



Published in final edited form as:

Drug Alcohol Depend. 2016 September 1; 166: 26–31. doi:10.1016/j.drugalcdep.2016.06.024.

Chronic pain, craving, and illicit opioid use among patients receiving opioid agonist therapy

Judith I. Tsui^a, Marlene C. Lira^b, Debbie M. Cheng^c, Michael R. Winter^d, Daniel P. Alford^{b,e}, Jane M. Liebschutz^{b,e,g}, Robert R. Edwards^f, and Jeffrey H. Samet^{b,e,g}

^aSection of General Internal Medicine, Department of Medicine, University of Washington School of Medicine, 325 9th Avenue Seattle, WA 98104

^bClinical Addiction Research and Education Unit, Section of General Internal Medicine, Department of Medicine, Boston Medical Center, 801 Massachusetts Ave., Second Floor, Boston, MA 02118

^cDepartment of Biostatistics, Boston University School of Public Health, 801 Massachusetts Ave., Third Floor, Boston, MA 02118

^dData Coordinating Center, Boston University School of Public Health, 801 Massachusetts Ave., Third Floor, Boston, MA 02118

^eSection of General Internal Medicine, Department of Medicine, Boston University School of Medicine, 801 Massachusetts Ave., Second Floor, Boston, MA 02118

^fDepartment of Anesthesia, Brigham and Women's Hospital, Pain Management Center, 850 Boylston Street, Chestnut Hill, MA 02467

^gDepartment of Community Health Sciences, Boston University School of Public Health, 801 Massachusetts Ave., Second Floor, Boston, MA 02118

Abstract

Corresponding Author: Judith I. Tsui, Section of General Internal Medicine, Harborview Hospital / University of Washington School of Medicine, 325 9th Avenue, Box 359780, Seattle, WA 98104, Phone: (206) 744-1835, Fax: (206) 744-9917, tsuij@uw.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Each author has contributed to the submission in the following manner:

Study concept: Judith I. Tsui, Robert E. Edwards, Jeffrey H. Samet

Study design: Judith I. Tsui, Debbie M. Cheng

Data collection: Judith I. Tsui, Marlene C. Lira

Data analysis: Judith I. Tsui, Michael R. Winter

Interpretation of data: all authors (Judith I. Tsui, Marlene C. Lira, Debbie M. Cheng, Michael R. Winter, Daniel P. Alford, Jane M.

Liebschutz, Robert R. Edwards, and Jeffrey H. Samet)

Drafting of manuscript: Judith Tsui

Revision of manuscript: all authors (Judith I. Tsui, Marlene C. Lira, Debbie M. Cheng, Michael R. Winter, Daniel P. Alford, Jane M.

Liebschutz, Robert R. Edwards, and Jeffrey H. Samet)

All authors have approved the final article.

Contributors: All authors have contributed significantly to claim authorship, and have seen and approved of the manuscript.

Conflict of Interest: There are no conflicts of interest.

Aims—In a sample of patients receiving opioid agonist therapy, we evaluated whether having chronic pain was associated with a) craving for opioids and b) illicit opioid use.

Methods—In a cross-sectional study of adults on buprenorphine or methadone maintenance recruited from an urban medical center, we examined any craving for opioids (primary dependent variable) in the past week and recent illicit opioid use (secondary dependent variable). Illicit opioid use was defined as a positive urine drug test (UDT) for opiates and chronic pain was defined as bodily pain that had been present for at least 3 months. Multivariable logistic regression models were fit for each outcome, adjusting for age, sex, and non-white race. Additional models adjusted for depression (PHQ-9) and anxiety (STAI).

Results—The sample included 105 adults on methadone or buprenorphine maintenance. Mean age was 43.8 (SD±9.4) years; 48% were female and 32% non-white; 19% were on methadone. Chronic pain was present in 68% of the sample, 51% reported craving opioids in the past week, and 16% had a positive UDT. Chronic pain was associated with 3-fold higher odds of reporting craving in the past week (aOR=3.10; 95% CI: 1.28–7.50, p-value=0.01). The relative odds for having a positive UDT were not statistically significant (aOR=2.52; 95% CI: 0.64–9.90, p=0.18).

Conclusion—In this sample of patients treated with opioid agonist therapy, those with chronic pain had higher odds of reporting craving for opioids. Chronic pain with associated opioid craving potentially places this population at risk for relapse.

Keywords

Opioid use disorder; pain; chronic pain; opioid agonist therapy; methadone; buprenorphine

1. INTRODUCTION

In 2014, an estimated 1.9 million people in the United States had an opioid use disorder related to prescription pain relievers, and an estimated 586,000 had an opioid use disorder related to heroin use (SAMHSA, 2015). Chronic pain is common in patients with opioid use disorders who are on opioid agonist therapy (OAT). Studies of patients maintained on methadone or buprenorphine suggest that a third to more than a half report pain that has been present 3 or more months (Barry et al., 2009a, 2013; Jamison et al., 2000; Rosenblum et al., 2003). Chronic pain is highly relevant to substance use outcomes, as it may serve as a barrier to treatment entry, retention or success, and a trigger for relapse. Among HIV-infected substance users, pain has been associated with persistent use of heroin (Tsui et al., 2013). In some studies, patients with chronic pain who received addiction treatment were more likely to relapse to drug use compared to patients without pain (Caldeiro et al., 2008; Larson et al., 2007). However, not all studies have demonstrated worse outcomes (Dhingra et al., 2015; Fox et al., 2012; Ilgen et al., 2006).

Drug craving is a subjective phenomenon conceptualized as an individual's desire or urges to use a previously experienced substance (Sayette et al., 2000; Tiffany and Wray, 2012). Opioid craving predicts opioid use among persons with heroin and prescription opioid use disorders (McHugh et al., 2014; Tsui et al., 2014), and treatment with methadone and buprenorphine reduces craving (Fareed et al., 2010). Pain may be associated with increased craving for opioids. Among patients with chronic pain, craving has been associated with

aberrant use of prescription opioids (Wasan et al., 2009), and among persons with prior heroin use, increased sensitivity to pain has been associated with opioid craving (Ren et al., 2009). Among patients with treated opioid use disorders, it is unknown whether chronic pain is associated with opioid craving and thereby an increased likelihood of relapse. In addition, the mechanisms whereby pain leads to craving or relapse are relatively unexplored. Prior research suggests that negative affect may be associated with heroin and other drug craving among persons in treatment for opioid use disorders (Epstein et al., 2009; Huhn et al., 2016), and in methadone maintenance treated samples, persons with chronic severe pain have been observed to have more symptoms of depression and anxiety (Barry et al., 2009a).

The study aim is to assess whether having chronic pain was associated with a) opioid craving and b) illicit opioid use in a sample of adults who were treated with buprenorphine or methadone for their opioid use disorders. In addition, we explored the roles of anxiety and depression in these relationships to assess whether they might be potential confounders or mediators.

2. MATERIALS AND METHODS

2.1 Objective and Study Design

This is secondary analysis of a cross-sectional study of adults on methadone or buprenorphine for treatment of opioid use disorders in the VIP (Viral Infections and Pain) study. The parent study explored the contributions of hepatitis C virus (HCV) infection to pain and pain hypersensitivity among persons with treated opioid use disorders on buprenorphine or methadone with and without HCV (Tsui et al., 2015). The current study included all participants whose data on their chronic pain status was available; one subject whose data was missing was excluded. We hypothesized that patients with chronic pain would be more likely to report craving opioids and to have recently used illicit opioids, as evidenced by a positive urine drug test, than those without chronic pain.

2.2 Participants

Study participants were recruited from January, 2012 through December, 2013 from the Boston Medical Center (BMC). Flyers advertising the study as open to persons who were treated with methadone or buprenorphine for addiction were distributed, and providers were asked to refer interested patients to the study coordinator for screening. Potential subjects were screened over the phone for eligibility and were then invited for a study visit, which included further screening and, if eligible, the study assessment and procedures.

Eligibility criteria included the following: between 18 and 65 years of age, English speaking, receiving primary care at BMC, on methadone or buprenorphine for treatment of an opioid use disorder for at least 4 weeks and receiving a stable dose for at least 2 weeks, and documented HCV and HIV status. Exclusion criteria included: current pregnancy, numbness in hands that would prevent sensation of pain or movement in response to pain, and acute intoxication or psychological distress precluding participation. Participants received \$50 store gift cards as compensation for time and effort involved in the in-person eligibility assessment and study visit. Written informed consent was obtained from all participants

prior to study participation. The study was approved by the Institutional Review Board of Boston University Medical Campus.

2.3 Research Visits/Measurements

Research visits took place in the General Clinical Research Unit at Boston University School of Medicine. Participants underwent a single study visit involving a face-to-face interview assessment with a research assistant and a urine toxicology test. Participants were asked to take their normal dose of buprenorphine or methadone on the day of the study visit. The study assessment included demographics (e.g., age, education, marital status, and disability status), duration and type of opioid agonist therapy, the short form Brief Pain Inventory to assess pain (Cleeland, 2009), State Trait Anxiety Inventory (STAI; Spielberger et al., 1983, 1995) to assess anxiety symptoms, and the Patient Health Questionnaire-9 (PHQ-9; Kroenke et al., 2001) to assess depressive symptoms. The BPI assesses pain at its “worst,” “least,” “average,” and “now” (current pain). In clinical trials, the items “worst” and “average” have each been used singly to represent pain severity; however, the scale developers recommend that all four severity items be used, because the models for validation of the BPI included all four items. The PHQ-9 is a diagnostic clinical and research tool which has been shown to be a reliable and valid measure of depression severity. It scores each of the 9 DSM-IV criteria as “0” (not at all) to “3” (nearly every day), providing a 0 to 27 severity score; PHQ-9 scores of 5, 10, 15, and 20 represented mild, moderate, moderately severe, and severe depression, respectively. The STAI Form is an administered analysis of reported anxiety symptoms, measuring both state and trait anxiety. The range of scores is 20–80, the higher the score indicating greater anxiety. A urine drug test using homogeneous enzyme immunoassays (Abbott/Microgenics) was conducted to assess recent use of opiates, cocaine, amphetamines, benzodiazepines, and barbiturates.

2.4 Main Independent Variable

The main independent variable of interest was chronic pain, defined as pain that had been present for at least 3 months. Current (past week) pain was assessed with the initial question on the Short Form Brief Pain Inventory (“During the past week have you had any bodily pain?”); persons who reported past week pain were subsequently asked about the duration of their current pain. Those who responded that their pain had been present for 3 months or longer were categorized as having chronic pain. In post-hoc analyses we evaluated a three level variable for chronic pain severity, defined as “no pain” (0), “mild pain” (1–4) and moderate to severe pain (>4). The threshold for moderate pain was the median severity score for participants with chronic pain in the sample, furthermore, it has been established as a threshold for moderate pain by other researchers (Farrar, 2010; Hoffman et al., 2010). Pain severity was assessed using the Brief Pain Inventory, rating pain from “0” (no pain) to “10” (pain as bad as you can imagine), using the mean of four responses for past week worst pain, least pain, average pain and current pain.

2.5 Dependent Variables

The primary outcome was self-reporting of any opioid craving. Opioid craving was assessed using a single item numeric scale (Rosenberg, 2009). Participants were asked: “On a scale of 0–10, please indicate how much craving you have experienced during the past week,” with

responses anchored at “0=no craving at all” and “10-strongest craving ever”. Participants were queried specifically about buprenorphine and methadone, as well as all other opioids (e.g., heroin, oxycodone, hydromorphone, etc.). Any response greater than zero for either question was considered positive for opioid craving; a dichotomous outcome (yes/no) was chosen as data were highly skewed and most subjects reported no craving (i.e., a score of “0”). The secondary outcome was recent illicit opioid use. This was defined as a urine drug test (UDT) at the study visit that was positive for opiates. As is the case with most standard UDT panels, it did not include identification synthetic and semi-synthetic opioids, and thus would not include detection of fentanyl, methadone, or buprenorphine (and oxycodone at lower doses).

2.6 Confounders

Potential confounders, chosen a priori, included demographics: age, sex, and non-white race. While these were chosen “a priori” for face validity, these factors have been correlated with pain (Campbell et al., 2005; Dao and LeResche, 2000; Gibson and Farrell, 2004) and substance use (Jones et al., 2015; Wu et al., 2011) and thus may confound the relationship between pain and our outcomes of interest. We also assessed the roles of anxiety (STAI) and depression (PHQ-9) in the relationship between chronic pain and the outcomes of interest to assess whether they are potential confounders or mediators (Asmundson and Katz, 2009; Bair et al., 2003; Edwards et al., 2005).

2.7 Statistical Analysis

Preliminary analyses were conducted using descriptive statistics to compare characteristics of participants with and without chronic pain using chi-square/Fisher’s exact tests for categorical variables and analysis of variance or Kruskal-Wallis tests as appropriate. The primary analyses used multivariable logistic regression models to assess whether chronic pain was associated with craving for opioids or, having recently used illicit opioids, after adjustment for the potential confounders of age, sex, and race. We ran additional confirmatory models adjusting for anxiety and depression in separate models to explore whether these factors play a role in the relationships between pain and craving and illicit opioid use, i.e., as confounders or mediators (Vittinghoff et al., 2005). We used a similar approach to assess whether craving plays a role in the association between chronic pain and recent illicit opioid use. Analyses were conducted using 2-sided tests; a p-value < 0.05 was considered statistically significant. All analyses were conducted using SAS version 9.3.

3. RESULTS

The sample included 105 persons, of the 106 total participants in the VIP study, who reported information on chronic pain. Median age was 45 (IQR: 37–51) years; 48% were female and 32% nonwhite. Most participants (81%) were treated with buprenorphine. The majority of the sample (84%) reported pain in the past week, 68% reported chronic pain and 38% reported moderate to severe chronic pain. The most frequent location of the pain was the back; the second most reported was the knees. Overall, about one-half (51%) of these participants reported craving opioids in the past week, and 16% had an opiate positive urine drug test. Demographics, depression, anxiety, and opioid-related outcomes overall and

stratified by chronic pain status are described in Table 1. Participants with chronic pain were significantly more likely to report opioid craving and to have more depression but did not differ on other factors.

In the multivariable logistic regression models (Table 2), participants who had chronic pain were significantly more likely to report craving opioids, even after adjusting for demographic factors. Adjustment for depression attenuated the association between chronic pain and opioid craving as evidenced by the odds ratio decreasing from 3.10 (95% CI: 1.28–7.50) to 2.63 (95% CI: 1.06–6.52) with the inclusion of depression in the regression model. However, chronic pain remained statistically significant, and the magnitude of the adjusted odds ratio remained notably large. Results were unchanged after adjustment for anxiety (AOR=3.10 (95% CI: 1.25–7.66)). In adjusted analyses, chronic pain was associated with higher odds of having a UDT positive for opiates (AOR=2.52 (95% CI: 0.64–9.90)) (Table 2), although the results were not statistically significant ($p=0.18$). Results were similar after adjustment for depression and anxiety, but the odds ratio attenuated to 1.91 (95% CI: 0.45–8.08) after adjustment for craving.

In secondary, post-hoc analyses, we examined associations between severity of chronic pain (no pain vs. mild pain or moderate to severe pain) and craving/illicit opioid use (Tables 3). The observed magnitudes of effect generally appeared larger for moderate-severe pain and opioid craving/recent opiate use, compared to mild pain.

4. DISCUSSION

In this study of adults maintained on methadone or buprenorphine for treatment of opioid use disorder, we found that participants with chronic pain had significantly higher odds of reporting craving for opioids, and that the association was highest with those with moderate to severe chronic pain. We were unable to detect an association between chronic pain and having a UDT positive for opiates. Depression is a potential confounder of the relationship between chronic pain and opioid craving.

This research is clinically relevant, as it demonstrates that patients with treated opioid use disorders who experience chronic pain may be vulnerable to opioid craving, and thereby to relapse. Opioid craving has been demonstrated to be a salient construct which predicts lapse to opiate use among persons with treated opioid use disorders (McHugh et al., 2014; Moore et al., 2014; Northrup et al., 2015; Tsui et al., 2014). We observed that adjusting for opioid craving attenuated the association between chronic pain and having a UDT positive for opiates, suggesting that increased opioid craving in the setting of chronic pain is a mechanism that leads to relapse. Chronic pain is common among persons with opioid use disorders: the prevalence of 68% for any chronic pain and 38% for moderate to severe chronic pain observed in this study is similar to that reported in other studies (Barry et al., 2009b; Rosenblum et al., 2003; Sheu et al., 2008; Voon et al., 2015). Given that chronic pain is such a common clinical problem that impacts drug craving and substance use outcomes, more research attention should be directed to screening for and testing interventions to reduce pain in these populations.

Our results add to the existing body of literature pointing to the importance of pain as a complicating factor for patients who are treated for opioid use disorders. In a prior early study (Rosenblum et al., 2003) examining both persons admitted to short-term residential (inpatient) substance abuse treatment and those being treated in methadone maintenance treatment programs (MMPT), chronic pain was highly prevalent in both samples and significant associations were observed between craving and chronic pain for the inpatient group (borderline significance for the MMTP group). A more recent study (Sheu et al., 2008) of patients attending outpatient drug and alcohol treatment programs also demonstrated higher mean drug craving among persons with chronic severe pain. In a study of chronic pain patients on opioids, pain severity was modestly associated with opioid craving (Martel et al., 2016), and craving was associated with aberrant use of opioids (Wasan et al., 2009). Our study is unique as it demonstrates a strong and significant association between chronic pain and opioid craving specifically among persons on opioid agonist therapy for treatment of opioid use disorders. Also, our results show that depression may be an important confounder of the relationship between pain and opioid craving for patients on opioid agonist therapy. Prior research suggests that negative affect may be associated with heroin and other drug craving among persons in treatment for opioid use disorders (Epstein et al., 2009; Huhn et al., 2016). Still, it is important to note that the association between any chronic pain and craving, although attenuated, remained strongly significant even after adjustment for depression suggesting independent effects.

Our study did not demonstrate a significant association between chronic pain and illicit opiate use as demonstrated by UDT, although post-hoc analyses demonstrated an association between moderate to severe chronic pain and positive UDT after adjustment for anxiety. Given the small number of positive UDT outcomes (16%) we did not have adequate power to assess this outcome. The literature on the impact of pain and chronic pain on relapse and substance use outcomes is mixed. Some studies have suggested worse substance use treatment outcomes (including opioid use) among persons with pain (Caldeiro et al., 2008; Larson et al., 2007). A study of opioid dependent patients treated with buprenorphine for detoxification found that pain was a significant predictor of self-reported opioid use within the past 30 days, but not positive UDT (Potter et al., 2010). Research on patients treated with methadone maintenance failed to observe an association between pain and self-reported illicit drug use (Ilgen et al., 2006), as well as positive UDT (Dhingra et al., 2015). However, a recent longitudinal study of adults with chronic pain treated with buprenorphine demonstrated persons with greater volatility of pain severity were less likely to be abstinent over time (Worley et al., 2015). More research is needed to disentangle relationships between pain and substance use among persons with treated opioid use disorders.

There are important limitations to consider in this study. The relatively small number of positive UDT events limited study power, particularly for our outcome of positive UDT; therefore these results should be considered exploratory and confirmed in larger samples. Our UDT assay assessed opiate use only, and did not assess use of synthetic or semi-synthetic opioids; therefore we could not fully ascertain the illicit use of all prescription opioids. We used a numeric measure of craving, rather than multi-dimensional scales that have been developed for opioid craving. Therefore, we are unable to understand which of the specific domains of craving are more highly impacted by chronic pain or whether the

“craving” experienced was a desire for analgesic pain relief rather than to get “high.” Due to the cross-sectional study design, directionality of associations cannot be ascertained and causality cannot be established. While we hypothesized that chronic pain may lead to opiate craving, it is also possible that patients who were more strongly craving and unstable in their drug use would be more likely to report chronic pain. Our sample of persons with opioid use disorders on opioid agonist therapy included small numbers on methadone (19%), therefore we were unable to perform sub-group analyses of persons on methadone versus buprenorphine. Both methadone and buprenorphine have been associated with improvements in pain severity after treatment initiation (Neumann et al., 2013), although some research suggests greater pain severity among persons on methadone maintenance (Dunn et al., 2015) compared to those on buprenorphine. To our knowledge, we are unaware of any prior research to suggest that relationships between pain and opioid craving might differ among patients treated with methadone versus buprenorphine.

In summary, this study demonstrated that among patients treated for an opioid use disorder with buprenorphine or methadone, those with chronic pain had higher odds of reporting craving for opioids. Results highlight that chronic pain is an important factor that can adversely impact substance use treatment outcomes among patients with opioid use disorders, even those on opioid agonist treatment. The findings suggest that it would be beneficial for patients who initiate treatment with buprenorphine or methadone for opioid use disorders to be screened for chronic pain. As this condition is common, the need to develop interventions to address chronic pain in this population is clear.

Acknowledgments

We wish to thank the participants of the study for their contributions.

Role of Funding: This study was supported by grant K23DA027367 from the National Institute on Drug Abuse, and through BU-CTSI Grant Number KL2 TR000158. The funding sources had no involvement in study activities.

REFERENCES

- Asmundson GJ, Katz J. Understanding the co-occurrence of anxiety disorders and chronic pain: state-of-the-art. *Depress. Anxiety*. 2009; 26:888–901. [PubMed: 19691031]
- Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. *Arch. Intern. Med.* 2003; 163:2433–2445. [PubMed: 14609780]
- Barry DT, Beitel M, Garnet B, Joshi D, Rosenblum A, Schottenfeld RS. Relations among psychopathology, substance use, and physical pain experiences in methadone-maintained patients. *J. Clin. Psychiatry*. 2009a; 70:1213–1218. [PubMed: 19607760]
- Barry DT, Beitel M, Joshi D, Schottenfeld RS. Pain and substance-related pain-reduction behaviors among opioid dependent individuals seeking methadone maintenance treatment. *Am. J. Addict.* 2009b; 18:117–121. [PubMed: 19283562]
- Barry DT, Savant JD, Beitel M, Cutter CJ, Moore BA, Schottenfeld RS, Fiellin DA. Pain and associated substance use among opioid dependent individuals seeking office-based treatment with buprenorphine-naloxone: a needs assessment study. *Am. J. Addict.* 2013; 22:212–217. [PubMed: 23617861]
- Caldeiro RM, Malte CA, Calsyn DA, Baer JS, Nichol P, Kivlahan DR, Saxon AJ. The association of persistent pain with out-patient addiction treatment outcomes and service utilization. *Addiction*. 2008; 103:1996–2005. [PubMed: 18855809]

- Campbell CM, Edwards RR, Fillingim RB. Ethnic differences in responses to multiple experimental pain stimuli. *Pain*. 2005; 113:20–26. [PubMed: 15621360]
- Cleeland CS. The Brief Pain Inventory User Guide. 2009 [accessed on Mar 17 2015] http://www.mdanderson.org/education-and-research/departments-programs-and-labs/departments-and-divisions/symptom-research/symptom-assessment-tools/BPI_UserGuide.pdf.
- Dao TT, LeResche L. Gender differences in pain. *J. Orofac. Pain*. 2000; 14:169–184. discussion 184–195. [PubMed: 11203754]
- Dhingra L, Perlman DC, Masson C, Chen J, McKnight C, Jordan AE, Wasser T, Portenoy RK, Cheatle MD. Longitudinal analysis of pain and illicit drug use behaviors in outpatients on methadone maintenance. *Drug Alcohol Depend*. 2015; 149:285–289. [PubMed: 25735466]
- Dunn KE, Finan PH, Tompkins DA, Fingerhood M, Strain EC. Characterizing pain and associated coping strategies in methadone and buprenorphine-maintained patients. *Drug Alcohol Depend*. 2015; 157:143–149. [PubMed: 26518253]
- Edwards RR, Sarlani E, Wesselmann U, Fillingim RB. Quantitative assessment of experimental pain perception: multiple domains of clinical relevance. *Pain*. 2005; 114:315–319. [PubMed: 15777856]
- Epstein DH, Willner-Reid J, Vahabzadeh M, Mezghanni M, Lin JL, Preston KL. Real-time electronic diary reports of cue exposure and mood in the hours before cocaine and heroin craving and use. *Arch. Gen. Psychiatry*. 2009; 66:88–94. [PubMed: 19124692]
- Fareed A, Vayalapalli S, Casarella J, Amar R, Drexler K. Heroin anticraving medications: a systematic review. *Am. J. Drug Alcohol Abuse*. 2010; 36:332–341. [PubMed: 20955107]
- Farrar JT. Cut-points for the measurement of pain: the choice depends on what you want to study. *Pain*. 2010; 149:163–164. [PubMed: 20347224]
- Fox AD, Sohler NL, Starrels JL, Ning Y, Giovanniello A, Cunningham CO. Pain is not associated with worse office-based buprenorphine treatment outcomes. *Subst. Abuse*. 2012; 33:361–365.
- Gibson SJ, Farrell M. A review of age differences in the neurophysiology of nociception and the perceptual experience of pain. *Clin. J. Pain*. 2004; 20:227–239. [PubMed: 15218407]
- Hoffman DL, Sadosky A, Dukes EM, Alvir J. How do changes in pain severity levels correspond to changes in health status and function in patients with painful diabetic peripheral neuropathy? *Pain*. 2010; 149:194–201. [PubMed: 20303665]
- Huhn AS, Harris J, Cleveland HH, Lydon DM, Stankoski D, Cleveland MJ, Deneke E, Bunce SC. Ecological momentary assessment of affect and craving in patients in treatment for prescription opioid dependence. *Brain Res. Bull*. 2016; 123:94–101. [PubMed: 26876756]
- Ilgen MA, Trafton JA, Humphreys K. Response to methadone maintenance treatment of opiate dependent patients with and without significant pain. *Drug Alcohol Depend*. 2006; 82:187–193. [PubMed: 16219429]
- Jamison RN, Kauffman J, Katz NP. Characteristics of methadone maintenance patients with chronic pain. *J. Pain Symptom Manage*. 2000; 19:53–62. [PubMed: 10687327]
- Jones CM, Logan J, Gladden RM, Bohm MK. Vital signs: demographic and substance use trends among heroin users - United States, 2002–2013. *MMWR*. 2015; 64:719–725. [PubMed: 26158353]
- Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J. Gen. Intern. Med*. 2001; 16:606–613. [PubMed: 11556941]
- Larson MJ, Paasche-Orlow M, Cheng DM, Lloyd-Travaglini C, Saitz R, Samet JH. Persistent pain is associated with substance use after detoxification: a prospective cohort analysis. *Addiction*. 2007; 102:752–760. [PubMed: 17506152]
- Martel MO, Finan PH, McHugh RK, Issa M, Edwards RR, Jamison RN, Wasan AD. Day-to-day pain symptoms are only weakly associated with opioid craving among patients with chronic pain prescribed opioid therapy. *Drug Alcohol Depend*. 2016; 162:130–136. [PubMed: 27021805]
- McHugh RK, Fitzmaurice GM, Carroll KM, Griffin ML, Hill KP, Wasan AD, Weiss RD. Assessing craving and its relationship to subsequent prescription opioid use among treatment-seeking prescription opioid dependent patients. *Drug Alcohol Depend*. 2014; 145:121–126. [PubMed: 25454409]

- Moore TM, Seavey A, Ritter K, McNulty JK, Gordon KC, Stuart GL. Ecological momentary assessment of the effects of craving and affect on risk for relapse during substance abuse treatment. *Psychol. Addict. Behav.* 2014; 28:619–624. [PubMed: 24128286]
- Neumann AM, Blondell RD, Jaanimagi U, Giambone AK, Homish GG, Lozano JR, Kowalik U, Azadfar M. A preliminary study comparing methadone and buprenorphine in patients with chronic pain and coexistent opioid addiction. *J. Addict. Dis.* 2013; 32:68–78. [PubMed: 23480249]
- Northrup TF, Stotts AL, Green C, Potter JS, Marino EN, Walker R, Weiss RD, Trivedi M. Opioid withdrawal, craving, and use during and after outpatient buprenorphine stabilization and taper: a discrete survival and growth mixture model. *Addict. Behav.* 2015; 41:20–28. [PubMed: 25282598]
- Potter JS, Chakrabarti A, Domier CP, Hillhouse MP, Weiss RD, Ling W. Pain and continued opioid use in individuals receiving buprenorphine-naloxone for opioid detoxification: secondary analyses from the Clinical Trials Network. *J. Subst. Abuse Treat.* 2010; 38(Suppl. 1):S80–S86. [PubMed: 20307799]
- Ren ZY, Shi J, Epstein DH, Wang J, Lu L. Abnormal pain response in pain-sensitive opiate addicts after prolonged abstinence predicts increased drug craving. *Psychopharmacology (Berl.)*. 2009; 204:423–429. [PubMed: 19172249]
- Rosenberg H. Clinical and laboratory assessment of the subjective experience of drug craving. *Clin. Psychol. Rev.* 2009; 29:519–534. [PubMed: 19577831]
- Rosenblum A, Joseph H, Fong C, Kipnis S, Cleland C, Portenoy RK. Prevalence and characteristics of chronic pain among chemically dependent patients in methadone maintenance and residential treatment facilities. *JAMA.* 2003; 289:2370–2378. [PubMed: 12746360]
- SAMHSA. Substance Use Disorders. 2015. <http://www.samhsa.gov/disorders/substance-use>
- Sayette MA, Shiffman S, Tiffany ST, Niaura RS, Martin CS, Shadel WG. The measurement of drug craving. *Addiction.* 2000; 95(Suppl. 2):S189–S210. [PubMed: 11002914]
- Sheu R, Lussier D, Rosenblum A, Fong C, Portenoy J, Joseph H, Portenoy RK. Prevalence and characteristics of chronic pain in patients admitted to an outpatient drug and alcohol treatment program. *Pain Med.* 2008; 9:911–917. [PubMed: 18346064]
- Spielberger, CD.; Gorsuch, RL.; Lushene, R.; Vagg, PR.; Jacobs, GA. *Manual for the State-Trait Anxiety Inventory.* Palo Alto, CA: Consulting Psychologists Press, Inc.; 1983.
- Spielberger, CD.; Reheiser, EC.; Ritterband, LM.; Sydeman, SJ.; Unger, KK. Assessment of emotional states and personality traits: measuring psychological vital signs. In: Butcher, JN., editor. *Clinical Personality Assessment: Practical Approaches.* New York: Oxford University Press; 1995.
- Tiffany ST, Wray JM. The clinical significance of drug craving. *Ann. N. Y. Acad. Sci.* 2012; 1248:1–17. [PubMed: 22172057]
- Tsui JI, Anderson BJ, Strong DR, Stein MD. Craving predicts opioid use in opioid-dependent patients initiating buprenorphine treatment: a longitudinal study. *Am. J. Drug Alcohol Abuse.* 2014; 40:163–169. [PubMed: 24521036]
- Tsui JI, Cheng DM, Coleman SM, Blokhina E, Bridden C, Krupitsky E, Samet JH. Pain is associated with heroin use over time in HIV-infected Russian drinkers. *Addiction.* 2013; 108:1779–1787. [PubMed: 23773361]
- Tsui JI, Lira MC, Cheng DM, Winter MR, Alford DP, Liebschutz JM, Mao J, Edwards RR, Samet JH. Hepatitis C virus infection and pain sensitivity in patients on methadone or buprenorphine maintenance therapy for opioid use disorders. *Drug Alcohol Depend.* 2015; 153:286–292. [PubMed: 26048638]
- Vittinghoff, E.; Glidden, DV.; Shiboski, SC.; McCulloch, CE. *Regression Methods in Biostatistics.* New York, NY: Springer; 2005.
- Voon P, Hayashi K, Milloy MJ, Nguyen P, Wood E, Montaner J, Kerr T. Pain among high-risk patients on methadone maintenance treatment. *J. Pain.* 2015; 16:887–894. [PubMed: 26101814]
- Wasan AD, Butler SF, Budman SH, Fernandez K, Weiss RD, Greenfield SF, Jamison RN. Does report of craving opioid medication predict aberrant drug behavior among chronic pain patients? *Clin. J. Pain.* 2009; 25:193–198. [PubMed: 19333168]
- Worley MJ, Heinzerling KG, Shoptaw S, Ling W. Pain volatility and prescription opioid addiction treatment outcomes in patients with chronic pain. *Exp. Clin. Psychopharmacol.* 2015; 23:428–435. [PubMed: 26302337]

Wu LT, Woody GE, Yang C, Pan JJ, Blazer DG. Racial/ethnic variations in substance-related disorders among adolescents in the United States. *Arch. Gen. Psychiatry.* 2011; 68:1176–1185. [PubMed: 22065533]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Highlights

Among individuals maintained on methadone or buprenorphine for opioid use disorders, chronic pain was present in 68% of the sample and 51% reported craving opioids in the past week.

Chronic pain was associated with 3-fold higher odds of reporting opioid craving in the past week.

Chronic pain with associated opioid craving may place persons with treated opioid use disorders at risk for relapse.

Table 1

Demographic Characteristics, Depression, Anxiety, Pain and Opioid Outcomes by Chronic Pain for Individuals on Opioid Agonist Therapy (n=105)

	No Chronic Pain (n=34)	Chronic Pain (n=71)	p-value
Age [mean years \pm SD]	44 (\pm 10)	44 (\pm 9)	0.96
Female n (%)	19 (56%)	31 (44%)	0.24
Non-white n (%)	11 (32%)	23 (32%)	0.99
Buprenorphine n (%)	29 (85%)	56 (79%)	0.43
Craving Opioids n (%)	11 (32%)	43 (61%)	<0.01
Numeric Craving Score [*] , methadone/buprenorphine [median; IQR]	0 (0, 0)	0 (0, 5)	0.02
Numeric Craving Score [*] , other opiates [median; IQR]	0 (0, 1)	0 (0, 3)	0.33
UDT Positive Opiates n (%)	3 (9%)	14 (20%)	0.16
PHQ-9 ^{**} [mean \pm SD]	9.1 (\pm 6.5)	12.1 (\pm 7.1)	0.04
STAI [†] [mean \pm SD]	35.4 (\pm 15.1)	37.4 (\pm 14.6)	0.52
Pain Severity [*] [median; IQR]	1 (0, 3.75)	4 (3, 5.75)	<0.01

* Range of possible scores 0–10

** Patient Health Questionnaire-9, range of possible scores 0–27

† State Trait Anxiety Inventory, range of possible scores 20–80

Table 2

Associations between Any Chronic Pain, Craving and a Urine Drug Test Positive for Opiates among Individuals on Opioid Agonist Therapy (n=105)

	Craving Opioids OR (95% CI)	p- value	Opiate Positive UDT OR (95% CI)	p- value
Unadjusted model for Any Chronic Pain *	3.21 (1.36–7.60)	0.01	2.54 (0.68–9.51)	0.17
Adjusted for demographics (age, sex, race)	3.10 (1.28–7.50)	0.01	2.52 (0.64–9.90)	0.18
Adjusted for demographics + depression **	2.63 (1.06–6.52)	0.03	2.62 (0.65–10.65)	0.18
Adjusted for demographics + anxiety †	3.10 (1.25–7.66)	0.01	2.66 (0.67–10.53)	0.16
Adjusted for demographics + craving			1.91 (0.45–8.08)	0.38

* N=71 for any chronic pain; N=34 for no chronic pain

** PHQ-9

† STAI

Table 3

Associations between Severity of Chronic Pain, Craving and a Urine Drug Test Positive for Opiates among Individuals on Opioid Agonist Therapy (n=105)

	Craving Opioids OR (95% CI)	p- value	Opiate Positive UDT OR (95% CI)	p- value
Unadjusted OR				
No pain (n=34)	Ref	0.01	Ref	0.16
Mild pain (n=31)	2.23 (0.82–6.10)		1.53 (0.31–7.46)	
Moderate-severe pain (n=40)	4.34 (1.64–11.53)		3.44 (0.86–13.75)	
Adjusted for demographics (age, sex, race)				
No pain	Ref	0.03	Ref	0.18
Mild pain	2.43 (0.86–6.86)		1.49 (0.29–7.64)	
Moderate-severe pain	3.81 (1.40–10.40)		3.69 (0.84–16.17)	
Adjusted for demographics + depression *				
No pain	Ref	0.10	Ref	0.10
Mild pain	2.31 (0.80–6.70)		2.31 (0.80–6.70)	
Moderate-severe pain	2.96 (1.05–8.37)		2.96 (1.05–8.37)	
Adjusted for demographics + anxiety **				
No pain	Ref	0.04	Ref	0.04
Mild pain	2.57 (0.89–7.41)		2.57 (0.89–7.41)	
Moderate-severe pain	3.64 (1.30–10.19)		3.64 (1.30–10.19)	
Adjusted for demographics + craving				
No pain			Ref	0.36
Mild pain			1.20 (0.22–6.57)	
Moderate-severe pain			2.70 (0.57–13.02)	

* PHQ-9

** STAI