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Treating chronic pain: the need for non-opioid options

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Chronic pain is a prevalent problem that exacts a significant toll on society. The medical system has responded to this issue by implementing pain management services centered on opioid pharmacotherapy. However, for many chronic pain patients, the analgesic efficacy of long-term opioids is limited. Moreover, chronic exposure to opioids can result in opioid misuse, addiction, and risk of overdose. As such, non-opioid treatment options are needed. This article first provides a selective review of cognitive, affective, and psychophysiological mechanisms implicated in chronic pain to be targeted by novel non-opioid treatments. Next, it briefly details one such treatment approach, Mindfulness-Oriented Recovery Enhancement, and describes evidence suggesting that this intervention can disrupt the risk chain linking chronic pain to prescription opioid misuse.

According to a report by the US Institute of Medicine, chronic pain (broadly construed in this report to include persistent pain in the low back, neck, knees, shoulders, fingers and hips) afflicts more patients than heart disease, diabetes and cancer combined [1]. Estimates of low back pain (the most prevalent chronic pain condition) obtained via surveys conducted in 2009 by the CDC and the National Center for Health Statistics indicate that more than one-quarter of US adults (28.1%) reported low back pain in the past 3 months [1]. Beyond the US prevalence, estimates in Western nations indicate that as many as one-third of the populace is affected by chronic pain conditions; 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 [2]. The scope of this problem is matched by its economic toll: one estimate suggested that in the USA alone, chronic pain results in a loss of $635 billion to medical costs and reduced work productivity each year [1]. However, this estimate encompassed costs from persons with a broad range of conditions including joint pain, arthritis and functional limitations. More focused estimates suggest that spinal pain conditions result in costs of approximately $85.9 billion a year in the US, and that such costs are increasing over time [3].

To treat this often serious and debilitating health issue, opioid analgesics are typically prescribed to chronic pain patients. Although opioids are an effective means of reducing acute pain, unfortunately, these pharmacological agents have a high abuse liability and are potentially toxic in elevated doses. Moreover, placebo-controlled trials indicate that, on average, opioids do not result in clinically significant reductions in chronic pain symptoms [4], and even in cases where opioid analgesia is adequate for the individual patient, analgesic effects are typically not maintained during a course of long-term opioid pharmacotherapy due to pharmacokinetic and pharmacodynamic tolerance [5,6]. Lastly, evidence suggests that among some patients, chronic exposure to opioids can result in hyperalgesia – that is, increased sensitization to the original painful condition and/or development of pain in body regions distal to the original treatment site [7].

Inadequately addressed chronic pain symptoms and physiological tolerance can result in opioid-seeking behaviors

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and opioid dose escalation, which in turn may increase the risk of prescription opioid misuse and addiction [8]. Although the majority of chronic pain patients take opioids as prescribed, a substantial subset of patients are at risk for developing addictive opioid use behaviors; a systematic review of 67 studies concluded that 11.5% of these patients misuse opioids, evidenced by aberrant drug-seeking attempts, use of opioids to self-medicate negative emotions and unauthorized dose escalation [9]. These behaviors present significant risks for overdose, unsafe drug interactions and manifold adverse social, legal and health consequences associated with abuse and dependence on any (licit or illicit) psychoactive drug.

Though long-term exposure to high doses of opioids can be hazardous, addictive and potentially fatal, most chronic pain patients require treatment to enhance their well-being and functioning. As such, novel, nonpharmacological interventions are needed to complement pharmacotherapy and prevent the cycle of behavioral escalation from appropriate opioid use to misuse and addiction. To be optimally effective, nonpharmacological interventions should target the manifold cognitive, affective and psychophysiological mechanisms implicated in chronic pain. Next, a selective review of a number of such mechanisms is presented, followed by a brief discussion of a new, targeted nonopioid treatment approach.

Biopsychosocial mechanisms that undergird chronic pain & increased risk of opioid misuse

Chronic pain is a biopsychosocial phenomenon [10]. While acute pain usually stems from injury and/or disease, in some cases, chronic pain may not be directly linked to an apparent physiological pathology. In these instances, the severity of chronic pain is only weakly or not at all correlated with the extent of actual tissue damage [11,12] and instead becomes a function of psychological and emotional reactions associated with episodes of pain. In this way, the anticipation of pain may result in somatic distress and/or functional impairment comparable to that evoked by the initial painful insult [13], and pain itself may become a pattern of nervous system activity that is partially independent of external noxious stimuli [14]. Similarly, social–emotional pain (such as that experienced during depression, loss or rejection) often embodied [15], and because of their shared neural substrates, may be conflated with the experience of physical pain [16].

Chronic pain arises from peripheral, autonomic, neuroinflammatory and CNS interactions [10,17]. As such, rather than passively receiving nociceptive information from the periphery and viscera, the brain actively regulates nociception by way of interactions between the descending pain modulatory system [18,19] and an array of corticocortical circuits [20]. The descending pain modulatory system attenuates or exacerbates nociceptive input from the spinal cord through a network of cortical, subcortical and brainstem structures including prefrontal cortex, anterior cingulate cortex, insula, amygdala, hypothalamus, periaqueductal gray, rostral ventromedial medulla and dorsolateral pons [21].

Through central–peripheral feedback loops, pain can induce a robustly aversive, emotional reaction that can then exacerbate pain severity and unpleasantness. Depending on how a given episode of pain is cognitively appraised (i.e., interpreted and understood), sensations of pain often lead to emotions of anger, sadness or fear. For example, when individuals catastrophize about pain, they interpret uncomfortable somatic sensations as reflecting the presence of a serious threat to health and well-being; such catastrophic appraisals result in fear of pain and increased functional disability [13,22]. By virtue of corticolimbic circuitry subserving cognitive appraisal and affective processes, negative emotions tune attention toward pain, exacerbate pain unpleasantness and amplify interoception [23,24]. Consequently, when chronic pain patients experience negative emotions due to increased pain or stress, amplified threat processing in the brain primes pain perception [25,26] and biases the interpretation of innocuous somatic sensations as painful [27–29]. In these ways, negative affect results in hypervigilance for and sustained attention to pain, which then increases its aversive quality [30,31]. Further compounding this pathogenic process, negative affect enhances pain-related sympathetic nervous system activation, which can manifest as heightened stress arousal and muscle tension [32–34]. As a result of these cognitive, affective and physiological mechanisms, negative emotional states are both consequences and causes of prolonged pain and suffering.

Unfortunately, opioids do not directly target many of these mechanisms. Rather, opioid agents relieve pain by targeting the descending pain modulatory system – most notably in the periaqueductal gray [35]. Opioids also produce analgesia by reducing sensory evaluation as evidenced by reduced activation in somatosensory cortex and the thalamus [36,37], and by altering neurotransmission in the substantia gelatinosa of the dorsal horn of the spine [38–40]. Other studies demonstrate that opioids reduce pain processing in brain regions that mediate affective dimension of pain – for example, amygdale [41]. Importantly, there is significant genetic variability with regard to the efficacy of opioid analgesia. For instance, melanocortin-1 receptor and catechol-*O*-methyltransferase gene variants affect analgesic responsiveness to opioids [42,43].

In addition to analgesic effects, acute opioid administration causes release of dopamine from the ventral tegmental area to the prefrontal cortex and nucleus accumbens, facilitating opioid-related reinforcement learning [44]. In this way, opioids and opioid-related cues are imbued with incentive salience and come to signal both pain relief and reward [45,46]. Such incentive salience may then drive the urge to consume opioids irrespective of pain. Appetitive reward responses (and concomitant feelings of euphoria) may be more robustly elicited by short-acting than by long-acting opioids with lower abuse liability (e.g., methadone), though experimental studies indicate that even long-acting opioids may produce euphoria [47].

It is of paramount importance to determine which patients may be at risk for developing addictive opioid use behaviors. Yet, such determinations can only be made with great difficulty among chronic pain patients, who are driven to seek opioids as

a means of pain relief. In that regard, some clinicians believe that the behavioral diagnostic criteria for prescription opioid abuse and dependence are inappropriate for opioid-using chronic pain patients. As an alternative, many pain and addiction specialists use the American Pain Society criteria to identify *prescription opioid addiction* among chronic pain patients including symptoms of impaired control over opioid use, compulsive opioid use, continued use despite harm and craving for opioids [48]. Although prescription opioid addiction is estimated to occur in only 3% of individuals with chronic pain [9] and tends to occur in individuals with substance abuse histories [49], more than one-in-ten patients exhibit opioid misuse behaviors [9], which may presage the transition from appropriate opioid use to addiction [8].

Like other addictive behaviors, the appetitive drive to use and misuse opioids involves neurocognitive operations that compel craving states and consummatory behavior [50,51]. Repeated substance use establishes automatic drug-use action schemas that coordinate consumption of the drug through sequences of context-dependent behavioral responses including the biasing of attention toward drug-related cues (e.g., the sight of an opioid pill bottle, a prescription slip or even the pharmacy where the opioids are dispensed) [52–54]. As such, opioid use may become a habit mediated by structural and functional changes in corticolimbic–striatal circuits [8,55]. As the opioid use habit is entrenched, neural circuitry mediating associations between drug cues and learned appetitive responses become strengthened, while the dopamine system becomes increasingly insensitive to natural rewards like food, sex or social connection, undermining the ability to experience natural pleasure from healthful objects and events [56]. This growing insensitivity to natural pleasure, coupled with physiological tolerance to opioid analgesis, may further entrench chronic pain patients in the cycle of opioid dose escalation in a desperate and futile attempt to achieve a state of well-being.

Nonopioid interventions for chronic pain: the example of MORE

While opioid pharmacotherapies seem to target sensory–emotional processes implicated in pain perception, they may have limited long-term efficacy because they fail to directly target and durably alter dysregulated neural circuits that govern cognitive processes and habit responses elicited by pain, stress and drug-related cues. Consequently, new interventions are needed to effectively address key cognitive–affective mediators of the risk chain from chronic pain to opioid misuse and addiction. There is a great need for novel pharmacotherapies that can substantially reduce chronic pain and pain-related disability without stimulating the mesocorticolimbic dopamine system; yet, at present, no such agents have progressed to late phase clinical trials. Moreover, pharmacological treatments may not modulate cognitive and behavioral habits as effectively as behavioral training interventions, which can be designed to install new, adaptive responses to pain through repetitive practice of coping skills in response to distressing somatic sensations.

Mindfulness-Oriented Recovery Enhancement (MORE) is a novel example of this kind of behavioral intervention [57]. MORE is a cognitive training program that aims to treat chronic pain while reducing the risk of prescription opioid misuse by combining instruction in mindfulness and reappraisal skills with techniques designed to increase natural reward processing. Mindfulness training, that is, the practice of cultivating a state of metacognitive awareness of present moment thoughts, emotions, sensations and perceptions, has been shown to result in reductions in chronic pain symptoms [58], drug craving [59] and attentional and autonomic responses to addictive cues [60]. Similarly, reappraisal, that is, the process whereby one adaptively reframes the meaning of an adverse or emotionally salient experience, has been shown to reduce negative affect [61] and substance craving by activating top-down cognitive control of bottom-up impulses [62]. At the same time, positive emotion regulation through savoring, that is, intentionally focusing attention on pleasant events as a means of increasing positive emotions, may enhance positive affect, reduce anhedonia and promote psychological resilience [63]. Because of the centrality of reward processing in addiction, this latter therapeutic component of savoring may be especially efficacious in reducing appetitive drive for opioids.

Recently, MORE was tested as an intervention for co-occurring chronic pain and prescription opioid misuse in a randomized controlled trial [64]. In this trial, 115 patients who had taken prescription opioids for >3 months for chronic pain were randomly assigned to receive either 8 weeks of MORE or 8 weeks of a social support group (the control condition in this study). Findings indicated that MORE led to significant reductions in pain severity and pain-related functional interference that were maintained for 3 months following the end of the treatment groups. Furthermore, MORE significantly decreased opioid craving and the risk of opioid misuse by at post-treatment. Subsequent analyses of neurocognitive data from the trial revealed several of MORE's potential mechanisms of action; MORE reduced hypervigilance toward pain-related information (pain attentional bias) [65], decreased subjective opioid cue reactivity [66] and enhanced autonomic nervous system responses to images representing natural rewards (e.g., photos of a sunset, romantic couples, smiling babies, etc.,) [66].

Expert commentary & five-year view

Initial results suggest that MORE appears to be a promising, nonopioid option for treating chronic pain and decreasing the risk of opioid misuse. Larger scale randomized controlled trials are needed to provide a definitive efficacy test of MORE and are being planned to be implemented within the next 5 years. Moreover, multimodal interventions that seek to combine cognitiive training regimens with somatic therapies (e.g., physical therapy, massage and/or acupuncture) and novel pharmacological agents may ultimately prove most efficacious in ameliorating the symptoms and adverse consequences of chronic pain. The pain management approach of the future may employ such multimodal interventions at critical periods during the

development of chronic pain. For instance, when a patient presents to a primary care setting with an acute pain condition the clinician might prescribe *both* an atypical opioid or opioid with mixed agonist–antagonist properties *and* participation in an intervention program that involves cognitive training (e.g., MORE) and manual therapy (e.g., exercise training). The clinician could make opioid refills contingent on participation in such a multimodal intervention program. The treatment plan would include a concrete schedule for titrating the patient off of the analgesic medication while simultaneously increasing his/her engagement in meaningful life activities. Elevated or intractable pain symptoms would be addressed through prescription of increased intensities of cognitive training and somatic therapies, rather than through opioid dose escalation. In this way, acute pain episodes might be effectively addressed before becoming entrenched in the nervous system as chronic pain conditions.

In sum, decades of neuropsychopharmacological research on opioids, chronic pain and addiction point to the sobering notion that, for vulnerable individuals, long-term opioid pharmacotherapy may create as many problems as it solves. Alternative methods of chronic pain management are needed that can address the panoply of pathogenic cognitive, affective and behavioral processes underpinning this significant threat to public health and well-being.

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Key issues

- Chronic pain is a prevalent health condition that is often treated with opioids.
- Although opioids can be highly effective in treating acute pain, for many patients, long-term opioid analgesia inadequately addresses the symptoms of chronic pain.
- More than 10% of chronic pain patients are at risk for misusing prescription opioids.
- Chronic pain may be subserved by maladaptive cognitive processes, dysregulated emotional responses and heightened sympathetic nervous system activation.
- Opioids do not directly target the cognitive mechanisms implicated in chronic pain, and due to their effects on the mesocorticolimbic dopamine system, may lead to development of addictive habits.
- Nonopioid treatment approaches for chronic pain might achieve optimal efficacy by integrating cognitive training regimens such as Mindfulness-Oriented Recovery Enhancement with somatic therapies and novel pharmacological agents.

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