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Publication Date

2023-11-20

DOI

10.1038/s41386-023-01766-2

Peer reviewed

American College of Neuropsychopharmacology

www.nature.com/npp

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# The role of endogenous opioids in mindfulness and sham mindfulness-meditation for the direct alleviation of evoked chronic low back pain: a randomized clinical trial

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Chronic low back pain (cLBP) is the most prevalent chronic pain condition. There are no treatments that haven been found to directly assuage evoked cLBP. To this extent, mindfulness-meditation is a promising pain therapy. Yet, it is unclear if meditation can be utilized to directly attenuate evoked chronic pain through endogenous opioids. A double-blind, randomized, and placebo-controlled clinical trial with a drug crossover design examined if mindfulness-meditation, as compared to sham mindfulness-meditation, attenuated straight leg-raise test evoked chronic pain during intravenous (0.15 mg/kg bolus + 0.15 mg/kg/hour maintenance) naloxone (opioid antagonist) and placebo-saline infusion. Fifty-nine individuals with cLBP (mean age = 46 years; 30 females) completed all study procedures. After the pre-intervention pain testing session, patients were randomized to a four-session (20-min/session) mindfulness ($n = 30$) or sham mindfulness-meditation ($n = 29$) intervention. After the interventions, mindfulness and sham mindfulness-meditation were associated with significant reductions in back pain during saline and naloxone infusion when compared to rest (non-meditation) in response to the cLBP-evoking straight leg-raise test. These results indicate that meditation directly reduces evoked chronic pain through non-opioidergic processes. Importantly, after the interventions, the mindfulness group reported significantly lower straight leg-raise induced pain than the sham mindfulness-meditation group during rest (non-meditation) and meditation. Mindfulness and sham mindfulness-meditation training was also associated with significantly lower Brief Pain Inventory severity and interference scores. The pain-relieving effects of mindfulness meditation were more pronounced than a robust sham-mindfulness meditation intervention, suggesting that non-reactive appraisal processes may be uniquely associated with improvements in chronic low-back pain.

**Trial Registration:** ClinicalTrials.gov identifier: NCT04034004

*Neuropsychopharmacology*; https://doi.org/10.1038/s41386-023-01766-2

## INTRODUCTION

Chronic low back pain (cLBP) is the most common clinical pain condition and the leading cause of disability [1]. It is often aggravated by movement, such as bending over to lift heavy objects, tying shoelaces, or engaging in low-flexion exercises, rendering movement as the primary driver of cLBP-related disability [2, 3]. The inability to directly alleviate acutely evoked cLBP exacerbates a spectrum of chronic pain symptoms and related comorbidities [4]. Yet, there are no known treatments that can be utilized to directly and immediately alleviate evoked chronic back pain.

Mindfulness-meditation is a self-facilitated technique that involves sustaining non-reactive attention to arising sensory and cognitive-affective events, and produces durable reductions in cLBP after eight weeks of training [5, 6]. However, the scarcity of mindfulness-specific, placebo-controlled clinical trials, mechanistic classification, and lengthy training requirements have hampered the clinical translation of mindfulness to treat chronic pain [7–10]. To address this, a "sham mindfulness-meditation" technique was designed to isolate the impact and unique mechanisms of mindfulness-specific instructions from the beliefs, respiration changes, expectations, conditioning, social support and other placebo-related effects that accompany participation in a meditation intervention [11, 12]. This control condition trains individuals to "take slow, deep breaths" in a meditative posture but omits the *mindfulness-specific* instructions (non-reactive attention to breath sensations) hypothesized to mediate pain relief [11, 12]. In healthy volunteers, sham mindfulness-meditation reduces heat-induced pain and engages mechanisms that parallel those supporting placebo-analgesia [11, 13, 14]. Yet, there is a lack of existing research that has examined the effects and mechanisms of mindfulness-meditation on acutely evoked chronic pain compared to a mindfulness-specific placebo.

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Received: 21 June 2023 Revised: 26 October 2023 Accepted: 2 November 2023
Published online: 20 November 2023

The endogenous opioidergic system is considered the primary pain modulatory system [15–17] and is engaged during pain-relief elicited by placebo [18–20], distraction [21], transcranial magnetic stimulation [22], and attention [21, 23]. In healthy volunteers, mindfulness-based pain relief is insensitive to opioidergic blockade [13, 24]. Further, patients with cLBP exhibit significantly lower opioid receptor availability [25–30]. Therefore, it is unknown if meditation-based cLBP relief is mediated by endogenous opioidergic signaling. It is also not known if mindfulness meditation can outperform a highly-analgesic and placebo-based sham-mindfulness meditation at reducing evoked cLBP.

To address these gaps, the present clinical trial (NCT04034004) employed a randomized, double-blind, crossover design to examine if mindfulness-meditation, as compared to sham mindfulness-meditation, attenuates cLBP during intravenous infusion of placebo-saline and naloxone. The straight leg-raise test, an ecologically validated cLBP evocation procedure, was used as an analog to the experience of evoked cLBP commonly reported during daily functioning [31]. Mindfulness-meditation was postulated to reduce evoked back pain during saline and naloxone-infusion. Based on prior findings in healthy volunteers [13, 24, 32], we predicted that sham mindfulness-meditation would reduce evoked cLBP, through the straight leg-raise test, during saline, but not naloxone infusion. We also expected that mindfulness-meditation would produce greater evoked cLBP pain relief as compared to sham mindfulness-meditation. Given the brevity of the interventions, we did not anticipate that either meditation training would produce significant reductions in stabilized chronic pain ratings, as measured by the Brief Pain Inventory (BPI).

## METHODS AND MATERIALS

### Design, setting and participants

The University of California San Diego's (UCSD) Institutional Review Board (IRB#190709) approved all procedures. Participants were recruited through three strategies: (1) HIPAA-waivered electronic medical chart review, (2) Research Match, an online clinical trial recruitment platform, and (3) distribution of flyers throughout the community. Exclusion criteria included those that tested positive for opioids, were pregnant, had prior meditation experience, were not responsive to the straight leg-raise test, and/or had back surgery within a year of the enrollment (see Supplementary Methods). Participants were not concurrently enrolled in other experiments and were not permitted to initiate new pain therapies during the study period. A total of eighty-eight individuals with cLBP for a minimum of three months were enrolled (see CONSORT Supplementary Fig. 1). All individuals provided written and informed consent. Data collection occurred during the global Coronavirus-19 pandemic (January 2020 to December 2021). Participants were compensated $400 for study completion.

### Psychophysical assessment of pain

Back pain was assessed using an 11-point numerical rating scale (NRS) where the minimum rating of "0" represented "no pain sensation" and "10" represented the "most intense pain imaginable".

### Acute chronic low back pain assessment

The straight leg-raise test is a common procedure employed to diagnose and evoke radicular cLBP [31, 33]. Two straight leg-raise procedures were performed in each of the three pain testing sessions (Fig. 1) for a total of six leg-raise tests performed per patient throughout the entire experiment. For each straight leg-raise test, pain ratings were collected while patients were lying supine and again seven minutes after performing the straight leg-raise test.

To perform the straight leg-raise test, a trained technician raised the patient's affected leg with the knee straightened and foot positioned in a 90°angle. Patients were instructed to notify the technician when they experienced a 2-point pain increase. When a 2-point increase was verbalized, the technician held said position for approximately 10 s and subsequently lowered the leg. After lowering the leg, the patient confirmed if the 2-point increase in pain was sustained. If a 2-point increase was not achieved, the leg-raise was repeated up to six times to reach the targeted 2-point increase. Patients were dismissed from the study if a two-point back pain increase could not be achieved through the leg-raise procedures ($n = 4$).

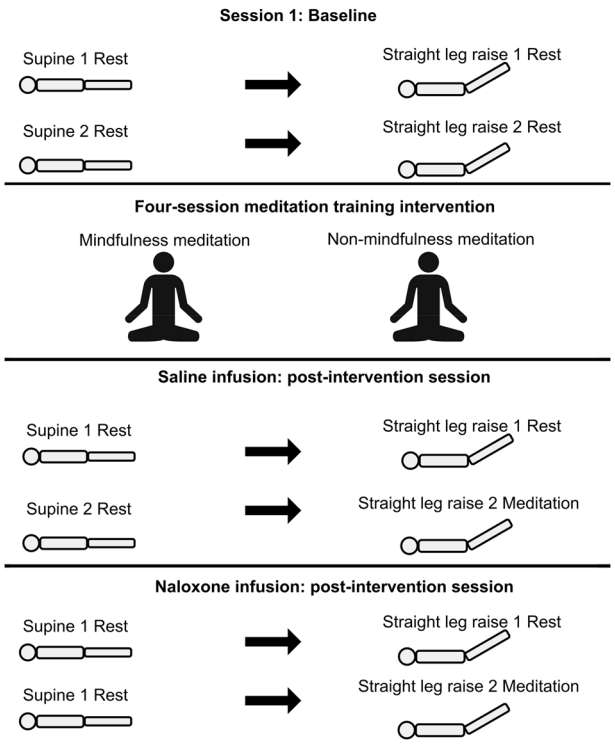


**Fig. 1 Study design.** During the initial study session (pre-intervention), numerical pain ratings were collected while lying supine (Supine 1 Rest) and seven minutes after performing the straight leg-raise test (Straight leg-raise 1 Rest) during rest. After 8 min, numerical pain ratings were collected again while lying in the supine (Supine 2 Rest) and after the straight leg-raise test (Straight leg-raise 2 Rest) during rest. Participants were then randomly assigned to one of two interventions: a four-session (20 min/session) mindfulness-meditation or sham mindfulness-meditation training. After successful completion of the interventions, numerical pain ratings were collected while lying supine (Supine 1 Rest) and seven minutes after performing the straight leg-raise test (Straight leg-raise 1 Rest) during rest. Half the participants (stratified by sex) received either saline or naloxone infusion during session six. Following an 8-minute bolus infusion (0.15 mg/kg), a maintenance (0.15/mg/kg/hr) infusion was initiated, and numerical pain ratings were collected again while lying in the supine (Supine 2 Rest) during rest. The straight leg-raise test (Straight leg-raise 2 Meditation) was then performed, after which participants were instructed to "begin meditation". Pain ratings were collected after seven minutes. The experimental procedures in session 7 paralleled session 6, except participants who received saline in session 6 were administered naloxone in session 7 and vice versa.

### Chronic pain assessments

The BPI [34] assessed cLBP severity and interference and measured the extent to which pain affected the ability to participate in activities such as walking, working, and maintaining relationships. The BPI was administered before and after each meditation intervention.

The 13-item Pain Catastrophizing Scale (PCS) [35] assessed the tendency to magnify chronic pain significance and learned helplessness. Higher scores indicate higher pain catastrophizing. The PCS was administered before and after each meditation intervention.

The 24-item Roland Morris Low Back Pain and Disability Questionnaire (RMDQ) [36] assessed the impact of cLBP on daily activities. Higher scores indicate higher disability. The RMDQ was administered before and after each meditation intervention.

### Thermal stimuli
For a separate investigation not related to the primary study, ten, 12 s plateaus of 49 °C were delivered to the unaffected calf (16 $mm^2$ thermal probe) before the first and after the second straight leg-raise test (data not presented).

### Drug administration
The procedures employed are well validated to comprehensibly inhibit endogenous opioidergic signaling without unblinding drug assignment [37]. As performed in previous studies [13, 24], a 0.15 mg/kg bolus dose of naloxone (Naloxone HCl; Amphastar Pharmaceuticals) or saline in 25 ml of normal saline was administered over 10 min via the intravenous line inserted into the antecubital vein of the nondominant arm. Onset of opioidergic antagonism occurs after 2 min of intravenous initiation and exhibits an average half-life of 64 min [37]. The duration of the experiment from the onset of bolus infusion to completion was approximately 25 min. To ensure opioidergic antagonism [37], a "maintenance" infusion (0.15 mg/kg/hour) immediately after the bolus ceased was supplemented until study completion (~15 minutes) [13, 24]. Drug assignment was blinded to patients, nurses, and experimenters. Only the study physicians, pharmacist, and coordinator were aware of drug assignment.

### Randomization
After completion of Experimental Session 1, randomization was performed using an Excel-based random number generator and was stratified by gender and drug order presentation. Cohort size included blocks of two and four. A study coordinator who did not collect any data randomized participants within three days of completing Experimental Session 1 using a 1:1 ratio into the mindfulness and sham mindfulness-meditation interventions. Thirty patients were randomized to receive naloxone during Session 6 and saline during Session 7, while 29 patients received saline during Session 6 and naloxone during Session 7.

### Study sessions
The proposed crossover design was validated during a previous study comparing the effects of mindfulness to sham mindfulness-meditation during noxious heat and saline and naloxone infusion in healthy, pain-free individuals [13].

*Pre-intervention: Session 1.* Patients first reported to UC San Diego's Altman Clinical and Translational Research Institute (ACTRI). In light of the Coronavirus-19 pandemic, 50 out of the 59 participants were mandated to wear face masks for the duration of all in-person experimental sessions. After providing informed consent, a urine sample was administered to assess for opioid use and pregnancy.

Straight leg-raise 1 (non-meditation rest): Patients were situated in the supine position and pain ratings were collected. The first straight leg-raise test was then performed (Fig. 1). Patients were instructed to "rest with your eyes closed" and after seven minutes, pain ratings were collected.

Pre-intervention bolus control: Patients were instructed to "continue resting with your eyes closed" (8 min). This served as a control for the time spent administering the drug/saline bolus in the subsequent sessions.

Straight leg-raise 2 (non-meditation): After 8 min of non-meditation rest ("rest with eyes closed"), back pain ratings were collected again. The second straight leg-raise test was then administered. Patients rested for another seven minutes before providing back pain ratings.

*Group Interventions: Sessions 2–5*

Mindfulness-meditation training regimen: Patients in the mindfulness group participated in four sessions (20 min/session) of mindfulness-based mental training (see Appendix 1 for script). Mindfulness training was facilitated by certified meditation instructors. In each training session, mindfulness-based instructions emphasized (1) acknowledging arising thoughts, feelings, and/or emotions, (2) that such sensations and emotions were "momentary" and "fleeting", and (3) to "return their attention back to the breath" whenever such discursive events occurred. During training day 4, participants were asked to practice while lying in the supine position and wearing a face mask to emulate the conditions in the post-intervention testing sessions.

Sham mindfulness-meditation training regimen: The purpose of the sham mindfulness-meditation group (see Appendix 1 for script) was to serve as an active control designed to differentiate the effects of the mindfulness-meditation intervention. Certified meditation instructors facilitated the sham mindfulness-meditation instruction, which was based on slow-breathing exercises and reiterating the notion that they were meditating. During each session, the participants were told, approximately every 2–3 min, to "take deep breaths as we sit in meditation." This intervention differed notably from the mindfulness training because participants were not given the guided instructions (focusing on discursive sensory/affective events) imperative for mindfulness-meditation. All other aspects (e.g., introductions, posture, facilitator) of the sham mindfulness-meditation intervention were matched to the mindfulness-meditation intervention.

*Post-intervention: Sessions 6 & 7.* Although intravenous naloxone completely metabolizes within minutes of infusion cessation [37], a 48 h washout period was imparted between Sessions 6 and 7. After drug, pregnancy, and psychological assessments, a study nurse administered (nondominant arm; antecubital vein) a continuous infusion (0.9% saline) to reduce perceptual changes from the initiation of the bolus (cold sensation).

Straight leg-raise 1 (non-meditation rest): Patients were instructed to rest with their eyes closed while lying down (i.e., non-meditation). Back pain ratings were then collected (Fig. 1). The first leg-raise test was then performed, and pain ratings were collected after 7 min.

Naloxone/saline bolus + maintenance: Patients were then instructed to "continue resting with your eyes closed." The nurse then initiated the naloxone/saline bolus (8-min) and maintenance (15-minutes) infusion.

Straight leg-raise 2 (meditation): Back pain ratings were collected in response to the lying in the supine position, and the second straight leg-raise test was subsequently performed. Immediately after lowering their leg, patients were instructed to "begin meditating." Pain ratings were collected after 7 min.

### Sample size determination
Power calculations estimates (G*power, 3.1) were based on effect sizes from a similar study conducted in healthy, pain-free volunteers using noxious heat [13]. The analysis employed an ANOVA that included indicator variables for group (mindfulness vs. sham mindfulness-meditation), session (pre-intervention vs. naloxone vs. saline), and manipulation (non-meditation rest vs. meditation). In said previous study [13], the observed 3-way interaction was associated with a medium effect size ($\eta_p^2 = 0.06$; $f = 0.25$), which was used for the power calculation in the present study. Including these parameters and a factor including two levels of the straight leg raise test (supine vs. post-straight leg-raise test), it was determined that a sample size (total $n = 60$) of 30 per group provided 81% power to detect a significant interaction between group and session effect with an alpha level set at 0.05 and a 0.5 correlation among measures.

### Primary outcome
Numerical pain ratings were collected before and seven minutes after performing the straight leg-raise test. A 2 (group) X 2 (supine vs. post-straight leg-raise test) X 2 (non-meditation rest vs. meditation) X 3 (session; pre-intervention vs. post-intervention saline vs. post-intervention naloxone) repeated measures ANOVA (NCT04034004) was conducted to determine if mindfulness and sham mindfulness-meditation attenuate evoked low-back pain through endogenous opioids. Simple effects tests investigated significant main effects and interactions to test primary study hypotheses and between-group differences.

### Secondary outcomes
Core outcomes for chronic pain-based clinical trials include the Brief Pain Inventory and the Roland Morris Low Back Pain and Disability Questionnaire [38]. Pain catastrophizing was administered because it is characterized as a potential mechanism for mindfulness-based analgesia [39, 40]. Half of the study participants received naloxone in session 6, while the other half received it in session 7. Thus, to ensure a comprehensive depiction of changes in secondary outcomes, only data from only the pre-

intervention and the final study session (Session 7) were considered, and data from Session 6 were excluded from secondary outcome analyses.

A 2 (group) X 2 (pre-intervention vs. post-intervention) repeated measures ANOVA examined if mindfulness-meditation and sham mindfulness-meditation training was associated with significant changes in BPI Pain Severity and Interference scores. A 2 (group) X 2 (pre-intervention vs. post-intervention) ANOVA tested if mindfulness-meditation and sham mindfulness-meditation training were associated with Pain Catastrophizing Scale and Roland Morris Low Back Pain and Disability Questionnaire improvements. Significant main effects and interactions were tested with Bonferroni corrected simple effects tests ($p = 0.013$).

To better appreciate potential group-specific meditation operational differences, between-group chi-squared tests assessed for between-group differences in the frequency of self-reported (a) focusing on the breath during their meditation and (b) non-evaluation during their meditation practice. Two independent researchers, both blinded to group assignment, coded responses for reports of "non-judgmental", "non-evaluation", and/or "non-reaction" (all categorized together) during meditation. The coders demonstrated a strong level of agreement in monitoring interview responses (Cohen's Kappa = 0.88). As performed in our previous work [13], multiple regression analyses examined if self-reported non-judgment during meditation varied by group and predicted straight leg-raise test pain during saline and naloxone infusion, respectively.

## RESULTS

### Primary outcome

Fifty-nine participants ($n = 30$ mindfulness; $n = 29$ sham-mindfulness) completed all study procedures (Table 1). The ANOVA revealed a significant three-way interaction between pain reported supine- vs. post-straight leg-raise test X non-meditation rest vs. meditation X session, $F(1, 57) = 21.45$, $p < 0.001$, $\eta_p^2 = 0.27$ (Supplementary Fig. 2; Supplementary Table 1). This three-way interaction was driven by a significant 7% increase in pain in response to both the first ($p < 0.001$; $CI_{95} = -1.31$; $-0.65$) and second straight leg-raise tests ($p < 0.001$; $CI_{95} = -1.28$; $-0.75$) during the pre-intervention session. In the post-intervention sessions, the first straight leg-raise test significantly increased pain by 15% in the saline session ($p < 0.001$; $CI_{95} = -1.41$; $-0.86$) and by 10% in the naloxone session ($p < 0.001$; $CI_{95} = -1.42$; $-0.86$). Notably, for patients in both the mindfulness-meditation and sham mindfulness-meditation groups, meditation inhibited straight leg-raise test induced pain during saline ($p = 0.97$; $CI_{95} = -0.23$; 0.24) and naloxone infusion ($p = 0.89$; $CI_{95} = -0.34$; 0.30) (Fig. 2).

The ANOVA also detected a significant three-way group X non-meditation rest vs. meditation X session interaction, $F(2, 57) = 3.35$, $p = 0.04$, $\eta_p^2 = 0.06$ (Fig. 3; Supplementary Table 1). Mindfulness meditation was associated with lower pain than sham mindfulness-meditation in the two post-intervention sessions when compared to the pre-intervention session. Before the interventions, there was no significant difference in pain between the two groups in response to the first ($p = 0.14$; $CI_{95} = -2.00$; 0.29) or second ($p = 0.33$; $CI_{95} = -1.84$; 0.64) leg-raise test. After the interventions, the mindfulness-meditation group reported significantly lower leg-raise-induced pain while resting, than the sham mindfulness-meditation group, in the saline ($p = 0.04$; $CI_{95} = -2.52$; $-0.07$) and naloxone ($p = 0.02$; $CI_{95} = -2.69$; $-0.29$) infusion sessions. Mindfulness-meditation during intravenous saline ($p = 0.02$; $CI_{95} = -2.84$; $-0.21$) and opioidergic blockade ($p = 0.003$; $CI_{95} = -3.18$; $-0.70$) was significantly more effective at reducing leg-raise evoked low back pain than sham mindfulness-meditation. There was not a significant, four-way group X non-meditation rest vs. meditation X session X supine- vs. post-straight leg-raise test interaction, $F(2, 114) = 0.09$, $p = 0.91$, $\eta_p^2 = 0.002$ detected. See Supplementary Results for full ANOVA report on the primary outcome.

### Secondary outcomes

BPI Interference scores significantly improved by 17% after mindfulness and sham mindfulness-meditation training when compared to pre-intervention values, $F(1, 57) = 19.52$, $p < 0.001$, $\eta_p^2 = 0.26$ (Table 2). There was no significant group X pre- vs. post-intervention interaction, $F(1, 57) = 1.24$, $p = 0.27$, $\eta_p^2 = 0.02$ or a between-group main effect, $F(1, 57) = 1.24$, $p = 0.27$, $\eta_p^2 = 0.02$. Mindfulness and sham mindfulness-meditation training lowered BPI Severity scores when compared to pre-intervention levels, $F(1, 57) = 3.15$, $p = 0.08$, $\eta_p^2 = 0.05$. Across all sessions, the mindfulness-meditation group reported lower pain severity scores when compared to the sham mindfulness-meditation group, $F(1, 57) = 4.30$, $p = 0.04$, $\eta_p^2 = 0.07$. However, these effects did not reach significance with Bonferroni multiple-comparison correction. There was no significant group X pre- vs. post-intervention interaction, $F(1, 57) = 1.73$, $p = 0.19$, $\eta_p^2 = 0.03$.

There were no significant changes in the Roland Morris Low Back Pain and Disability Questionnaire scores from pre to post intervention, $F(1, 56) = 0.58$, $p = 0.45$, $\eta_p^2 = 0.01$, group, $F(1, 56) = 0.96$, $p = 0.33$, $\eta_p^2 = 0.02$ or group X session interaction, $F(1, 56) = 1.33$, $p = 0.25$, $\eta_p^2 = 0.02$ (Table 2).

Pain Catastrophizing Scale: The mindfulness (−17%) and the sham mindfulness-meditation (-11%) groups, $F(1, 57) = 7.22$, $p = 0.009$, $\eta_p^2 = 0.11$, significantly lowered pain catastrophizing from pre- to post-intervention ($p = 0.009$; $CI_{95} = -4.87$; $-0.71$; Table 2). There was no significant main effect of group, $F(1, 57) = 0.76$, $p = 0.39$, $\eta_p^2 = 0.01$ or a group X session interaction, $F(1, 57) = 0.18$, $p = 0.67$, $\eta_p^2 = 0.00$.

Meditation group manipulation check: The mindfulness group (60%) reported practicing non-reactive attention during their meditation practice more than the sham mindfulness-meditation group (20%), ($U = 378.50$, $p < 0.001$, $Z = -1.63$). Ninety percent of participants in both groups reported that they "focused on the breath" during their meditation practice. There were no significant between group differences ($U = 378.50$, $p < 0.001$, $Z = -1.63$; Supplementary Table 2).

Regression revealed, $F(2, 56) = 3.48$, $p = 0.04$, $R^2 = 0.11$, that the relationship between straight leg-raise test-induced pain and non-judgment ($B = -0.83$, $SE = 0.64$, $p = 0.20$) during meditation and saline varied by group ($B = 2.15$, $SE = 0.82$, $p = 0.01$; Supplementary Table 3). Higher self-reported non-reactivity during mindfulness-meditation ($r = -0.35$; $p = 0.06$) but not sham mindfulness-meditation ($r = 0.04$; $p = 0.84$) was associated with lower pain.

The significant regression model, $F(2, 56) = 6.57$, $p = 0.003$, $R^2 = 0.19$ (Supplementary Table 4), found that the relationship between straight leg-raise-induced pain during naloxone administration and non-judgment ($B = -1.05$, $SE = 0.58$, $p = 0.07$) varied by group ($B = 2.69$, $SE = 0.74$, $p < 0.001$). Higher non-reactivity during mindfulness-meditation ($r = -0.38$; $p = 0.04$) but not sham mindfulness-meditation ($r = -0.07$; $p = 0.71$) predicted lower pain.

## DISCUSSION

The present mechanistically focused clinical trial utilized a double-blinded, naloxone-based crossover design to determine if mindfulness-meditation reduces exacerbated cLBP when compared to an operationally well-matched sham mindfulness-meditation technique. Groups did not significantly differ in any study outcomes before the interventions. After the interventions, mindfulness and sham mindfulness-meditation effectively attenuated straight leg-raise-induced pain (Fig. 2). Hypotheses were partially supported as analgesia was not reversed during opioidergic antagonism during mindfulness or sham mindfulness-meditation. These findings are novel because they demonstrate that mindfulness-meditation training was more effective at reducing evoked chronic pain when compared to a placebo-mindfulness technique (i.e., sham-mindfulness). We provide supplemental and compelling evidence that mindfulness-based meditation is more effective and distinct from placebo-based analgesia. Thus, this work is an integral step in fostering the

**Table 1.** Participant demographics.

| | Mindfulness | | Sham | | Total | |
|---|---|---|---|---|---|---|
| Gender | N | % | N | % | N | % |
| Female | 15 | 50.0% | 15 | 51.7% | 30 | 50.8% |
| Male | 15 | 50.0% | 14 | 48.2% | 29 | 49.2% |
| Ethnicity | N | % | N | % | N | % |
| Hispanic | 6 | 20.0% | 5 | 17.2% | 11 | 18.6% |
| Not Hispanic | 24 | 80.0% | 24 | 82.8% | 48 | 81.4% |
| Race | N | % | N | % | N | % |
| Asian | 1 | 3.3% | 2 | 6.9% | 3 | 5.1% |
| Black or African American | 1 | 3.3% | 3 | 10.3% | 4 | 6.8% |
| White | 26 | 86.7% | 19 | 65.5% | 45 | 76.3% |
| Other | 2 | 6.7% | 5 | 17.2% | 7 | 11.9% |
| Employment Status | N | % | N | % | N | % |
| Working full-time | 12 | 40.0% | 9 | 31.0% | 21 | 35.6% |
| Working part-time | 4 | 13.3% | 3 | 10.3% | 7 | 11.9% |
| Looking for work | 1 | 3.3% | 3 | 10.3% | 4 | 6.8% |
| Disabled due to back pain | 1 | 3.3% | 5 | 17.2% | 6 | 10.2% |
| Disabled for other reasons | 4 | 13.3% | 1 | 3.4% | 5 | 8.5% |
| Student | 2 | 6.7% | 1 | 3.4% | 3 | 5.1% |
| Temporarily laid off | 0 | 0.0% | 2 | 6.9% | 2 | 3.4% |
| Retired | 2 | 6.7% | 2 | 6.9% | 4 | 6.8% |
| Keeping house | 1 | 3.3% | 2 | 6.9% | 3 | 5.1% |
| Other | 3 | 10.0% | 1 | 3.4% | 4 | 6.8% |
| Education Level | N | % | N | % | N | % |
| High school graduate | 3 | 10.0% | 4 | 13.8% | 7 | 11.9% |
| Some college, no degree | 8 | 26.7% | 10 | 34.5% | 18 | 30.5% |
| Occupational/technical/vocational program | 2 | 6.7% | 0 | 0.0% | 2 | 3.4% |
| Associate degree | 1 | 3.3% | 3 | 10.3% | 4 | 6.8% |
| Bachelor's degree | 13 | 43.3% | 5 | 17.2% | 18 | 30.5% |
| Master's degree | 3 | 10.0% | 4 | 13.8% | 7 | 11.9% |
| Doctoral degree | 0 | 0.0% | 3 | 10.3% | 3 | 5.1% |
| Income | N | % | N | % | N | % |
| Less than $25,000 | 5 | 16.7% | 11 | 37.9% | 16 | 27.1% |
| $25,000 - $34,999 | 6 | 20.0% | 2 | 6.9% | 8 | 13.6% |
| $35,000 - $49,999 | 2 | 6.7% | 1 | 3.4% | 3 | 5.1% |
| $50,000 - $74,999 | 5 | 16.7% | 9 | 31.0% | 14 | 23.7% |
| $75,000 - $99,999 | 6 | 20.0% | 1 | 3.4% | 7 | 11.9% |
| $100,000 - $149,999 | 4 | 13.3% | 3 | 10.3% | 7 | 11.9% |
| Over $150,000 | 2 | 6.7% | 2 | 6.9% | 4 | 6.8% |
| Cigarette Smoking | N | % | N | % | N | % |
| Never smoked | 19 | 63.3% | 22 | 75.9% | 41 | 69.5% |
| Current smoker | 3 | 10.0% | 4 | 13.8% | 7 | 11.9% |
| Used to smoke but quit | 8 | 26.7% | 3 | 10.3% | 11 | 18.6% |
| "Affected" leg | N | % | N | % | N | % |
| Left | 12 | 40.0% | 17 | 58.6% | 29 | 49.2% |
| Right | 17 | 56.7% | 9 | 31.0% | 26 | 44.1% |
| Both | 1 | 3.3% | 2 | 6.9% | 3 | 5.1% |

Self-reported demographics of study population ($n = 59$). The Mindfulness column represents the demographics of patients who completed the mindfulness-meditation intervention ($n = 30$). The Sham column displays the demographics of participants who completed the sham mindfulness-meditation intervention ($n = 29$). The Total column shows the demographics of participants combined across groups ($n = 59$). "Affected" leg is defined as the leg that was lifted during the back pain-inducing procedure, i.e., the straight leg-raise test.

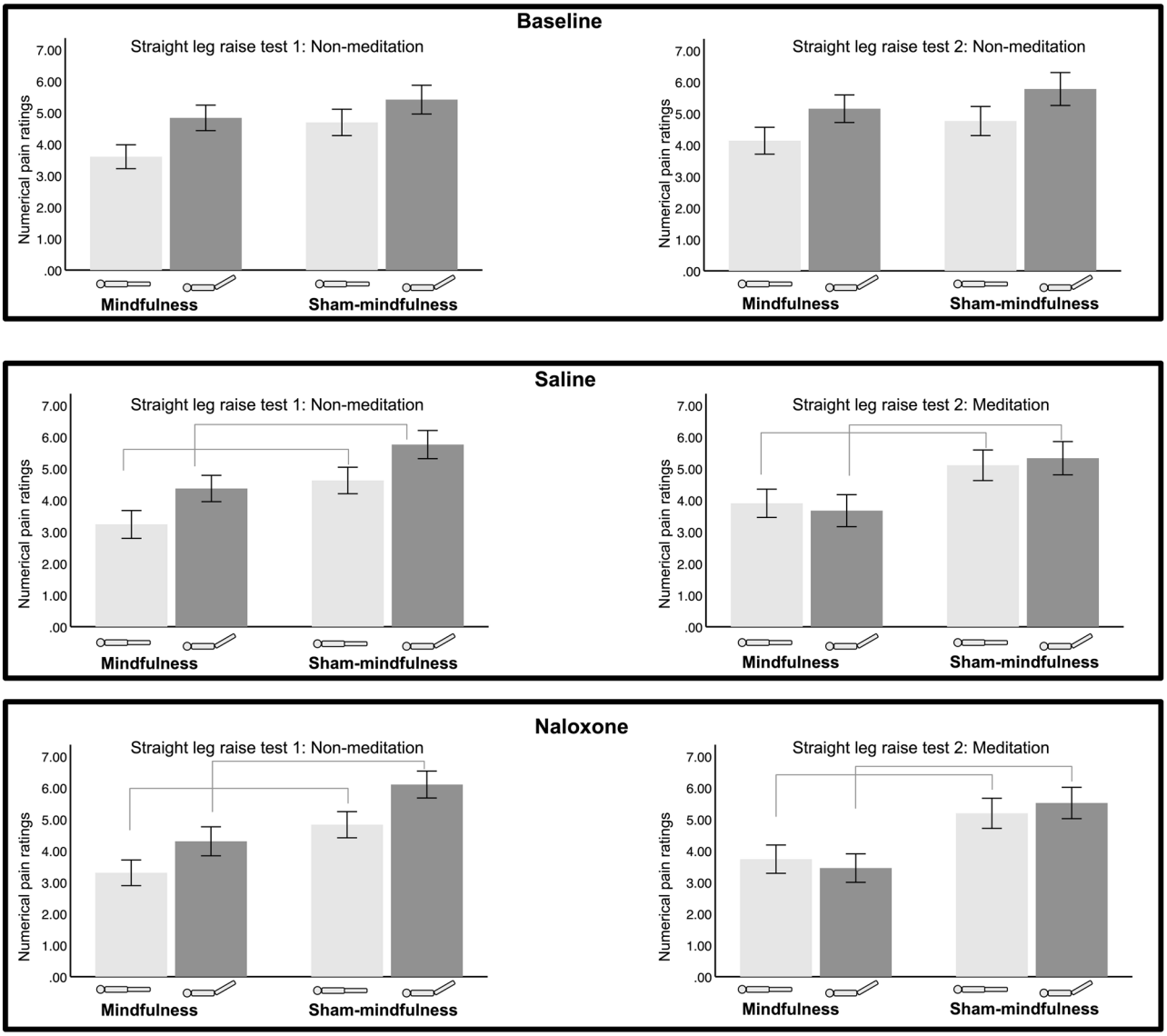


**Fig. 2 Pain ratings in response to lying supine and straight leg-raise test across participants.** Time series depicting numerical pain ratings during pre-intervention, placebo-saline infusion, and naloxone infusion (opioid antagonism) across all participants/groups. During the non-meditation condition, pain increased in response to both straight leg-raise tests (straight leg-raise test 1 & 2) when compared to lying in the supine ($ps < 0.001$). During saline and naloxone infusion, the straight leg-raise test increased pain compared to lying in the supine during rest (straight leg-raise test 1; $p < 0.001$), but not during meditation (straight leg-raise test 2; $ps > .86$). Error bars = +/− 1 standard error of the mean. ***$p < 0.001$.

behavioral and mechanistic validity of mindfulness meditation as a reliable treatment of chronic pain.

After the interventions, the mindfulness-meditation group reported lower pain before and after the straight leg-raise test when resting and during meditation when compared to the sham mindfulness-meditation group. Thus, mindfulness-specific didactics could improve chronic pain outcomes relative to slow breathing interventions [11–14]. Mindfulness meditation engages distinct mechanisms from sham mindfulness-meditation in healthy individuals [12–14]. That is, greater mindfulness-based pain relief is associated with lower pain [12, 13], higher heart rate variability [14], and attenuated thalamic and default mode network processing [41]. Across both groups, 90% of participants reported "attending" to the breath sensations as an operational feature of their meditation. In our previous work in healthy, pain-free individuals, attention to breath was associated with non-opioidergic pain modulation [13]. Attention to the breath is thought to increase meta-cognitive processes that promote unique non-reactive reappraisal processes [42–44]. Therefore, the normally high salience of acute cLBP exacerbations may be reappraised by voluntarily redirecting attention to the breath, thereby diminishing the intensity of said nociceptive events [24, 32, 45].

The majority of the mindfulness-meditation group (60%) reported employing non-reactive awareness during their practice. Non-reactive evaluation predicted lower pain ratings during mindfulness but not sham mindfulness-meditation. Thus, the unique non-reactive appraisal aspect of mindfulness may be associated with enduring improvements in chronic pain exhibited in more extant mindfulness interventions [5, 6, 46–48]. Non-evaluative and positive-based reappraisal are two hypothesized psychological mechanisms supporting mindfulness-based analgesia. Future work could include psychological assessments (i.e., Mindful Reappraisal of Pain Sensations Scale) [49] and/or

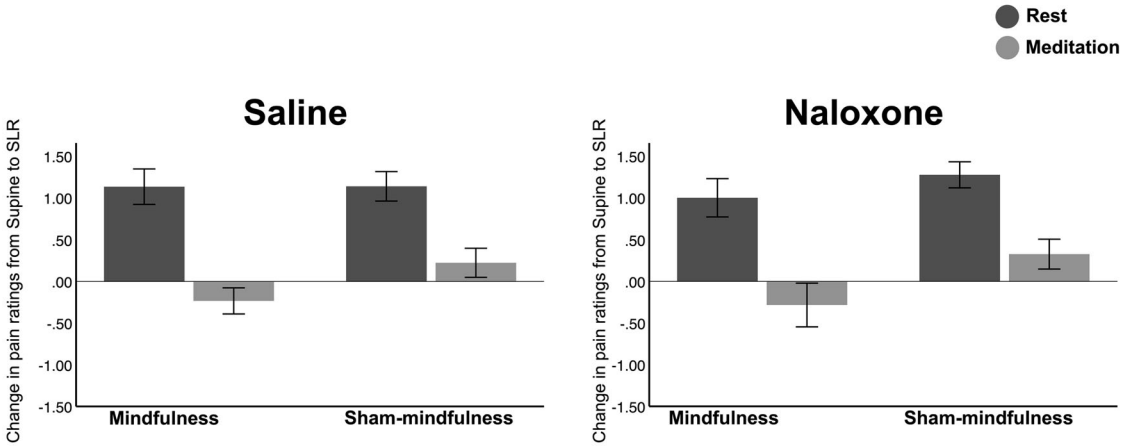


**Fig. 3 Mindfulness and sham mindfulness-meditation group-based pain ratings in response to lying supine and straight leg-raise test during experimental sessions.** Time series illustrating the distribution of numerical ratings of lower back pain for the sham and mindfulness groups during pre-intervention, intravenous placebo-saline infusion, and intravenous naloxone infusion (opioidergic antagonism) session. There were no statistically significant between-group differences in pain evoked by the straight leg-raise test 1 ($p = 0.14$) or 2 ($p = 0.33$) before the interventions (pre-intervention). During saline infusion, the mindfulness group reported significantly lower pain than the sham group during both rest (straight leg-raise test 1; $p = 0.04$) and meditation (straight leg-raise test 2; $p = 0.02$). Similarly, during opioidergic antagonism, the mindfulness group reported lower pain than the sham mindfulness-meditation group during both rest (straight leg-raise test 1; $p = 0.02$) and meditation (straight leg-raise test 2; $p = 0.003$). $^{**}p < 0.01$, $^{*}p < 0.05$.

**Table 2.** Mean and standard deviation of secondary outcomes.

| Group | BPI Severity: Pre-intervention | BPI Severity: Post-intervention | BPI Interference: Pre-intervention | BPI Interference: Post-intervention | PCS: Pre-intervention | PCS: Post-Intervention | RMDQ: Pre-intervention | RMDQ: Post-intervention |
|---|---|---|---|---|---|---|---|---|
| Mindfulness | 4.47 (1.79) | 3.94 (1.83) | 4.40 (2.72) | 3.38 (2.34) | 18.57 (13.21) | 15.33 (10.53) | 12.86 (5.61) | 12.03 (5.71) |
| Sham | 5.22 (1.91) | 5.15 (2.17) | 5.17 (2.50) | 4.57 (2.80) | 20.83 (12.85) | 18.48 (13.43) | 13.85 (6.34) | 14.02 (6.41) |
| Total | 4.83 (1.88) | 5.53 (2.08) | 4.78 (2.63) | 3.94 (2.62) | 19.68 (12.97) | 16.88 (12.04) | 13.36 (5.95) | 13.02 (6.09) |

Mean (standard deviation) of secondary outcomes for the mindfulness and non-mindfulness groups at pre-intervention (Session 1) and post-intervention (Session 7). *BPI* Brief Pain Inventory, *PCS* Pain Catastrophizing Scale, *RMDQ* Roland-Morris Disability Questionnaire.

functional MRI to disentangle the spectrum of appraisal approaches utilized to modulate pain.

Contrary to previously held assumptions, temporally extant mental training was not required to alleviate evoked cLBP. Mindfulness and sham mindfulness-meditation training were associated with significant improvements in pain interference and pain catastrophizing after 80-min of mental training (Supplementary Table 2). Nevertheless, it is important to note that the durability of these benefits remains uncertain. However, longer training interventions, such as the eight-week Mindfulness-Oriented Recovery Enhancement [46] program, have demonstrated sustained chronic pain reductions (≥9 months).

The effectiveness of sham mindfulness-meditation, a slow-breathing technique, may also be impactful to other pain conditions because it is less cognitively demanding and easier to operationalize than mindfulness-meditation. In light of the present and others' findings, we predict that meditation may engage a combination of dopaminergic [50], glutamatergic [13, 51], and/or endocannabinoid [52] systems to uniquely facilitate mindfulness-meditation-induced pain relief. The proposed findings demonstrate that meditation can be used to immediately reduce evoked pain through non-opioidergic processes. These findings corroborate contemplative text [53] and empirical evidence [12, 54, 55] indicating that meditation uniquely impacts pain-related affective and comorbid-related outcomes than sensory dimensions of the nociceptive experience. Mindfulness-based mental training was more efficacious at reducing evoked back pain than slow-breathing meditation, indicating that non-reactive reappraisal processes unique to mindfulness-based mental training can produce reliable reductions in radicular chronic pain, a critical finding for the millions of individuals living with chronic pain seeking a fast-acting, user-friendly, and non-opioidergic pain treatment.

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Concept and Design: F.Z. Acquisition of Data: LK, NEG, JGD, GR, JB, VO, GC, KC, JM, MP, H-CK. Statistical Analysis, Interpretation of Data, and Drafting of the Manuscript: LK, JGD, FZ. Critical Revision of the Manuscript: LK, JGD, FZ. Supervision: FZ.

## FUNDING

This work was supported by the National Center for Complementary and Integrative Health (Zeidan R21-AT010352, R01-AT009693, R00-AT008238) and the UC San Diego Denny T. Sanford Institute for Empathy and Compassion.

## COMPETING INTERESTS

The authors declare no competing interests.

## ADDITIONAL INFORMATION

**Supplementary information** The online version contains supplementary material available at https://doi.org/10.1038/s41386-023-01766-2.

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