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Mindfulness-Oriented Recovery Enhancement Reduces Opioid Dose in Primary Care by Strengthening Autonomic Regulation During Meditation

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Abstract

Objective.—The current opioid crisis was fueled by escalation of opioid dosing among patients with chronic pain. Yet, there are few evidence-based psychological interventions for opioid dose reduction among chronic pain patients receiving long-term opioid analgesics. Mindfulness-Oriented Recovery Enhancement (MORE), which was designed to target mechanisms underpinning chronic pain and opioid misuse, has shown promising results in two randomized clinical trials (RCTs), and could facilitate opioid sparing and tapering by bolstering self-regulation. Here we tested this hypothesis with secondary analyses of data from a Stage 2 RCT.

Method.—Chronic pain patients (N = 95) on long-term opioid therapy were randomized to 8 weeks of MORE or a support group (SG) control delivered in primary care. Opioid dose was assessed with the Timeline Followback through 3-month follow-up. Heart rate variability (HRV) during mindfulness meditation was quantified as an indicator of self-regulatory capacity.

Results.—Participants in MORE evidenced a greater decrease in opioid dosing (a 32% decrease) by follow-up than the SG [$F(2,129.77) = 5.35$, $p = .006$, $d = 1.07$]. MORE was associated with a significantly greater increase in HRV during meditation than the SG. Meditation-induced change in HRV partially mediated the effect of MORE on opioid dose reduction [$p = .034$].

Conclusions.—MORE may boost self-regulatory strength via mindfulness and thereby facilitate self-control over opioid use, leading to opioid dose reduction in people with chronic pain.

Keywords

addiction; heart rate variability; mindfulness; opioid tapering; self-regulation

According to the 2015 National Survey on Drug Use and Health, over a third of U.S. adults used prescription opioids in the past year, and 15.3 million Americans met criteria for an

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opioid use disorder (OUD) (Han et al., 2017). The over-prescription of opioid medications to treat chronic pain contributed to the current OUD epidemic. Over-prescribing has proven pernicious, as chronic, high dose, opioid analgesic use increases the risk of developing opioid misuse and OUD (Chou et al., 2015). One of the common pathways to OUD begins with a valid opioid prescription for pain management and leads, via opioid dose escalation, to opioid misuse and eventually to the loss of control over opioid use that is characteristic of addiction.

The downward spiral linking chronic pain to opioid dose escalation, opioid misuse, and OUD is thought to be driven by the neuropsychopharmacologic effects of chronic opioid exposure on dysregulation of brain stress and reward systems (Garland et al., 2013). During this process, known as allostasis, chronic opioid use triggers a cascade of neurobiological processes in corticostriatal circuits that disrupt hedonic homeostasis, increasing sensitization to drug-related cues that entrenches opioid use as a habitual behavior while reducing the reward derived from natural reinforcers in the socioenvironment (Koob & Volkow, 2016). Simultaneously, allostatic effects of chronic, high dose opioid use on corticolimbic circuitry results in increased reactivity to stressors, including pain (Shurman et al., 2010). Furthermore, chronic opioid exposure can weaken cognitive control (Baldacchino et al., 2012), undermining the capacity for self-regulation of the opioid use habit, particularly under conditions of heightened stress – which has been shown to prompt habitual behaviors (Schwabe & Wolf, 2009). Weakened self-regulatory capacity coupled with increasing opioid tolerance and overwhelming distress and pain drives opioid dose escalation as a means of obtaining hedonic equilibrium, further propelling the downward spiral of allostasis and increasing dependence on opioids (Garland et al., 2013). Thus, chronic opioid users with pain become caught in a vicious cycle where the perceived solution (i.e., opioid use) to their problem (i.e., pain and distress) only magnifies the problem. Alternative treatments are urgently needed to halt opioid dose escalation among people with chronic pain.

Mindfulness-Oriented Recovery Enhancement (MORE) is a mindfulness-based intervention that was developed to reduce opioid use and misuse among people with chronic pain via a treatment sequence involving three distinct, yet interrelated, therapeutic components: mindfulness, reappraisal, and savoring (Garland, 2013). MORE begins with a foundation of mindfulness training to increase attentional control and metacognitive awareness. Next, MORE draws from the cognitive-behavioral tradition, providing direct instruction in cognitive reappraisal to improve negative emotion regulation. Finally, MORE introduces savoring, a technique designed to boost natural reward processing and positive emotion regulation. Results from two, Stage 2 randomized clinical trials (N = 115 and N = 95) of opioid-treated chronic pain patients indicate significant effects of MORE on pain severity, stress arousal, desire for opioids, and opioid misuse risk as well as on positive psychological functioning (e.g., positive affectivity, meaning in life) relative to a therapist-led support group control condition (Garland et al., 2014a; Garland, Hanley, Riquino, et al., 2019). Although a broad spectrum of intervention effects have been observed, MORE's effect on opioid dose escalation has yet to be established.

Preventing opioid dose escalation is likely dependent on improving self-regulation. Among pain management patients in primary care, opioid dosing is self-administered, and given that patients are often prescribed ≥ 30-day supplies (Mundkur et al., 2018), patients may take higher doses than prescribed. In light of the powerfully reinforcing effects of opioids, opioid dose escalation has been shown to occur over time among some individuals with chronic pain (Henry et al., 2015; Mystakidou et al., 2003; Paice et al., 1996; Zenz et al., 1992). Prospective cohort studies indicate that 19% of chronic pain patients double their dose over two years (Morasco et al., 2020), with national epidemiologic data indicating that 34% double their dose over five years (Fredheim et al., 2013). Plausibly, such opioid dose escalation is likely to occur in the absence of effective self-regulation. In their neurovisceral integration model, Thayer & Lane (2000) propose self-regulation is comprised of three core components: control of attention, emotion, and autonomic function. Within this model, attention and emotion regulation are subserved by the same functional and structural brain networks as autonomic control (Jennings et al., 2015); by virtue of this common neural architecture, regulating attention and emotion should also regulate autonomic processes. Mindfulness training, which has been shown to improve self-regulatory capacities (Ostafin et al., 2015), is intended to strengthen both attention and emotion regulation (Tang, Hölzel, & Posner, 2015; Vago & Silbersweig, 2012), and MORE, which rests on a foundation of mindfulness training, has been shown to enhance both of these capacities. Specifically, MORE improves the capacity to regulate attention to emotional information, as revealed by dot probe (Garland, Baker, et al., 2017; Garland & Howard, 2013) and emotional go/no-go tasks (Garland, Bryan, Priddy, et al., 2019). In addition, MORE improves top-down regulation of emotional responses, as revealed by neurophysiology (Froeliger et al., 2017; Garland, Atchley, Hanley, et al., 2019). Following the neurovisceral integration model, to the extent that MORE strengthens self-regulatory capacity, such improvements should be reflected in increased autonomic control.

According to the neurovisceral integration model, self-regulation in the face of homeostatic perturbations (such as those evoked by chronic pain and/or the urge to consume opioids) is thought to elicit downstream activation of a central-autonomic network that modulates attention and emotion (e.g., medial prefrontal cortex → anterior cingulate cortex and anterior insula → central nucleus of the amygdala → hypothalamus → nucleus of the solitary tract → ventrolateral medullary) with downstream effects on visceral physiological responses, including the beat-to-beat modulation of heart rate by the vagus nerve, known as heart rate variability (HRV) (Thayer & Lane, 2009; Thayer & Lane, 2000). Prefrontal cortical activation is significantly positively associated with HRV (Thayer, Åhs, Fredrikson, Sollers III, & Wager, 2012). Thus, HRV may index top-down, prefrontally-mediated self-regulation of brainstem activity and autonomic responses. In that regard, a meta-analysis including 123 studies found a statistically significant, albeit small, relation between HRV and various measures of self-regulation (Holzman & Bridgett, 2017), including the capacity to regulate appetitive urges. For example, in a classic experiment, Segerstrom and Nes (2007) found that exerting self-regulation strength to resist the urge to eat an appetizing food increased HRV relative to indulging in the urge. In contrast, decreased HRV is associated with reduced self-regulation of craving for other substances, including alcohol (Garland et al., 2012; Quintana et al., 2013), methamphetamine (Wang et al., 2019), nicotine (Ashare et al., 2012), and opioids (Baker & Garland, 2019; Garland, Bryan, et al., 2017).

As a self-regulatory strategy, mindfulness meditation should impact HRV. In that regard, Krygier et al. (2013) identified increases in HRV during mindfulness Vipassana meditation among novice practitioners during a 10-day mindfulness retreat. Practitioners of an integrative body-mind training involving mindfulness meditation showed similarly elevated levels of HRV during meditation that were correlated with increases in activation in the anterior cingulate cortex (Tang et al., 2009) – a key region implicated in the frontoparietal control system, which may suggest a cortical (attentional) control mechanism over autonomic function. Furthermore, Takahashi et al., (2005) found that Zen-meditation also increased HRV and frontal slow-alpha/theta EEG rhythms, again suggesting attention regulation over autonomic function during meditation. With respect to MORE, significant HRV effects have been observed during attention to drug-related stimuli and other emotionally salient cues in the context of cognitive tasks (Garland et al., 2014; Garland et al., 2010; Garland, Howard, et al., 2017). These findings demonstrate that MORE modulates HRV during attention to exteroceptive stimuli. However, to date, no study has directly examined effects of MORE on autonomic control during mindfulness meditation with an internal locus of attention on cognitive, affective, and interoceptive experience, nor has any study tied self-regulation of autonomic responses via meditation to opioid use.

The present study examined effects of MORE on opioid dosing and HRV during meditation among a sample of patients with opioid-treated chronic pain participating in a recently completed Stage 2 RCT (NCT03298269). Self-reported outcomes from this trial demonstrated that MORE significantly decreased chronic pain severity and opioid misuse risk by 3-month follow-up (Garland, Hanley, Riquino, et al., 2019). In this secondary analysis of proximal outcome data from this trial, we hypothesized that patients with opioid-treated chronic pain allocated to MORE would report significantly greater increases in HRV during meditation than patients allocated to an active support group (SG) control condition, and that this increase in HRV would mediate the effect of MORE on reducing opioid dosing by 3-month follow-up.

METHODS

Participants

Participants met study inclusion criteria if they reported chronic non-cancer pain on more days than not and had been prescribed and taking opioid analgesics nearly every day for at least 90 days. Participants were recruited from primary care clinics in Salt Lake City, UT through a variety of means, including electronic health record, opt out letters, flyers, and radio advertisements. Participants were excluded if they were actively suicidal or psychotic (determined by the Mini-International Neuropsychiatric Interview 6.0, Sheehan et al., 1998) or had previously completed an 8-week mindfulness-based intervention (e.g., Mindfulness-Based Cognitive Therapy, MBCT). Over two-years, 304 patients were screened, 95 of whom met study criteria and were randomly assigned to MORE (n=50) or SG (n=45) conditions (see CONSORT chart in Garland, Hanley, Riquino, et al., 2019b). Of these participants, 76 (80% of the randomly allocated sample; 74% of MORE participants and 86% of SG participants) completed treatment - defined as attending ≥4 treatment sessions, a threshold established in the original MBCT efficacy trial (Teasdale et al., 2000). Of participants allocated to MORE, 72% completed post-treatment assessments, and 68% completed the 3-month follow-up. Of participants allocated to SG, 84% completed post-treatment assessments, and 69% completed the 3-month follow-up.

Procedures

Following screening, individuals who met eligibility criteria and gave informed consent completed a series of validated questionnaires (reported in Garland, Hanley, Riquino, et al., 2019b). Next, participants were interviewed by a clinically trained research assistant using the Timeline Followback procedure (Sobell & Sobell, 1992) to assess their daily opioid use. After the pre-treatment assessment, participants were randomly allocated by a project coordinator, who was uninvolved with assessment or treatment, to one of two undisclosed treatment groups. Participants were informed that they would be randomized to a behavioral treatment group that would help them to cope with pain, stress, and opioid-related problems by providing either mindfulness training or group support. To prevent bias and maintain allocation concealment, the identity of treatment allocation was not revealed to the participant until he or she arrived to the first treatment session. The allocation sequence (which was inaccessible to research staff involved in assessment or treatment) was generated via computerized random number table by a researcher who was uninvolved in assessment, treatment, or enrollment using simple randomization in blocks of varying sizes (2 - 4) to preserve allocation unpredictability. Assessments were conducted by research staff blinded to group assignment (which remained concealed throughout the study), and participants were reminded to not disclose their group assignment to research staff before or during each assessment. After participants had completed the 8-week MORE or SG treatment, they returned to the lab to complete a post-treatment assessment consisting of: 1) the same questionnaires administered at pre-treatment, 2) the Timeline Followback to assess for opioid use, and 3) a laboratory-based, mindfulness practice session during which HRV was assessed. Participants returned for a 3-month follow-up where they again completed the Timeline Followback. All study procedures were IRB approved.

Study Interventions

MORE intervention.—The manualized MORE intervention (Garland, 2013) was delivered by a Master's level social worker in 8 weekly, 2-hour group therapy sessions conducted in a community-based primary care clinic. MORE sessions involved: 1) mindfulness training to facilitate self-regulation of cognitive, affective, and physiological responses; 2) reappraisal training to reframe adversity as an opportunity for psychological growth; and 3) training in savoring pleasant events to boost positive affective responses and promote natural reward processing. MORE treatment sessions addressed the following topics on successive weeks: distinguishing nociception from pain and suffering; cultivating mindful awareness of automaticity in the context of chronic pain and opioid use; elucidating the role of cognitive reappraisal in fueling negative emotions and pain catastrophizing; shifting attention from pain and stress to savor pleasant experiences; self-regulating opioid use and misuse through mindful attention and awareness; reducing stress as a means of preventing opioid misuse; finding meaning in life through self-transcendence; and developing a mindful recovery plan. No explicit motivation or instruction for opioid dose reduction was provided in the intervention groups. Mindfulness training involved mindful breathing and body scan techniques, with specific instructions to help patients shift from affective to sensory processing of pain sensations and savor positive emotions and pleasant body sensations (Hanley & Garland, 2019), as well as develop meta-awareness. Participants were asked to engage in daily 15-minute mindfulness practice sessions at home guided by an audio recording. In addition, participants were asked to pause before taking their next opioid dose to practice three minutes of mindful breathing. This mindfulness practice aimed to disrupt habitual (automatic) use of opioids, and was intended to clarify whether opioid use was driven by craving or a legitimate need for pain relief. Ultimately, this set of techniques was intended to strengthen self-regulatory capacity and provide a means of reducing unneeded opioid dosing.

Support group intervention.—To control for non-specific factors including attention by a caring professional, therapeutic expectancy, and social support, we employed a therapist-led support group (SG) as the active control condition in this study. The SG consisted of 8 weekly, 2-hour group sessions, in which a Master's level social worker led discussion on topics pertinent to chronic pain and long-term opioid use that were selected to roughly match corresponding themes in the MORE intervention: the lived experience of chronic pain; ways of coping with chronic pain; ways of coping with negative emotions; how stressful life events impact pain; the stigma of opioid use and dependence; adverse effects of opioids; acceptance versus denial; and plans for the future. To match the MORE homework requirement, SG participants were asked to engage in 15 minutes of journaling a day on the weekly session topics. This Rogerian SG format, which did not involve learning of any experiential skills, was validated as a control condition in several prior trials of MORE (Garland, Manusov, et al., 2014; Garland, Gaylord, Boettiger, & Howard, 2010) and was largely based on the active intervention condition outlined in the Matrix Model intensive outpatient treatment manual (Rawson & McCann, 2006). During the SG sessions, participants were guided via client-centered reflective listening techniques to disclose feelings and thoughts about group topics, as well as to provide advice and emotional support for their peers. Therapists engaged in empathic responding and promoted mutual support among group members, but no specific recommendations for change were provided. This intervention, which typifies a widely-available form of conventional, process-oriented group therapy, was found in three prior RCTs to have equivalent perceived credibility to mindfulness-based interventions (Garland et al., 2010, 2014; Gaylord et al., 2011). MORE and SG sessions were held in a primary care clinic in groups of 8 to 12 people, were 2 hours in length, and were administered by Masters-level therapists supervised by the first author.

Treatment fidelity.—MORE therapist competence was rated on a Likert scale (1 = very poor, 4 = adequate, 7 = excellent) while therapist adherence was rated on a similar Likert scale (1 = not at all, 4 = somewhat, 7 = extensively) across 16 items developed by the first author (validated in R34DA037005). Therapist competence and adherence to the SG treatment manual were rated with similar Likert scales across 14 items (also validated in R34DA037005). As reported in Garland, Hanley, Riquino, et al. (2019b), MORE and SG therapists achieved a high level of fidelity (MORE competence = 5.9, SD = 0.7, MORE adherence = 5.9, SD = 0.6; SG competence = 6.4, SD = 0.4, SG adherence = 5.6, SD = 0.6). The first author reviewed all MORE and SG treatment session recordings weekly to monitor fidelity and provide clinical supervision until a level of adequate or greater therapist competence and adherence had been achieved (mean scores > 4). At this time, clinical supervision was provided every few weeks, and clinically trained research staff (e.g., graduate-level social workers and psychologists) continued to conduct fidelity monitoring on a random sample of ≥ two sessions per cohort.

Measures

Opioid dose.—Average daily opioid dose throughout the study was assessed using the validated Timeline Followback procedure (Sobell & Sobell, 1992). Self-reports of opioid dosing data were triangulated through electronic health record review of opioid prescription data. Opioid dose was converted in morphine milligram (mg) equivalents.

Heart rate variability during mindfulness practice.—At the beginning of the experimental laboratory session, disposable Ag-AgCl adhesive electrodes were attached to participants' right and left pectoral muscles and electrocardiogram (ECG) data were continuously sampled at 1,000 Hz on a Biopac MP 150 system (Biopac Systems, Goleta, CA). Baseline HRV was collected during a 5-minute period in which participants were asked to remain silent and motionless, after which they completed the 10-minute mindfulness practice. For this practice all participants received the same instruction: "Now practice mindfulness, which means focusing on your thoughts, feelings and body sensations in the present moment in a nonjudgmental way, without reacting to them." In keeping with methods used in previous mindfulness studies (E. L. Garland, Atchley, Hanley, et al., 2019), to control for demand characteristics, these task instructions were kept constant across both treatment conditions (MORE and SG), allowing us to isolate the effects of mindfulness training through the MORE intervention from any potential instruction effects. We assumed that meditation-naive participants randomized to the SG control would be unable to successfully practice mindfulness meditation with such nondescript instructions, whereas participants randomized to MORE would be able to use these simple instructions to successfully practice mindfulness following 8 weeks of training in the MORE intervention.

During the resting baseline and mindfulness practice session, R-R intervals in the ECG waveforms were initially detected automatically in Acqknowledge 4.1 (BIOPAC, Inc.), and then visually inspected to correct missed or incorrectly identified R-waves. Kubios 2.0 (Biosignal Analysis and Medical Imaging Group, University of Finland) was used for time domain analysis of R-waves. The root mean square of successive differences (RMSSD) in R-R intervals was used to compute HRV. This measure has been well-established to be sensitive to short-term fluctuations in HRV (Task Force of the European Society of Cardiology the North American Society of Pacing and Electrophysiology, 1996). Although some researchers suggest RMSSD is not a pure measure of vagal control of the heart (Berntson et al., 2007), we selected RMSSD as our primary measure of HRV in this study given that it less affected by respiratory influences than spectral frequency-domain HRV measures (Hill et al., 2009). RMSSD is recommended as a psychophysiological measure of phasic, short-term changes in HRV in multiple best practice guidelines (Laborde et al., 2017; Shaffer & Ginsberg, 2017; Smith et al., 2020). It has been demonstrated that RMSSD is preferable to spectral frequency-domain HRV (e.g.., high frequency HRV, HF-HRV) measures in experiments where respiratory confounds are likely to be present (Hill et al., 2009; Penttilä et al., 2001). Indeed, HF-HRV is well-known to be confounded by respiration effects (Shaffer & Ginsberg, 2017). In light of well-documented effects of opioids on respiratory depression (Boom et al., 2012; Jarzyna et al., 2011), as well as the effects of mindfulness training on respiration rate (Adler-Neal et al., 2019; Wielgosz et al., 2016), we selected RMSSD as our primary HRV measure in an effort to remove the potentially confounding influence of respiration inherent to spectral frequency-domain measures of HRV. As an ancillary HRV measure, we also report HF-HRV. HRV values were averaged across the 5-min baseline and the 10-minute mindfulness induction.

Therapeutic skill practice.—Each day during the 8-week MORE intervention, participants completed ecological momentary assessments (EMAs) via smartphones to report the number of minutes they spent engaged in each type of therapeutic skill (i.e., mindful breathing, reappraisal, and savoring) that day. We asked participants to report skill practice daily to prevent retrospective memory biases.

Statistical Analysis—Intendon-to-treat (ITT) analyses were conducted on the entire randomized sample. To analyze patterns of missing data, we performed Little's MCAR test (Little, 1988). The nonsignificant MCAR test ($\chi^2 = 75.32$, $df = 75$, $p = .47$) and pattern of missing data were consistent with data being missing completely at random; thus, maximum likelihood estimation (MLE) was employed to handle missing data. To reduce bias resulting from listwise deletion, MLE estimates the variance-covariance matrix for all available data, including data from cases assessed at only one time point. Given that all available data were used for ITT analysis, raw means from the available data for the entire sample (without listwise deletion, in mean ± 1 standard error) were reported for interpretation of study findings (e.g., changes in opioid dose).

We undertook a stepwise analytic approach. We first employed linear mixed modeling in SPSS 24.0 to assess effects of MORE on opioid dose trajectories from pre-treatment to followup. This model was composed of variables representing treatment group (Group) and assessment time point (Time), as well as their interaction, and was specified with a random intercept. In the SG, two participants had very high opioid dose values (i.e., greater than 1000 mg of morphine equivalents at 3-month follow-up). As such, the opioid dosing variable was found to be skewed (skewness = 6.33, SE = .16). To account for these outliers and adjust for the non-normality of the data, opioid dose at each study timepoint was natural log transformed before analysis, resulting in distributions that did not significantly differ from normal (one-sample Kolmogorov-Smirnov test *p*s= .20). After establishing differences in opioid dose trajectory by treatment condition, we then conducted a path analysis (Baron & Kenny, 1986) to test mindfulness-induced change in HRV at post-treatment as a mediator of the effects of opioid dose reduction by 3-month followup. This path model was composed of a single independent variable representing treatment group (Group), a mediator variable representing change in HRV (RMSSD during mindfulness meditation – resting baseline RMSSD at post-treatment), and dependent variable representing change in opioid dose by follow-up. The R Lavaan package obtained direct and indirect effects with bootstrapping (Preacher & Hayes, 2008) to test the significance of the indirect effect.

Finally, to better determine which therapeutic skill (i.e., mindfulness, reappraisal, and savoring) was most strongly related to the effect of MORE on increased HRV during mindfulness meditation and lowered opioid dose at 3-month follow-up, we examined Pearson correlations between the total number of self-reported minutes of each type of therapeutic skill practice over the 8-week intervention and opioid dose and HRV outcomes.

RESULTS

Sample Characteristics

Participants were predominately Caucasian (89.5%) and female (66.3%), with a mean age of 56.6 ± 1.21 years. Approximately half of participants (53.6%) had no more than a high school education, and the majority (69.5%) had an annual household income < $49,999. Back pain was the most commonly reported pain location (38.9%), followed by pain in the joints (13.7%), lower extremities (11.6%), and neck/shoulders (8.4%), with the remaining participants reporting other types of pain as their primary pain condition. The mean pain severity was 5.29 ± 0.15 out of 10. Participants had used opioids for an average of 10.2 ± 0.8 years. Hydrocodone was the most commonly reported primary opioid type (40.0%), followed by oxycodone (20.0%), tramadol (15.7%), and morphine (10.5%), with fewer participants reporting use of other opioids.

Effect of MORE On Opioid Dose

In ITT analysis via linear mixed modeling, although neither the main effect of Group (F(1,92.68) = 1.41, p = .24 nor Time (F(2,129.77) = .99, p = .38), were significant, a significant Group X Time interaction was observed on the log-transformed opioid dose variable (Figure 1), F(2,129.77) = 5.35, p = .006, d = 1.07, such that participants in MORE evidenced a significantly greater decrease in opioid dosing from pre- to post-treatment and 3-month follow-up than the SG. Inspection of the available opioid dose data (non-transformed for ease of interpretation) revealed that by 3-month follow-up, participants in MORE reported a 31.8% reduction in opioid dose (from 66.31 ± 10.75 mg at pre-treatment to 45.24 ± 10.08 mg at follow-up), compared to a 124.0% increase in opioid dose among participants in the SG (from 69.56 ± 15.05 mg at pretreatment to 155.84 ± 63.82 mg at follow-up). In a sensitivity analysis dropping the two outliers from the SG, the Group X Time interaction remained significant, F(2,59.92) = 4.41, p = .016, d = .77, with the SG reporting a 16.1% increase in opioid dose (from 61.04 ± 14.05 mg at pretreatment to 70.89 ± 19.54 mg at follow-up).

HRV During Meditation as a Mediator of Treatment Effect on Opioid Dose

Participation in MORE was associated with significantly greater increases in RMSSD from resting baseline through mindfulness meditation (baseline: 32.81 ± 4.55, meditation: 38.51 ± 4.62) than the support group (baseline: 30.36 ± 4.62, meditation: 29.65 ± 4.69); this difference was statistically significant (B = 6.41, SE = 2.78, p = .02, see Figure 1). MORE was also associated with greater increases in HF-HRV from resting baseline through meditation (baseline: 251.04 ± 144.38, meditation: 689.18 ± 271.92) than the support group (baseline: 383.35 ± 146.69, meditation: 353.28 ± 276.27), but this effect was not statistically significant (p = .16).

In our path model (Figure 2), the direct effect of Group on change in RMSSD from resting baseline through mindfulness meditation in the post-treatment laboratory session was significant (‘a’ path: B = 6.48, SE = 2.36, $p = .006$). Mindfulness-induced change in RMSSD significantly predicted changes in opioid dose by 3-month follow-up (‘b’ path: B = −.03, SE = .008, $p = .001$), such that individuals who evidenced the largest increases in RMSSD during mindfulness meditation at the post-treatment laboratory assessment evidenced the greatest decreases in opioid dose over time. The direct effect of Group on opioid dose remained significant (‘c’ path: B = −.58, SE = .20, $p = .004$). The indirect effect of Group on opioid dose reduction via change in RMSSD was significant (B = −.17, SE = .07, $p = .034$).

Therapeutic Skill Practice and its Relation to Study Outcomes

With regard to home therapeutic skill practice, participants in MORE reported a daily mean practice of mindful breathing for 17.4 (SD = 8.9), reappraisal for 10.5 (SD = 7.6), and savoring for 17.0 (SD = 17.1) minutes. Further analysis indicated that the total number of minutes of mindful breathing practice over the 8 weeks of the intervention correlated significantly with both RMSSD increases during meditation ($r = .42$, $p = .048$) and opioid dose at the 3-month follow-up ($r = -.40$, $p = .046$). Total number of minutes practicing savoring also correlated significantly with opioid dose at the 3-month follow-up ($r = -.39$, $p = .049$), but not with RMSSD during meditation ($r = .25$, $p = .25$). Total number of minutes of reappraisal practice showed no significant correlations with either RMSSD during meditation ($r = .25$, $p = .26$) or opioid dose at the 3-month follow-up ($r = -.38$, $p = .08$).

DISCUSSION

Mindfulness-based interventions are theorized to improve self-regulation (Tang et al., 2015; Vago & Silbersweig, 2012), and self-regulation may be critical for managing opioid medications over time. Previous evidence suggests MORE improves attentional and emotional markers of self-regulation (Garland, Baker, et al., 2017; Garland, Atchley, Hanley, et al., 2019; Garland, Bryan, Priddy, et al., 2019; Garland & Howard, 2013) and decreases opioid misuse (Garland et al., 2014a; Garland, Hanley, Riquino, et al., 2019). Here we tested whether MORE could strengthen self-regulation of autonomic function (i.e., HRV) during an acute meditative state and whether meditation-related increases in HRV during meditation predict less opioid use 3-months after treatment ends. Results from the present study indicate that MORE significantly reduced opioid dosing by three-month follow-up in a sample of primary care patients prescribed opioid pain management. Comparatively, opioid use increased in the SG control condition over the same time period. Additionally, MORE increased HRV during meditation, and these HRV increases predicted less opioid use at three-month follow-up. Taken together, study results suggest that MORE may reduce opioid dose by strengthening self-regulation of autonomic function during mindfulness practice.

Evidence that behavioral interventions can reduce prescribed opioid dose in chronic pain patients is limited (Eccleston et al., 2017; Frank et al., 2017). However, a recent systematic review and meta-analysis concluded that mindfulness-based interventions showed particular promise for opioid-treated chronic pain patients (Garland, Brintz, et al., 2020). To date, only six RCTs of behavioral interventions are known to have reported positive opioid-related outcomes in samples of chronic pain patients (Garland et al., 2014b; Garland, Hanley, Kline, et al., 2019; Garland, Hanley, Riquino, et al., 2019; Jamison et al., 2010; Naylor et al., 2010; Wilson et al., 2015). Cognitive-behavioral therapy was tested in three of the six studies, whereas MORE was tested in the remaining three. Jamison et al. (2010) found that an in-person cognitive-behavioral intervention decreased opioid misuse among chronic pain patients. Naylor et al. (2010) found an automated cognitive behavioral therapy maintenance enhancement program delivered via telephone reduced chronic pain patients' opioid dose at 4-month and 8-month follow-ups. Wilson et al. (2015) found a cognitive behaviorally based pain self-management program delivered via the internet decreased chronic pain patients' opioid misuse at post-treatment. In two previous, stage 2 RCTs Garland and colleagues found that MORE decreased chronic pain patients' opioid misuse at post-treatment (Garland et al., 2014b), and at 3-month follow-up (Garland, Hanley, Riquino, et al., 2019). Additionally, a stage 1 RCT found MORE decreased moment-to-moment opioid craving (as indexed by ecological momentary assessment), and increased self-control over craving among individuals with OUD and chronic pain (Garland, Hanley, Kline, et al., 2019). Findings from the present study compliment and extend these previous results, providing the first evidence in the scientific literature that a mindfulness-based intervention can reduce opioid dosing among people prescribed opioid analgesics.

MORE's ability to improve opioid-related outcomes is likely dependent on improving self-regulation through mindfulness meditation – a practice of cultivating meta-awareness to self-regulate thoughts, emotions, and body sensations (Tang et al., 2015). Self-regulation is held to be integral to restraint of addictive behavior, and evidenced by the exertion of self-control over the impulse to consume the appetitive substance (Baumeister & Vonasch, 2015; Heatherton & Wagner, 2011). Yet, self-regulation failure occurs when resources for self-control are depleted over time (Baumeister et al., 2018). In the present study, we assessed HRV during mindfulness as an indicator of self-regulatory strength. Meta-analyses suggest that HRV is positively associated with self-regulation (Holzman & Bridgett, 2017) and self-control (Zahn et al., 2016). With respect to addictive behavior, HRV has been shown to index self-control strength over appetitive responses to food (Geisler et al., 2016; Segerstrom & Nes, 2007) and alcohol (Garland et al., 2012; Ingjaldsson et al., 2003), and in meta-analyses individuals with substance use disorders evidence reduced resting HRV (Cheng et al., 2019) and attenuated task-elicited HRV (Beauchaine et al., 2019). Specific to problematic opioid use, blunted HRV among opioid misusers is associated with deficits in self-regulation of attention (Garland et al., 2015) and emotion (Garland, Bryan, et al., 2017). Here we show that mindfulness meditation, which has been shown to counteract self-control depletion (Friese et al., 2012), may increase physiological resources for self-regulation. In support of this contention, we observed that participants receiving 8 weeks of mindfulness training through the MORE intervention exhibited increases in HRV during mindfulness meditation from resting baseline levels that mediated the effect of MORE on reducing opioid dose. Plausibly, these findings may reflect MORE participants' increased capacity to use mindfulness to regulate autonomic reactions to homeostatic perturbations incurred by internal (e.g., pain) and external stimuli (e.g., opioid cues). Of note, because participants in MORE received 8 weeks of mindfulness training whereas those in the SG did not, HRV responses in the SG likely reflected a resting state whereas HRV responses in the MORE group likely indexed the autonomic effects of mindfulness practice. Thus, the current design was able to assess the state effects of mindfulness practice on HRV and their associations with opioid dose escalation, but could not evaluate trait-like changes in HRV produced by the intervention. Plausibly, if chronic pain patients learn to use mindfulness as an endogenous means of effectively self-regulating their internal milieu back to homeostasis, this may reduce the demand for opioids as an exogenous means of self-regulating the body's internal state.

Mindfulness is a skill, and like other skills, requires practice. This notion suggests that the greater duration of mindfulness practice, the greater self-regulatory strength one may cultivate and therefore be able to exert over opioid use in the face of chronic pain. In the present study, we found that number of minutes of mindful breathing practice were associated with increases in HRV during meditation and opioid dose. In data from another RCT, we observed parallel findings: greater duration of mindfulness practiced during the intervention period predicted a greater extent of emotional response inhibition observed in a laboratory task, that was in turn correlated with reduced pain interference (Garland, Bryan, Priddy, et al., 2019). That said, MORE is a multimodal intervention comprised of mindfulness, reappraisal, and savoring techniques. It is possible that techniques other than mindfulness meditation might account for the observed results. Although neither savoring nor reappraisal practice minutes were associated with HRV during the laboratory-based mindfulness meditation session, the number of minutes of savoring practice was indeed associated with opioid dose by 3-month follow-up. This result is perhaps unsurprising given that MORE uses savoring techniques to increase responsivity to natural rewards, which in prior psychophysiological studies has been associated with reduced opioid craving (Garland et al., 2014) and misuse (Garland, Howard, et al., 2017). Future studies should employ tasks from cognitive and affective neuroscience to parse the independent and interactive contributions of mindfulness, reappraisal, and savoring on HRV and opioid dosing.

The current study has several other limitations. First, the Timeline Followback measure of opioid dose is based on participant recall, and could be prone to errors due to participants forgetting or intentionally misrepresenting their opioid dose. Although there is no gold standard means of quantifying medication adherence (Weiss, 2004), the Timeline Followback has been shown through meta-analysis to validity detect substance use and to evidence agreement rates with biological measures of opioid use as high as 94% (Hjorthoj et al., 2012). A more accurate quantification of opioid use and misuse would require triangulation of self-reports, clinician evaluation, electronic monitoring systems (e.g., MEMS caps), statewide monitoring of prescription data, and urine toxicology screens. Second, due to the demographic characteristics of the study location, the sample recruited for this study was rather homogenous with respect to ethnicity and race. Future studies should increase participant racial and ethnic heterogeneity to obtain greater generalizability of study results. Third, as a Stage 2 RCT, the study sample size was relatively small, thus reducing statistical power. A future Stage 3 RCT with three to four times the sample size would improve our ability to test effects of MORE on HRV and opioid dosing outcomes. Lastly, we followed a reasonable conjecture that the mindfulness component of MORE was causally responsible for generating the observed effect of increased HRV during meditation at post-treatment, but it still remains to be seen exactly which components of MORE may have causally contributed to the observed effects on HRV and opioid dose, as MORE is an integrated bio-behavioral intervention program that unites three therapeutic components: mindfulness, reappraisal, and savoring. We were unable to examine the differential effects of each of these practices because high multicollinearity between practice duration measures precluded multiple regression analysis. Also, when the present study was conducted, we did not have a decisive means to decipher presumably complex chains of causes and effects that synergistically emerge in the actual delivery of MORE to pain patients who can greatly benefit from it in many ways. A future study employing ecological momentary assessment (EMA) may address this type of question relevant to intervention-induced dynamics of change.

In summary, we show that MORE, a mindfulness-based intervention for chronic pain patients on long-term opioid therapy, can reduce opioid dosing by 3-month follow-up. Increases in HRV during mindfulness meditation were found to mediate the effect of treatment on dose reduction, with larger HRV increases associated with greater dose reductions. Plausibly, the mindfulness meditation component of MORE provides a means of cultivating self-regulatory strength, as reflected by autonomic function, which might in turn be useful for exerting self-control over opioid dosing. In light of a recent systematic review of the efficacy of mind-body therapies for opioid-treated pain (Garland, Brintz, et al., 2019), this study represents the first RCT to demonstrate the effects of a mindfulness-based intervention on quantitative reductions in opioid dose. Effects of MORE on opioid dose, coupled with other clinical outcomes such as reduced pain, craving, and misuse demonstrated in previous studies (Garland et al., 2014b; Garland, Hanley, Kline, et al., 2019; Garland, Hanley, Riquino, et al., 2019), indicate robust empirical support for MORE as an intervention to combat the current opioid epidemic. Lastly, the present study provides intriguing implications for the question of how to best optimize the approach to opioid dose reduction as the goal of the intervention. Although no motivational enhancement therapy or explicit instructions for dose reduction were integrated into the intervention, participants in MORE, relative to those in SG, acquired skills to boost self-regulatory capacity and thereby self-initiated opioid dose reduction. Thus, MORE might be useful as part of a comprehensive opioid sparing or tapering strategy for patient-centered reduction of long-term opioid analgesic therapy (Dowell et al., 2016). Future treatment development research should address what optimized intervention factors and therapeutic requirements (e.g., motivational interviewing, see Rollnick & Miller, 1995) will be ultimately responsible for facilitating opioid dose reduction for patients undergoing an integrated treatment program such as MORE. This is an empirically tractable problem that will be pursued in our future research program.

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Public significance:

Mindfulness-Oriented Recovery Enhancement reduced opioid dose among people with chronic pain by increasing heart rate variability – a marker of self-control strength.

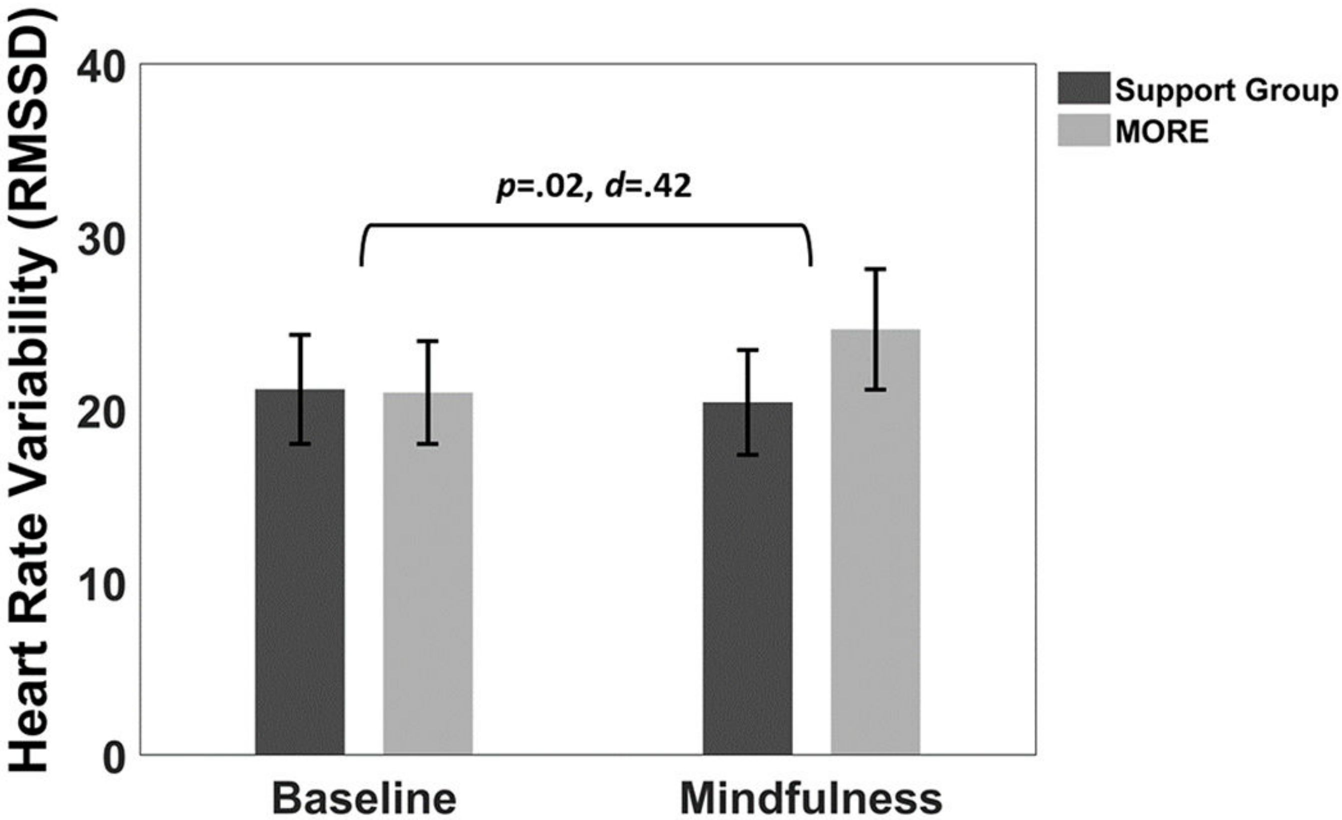

Figure 1.
Effects of Mindfulness-Oriented Recovery Enhancement (MORE) versus a Support Group control condition on heart rate variability (mean RMSSD ± 1 S.E.; RMSSD = root mean square of successive differences) during a laboratory-based mindfulness meditation practice session and resting baseline at post-treatment.

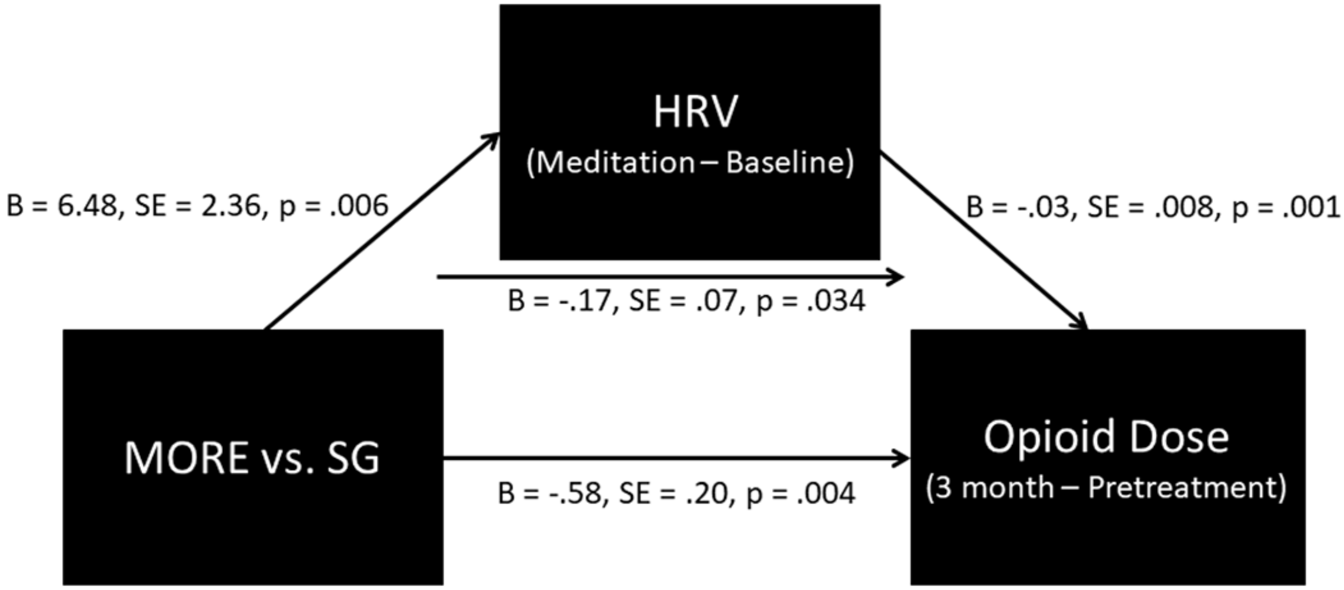

Figure 2.

Path model indicating that the effect of Mindfulness-Oriented Recovery Enhancement (MORE) versus a Support Group (SG) control condition on reducing opioid dose was statistically mediated by increasing heart rate variability (HRV) during mindfulness meditation.