Published in final edited form as:

Drug Alcohol Depend. 2015 January 1; 0: 1–6. doi:10.1016/j.drugalcdep.2014.10.023.

Psychophysiology of pain and opioid use: Implications for managing pain in patients with an opioid use disorder

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Abstract

Background—Opioid therapy is one component of an effective pain management regimen for patients with chronic pain and the majority of these patients use their medications responsibly. However, there are a growing number of these patients who develop an opioid use disorder and in some cases require opioid replacement therapy. Managing these patients is complex and the underlying mechanisms of pain and addiction are not well understood. Developing an effective interdisciplinary treatment program for the individual with pain and an opioid use disorder will depend on enhancing our knowledge of the psychophysiology of pain and addiction.

Method—Authors gathered key empirical and theoretical papers examining the psychophysiology of comorbid pain and opioid misuse disorders.

Results—This article reviews the current theory of the effect of pain on patients with pain and concomitant addiction, the psychophysiology of pain, opioid use and addiction, and future research in this area.

Conclusions—Individuals with a history of opioid misuse have greater levels of hyperalgesia which may be due to alterations in psychophysiological pathways. More research is needed into the psychophysiological biomarkers among individuals with comorbid pain and addiction in order to develop better treatment approaches and improve outcomes among this difficult to treat population.

Keywords

pain; opioids; addiction; psychophysiology

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1. INTRODUCTION

Approximately 40% of Americans experience non-malignant chronic or persistent pain (Tsang et al., 2008) and opioid therapy has been a major component of pain management with a historical trend of increased rates of prescribing (Crum, 2006; Gilson et al., 2004). With greater access to opioids there has been a parallel rise in reported cases of misuse and abuse of opioid analgesics (Crum, 2006; Compton and Volkow, 2006) and opioid-related overdose fatalities (Jones et al., 2010). In 2012 it was estimated that 4.9 million individuals 12 years or older were current nonmedical users of pain relievers (SAMHSA, NSDUH, 2013), there were 488,004 emergency department visits related to nonmedical use of opioids in 2011 (SAMHSA, DAWN, 2013) and there were 186,986 admissions to treatment facilities for opioid use disorders (SAMHSA, TEDS, 2013).

A significant proportion of patients requiring treatment for opioid use disorders (OUD) experience pain. For example of the patients with OUDs entering methadone treatment, 80% report recent pain, and 37% report chronic pain (Hser et al., 2001; Prater et al., 2002; Rosenblum et al., 2003). Jamison (2000) interviewed 248 methadone maintenance patients. Sixty one percent of the sample acknowledged experiencing chronic pain. Patients with pain as compared to patients without pain experienced significantly greater physical and mental health problems, higher use of prescription and nonprescription medication and 44% of the patients with pain held the belief that opioids prescribed for their pain led to their opioid use disorder. This and other literature suggests that pain and addiction commonly co-occur. There are two hypotheses on how this pain-addiction comorbidity develops: 1) patients with pain are exposed to opioids as a component of pain management and then develop an OUD; and 2) patients with a prior history of a substance use disorder (SUD) develop subsequent pain syndromes. Both populations may seek treatment for SUD in methadone maintenance programs. Managing pain in patients with SUDs, even for those in methadone maintenance is particularly challenging and most physicians may be reluctant to even attempt treatment. A major barrier to providing pain treatment in this complex patient population is our limited knowledge of the impact of SUD on the emotional and physiological reactivity to pain. Without a clear understanding of the mechanisms of how pain differentially affects those with a history of OUD, we cannot fully develop an effective treatment program. In this paper, we will review the current theory of the effect of pain on individuals with co-occurring OUD and pain, review the psychophysiology of pain, the psychophysiology of opioid use and SUD, and finally examine how pain is experienced by individuals with a SUD.

2. PSYCHOPHYSIOLOGY OF PAIN

Pain is a complex phenomenon with sensory, motivational and affective dimensions. The sensory component, referred to as nociception, is the detection of a noxious stimulus by specialized sensors (nociceptors), which transmit impulses to the spinal cord and brain. The primary neuron cell body is in the dorsal root ganglion or trigeminal ganglion, and synapses with a second order neuron in the spinal cord or brainstem, which further relays signals to the thalamus and eventually to the somatosensory cortex, where the information may be interpreted consciously as pain. It has been postulated that the affective component of pain is

mediated by a parallel system, which also ascends in the spinal cord, projects to the thalamus, and then connects to a number of brain regions thought to be key for emotional experience including the anterior cingulate cortex and the limbic system (Lumley et al., 2011). Pain is also closely linked with activation of the autonomic nervous system, leading acutely to increases in heart rate, blood pressure and cardiac output, preparing the organism to escape from the source of potential physical damage (fight or flight experience).

Persistent pain may be contributed to by central sensitization, a phenomenon of plasticity whereby persistent stimulation, inflammation, or injury leads to changes in the brain and spinal cord that augment pain perception. Sensitization can cause an enhanced response to painful stimuli (hyperalgesia), a response to previously non-painful stimuli (allodynia), or even spontaneous pain. The affective pathways of pain perception are often dysregulated in persistent pain conditions, contributing to a complex cyclical interaction where fear and anxiety, emotions initially important in a defensive response, amplify pain, which then creates anticipatory anxiety, distress, and suffering. To further complicate the picture, previous life experiences such as history of trauma or stressful life events may also modify perception of pain (Lumley et al., 2011).

Pain perception may be characterized by multiple different measurements. Pain threshold is defined as the level of noxious stimulus that is needed for the individual to identify the stimulus as “pain.” Pain tolerance is the amount of time an individual can withstand painful stimuli prior to seeking to escape or reduce the pain experience. Pain sensitivity is how painful the individual rates a stimulus, often on a 0–100 or 0–10 scale. Opioid induced hyperalgesia is closely related to these pain measurements; in the context of opioid use an individual experiences a decrease in pain threshold and/or an escalation in pain sensitivity in response to noxious stimuli.

One may argue that the experience of pain is so subjective that it cannot be studied experimentally. However, Brown (2011) demonstrated that fMRI supported by a machine learning algorithm can accurately assess pain in the absence of self report. In addition, several experimental models have been developed to objectively study psychological and physiological aspects of pain. These models include the electrical stimulation test, the mechanical pressure test, the heat tolerance test, the ischemic pain test, and the cold pressor test (Krishnan et al., 2012). Of these, the cold pressor test has been proposed to best mimic the qualities of chronic, aching pain, such as back pain, orofacial pain and osteoarthritis, and appears to be the most applicable method of detecting the effect of opioids on pain (Krishnan et al., 2012; Chen et al., 1989). In the cold pressor test, a subject’s arm is placed first in a warm water bath, and then into an ice-water bath. A blood pressure cuff is used to minimize blood flow to the immersed hand. The subject indicates when he or she first feels pain (pain threshold), and then when the pain is no longer tolerable (pain tolerance). Autonomic sympathetic responses such as increased heart rate, blood pressure, galvanized skin response, and muscle tension are correlated to pain severity during the cold pressor test (Petrovic et al., 2004; Peckerman et al., 1994; Schachter et al., 1957; Schneiderman et al: 2000).

Using the cold pressor test as a tonic pain model, Chen (1989) divided 205 subjects into pain sensitive and pain tolerant groups based on length of time the subjects could tolerate the cold water, and examined several psychological factors correlated with pain sensitivity. For the pain sensitive, but not pain tolerant group, pain perception was significantly associated with the level of state anxiety, “absorbance” (perceptual style), and the level of fear. In effect, subjects who were more sensitive to pain also had more situational anxiety and fear. Interestingly, they found that for pain sensitive individuals 36% of the variance in pain score could be predicted by the psychological factors. Thus, the multidimensional aspects of pain may be explored experimentally.

While research in the clinical setting is not as extensive and sensitive as in experimental induction of pain, the phenomenon of opioid induced hyperalgesia has been explored in postoperative patients. During significant abdominal surgery in non-opioid dependent patients, half of the participants were given large intra-operative dosages of a short acting opioid. Patients and post-operative staff were blinded to patient group status. The investigators measured post-operative pain levels and morphine use. Patients who received the short acting opioid during surgery experienced post-surgical opioid induced hyperalgesia and required significantly higher doses of morphine to control post-operative pain (Guignard et al., 2000).

It is important to note that physiological reactivity to pain is not static. It can be altered by external factors (e.g., environment, socioeconomic status) and internal factors (e.g., mood, cognitive focus). Even more importantly, psychoeducation and training can effectively alter an individual’s psychophysiological response to pain (Wachholtz and Pargament, 2005, 2008). In a study on modifying pain psychophysiology, sixty healthy adults were randomly assigned to self-regulation (SR) /meditation groups and taught a SR technique to practice over 2 weeks. Pre-post assessments included psychological (mood, affect, anxiety, pain self-efficacy), physiological (heart rate, blood pressure), and objective (duration of pain contact) assessments in response to a cold pressor pain task. This study found that a physiological response to pain does not always correlate with the psychological response and provides unique insight into psychophysiological distress tolerance. Further, with only two weeks of SR training and practice, healthy individuals can decrease psychophysiological pain reactivity (Wachholtz and Pargament, 2005). In a chronic pain population, this process may take longer (Wachholtz and Pargament, 2008), but self-regulation training can still alter pain psychophysiological reactivity in a relatively short period of time. Likely these observed changes in reactivity are mediated by changes in the underlying neurobiology reflective of plasticity.

3. PSYCHOPHYSIOLOGY OF OPIOID USE

Opioids have been employed for a millennium to reduce both physical and psychological pain. In recent years, the mechanism by which opioids exert their anti-nociceptive effect during short-term use has become clearer. At a molecular level, opioids bind to G-protein coupled receptors in the brain and spinal cord. Signaling through opioid receptors results in a variety of secondary effects including decreased exocytosis of excitatory amino acids and neuropeptides, and hyperpolarization of post-synaptic neurons leading to decreased

transmission of nociceptive signals from the periphery to the dorsal horn of the spinal cord. Opioids also act centrally to limit our awareness of noxious stimuli (Ossipov et al., 2004). Opioid administration results in decreased blood pressure, heart rate, drowsiness, increased smooth muscle tone, and, at high doses sedation and respiratory depression. In addition to their analgesic effect, acutely opioids can have anxiolytic qualities, cause euphoria, and increase tolerance to distress. It has also been postulated that since both endogenous opioids (endorphins, enkephalins) and exogenous opioids interact with the serotonergic system, they can produce a pronounced antidepressant or hedonic effect (Berrocoso et al., 2009).

A well-known consequence of prolonged opioid use is tolerance, or need for increased doses of the drug over time to provide the same therapeutic effect. This is thought to be caused by down regulation of opioid receptors (a normal, homeostatic response to prolonged receptor agonism from an exogenous ligand). Another common effect of chronic opioid exposure is withdrawal, caused by abruptly discontinuing or lowering the dose of the drug. Patients may experience a flu-like state with muscle aches and pain, abdominal cramping, and sympathetic hyperactivity, along with fatigue and dysphoria.

Distinct from tolerance and withdrawal is the phenomenon of opioid-induced-hyperalgesia, defined as increased sensitivity to pain as a consequence of opioid use. Hyperalgesia occurs in the absence of the underlying disease progressing or opioid withdrawal. Whereas escalating the dose of opioid may provide pain relief in tolerant patients, it can worsen pain in patients with hyperalgesia. The molecular mechanisms of hyperalgesia are still poorly understood, with most mechanistic studies performed in animals. Proposed mechanisms include mechanisms consistent with central sensitization such as increased activation of NMDA (N-methyl-D-aspartate) receptors leading to sensitization of spinal neurons, activation of descending pathways from the brain stem, and the ascending pathways in the dorsal horn of the spinal column (Angst and Clark, 2006).

Clinical studies have shown that hyperalgesia may develop as soon as a month after initiation of short acting opioids. A small study examined the trajectory of pain and opioid tolerance among chronic low back pain patients who were initiated on steady-state short-acting (prn) oral opioids for chronic pain treatment. Within one month, all of the patients with pain on this regimen showed both hyperalgesia and opioid tolerance during testing (Chu et al., 2006). A subsequent experimental pain study utilizing a long-acting opioid preparation found that hyperalgesia but not tolerance could be prevented (Chu et al., 2012). The extent to which the results of this study and others using experimental methods can be extrapolated to chronic pain patients in the clinical setting is not known.

While some types of opioid medications have been shown to be more likely to create opioid-induced hyperalgesia (e.g., remifentanyl) and some non-medication interventions have been explored (e.g., use of NO₂ during surgery) there are few studies on patient-dependent variables that affect the likelihood of developing hyperalgesia (Lee et al., 2011; Martinez and Fletcher, 2012). Clearly there are a number of questions that still need to be answered about the relationship between opioid tolerance and opioid-induced hyperalgesia (Richebe et al., 2012).

A certain percentage of patients using opioids for pain will develop an OUD with the estimated percentage ranging anywhere from 1% to 40% depending on the criteria used to define an OUD (Fishbain et al., 2008; Reid et al., 2002; Katz et al., 2003; Ives et al., 2006; Martell et al., 2007). Patients may also engage in problematic drug seeking behavior estimated as occurring in 3% to 62% of patients with pain receiving long-term opioid therapy (Martell et al., 2007; Ballantyne and LaForge, 2007; Webster and Webster, 2005; Fleming et al., 2008). There has been a great deal of confusion in rendering an accurate diagnosis of “addiction” in patients with pain receiving long term opioid therapy (Heit, 2003; Cheattle and O’Brien, 2011). The *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, DSM-IV-TR, 2000) was the gold standard for diagnosing “dependence” (addiction) and outlined seven criteria including tolerance and dependence which occur naturally in patients using opioids long term and not necessarily reflective of addiction thus potentially leading to misdiagnosis in this patient population. The recently published DSM-5 (American Psychiatric Association DSM-5, 2013) has mitigated some of these issues by eliminating the terms abuse and dependence and instead using OUD with mild, moderate and severe designations. Furthermore the criteria of tolerance and dependence are excluded in the diagnostic formulation if the patient is taking opioids under medical supervision. The liaison committee on pain and addiction with representation from the American Pain Society, American Academy of Pain Medicine and the American Society of Addiction Medicine (Savage et al., 2003) defined addiction using the “4 Cs”: “behaviors that include one or more of the following: impaired Control over drug use, Compulsive use, Continued use despite harm, and Craving”. In addiction, patients experience profound negative emotional symptoms during abstinence, including extreme dysphoria, irritability, anxiety, emotional pain, and preoccupation with obtaining opioids (craving). The severity of the negative symptoms leads to anticipatory craving—a drive to avoid the dysphoria and emotional distress experienced during withdrawal and abstinence. Whereas initially the drug may have provided euphoric effects and reward, over time, the drug is taken to avoid the negative consequences. This change is mirrored in the underlying brain structures thought to mediate reward. The function of the reward system becomes impaired, with decreased dopamine and endogenous opioid activity in the reward centers of the brain. Simultaneously, there is increased activity in the amygdala, the brain stress/fear system.

Shurman (2010) has hypothesized that addiction and hyperalgesia may share the same neural substrate: the central nucleus of the amygdala, which is implicated in processing emotional components of pain perception, and also may be responsible for negative emotional responses to abused drugs. In addition, exogenous administration of opioids likely affects regulation of endogenous opioids which are important regulators of pain and mood. Thus, in a patient suffering from SUD, one might predict that perception of pain and reactivity to pain would be altered.

4. PAIN AND THE BRAIN IN ADDICTED PATIENTS

Studies of pain perception in patients with SUD are still in early stages. Most studies in patients with SUD measure two variables, specifically, threshold to feeling pain, and intensity of pain. Utilizing the experimental model of the cold pressor test, in a small study

(16 patients per group) comparing methadone maintained patients to healthy controls, methadone patients showed significantly greater sensitivity and less tolerance to cold pressor pain during trough methadone levels, and less tolerance during peak methadone levels when compared to controls (Doverly et al., 2001a). Patients on methadone maintenance in this study were considered to be hyperalgesic to cold pressor pain. In later studies using similar methods, the same investigators found that methadone maintenance patients are cross-tolerant to the antinociceptive effects of morphine. They also continued to detect pain earlier and have less tolerance to pain in the cold pressor test after receiving a conventional dose of morphine, despite having significantly higher plasma levels of morphine than controls (Doverly et al., 2001b). Athanasos (2006) discovered that even very high morphine doses (55mg, almost 5 times the effective dose for healthy controls) failed to significantly change pain tolerance for methadone patients, even though the dose did result in some respiratory depression. A larger study randomized 82 treatment-seeking heroin-dependent adults to treatment with either methadone or buprenorphine, and compared pain responses prior to treatment, during initiation, and during maintenance, asking if either therapy resulted in decreased hyperalgesia over time. They found that prior to starting therapy, patients with an OUD were hyperalgesic, and maintenance therapy with either methadone or buprenorphine did not significantly change tolerance or sensitivity to pain over the 12–18 week course of the study (Compton et al., 2012). Even previously heroin dependent patients who are then abstinent for months may remain hyperalgesic (Compton et al., 2012; Ren et al., 2009; Wachholtz and Gonzalez, 2014). Although the above studies clearly show that patients with a history of OUD maintained on opioid substitution therapy are more sensitive to pain, they do not provide any measures of psychological markers related to pain, and little insight into a physiological mechanism.

In a study reminiscent of early psychophysiological studies, Ren (Ren et al., 2009) evaluated 54 subjects with a history of OUD who were abstinent for greater than 5 months and 46 healthy controls, and demonstrated that pain sensitivity and drug craving were linked. The subjects with a history of OUD were exposed to drug related cues (to induce craving), and then both groups were subjected to the cold pressor test. They measured pain tolerance (time able to withstand the cold water), pain intensity (rated by visual analog scale), pain distress, cue-related craving, and cue-related anxiety. As a group, the subjects with a history of OUD had less pain tolerance than controls (as expected), but no difference in pain intensity ratings. They did have more distress, implying that pain distress (affect) could be dissociated from pain intensity. Pain distress, but not intensity, was correlated with degree of craving induced by the drug related cues in the OUD subjects. In addition, when they divided the abstinent subjects into pain sensitive and pain tolerant groups, the pain sensitive subjects had more cue-induced craving for drug than pain tolerant subjects. Thus pain sensitivity was correlated with experience of craving, a key component of addiction.

Supporting the hypothesis that pain perception and SUD share similar neural pathways and are closely linked, untreated or undertreated pain is a critical factor in relapse. Individuals with comorbid pain and OUD are 3–5 times more likely to relapse than those with opioid use disorder but no pain (Larson et al., 2007).

5. POTENTIAL TREATMENTS

There is greater recognition of the burgeoning prevalence of comorbid OUD and chronic pain. As a result, it is critical to develop more efficacious and effective interventions for this difficult to treat population. While as a field, we can speak somewhat knowledgeably about the psychophysiology of pain and the psychophysiology of SUD, and have developed treatments for the individual disorders, treating the comorbidity adds increased complexity. As such, each issue is often treated separately, rather than in an integrated treatment (Cheatle and O'Brien, 2011; Currie et al., 2003). There have been a few promising attempts at pharmacological treatment of hyperalgesia in OUD patients including gabapentin, alpha 2 agonists, and long acting opioid preparations (Compton et al., 2010). However, effects of pharmacological treatments so far have been modest. Even treatment with opioid maintenance for pain among those with an OUD history continues to be a controversial topic (Gonzalez et al., 2004) due to concerns that long-term opioid maintenance enhances hyperalgesia (Doverty et al., 2001b).

Sole reliance on medication management to treat these complex cases is controversial (Collins and Streltzer, 2003), and there is a need to provide both pharmacologic and non-pharmacologic (cognitive behavior therapy, support groups, activating physical therapy etc) treatments to support patients to enter and maintain recovery in the context of concomitant OUD and pain. There are few empirically validated psycho-social protocols to address this complexity; however multiple protocols are in development. Some of the psychosocial treatments that show promise include motivational interviewing, cognitive behavioral therapy, self-regulation therapy, group and interpersonal therapy, acceptance and commitment therapy among others. It is hopeful that as these protocols develop and are empirically validated, there will be more options for clinicians seeking to treat this complex treatment population. While it is important to begin developing efficacious interdisciplinary treatment protocols, it is also critical that we understand the unique psychological and physiological issues that are inherent to this patient group.

6. CONCLUSION

While there are still a number of questions that need to be answered regarding the complex relationship between opioid use, hyperalgesia, and tolerance, there is persuasive research that individuals receiving opioid maintenance therapy have greater levels of hyperalgesia. Further research is needed to determine what changes in the psychological or physiological indicators of pain among those on opioid maintenance therapy. It is also unclear how physiological biomarkers of pain differ among partial versus full mu-opioid agonist maintained patients, those in sustained abstinence from opioid use, or healthy controls. Lastly, yet to be identified is how exactly opioid induced hyperalgesia is related to dysfunction in the neural circuits moderating the affective component of the pain experience (Melzack, 1999). Machine-learning supported fMRI may be one method to start to address these unknowns (Brown et al., 2011).

A better understanding of these issues would allow us to identify the best pathways to address pain in opioid agonist maintained patients and among patients with a remote history

of OUD. Identifying the distinctive psychological and physiological aspects of pain reactivity amongst individuals with an OUD would foster the development of novel, new integrated treatments to improve outcomes in these complex patients.

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Highlights

- Managing patients with comorbid pain and opioid use disorder is complex and the underlying mechanisms of pain and addiction are not well understood.
- Authors reviewed key empirical and theoretical papers examining the psychophysiology of comorbid pain and opioid misuse disorders.
- Individuals with a history of opioid misuse appear to have greater levels of hyperalgesia due to alterations in psychophysiological pathways.
- Developing an effective interdisciplinary treatment program for the individuals with pain and an opioid use disorder will require thorough knowledge of the psychophysiology of pain and addiction.