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Review

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.

Contents

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, 2013a), there were 488,004 emergency department visits related to nonmedical use of opioids in 2011

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(SAMHSA, 2013b) and there were 186,986 admissions to treatment facilities for opioid use disorders (SAMHSA, 2013c).

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 et al. (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 et al. (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, 1957; Schneiderman et al., 2000).

Using the cold pressor test as a tonic pain model, Chen et al. (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