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Co-morbid pain and opioid addiction: Long term effect of opioid maintenance on acute pain

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ABSTRACT

Introduction: Medication assisted treatment for opioid dependence alters the pain experience. This study will evaluate changes pain sensitivity and tolerance with opioid treatments; and duration of this effect after treatment cessation.
Method: 120 Individuals with chronic pain were recruited in 4 groups ($N = 30$): 1-methadone for opioid addiction; 2-buprenorphine for opioid addiction; 3-history of opioid maintenance treatment for opioid addiction but with prolonged abstinence ($M = 121$ weeks; SD = 23.3); and 4-opioid naïve controls. Participants completed a psychological assessment and a cold water task including, time to first pain (sensitivity) and time to stopping the pain task (tolerance). Data analysis used survival analyses.
Results: A Kaplan–Meier–Cox survival analysis showed group differences for both pain sensitivity (log rank = 15.50; $p < .001$) and tolerance (log rank = 20.11; $p < .001$). Current or historical use of opioid maintenance resulted in differing pain sensitivity compared to opioid naïve (p's < .01). However, tolerance to pain was better among those with a history of opioid maintenance compared to active methadone patients ($p < .05$), with the highest tolerance found among opioid naïve control group participants (p's<.001). Correlations within the prolonged abstinent group indicated pain tolerance was significantly improved as length of opioid abstinence increased ($R = .37$; $p < .05$); but duration of abstinence did not alter sensitivity (ns).
Conclusion: Among individuals with a history of prolonged opioid maintenance, there appears to be long-term differences in pain sensitivity that do not resolve with discontinuation of opioid maintenance. Although pain sensitivity does not change, pain tolerance does improve after opioid maintenance cessation. Implications for treating co-morbid opioid addiction and pain (acute and chronic) are discussed.

1. Introduction

Recent years have seen increasing recognition of the critical intersection between opioid addiction and chronic (non-malignant) pain. However, despite the increased interest in this topic, there is little known about the psycho-physiological links between opioid addiction and pain and extremely few empirically validated treatments (Wachholtz et al., 2011a,b).

Approximately one half to one third of Americans experience non-malignant chronic or repeating pain (Elliott et al., 1999; Tsang et al., 2008) and opioid prescribing to treat pain is on the rise (Crum, 2006; Gilson et al., 2004). There is a simultaneous rise in reported cases of abuse, or mis-use of opioid analgesics (Compton and Volkow, 2006; Crum, 2006; Drug Abuse Warning Network, 2004) with estimates of pain-related opioid abuse/addiction up to 50% (Boscarino et al., 2011; Højsted and Sjøgren, 2007; Ives et al., 2006; Reiger et al., 1990). Boscarino et al. (2011) estimate that lifetime prevalence for opioid abuse disorders among chronic pain patients is approximately 35% across both DSM-4 (35.5%) and DSM-5 (34.9%)diagnostic criteria. Longitudinal research has provided a clear picture of the negative effects of opioid abuse (Hser et al., 2001). In a study of almost 400 patients with opioid addiction entering methadone treatment, 80% reported recent pain, and 37% of patients reported chronic pain (Rosenblum et al., 2003). Of those with pain, 65% described the pain as severe or moderately severe. Comorbid pain and addiction patients also report abusing illegal drugs, alcohol, or prescription medications to treat their pain (Brands et al., 2004; Cheatle and Gallagher, 2006). The frequency of comorbid pain and opioid addiction necessitates a better understanding of the psycho-physiological links between pain and opioid

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addiction, and the need to provide empirically validated treatment options.

For the purposes of this study, we will use the terms for addiction and pain as agreed upon by the Liaison Committee of Pain and Addiction. This combined working group of experts from the individual fields of pain and addiction defines addiction as "behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving" (Savage et al., 2003). The International Association for the Study of Pain defines pain as, "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (IASP Task Force on Taxonomy, 1994). It should also be noted that the recent release of DSMV has included new diagnostic criteria for "Opioid Use Disorder." While this criteria was not directly used in the conceptualization or patient diagnosis for this study, the newly released diagnostic criteria should be acknowledged as providing novel diagnostic criteria and a new way to conceptualize problematic opioid use.

Opioid addiction and pain reactivity is still in the early stages of research. Even treatment with opioid maintenance for pain among those with a opioid addiction history continues to be hotly debated (Gonzalez et al., 2004), due to concerns that long-term opioid maintenance enhances hyperalgesia (Doverty et al., 2001a,b). Animal studies exploring potential physiological mechanisms for the hyperalgesia have ranged from genetics, to specific NMDA or glutamate pathways, to descending pathways from the brain stem and the ascending pathways in the dorsal horn of the spinal column (Angst and Clark, 2006). Even environmental effects creating associative hyperalgesia, thought to be partially moderated by NMDA receptors, have received recognition as influencing hyperalgesia (Angst and Clark, 2006). Because of concerns that patients will resume addiction behaviors if opioid analgesics are administered in response to acute pain, there is a great debate in the literature about treating acute pain with opioid analgesics for individuals with an opioid addiction history (Wachholtz et al., 2011a). There is also little recognition of how hyperalgesia affects the treatment of acute pain among patients with a history of addiction to opioids (Collins and Streltzer, 2003; Lee et al., 2011). As a result, there is a limited understanding of opioid addiction related hyperalgesia in the treatment literature, and limited awareness of the psychological and physiological aspects that inform the pain experience in individuals with a history of opioid addiction.

Psychological and medical science has an extremely limited understanding of the impact of opioid mu-agonist maintenance therapy (e.g., buprenorphine or methadone) on the emotional and physiological reactivity to pain. If we do not understand how pain differentially affects those with a history of opioid addiction, how can we begin to treat it? Some earlier work has shown that individuals using chronic opioid maintenance treatment or recently abstinent from opioids show diminished pain tolerance compared to healthy controls (Compton et al., 2001; Pud et al., 2006). However, research into how maintenance doses of opioids for individuals with co-morbid chronic pain is lacking, as is any further information as to how individuals with a co-morbid pain and opioid use react psychologically and physiologically to pain.

Opioid maintenance treatment for opioid addiction (e.g., buprenorphine or methadone) alters the pain experience among individuals with co-morbid chronic pain. The current study seeks to begin to fill this gap in the scientific literature. The purpose of this study is to evaluate differences in pain sensitivity and tolerance among individuals with co-morbid pain and opioid addiction treated with methadone, and buprenorphine; and to assess whether this effect remains after treatment cessation.

Participants engaging in opioid maintenance treatment for opioid addiction with co-morbid chronic pain will have increased pain reactivity (physiological, behavioral, and psychological) compared to those with a history of treatment for opioid addiction with chronic pain who have sustained abstinence (6+ months), but currently without opioid assisted treatment, and compared to opioid naïve controls (those with chronic pain were considered opioid naïve if they have less than one month of cumulative lifetime history of PRN opioid use and no history of opioid abuse).

2. Method

One hundred and twenty individuals with history of non-malignant chronic pain and currently rating pain over 54.3. (SD = .91) in scale 0 to 100 were recruited in 4 groups ($N = 30$): (1)-current methadone for opioid addiction; (2)-current buprenorphine for opioid addiction; (3)-history of opioid maintenance for opioid addiction but with current prolonged abstinence of opioids ($M = 121$ weeks; SD = 23.3); and (4)-opioid naïve. Participants completed a psychological assessment and a cold water pain task. Time to first pain report (sensitivity) and time to disengagement from the pain task (tolerance) were recorded. The main data analyses used survival (time to event) analysis. Diagnoses were confirmed by DSM-IV criteria via IGD interview (Zimmerman, 1994) and urine drug screen verifying no drug abuse within the past 72 h.

2.1. Measures

Immediate craving: 0–100 Subjective rating of current craving intensity.

Pain rating: 0–100 Subjective pain rating of the cold pressor task.

Pain sensitivity: Duration of contact with the cold water until the participant reports the first experience of pain.

Pain tolerance: Duration of contact with the painful stimuli. Pain tolerance will be the observed time that participants maintain the placement of their hand in the cold water up to the wrist. Maximum time allowed 300 s.

General pain levels: The SF-36 (Brazier, 1992) is a 36 question survey assessing 8 subscales (physical functioning, role limitations due to physical issues, role limitations due to emotional issues, energy/fatigue, emotional well-being, social functioning, pain, and general health). For the purposes of this study, we used the pain subscale. Scoring measures the domain on a 0–100 scale with higher score indicating greater endorsement of that subscale.

Desires for drug (DDQ): The DDQ is a 14-question survey (Franken et al., 2002) that covers three drug craving domains (desire and intention; negative reinforcement; control). Each question is answered on a 1–7 Likert scale and summed within each domain with higher scores indicating greater endorsement of that subscale.

2.2. Procedures

Recruitment: Participants with a history of opioid dependence and non-malignant chronic pain were recruited from methadone and buprenorphine treatment centers, and Narcotic Anonymous groups. No participants were being treated solely with an opioid antagonist treatment (e.g., naltrexone) without an opioid agonist. Additionally, healthy community participants with non-malignant chronic pain were recruited via advertising on radio, and public access TV, and flyers posted in public venues. Participants received $20 for the one hour study. Potential participants were screened by telephone to determine eligibility. Eligible participants received an appointment for the in lab study. Immediately after signing the informed consent, participants completed urine drug screens to be cleared for inclusion in the study, reported their current pain severity, location and functional impact. All procedures were approved by the UMass Medical School IRB.

Pre-test assessment: At pretest, participants completed a survey packet that included a demographic questionnaire, the Desire for Drug Questionnaire, and SF-36 (Franken et al., 2002).

Pain task: After the pre-test assessment, participants placed their dominant hand up to the wrist in cold water (2 °C). They were instructed to let the assessor know when they first experience pain and to keep their hand in the water "until it is too painful" at which point they would remove their hand.

Post-test assessment: After the pain task, subjects completed another survey packet including a report of the level of pain they experienced during the cold pressor task, and assessment of their current craving for opioids in a Likert scale and Desires for Drug Questionnaire.

Debriefing: If patients reported an escalated craving level a therapeutic talk down intervention was provided.

2.3. Data analysis

Variables from the current and past opioid maintained participants and opioid naïve controls were compared across the four groups using MANOVA and, as appropriate, LSD post hoc tests. Kaplan- Meier time-to-event analysis, and follow up Cox analyses were used to evaluate group differences on pain sensitivity and pain tolerance. A Pearson R correlation was also used to assess relationship between pain variables and duration of opioid abstinence among the prolonged abstinent group. Data analysis was completed using SPSS v.21.