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ARTICLE

Disrupting the Downward Spiral of Chronic Pain and Opioid Addiction With Mindfulness-Oriented Recovery Enhancement: A Review of Clinical Outcomes and Neurocognitive Targets

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ABSTRACT

Prescription opioid misuse and addiction among chronic pain patients are problems of growing medical and social significance. Chronic pain patients often require intervention to improve their well-being and functioning, and yet, the most commonly available form of pharmacotherapy for chronic pain is centered on opioid analgesics—drugs that have high abuse liability. Consequently, health care and legal systems are often stymied in their attempts to intervene with individuals who suffer from both pain and addiction. As such, novel, non-pharmacologic interventions are needed to complement pharmacotherapy and interrupt the cycle of behavioral escalation. The purpose of this paper is to describe how the downward spiral of chronic pain and prescription opioid misuse may be targeted by one such intervention, Mindfulness-Oriented Recovery Enhancement (MORE), a new behavioral treatment that integrates elements from mindfulness training, cognitive-behavioral therapy, and positive psychology. The clinical outcomes and neurocognitive mechanisms of this intervention are reviewed with respect to their effects on the risk chain linking chronic pain and prescription opioid misuse. Future directions for clinical and pharmacologic research are discussed.

KEYWORDS addiction, chronic, mindfulness, misuse, neurocognitive, opioid, pain, pharmacotherapy

INTRODUCTION

Chronic pain is a prevalent problem in Western society, with estimates suggesting that as many as one third of the populace is afflicted by this often debilitating condition; a meta-analysis of 13 studies reported a weighted mean prevalence of 35.5% for chronic pain of any kind and a weighted mean prevalence of 11% for severe chronic pain.[1] Despite the widespread nature and serious impact of this issue, the most commonly available pain management approach, opioid pharmacotherapy, has not adequately addressed the problem. Indeed, placebo-controlled efficacy studies indicate that on average, opioids do not significantly decrease pain among chronic pain patients.[2] In addition, the analgesic effects of opioids, even if initially adequate for the individual patient, are not often sustained during continuous and long-term opioid pharmacotherapy.[3] Opioid-seeking behaviors and opioid dose escalation may result from such inadequately addressed pain, increasing the risk of prescription opioid misuse and addiction. Although most patients with chronic pain take medicines as prescribed, a subset of patients are at significant risk for escalating from appropriate opioid use to misuse and finally to opioid addiction. A review of 67 methodologically rigorous studies including thousands of chronic pain patients concluded that 11.5% of these patients evidence signs of opioid misuse such as aberrant drug-seeking behaviors and unauthorized dose escalation.[4] Although the paths from appropriate opioid use to misuse and addiction

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among chronic pain patients have not been fully delineated, some progress has been made toward elucidating the downward spiral linking chronic pain to addictive use of prescription opioids.[5] The purpose of this paper is to first describe the neuropsychopharmacologic mechanisms underpinning the problem of co-occurring chronic pain and prescription opioid misuse, and then to detail a novel behavioral intervention designed to alleviate this problem.

THE DOWNWARD SPIRAL OF CHRONIC PAIN, PRESCRIPTION OPIOID MISUSE, AND ADDICTION

Prolonged use of opioids produces physical dependence via neuroadaptations resulting in tolerance, withdrawal, and, in some cases, opioid-induced hyperalgesia. Risk for developing addictive behaviors may be compounded by these neuropharmacologic effects of long-term opioid use, can induce sensitization to painful stimuli.[6] Patients exhibiting opioid-induced hyperalgesia may experience increased sensitivity to the chronic painful condition for which they sought treatment, or pain in body regions distal to the original treatment site.[3] Such heightened pain responses, when coupled with tolerance to the analgesic effects of opioids, can result in increased opioid craving[7] and consumption.[8] Moreover, the aversive nature of pain can evoke a powerful emotional reaction that feeds back to modulate pain perception. Pain often results in feelings of anger, sadness, and fear depending on how the pain is cognitively appraised. For instance, when individuals engage in pain catastrophizing, they interpret bodily sensations as indicating the presence of a serious threat, and they underestimate their ability to cope with those sensations. Such catastrophic appraisals promote fear, intensified pain, and greater functional disability.[9,10] The reciprocal effects of negative emotion on pain stem from their shared neurobiologic substrates; primary nodes of the neural circuits subserving negative emotional processes, including the amygdala, anterior cingulate cortex, and anterior insula, are also primary nodes of the pain neuromatrix that tune attention toward pain, intensify pain unpleasantness, and amplify interoception.[11,12] Thus, when individuals experience negative emotions as a result of pain or other emotionally salient events and stressors, the heightened neural processing of threat in affective brain circuits primes the subsequent perception of pain[13,14] and increases the likelihood that sensations from within the body will be interpreted as painful.[15–17] Such enhanced negative emotional processing of health-related threat is associated with hypervigilance for and sustained attention to pain-related stimuli.[18,19] Thus, negative affect biases attention toward pain, which then increases its aversive quality. Furthermore, stress and negative affect intensify sympathetic nervous system activity associated with pain, which manifests in increased symptoms of anxiety and tension that may be perceived as painful muscle spasms.[20–22] Thus, negative affective states (e.g., anger, sadness) may result from chronic pain and feed back into biobehavioral processes that amplify pain perception and exacerbate suffering.

In turn, negative emotions may increase the urge to use and misuse opioids.[23] In that regard, chronic pain patients may misuse opioids to self-medicate[24,25] the negative affective states and autonomic arousal that cause, co-occur with, or result from pain.[26] In addition to these affective factors, like other addictive behaviors, the appetitive drive to engage in opioid misuse involves implicit neurocognitive operations that promote craving and aberrant drug taking.[27,28] Repeated substance misuse is thought to establish drug-use action schemas, i.e., memory structures that compel and coordinate consumption of the substance through automatized sequences of stimulus-bound, context-dependent behavior, including the biasing of attention towards substance-relevant cues and consequent initiation of drug-seeking behaviors.[29,30] In other words, external (e.g., the sight of a pill bottle) and internal (e.g., pain, stress) cues associated with past episodes of opioid use come to automatically and preferentially capture attention. This phenomenon, known as addiction attentional bias (AB), can be measured with a computer-based behavioral test, has been established for multiple drugs of abuse (alcohol, cocaine, heroin), and has been associated with increased craving and substance use.[31] Recent research in my laboratory provided the first evidence of an AB towards prescription opioids among chronic pain patients meeting DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders*, fourth edition) criteria for prescription opioid dependence.[32] In this study of chronic pain patients taking long-term prescription opioids, opioid-dependent patients exhibited significantly greater opioid AB than nondependent opioid users, and opioid AB scores were correlated with stronger craving for opioids.

When cues associated with past opioid use capture attention, they may trigger dopamine release and activate habitual drug-use routines subserved by neuroplastic alterations to cortico-limbic-striatal circuits.[33,34] In this respect, addictive opioid use results from cue-elicited neurobehavioral habits that can operate in the absence of pharmacologic reward or conscious decision-making.[35] Thus, although chronic use of opioids may produce limited

analgesic effects, once the habit of opioid misuse has been established, it may continue despite countervailing health, social, and legal reasons to adhere to the prescribed medication regimen. In other words, whether or not opioid use works to relieve pain (or even produces hyperalgesia), it may persist as an ingrained habit triggered by sensations of pain and external drug-related cues that were originally imbued with motivational salience during the acquisition of the habit of opioid use.[36]

Furthermore, theory suggests that addictive drug use occurs when the appetitive drive to obtain natural rewards is reorganized around seeking drug-induced reward and the desire to alleviate dysphoria induced by withdrawal and aversive experiences (e.g., pain and stress).[37,38] Concomitantly, opioid dependence is associated with impaired processing of natural rewards, such that as individuals become increasingly dependent on opioids, they experience less pleasure from natural rewarding stimuli in the environment.[39–42] Decreased responsiveness to natural rewards observed among opiate-dependent individuals[43] is robustly predictive of future opiate consumption.[44] As such, persons afflicted with pain and negative affect may find their attention involuntarily drawn towards opioids, motivating them to consume higher doses to achieve hedonic equilibrium as natural rewards become less pleasurable. This insidious process can ensnare the individual in a downward spiral that ultimately results in opioid hyperalgesia, unremitting pain, and severe opioid addiction.

TARGETING COGNITIVE-AFFECTIVE MECHANISMS OF CHRONIC PAIN AND OPIOID MISUSE WITH MINDFULNESS-ORIENTED RECOVERY ENHANCEMENT

In light of the complex network of processes outlined above, multimodal interventions are needed to target the manifold links in the risk chain underpinning chronic pain, prescription opioid misuse, and addiction. Novel therapies that can facilitate top-down cognitive regulation of pain-related emotional reactivity and enhance positive affect while reducing pain severity and functional impairment may be especially efficacious adjuvants for chronic pain. At the same time, treatments that target and undo habit-learning mechanisms by strengthening cognitive control may be needed to address the habitual behavioral routines that may develop in the transition from opioid use to misuse and addiction. In these ways, Mindfulness-Oriented Recovery Enhancement (MORE),[45] a new multimodal behavioral intervention that integrates techniques from mindfulness training, cognitive-behavioral therapy (CBT), and principles of positive psychology into a comprehensive mental training program, may be an especially effective complement to opioid pharmacotherapy, with the potential to reduce opioid seeking and misuse.

MORE is centered on mindfulness training—a mental discipline rooted in ancient contemplative traditions that has been translated into modernized and secularized interventions for stress-related conditions. Mindfulness training involves meditative practices designed to foster a nonjudgmental, present-oriented state of awareness in which the practitioner observes thoughts, emotions, and body sensations without reacting to them negatively. The *practice* of mindfulness involves sustaining attention on an object (e.g., the sensation of breathing; sensation of the body's internal state; the sensation of walking) while the practitioner alternately acknowledges and releases distracting thoughts and emotions. As mindfulness practice deepens, a state of metacognitive awareness is cultivated wherein mental contents and difficult experiences (such as the experience of pain) are allowed to arise unperturbed without suppression or distraction while the practitioner maintains the perspective of a dispassionate observer. By instructing patients in these attentional strategies, mindfulness-based therapies have been shown to strengthen the cognitive regulation of attention and emotion[46] and thereby reduce anxiety and depression.[47]

Prior studies have demonstrated that mindfulness training interventions can decrease pain catastrophizing[48] and reduce pain severity.[49–51] Clinical research suggests that mindfulness training decreases pain by attenuating emotional reactivity to distressing thoughts and emotions and by shifting attention from the emotional to the sensory aspects of the pain experience.[48] These changes may parallel increased activation in brain regions such as the anterior cingulate cortex and anterior insula observed among mindfulness meditators during experimental pain stimulation.[52] Altered function in these brain regions, which are involved in regulating emotional reactions and representing the sensations of the body in conscious awareness, further supports the notion that the pain-reducing effects of mindfulness training may be due to enhanced awareness of bodily sensations coupled with increased regulation of emotional reactions to those sensations. In addition, recent studies indicate that mindfulness training decreases attentional hypervigilance for pain (i.e., pain AB).[53,54] Through mindfulness, chronic pain patients may learn to disengage from negative cognitive appraisals of bodily sensations (e.g., the thought

"This pain is a sign that my health is taking a serious turn for the worse") and reorient their attention to the sensory quality of somatic experience. In so doing, chronic pain patients may come to appraise such sensations as innocuous and eminently manageable.

The mindfulness training component of MORE may also be useful for regulating addictive responses to opioids. Indeed, mindfulness-based interventions have been shown to reduce substance use and craving,[55] and decrease drug-use urges triggered by negative emotions.[56] Moreover, mindfulness training can modify addiction AB and enhance parasympathetic nervous system recovery from stress and addiction-related cues.[57] A recent conceptual review outlined the neurocognitive mechanisms by which mindfulness-centered regulation of addictive behaviors might operate.[58] This review suggested that mindfulness training enhances top-down regulation of limbic-striatal brain circuitry involved in craving and habit responses by strengthening connectivity between prefrontal and parietal brain regions involved in cognitive control and attention. Hypothetically capitalizing on these neural mechanisms, during MORE, participants are taught to refocus their attention on the sensory quality of bodily sensations when craving opioids, similar to the chronic pain technique outlined above. In addition, participants are taught to use mindful attention and awareness to contemplate the consequences of engaging in inappropriate opioid use as a means of reducing addictive behaviors.

In addition to mindfulness, MORE is also centered on reappraisal and savoring techniques drawn from CBT and positive psychology, respectively. Reappraisal, a cornerstone of CBT, is the process of reframing or reinterpreting the meaning of a stressful life circumstance so as to reduce the negative emotional impact of that event.[59] In MORE, patients are taught to reappraise adversity as an opportunity for personal growth or a means of discovering a sense of meaning in life. Prior research demonstrates that reappraisal can significantly reduce substance craving[60] and down-regulate sympathetic arousal.[59] At the same time, MORE teaches patients to mindfully focus their attention on and savor pleasant, healthful experiences (e.g., the sight of a beautiful landscape, the feeling of emotional connection with a loved one) as a means of countering the insensitivity to natural rewards that develops during chronic pain and dependence on opioids. Empirical research suggests that savoring pleasant experiences can significantly increase positive emotions.[61] Moreover, a recent review of a number of basic experimental studies indicates that the induction of positive emotions can produce analgesia to acute, experimental pain,[62] although it is unknown to what extent positive affect analgesia may influence chronic pain.

MORE was tested as an intervention for co-occurring chronic pain and prescription opioid misuse in a recent randomized controlled trial.[63] In this trial, 115 patients who had taken prescription opioids for more than 3 months for chronic pain conditions such as lumbago, cervicalgia, and arthritis were randomly assigned to receive either 8 weeks of a MORE treatment group or 8 weeks of a social support group led by a therapist. More than two thirds of these patients were at risk for opioid misuse, as evidenced by scores on the Current Opioid Misuse Measure (COMM).[25] In the MORE group, participants attended 2-hour-long sessions that involved mindfulness training, group process, psychoeducation, and experiential skill practice. MORE sessions provided instruction in applying mindfulness, reappraisal, and savoring skills to a variety of topics salient to the problem of chronic pain and opioid misuse (Table 1).

Mindfulness training involved mindful breathing and body scan techniques, with an emphasis on developing metacognitive awareness and shifting attention from emotional to sensory processing of pain and craving sensations. Each week, participants were instructed to practice mindfulness, reappraisal, and savoring skills for a total of 15 minutes a day at home guided by a CD. In addition, participants were asked to practice 3 minutes of mindful breathing prior to taking each dose of opioids throughout the day. This purpose of this exercise was to increase awareness of craving for opioids, reveal whether opioid use was motivated by craving versus a legitimate need for relief from pain, prevent unnecessary opioid dosing by providing a nonpharmacologic means of reducing pain, and to synergistically increase the efficacy of opioid analgesia.

Published findings from this randomized clinical trial indicated that MORE led to significant reductions in pain severity ($P = .014$) and pain-related functional interference ($P = .002$) that were maintained for 3 months following the end of the treatment groups.[63] Although the magnitude of changes in pain severity was modest, participation in MORE reduced the impact of pain on daily functioning by nearly one quarter from pretreatment levels of impairment. Following treatment with MORE, participants reported significant reductions in the extent to which pain interfered with their general activity level, mood, normal work, walking ability, relationships, sleep, and enjoyment of life. Furthermore, participants reported significant increases in nonreactivity to distressing thoughts and emotions ($P < .05$), and significant increases in the capacity to reinterpret

TABLE 1. Session Structure of Mindfulness-Oriented Recovery Enhancement for Chronic Pain and Prescription Opioid Misuse

Session	Topic and skills
1	Distinguishing between nociception, pain, and emotional suffering; introduction to the concept of mindfulness and the skill of mindful breathing
2	Enhancing awareness of maladaptive, automatic pain coping habits through mindfulness; introduction to the skill of the body scan
3	Understanding the role of cognitive appraisal in stress, pain, and coping; using mindful reappraisal to interrupt the link between negative emotions and pain; mindful breathing
4	Using mindfulness savoring to reorient attention from stress and pain to refocus on pleasant experiences and positive emotions
5	Understanding opioid dependence and craving; regulating opioid craving through mindful attention and awareness
6	Understanding the link between stress, pain, and opioid craving; decreasing opioid craving through engaging the mindful relaxation response
7	Using mindfulness to accept adversity as an alternative to suppression of emotional and physical pain
8	Developing a plan to continue using skills learned in the group to maintain recovery from pain and opioid misuse

pain sensations as innocuous sensory information ($P < .05$).[63] Crucially, formal statistical mediation analysis revealed that the pain-reducing effects of MORE were mediated by these two potential cognitive-affective mechanisms (Sobel test, Ps $< .05$).[63] These mediational findings are congruent with results from a previous study that indicated that the therapeutic effects of mindfulness training on chronic abdominal pain in irritable bowel syndrome were mediated by increased nonreactivity and reinterpretation of pain sensations.[48] The replication of these results across two distinct studies with different chronic pain samples provides strong evidence that mindfulness may decrease pain by reducing emotional reactivity and fostering sensory versus affective processing of pain sensations.

With regard to opioid-related outcomes, MORE was found to significantly decrease the desire for opioids (i.e., opioid craving) at posttreatment ($P = .02$).[63] Furthermore, a significantly greater proportion of participants in the MORE group no longer met criteria for prescription opioid use disorder (as indicated by a cutoff on the COMM) following treatment compared with participants in the support group (63% versus 32%; $P = .05$).[63] Participants who reportedly became less reactive to distressing thoughts and emotions following treatment with MORE were less likely to meet criteria for opioid use disorder. In addition, MORE reduced the association between opioid craving and opioid misuse; prior to treatment, opioid craving and misuse were significantly correlated ($r = .53$), whereas following treatment with MORE, opioid craving was uncorrelated with opioid misuse ($r = -.00$).[63] In other words, MORE seemed to reduce inappropriate opioid use that in the past would have been triggered by opioid craving. The effects of MORE on opioid craving and misuse, while robust, were not maintained by 3-month follow-up, suggesting that booster sessions or continued mindfulness homework practice is needed to sustain therapeutic effects on addictive responses. This is perhaps unsurprising, given the fact that most participants had taken opioids on a daily basis for years. Given the chronicity of the opioid use habit, continued practice would likely be required to reverse addiction-related neuroplasticity and preserve behavioral changes in the long term.

Using data obtained from this clinical trial, two other studies have been published to further elucidate the mechanisms by which MORE ameliorate chronic pain and opioid misuse. In one study, MORE was found to significantly reduce pain AB for pain-related images presented for 2000 ms ($P = .001$), and participants who evidenced the largest decreases in pain AB reported the greatest perceived control over pain following treatment ($P = .04$).[53] This study suggested that MORE improves attentional disengagement from pain-related information, and provided the first evidence in the scientific literature that a mindfulness-based intervention can reduce pain AB in the context of a randomized controlled trial. In another published study, MORE was found to significantly reduce subjective reactivity to images of prescription opioids presented in the laboratory, and to enhance autonomic responsiveness to images representing natural rewards (e.g., photos of a sunset, romantic couples, smiling babies, etc.).[64] In this study, MORE led to large, statistically significant decelerations in heart rate ($P = .04$) while participants focused attention on opioid-related, pain-related, and natural reward cues (mean pre-post treatment decrease of 7 beats per minute [BPM] to opioid cues, 7.2 BPM to pain cues, and 9.6 BPM to natural reward cues). Heart rate variability analysis indicated that these heart rate decelerations were driven by increased parasympathetic nervous system activity. Importantly, the effects of MORE on reducing opioid craving were statistically mediated by increased

autonomic responsiveness to natural reward stimuli (Sobel test, $P = .015$), but were not mediated by responses to opioid- or pain-related stimuli.[64] Although additional studies are needed to discern whether changes in reward responsiveness were a result or a determinant of reductions in opioid misuse and craving, this study provides the first evidence that a behavioral intervention can increase physiological sensitivity to reward in a drug-dependent sample, and suggests that MORE may reduce opioid craving by restructuring responsiveness to natural reward.

FUTURE NEUROCOGNITIVE, CLINICAL, AND PSYCHOPHARMACOLOGIC RESEARCH ON MINDFULNESS-ORIENTED RECOVERY ENHANCEMENT

Work in my laboratory is ongoing to investigate other cognitive, affective, and psychophysiological pathways by which MORE may produce therapeutic effects on chronic pain and prescription opioid misuse. As yet unpublished data suggest that MORE increases autonomic flexibility (as evidenced by significantly increased heart rate variability; $P < .05$) during responding to emotional laboratory stimuli. In addition, MORE enhances cognitive control in the context of emotional interference by pain-related images (as evidenced by accuracy on an Emotional GoNoGo task; $P < .05$). New clinical trials are being planned and implemented to investigate the effects of MORE on opioid dosing and misuse, using careful review of prescription history via electronic medical records and triangulated by physician-conducted interviews and urine toxicology screens. If MORE can improve pain management while reducing opioid dosing, this intervention may increase the efficacy of pain pharmacotherapy and prevent associated risks. In that regard, a recent case report from a participant in the aforementioned clinical trial of MORE suggested that mindfulness practice increased the subjective analgesic efficacy of daily opioid dosing.[65] This clinical anecdote requires confirmation via careful psychopharmacologic testing using psychophysical approaches to establish changes in pain thresholds and pain sensitivity under double-blinded opioid and placebo administration during mindfulness practice and a comparable control condition.

Should MORE continue to demonstrate positive effects on chronic pain and prescription opioid misuse in additional, larger-scale efficacy and effectiveness trials, it could be incorporated into a multidisciplinary pain management approach that integrates psychological interventions with pharmacotherapy and physical medicine/rehabilitation. Such an approach might prove to be cost-effective in the long term and reduce adverse consequences of chronic opioid dosing such as overdose, occupational impairment, and addiction. Although research on MORE remains at the early phases of treatment development and pilot testing, and has yet to advance to conclusive efficacy testing in multisite clinical trials, the extant data suggest that this intervention, founded on translation of findings from basic cognitive science and neurobiology into "real-world" clinical applications, may hold promise as a means of disrupting the downward spiral linking chronic pain and prescription opioid misuse.

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