot study." Mol Pain 8: 74.
Dowell, D., T. M. Haegerich and R. Chou (2016). "CDC Guideline for Prescribing Opioids for Chronic Pain - United States, 2016." MMWR Recomm Rep 65(1): 1-49.
Eippert, F., U. Bingel, E. D. Schoell, J. Yacubian, R. Klinger, J. Lorenz and C. Buchel (2009). "Activation of the opioidergic descending pain control system underlies placebo analgesia." Neuron 63(4): 533-543.
Fardon, D. F. (2001). "Nomenclature and classification of lumbar disc pathology." Spine (Phila Pa 1976) 26(5): 461-462.
Fardon, D. F., A. L. Williams, E. J. Dohring, F. R. Murtagh, S. L. Gabriel Rothman and G. K. Sze (2014). "Lumbar disc nomenclature: version 2.0: Recommendations of the combined task forces of the North American Spine Society, the American Society of Spine Radiology and the American Society of Neuroradiology." Spine J 14(11): 2525-2545.
Goldstein, A. and P. Grevert (1978). "Placebo analgesia, endorphins, and naloxone." Lancet 2(8104-5): 1385.
Gracely, R. H., R. Dubner, P. J. Wolskee and W. R. Deeter (1983). "Placebo and naloxone can alter post-surgical pain by separate mechanisms." Nature 306(5940): 264-265.
Grevert, P., L. H. Albert and A. Goldstein (1983). "Partial antagonism of placebo analgesia by naloxone." Pain 16(2): 129-143.
Han, B., W. M. Compton, C. M. Jones and R. Cai (2015). "Nonmedical Prescription Opioid Use and Use Disorders Among Adults Aged 18 Through 64 Years in the United States, 2003-2013." JAMA 314(14): 1468-1478.
Harris, R. E., D. J. Clauw, D. J. Scott, S. A. McLean, R. H. Gracely and J. K. Zubieta (2007). "Decreased central mu-opioid receptor availability in fibromyalgia." J Neurosci 27(37): 10000-10006.
Hosobuchi, Y., J. E. Adams and R. Linchitz (1977). "Pain relief by electrical stimulation of the central gray matter in humans and its reversal by naloxone." Science 197(4299): 183-186.
Hoy, D., C. Bain, G. Williams, L. March, P. Brooks, F. Blyth, A. Woolf, T. Vos and R. Buchbinder (2012). "A systematic review of the global prevalence of low back pain." Arthritis Rheum 64(6): 2028-2037.
Institute of Medicine (US) Committee on Advancing Pain Research, C., and Education (2011). Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington D.C, National Academies Press.

Jacob, J. A. (2016). "As Opioid Prescribing Guidelines Tighten, Mindfulness Meditation Holds Promise for Pain Relief." JAMA 315(22): 2385-2387.
Jamison, R. N., E. L. Ross, E. Michna, L. Q. Chen, C. Holcomb and A. D. Wasan (2010). "Substance misuse treatment for high-risk chronic pain patients on opioid therapy: a randomized trial." Pain 150(3): 390-400.
Jones, A. K., V. J. Cunningham, S. Ha-Kawa, T. Fujiwara, S. K. Luthra, S. Silva, S. Derbyshire and T. Jones (1994). "Changes in central opioid receptor binding in relation to inflammation and pain in patients with rheumatoid arthritis." Br J Rheumatol 33(10): 909-916.
Jones, A. K., N. D. Kitchen, H. Watabe, V. J. Cunningham, T. Jones, S. K. Luthra and D. G. Thomas (1999). "Measurement of changes in opioid receptor binding in vivo during trigeminal neuralgic pain using [11C] diprenorphine and positron emission tomography." J Cereb Blood Flow Metab 19(7): 803-808.
Jones, A. K., H. Watabe, V. J. Cunningham and T. Jones (2004). "Cerebral decreases in opioid receptor binding in patients with central neuropathic pain measured by [11C]diprenorphine binding and PET." Eur J Pain 8(5): 479-485.
Klega, A., T. Eberle, H. G. Buchholz, S. Maus, C. Maihofner, M. Schreckenberger and F. Birklein (2010). "Central opioidergic neurotransmission in complex regional pain syndrome." Neurology 75(2): 129-136.
Kwong, E. H., N. Virani, M. Robert, K. Gerry, A. Harding, M. S. Rose, S. P. Dukelow and P. M. Barton (2013). "Inter-rater reliability of the Active Straight-Leg Raise and One-Leg Standing tests in non-pregnant women." J Rehabil Med 45(10): 1058-1064.
Levine, J. D. and N. C. Gordon (1986). "Method of administration determines the effect of naloxone on pain." Brain Res 365(2): 377-378.
Levine, J. D., N. C. Gordon and H. L. Fields (1978). "The mechanism of placebo analgesia." Lancet 2(8091): 654-657.
Lobanov, O. V., F. Zeidan, J. G. McHaffie, R. A. Kraft and R. C. Coghill (2014). "From cue to meaning: brain mechanisms supporting the construction of expectations of pain." Pain 155(1): 129-136.
Loggia, M. L., J. Kim, R. L. Gollub, M. G. Vangel, I. Kirsch, J. Kong, A. D. Wasan and V. Napadow (2013). "Default mode network connectivity encodes clinical pain: an arterial spin labeling study." Pain 154(1): 24-33.
Maarrawi, J., R. Peyron, P. Mertens, N. Costes, M. Magnin, M. Sindou, B. Laurent and L. Garcia-Larrea (2007). "Differential brain opioid receptor availability in central and peripheral neuropathic pain." Pain 127(1-2): 183-194.
Mangold, D., M. E. McCaul, M. Ali and G. S. Wand (2000). "Plasma adrenocorticotropin responses to opioid blockade with naloxone: generating a dose-response curve in a single session." Biol Psychiatry 48(4): 310-314.
Martikainen, I. K., M. Pecina, T. M. Love, E. B. Nuechterlein, C. M. Cummiford, C. R. Green, R. E. Harris, C. S. Stohler and J. K. Zubieta (2013). "Alterations in endogenous opioid functional measures in chronic back pain." J Neurosci 33(37): 14729-14737.

May, L. M., P. Kosek, F. Zeidan and E. T. Berkman (2018). "Enhancement of Meditation Analgesia by Opioid Antagonist in Experienced Meditators." Psychosom Med.
Mayer, D. J., D. D. Price and A. Rafii (1977). "Antagonism of acupuncture analgesia in man by the narcotic antagonist naloxone." Brain Res 121(2): 368-372.
Mens, J. M., A. Vleeming, C. J. Snijders, H. J. Stam and A. Z. Ginai (1999). "The active straight leg raising test and mobility of the pelvic joints." Eur Spine J 8(6): 468-473.
Nelson, L. S., D. N. Juurlink and J. Perrone (2015). "Addressing the Opioid Epidemic." JAMA 314(14): 1453-1454.
Ngai, S. H., B. A. Berkowitz, J. C. Yang, J. Hempstead and S. Spector (1976). "Pharmacokinetics of naloxone in rats and in man: basis for its potency and short duration of action." Anesthesiology 44(5): 398-401.

Pereira, M. P., M. U. Werner, T. K. Ringsted, M. C. Rowbotham, B. K. Taylor and J. B. Dahl (2013). "Does naloxone reinstate secondary hyperalgesia in humans after resolution of a burn injury? A placebo-controlled, double-blind, randomized, cross-over study." PLoS One 8(5): e64608.
Posner, J. and C. A. Burke (1985). "The effects of naloxone on opiate and placebo analgesia in healthy volunteers." Psychopharmacology (Berl) 87(4): 468-472.
Rebain, R., G. D. Baxter and S. McDonough (2002). "A systematic review of the passive straight leg raising test as a diagnostic aid for low back pain (1989 to 2000)." Spine (Phila Pa 1976) 27(17): E388-395.
Rosier, E. M., M. J. Iadarola and R. C. Coghill (2002). "Reproducibility of pain measurement and pain perception." Pain 98(1-2): 205-216.
Roussel, N. A., J. Nijs, S. Truijen, L. Smeuninx and G. Stassijns (2007). "Low back pain: clinimetric properties of the Trendelenburg test, active straight leg raise test, and breathing pattern during active straight leg raising." J Manipulative Physiol Ther 30(4): 270-278.
Saloner, B. and S. Karthikeyan (2015). "Changes in Substance Abuse Treatment Use Among Individuals With Opioid Use Disorders in the United States, 2004-2013." JAMA 314(14): 1515-1517.
Schoell, E. D., U. Bingel, F. Eippert, J. Yacubian, K. Christiansen, H. Andresen, A. May and C. Buechel (2013). "The effect of opioid receptor blockade on the neural processing of thermal stimuli." PLoS One 5(8): e12344.
Sharma, H. A., R. Gupta and W. Olivero (2011). "fMRI in patients with lumbar disc disease: a paradigm to study patients over time." J Pain Res 4: 401-405.
Skrabanek, P. (1978). "Naloxone and placebo." Lancet 2(8093): 791.
Spiegel, D. and L. H. Albert (1983). "Naloxone fails to reverse hypnotic alleviation of chronic pain." Psychopharmacology (Berl) 81(2): 140-143.
Springborg, A. D., E. K. Jensen, B. K. Taylor and M. U. Werner (2016). "Effects of target-controlled infusion of high-dose naloxone on pain and hyperalgesia in a human thermal injury model: a study protocol: A randomized, double-blind, placebo-controlled, crossover trial with an enriched design." Medicine (Baltimore) 95(46): e5336.
Steglitz, J., Buscemi, J., Ferguson, M.J. (2012). "The future of pain research, education, and treatment: a summary of the IOM report “Relieving pain in American: a blueprint for transforming prevention, care, education, and research”." Transl Behav Med 2(1): 6-8.
Stephenson, J. B. (1978). "Reversal of hypnosis-induced analgesia by naloxone." Lancet 2(8097): 991-992.
Summers, B., K. Malhan and V. Cassar-Pullicino (2005). "Low back pain on passive straight leg raising: the anterior theca as a source of pain." Spine (Phila Pa 1976) 30(3): 342-345.
Taylor, J. J., J. J. Borckardt, M. Canterberry, X. Li, C. A. Hanlon, T. R. Brown and M. S. George (2013). "Naloxone-Reversible Modulation of Pain Circuitry by Left Prefrontal rTMS." Neuropsychopharmacology.
Taylor, J. J., J. J. Borckardt and M. S. George (2012). "Endogenous opioids mediate left dorsolateral prefrontal cortex rTMS-induced analgesia." Pain 153(6): 1219-1225.
Thompson, S. J., M. H. Pitcher, L. S. Stone, F. Tarum, G. Niu, X. Chen, D. O. Kiesewetter, P. Schweinhardt and M. C. Bushnell (2018). "Chronic neuropathic pain reduces opioid receptor availability with associated anhedonia in rat." Pain.
Wasan, A. D., G. Davar and R. Jamison (2005). "The association between negative affect and opioid analgesia in patients with discogenic low back pain." Pain 117(3): 450-461.
Wasan, A. D., M. L. Loggia, L. Q. Chen, V. Napadow, J. Kong and R. L. Gollub (2011). "Neural correlates of chronic low back pain measured by arterial spin labeling." Anesthesiology 115(2): 364-374.
Zeidan, F., A. L. Adler-Neal, R. E. Wells, E. Stagnaro, L. M. May, J. C. Eisenach, J. G. McHaffie and R. C. Coghill (2016). "Mindfulness-Meditation-Based Pain Relief Is Not Mediated by Endogenous Opioids." J Neurosci 36(11): 3391-3397.
Zeidan, F., N. M. Emerson, S. R. Farris, J. N. Ray, Y. Jung, J. G. McHaffie and R. C. Coghill (2015). "Mindfulness Meditation-Based Pain Relief Employs Different Neural Mechanisms Than Placebo and Sham Mindfulness Meditation-Induced Analgesia." J Neurosci 35(46): 15307-15325.

Zeidan, F., N. S. Gordon, J. Merchant and P. Goolkasian (2010). "The effects of brief mindfulness meditation training on experimentally induced pain." J Pain 11(3): 199-209.
Zeidan, F., J. A. Grant, C. A. Brown, J. G. McHaffie and R. C. Coghill (2012). "Mindfulness meditation-related pain relief: evidence for unique brain mechanisms in the regulation of pain." Neurosci Lett 520(2): 165-173.
Zeidan, F., S. K. Johnson, B. J. Diamond, Z. David and P. Goolkasian (2010). "Mindfulness meditation improves cognition: evidence of brief mental training." Conscious Cogn 19(2): 597-605.
Zeidan, F., S. K. Johnson, N. S. Gordon and P. Goolkasian (2010). "Effects of brief and sham mindfulness meditation on mood and cardiovascular variables." J Altern Complement Med 16(8): 867-873.
Zeidan, F., O. V. Lobanov, R. A. Kraft and R. C. Coghill (2015). "Brain mechanisms supporting violated expectations of pain." Pain 156(9): 1772-1785.
Zeidan, F., O. V. Lobanov, R. A. Kraft and R. C. Coghill (2015). "Brain Mechanisms Supporting Violated Expectations of Pain." Pain.
Zeidan, F., K. T. Martucci, R. A. Kraft, N. S. Gordon, J. G. McHaffie and R. C. Coghill (2011). "Brain mechanisms supporting the modulation of pain by mindfulness meditation." J Neurosci 31(14): 5540-5548.
Zeidan, F., K. T. Martucci, R. A. Kraft, J. G. McHaffie and R. C. Coghill (2014). "Neural correlates of mindfulness meditation-related anxiety relief." Soc Cogn Affect Neurosci 9(6): 751-759.
Zeidan, F., T. Salomons, S. R. Farris, N. M. Emerson, A. Adler-Neal, Y. Jung and R. C. Coghill (2018). "Neural mechanisms supporting the relationship between dispositional mindfulness and pain." Pain 159(12): 2477-2485.
Zubieta, J. K., Y. R. Smith, J. A. Bueller, Y. Xu, M. R. Kilbourn, D. M. Jewett, C. R. Meyer, R. A. Koeppe and C. S. Stohler (2001). "Regional mu opioid receptor regulation of sensory and affective dimensions of pain." Science 293(5528): 311-315.
Zubieta, J. K., Y. R. Smith, J. A. Bueller, Y. Xu, M. R. Kilbourn, D. M. Jewett, C. R. Meyer, R. A. Koeppe and C. S. Stohler (2002). "mu-opioid receptor-mediated antinociceptive responses differ in men and women." J Neurosci 22(12): 5100-5107.

23. FUNDING SUPPORT FOR THIS STUDY

The proposed study is an R21 funded by the National Center for Complementary and Integrative Health (NCCIH). The grant will go through USCD as an existing grant. The corresponding program officer at NCCIH for this grant will be Dr. Inna Belfer at inna.belfer@nih.gov, 301-435-1573.

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

Not applicable.

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

IND Exemption Form (attached)

26. IMPACT ON STAFF

Not applicable

27. CONFLICT OF INTEREST

The PI and all key personnel report no conflicts of interest.

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

Not applicable

29. OTHER APPROVALS/REGULATED MATERIALS

Not applicable

30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT

Not applicable