Published in final edited form as:

Drug Alcohol Depend. 2014 December 1; 145: 143–149. doi:10.1016/j.drugalcdep.2014.10.010.

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

Amy Wachholtz and Gerardo Gonzalez

Division of Addiction Psychiatry, Dept of Psychiatry, University of Massachusetts Medical School

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.

Keywords

pain; opioid addiction; methadone; buprenorphine; comorbidity; abstinence

© 2014 Elsevier Ltd. All rights reserved.

Corresponding author: Amy Wachholtz, Dept of Psychiatry, UMass Medical School, Worcester, MA 01655, Amy.wachholtz@umassmemorial.org, +01- 508-334-2164.

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.

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, 2011b).

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 and colleagues (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 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 (Doverly et al., 2001a, 2001b). 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 = 0.91) 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 hours.

2.1 Measures

2.1.1 Immediate craving—0–100 subjective rating of Current Craving intensity.

2.1.2 Pain rating—0–100 subjective pain rating of the cold pressor task.

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

2.1.4 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 seconds.

2.1.5 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.

2.1.6 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

2.2.1 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.

2.2.2 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).

2.2.3 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 they will keep their hand in the water “until it is too painful” at which point they removed their hand.

2.2.4 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.

2.2.5 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.

3. RESULTS

The demographics and baseline assessment for the full sample and by group membership can be found in Table 1. The study sample were predominately Caucasian (84%), women (60%), and in their early 40s ($M = 42$ years, $SD = 11$). 80% of the sample reported musculoskeletal based pain, and had a mean pain score of 54.3 ($SE=0.91$) on the SF-36. There was no significant difference between the groups on demographic variables.

While the rating of pain level induced by the cold pressor task was not significantly different between all the groups with an overall mean pain score of 63.8 ($SE = 2.29$), the groups receiving current and past treatment with opioid maintenance medication (methadone, buprenorphine and prolonged abstinence) had increased sensitivity (mean = 28.2 sec) and decreased tolerance (mean = 61.4 sec) to pain induced by the task relative to the opioid naïve control group (sensitivity = 54.4 sec; tolerance = 137.1 sec; $p<0.001$ respectively). The methadone, buprenorphine, and prolonged abstinence groups did not significantly differ from each other (see Table 2). There was no difference between the groups on the rating of the pain level induced by the cold pressor task.

A one-way ANOVA and LSD post-hoc test assessed differences in the cravings on the three subscales of the DDQ after a pain induction (Table 2). There were no statistically significant differences among the methadone, buprenorphine and prolonged abstinent groups ($p's = ns$) but these groups were significantly different to the opioid naïve control group ($p's<.05$) on both the DDQ-Desire subscale, and the DDQ-Negative Reinforcement subscale. However, the prolonged abstinence group was similar to the opioid naïve control group and notably

different from the active opioid maintenance group (Buprenorphine and Methadone) on the DDQ-Control subscale ($p < .05$). The opioid naïve control group was removed from this analysis and the data was reassessed since the opioid naïve control group had such limited opioid exposure that they would not be expected to have opioid cravings. However, the results were similar. There were no significant differences among the three active or historical opioid treatment groups on the DDQ Desire or Negative Reinforcement subscale (p 's=ns).

However, the DDQ Control subscale was a different story. Significant differences did occur on the DDQ Control subscale ($p < .001$), indicating that the prolonged abstinence group did not differ on cravings, desire, or focus on negative events that could occur if they used opioids in response to pain. Where the prolonged abstinence group differed was on their sense of control over those cravings and thoughts. The prolonged abstinence group showed significantly more control than those in the two active opioid treatment groups (p 's<.05) subsequent to the pain induction. The prolonged abstinence group was similar to the opioid naïve control group on the level of control they had over their desire to use.

In addition, the time to event analysis (Kaplan-Meier) also showed significant group differences for pain sensitivity (Log rank (3) = 15.50; $p < .001$; Figure 1). A follow up Cox analysis (Table 3), found that any current or historical use of opioid maintenance treatment resulted in significant worsening of pain sensitivity compared to individuals in the opioid naïve control group (p 's<.001). Tolerance to pain showed a similar pattern (Log rank (3) = 20.11; $p < .001$; Figure 2, Table 4) with no significant difference among the three active or historical opioid treatment groups and with the highest tolerance to pain found among opioid naïve control participants (p 's<.001).

To evaluate the effect of duration of abstinence on pain sensitivity and tolerance, we performed Pearson R correlations that showed pain tolerance significantly improved as the weeks since last opioid dose increased among the prolonged abstinent group, ($R = .37$; $p < .05$; see Table 5, Figure 3); but duration of abstinence did not alter how painful participants rated the experience ($R = -0.79$, $p = ns$).

4. DISCUSSION

Similar to previous research, individuals currently on methadone or buprenorphine maintenance for opioid addiction displayed hyperalgesic responses to the pain task (Compton et al., 2001; Doverty et al., 2001a). What makes this study unique, is the findings related to those who have achieved prolonged abstinence in comparison to the actively maintained opioid treatment group.

All participants rated the cold water test as equally painful, therefore, the lack of differences in pain rating suggests that individuals with and without a history of opioid abuse do not change their cerebral rating of how painful an experience is to their body. However, sensitivity to pain and ability to tolerate that level of pain is significantly lower among those with an opioid addiction history compared to opioid-naïve individuals. Even after a prolonged abstinence from opioid treatment, this level of sensitivity and tolerance does not change. This suggests that there are fundamental differences among individuals with a

history of opioid abuse and opioid maintenance, either due to the prolonged exposure to opioids on the mu-receptors (e.g., environmental factor), or on a pre-morbid genetic factor that pre-disposes these individuals to increased pain sensitivity which may induce a chronic pain patient to abuse a prescribed opioid analgesic.

There was no difference in pain sensitivity or tolerance among those in current or historical opioid maintenance. The observed differences in pain sensitivity do not appear to resolve after treatment cessation. However, tolerance to pain does slowly improve after the cessation of opioid maintenance.

Individuals who successfully have achieved prolonged abstinence report a significantly higher level of control over opioid cravings even in the context of a pain challenge, compared to those who are actively engaged in opioid maintenance. Their sense of control is even above that of opioid naïve individuals after a pain experience. With no differences in the level of pain experienced or the desire to use opioids after a pain event, the sense of control over opioids appears to be what differentiates active opioid users from those who have achieved prolonged abstinence.

Therefore, it may be that helping individuals with comorbid pain and opioid addiction improve their pain tolerance and their sense of control over pain and opioid use is the critical component to helping patients maintain long term sobriety even in the context of pain challenges.

Pain tolerance is a psychological phenomenon, not simply a biological one (Keefe et al., 2005; Wachholtz and Pearce, 2009). Therefore, any treatments addressing co-morbid pain and opioid addiction need to use the cognitive behavioral tools empirically developed by pain psychologists to improve pain tolerance and pain self-efficacy. With the integrated components of increasing tolerance to pain, self-efficacy, and control over opioid use into a psycho-social treatment, we may be able to improve the efficacy of treatment for this difficult to treat disorder.

4.1 Implications

Once an individual has a history of prolonged opioid use, there may be permanent damage to the opioid system, which increases an individual's sensitivity to pain, and decreases their tolerance to that pain level. However, some individuals are able to sustain long-term abstinence from opioids, even in the context of chronic pain. The notable difference between those who sustain abstinence is an extremely strong sense of control over opioid use. Therefore, treatments focused on moving individuals from opioid maintenance to complete abstinence need to focus on increasing a sense of control even in the context of multiple physiological and environmental stressors.

4.2 Future directions/Limitations

There are a few areas that would enhance and expand these findings. The current study is a laboratory study that provides a single point of evidence rather than a longitudinal picture of individuals with chronic pain who also have opioid addiction. Future research would ideally be able to engage in longitudinal research to identify trajectories for individuals

experiencing comorbid chronic pain and opioid addiction. In addition, follow-up studies could further expand our understanding of the long term impact of opioid use by including participants with chronic pain who have been treated with morphine or morphine-like ligands that can activate distinct signal transduction pathways and have a different pain sensitivity and tolerance response pattern to pain compared to treatment with methadone and buprenorphine (Morgan and Nicholson, 2011; Raehal and Bohn, 2011; Yekkirala et al., 2012).

Additionally, while we verified no current drug use using urine toxicology, the duration of participants' opioid abstinence relied on self-report. However, recruiting assistance from contacts in Narcotics Anonymous and other long-term abstinence support groups run in local addiction treatment centers provided trustworthy sources of those who have maintained long term abstinence from opioids.

Another fascinating future direction would be to include a comparison group with individuals who had chronic pain who were treated with long-term opioid treatment without developing an opioid use disorder. While few of those individuals would be currently treated solely with buprenorphine or methadone, which may complicate the psycho-physiological assessment, it may provide some information in preparation for a longitudinal study identifying psychological, social, genetic, and physiological differences among those who develop opioid use disorders in the context of chronic pain.

4.3 Conclusion

Among individuals with a history of prolonged opioid treatment, there appears to be long-term differences in pain sensitivity that do not resolve with discontinuation of opioid treatment. Although sensitivity does not change, tolerance to pain does appear to increase after the completion of treatment. This has significant implications for treating individuals with co-morbid opioid addiction and pain, including both chronic pain and acute pain conditions.

References

- Angst MS, Clark JDM. Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology*. 2006; 104:570–587. [PubMed: 16508405]
- Boscarino JA, Rukstalis MR, Hoffman SN, Han JJ, Erlich PM, Ross S, Gerhard G, Stewart WF. Prevalence of prescription opioid-use disorder among chronic pain patients: comparison of the DSM-5 vs. DSM-4 diagnostic criteria. *J Addict Dis*. 2011; 30:185–194. [PubMed: 21745041]
- Brands B, Blake J, Sproule B, Gourlay D, Busto U. Prescription opioid abuse in patients presenting for methadone maintenance treatment. *Drug Alcohol Depend*. 2004; 73:199–207. [PubMed: 14725960]
- Brazier JE. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ*. 1992; 305:160. [PubMed: 1285753]
- Cheatle MD, Gallagher RM. Chronic pain and comorbid mood and substance use disorders: a biopsychosocial treatment approach. *Curr Psychiatry Rep*. 2006; 8:371–376. [PubMed: 16968617]
- Collins ED, Streltzer J. Should opioid analgesics be used in the management of chronic pain in opiate addicts? *Am J Addict*. 2003; 12:93–100. [PubMed: 12746085]
- Compton P, Charuvastra VC, Ling W. Pain intolerance in opioid-maintained former opiate addicts: effect of long-acting maintenance agent. *Drug Alcohol Depend*. 2001; 63:139–146. [PubMed: 11376918]

- Compton WM, Volkow ND. Major increases in opioid analgesic abuse in the United States: concerns and strategies. *Drug Alcohol Depend.* 2006; 81:103–107. [PubMed: 16023304]
- Crum, R. Epidemiology of opioid use, abuse, and dependence. In: Strain, EC.; Stitzer, ML., editors. *The Treatment Of Opioid Dependence*. Johns Hopkins Press; Baltimore: 2006. p. 43-55.
- Doverly M, Somogyi AA, White JM, Bochner F, Beare CH, Menelaou A, Ling W. Methadone maintenance patients are cross-tolerant to the antinociceptive effects of morphine. *Pain.* 2001a; 93:155–163. [PubMed: 11427327]
- Doverly M, White JM, Somogyi AA, Bochner F, Ali R, Ling W. Hyperalgesic responses in methadone maintenance patients. *Pain.* 2001b; 90:91–96. [PubMed: 11166974]
- Drug Abuse Warning Network. *National Estimates Of Drug-Related Emergency Department Visits*. Department of Health and Human Services; Washington, DC: 2004.
- Elliott AM, Smith BH, Penny KI, Smith WC, Chambers WA. The epidemiology of chronic pain in the community. *Lancet.* 1999; 354:1248–1252. [PubMed: 10520633]
- Franken IHA, Hendriks VM, van den Brink W. Initial validation of two opiate craving questionnaires: The Obsessive Compulsive Drug Use Scale and the Desires for Drug Questionnaire. *Addict Behav.* 2002; 27:675–685. [PubMed: 12201376]
- Gilson AM, Ryan KM, Joranson DE, Dahl JL. A reassessment of trends in the medical use and abuse of opioid analgesics and implications for diversion control: 1997–2002. *J Pain Symptom Manage.* 2004; 28:176–188. [PubMed: 15276196]
- Gonzalez G, Oliveto A, Kosten TR. Combating opiate dependence: a comparison among the available pharmacological options. *Expert Opin Pharmacother.* 2004; 5:713–725. [PubMed: 15102558]
- Højsted J, Sjøgren P. Addiction to opioids in chronic pain patients: a literature review. *Eur J Pain.* 2007; 11:490–518. [PubMed: 17070082]
- Hser YI, Hoffman V, Grella CE, Anglin MD. A 33-year follow-up of narcotics addicts. *Arch Gen Psychiatry.* 2001; 58:503–508. [PubMed: 11343531]
- IASP Task Force on Taxonomy. Part III: pain terms, a current list with definitions and notes on usage. In: Merskey, H.; Bogduk, N., editors. *Classification of Chronic Pain*. IASP Press; Seattle: 1994. p. 209-214.
- Ives TJ, Chelminski PR, Hammett-Stabler CA, Malone RM, Perhac JS, Potisek NM, et al. Predictors of opioid misuse in patients with chronic pain: a prospective cohort study. *BMC Health Serv Res.* 2006; 6:46. [PubMed: 16595013]
- Keefe FJ, Abernethy AP, Campbell LC. Psychological approaches to understanding and treating disease-related pain. *Annu Rev Psychol.* 2005; 56:601–630. [PubMed: 15709948]
- Lee M, Silverman S, Hansen H, Patel V, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. *Pain Physician.* 2011; 14:145–161. [PubMed: 21412369]
- Morgan RW, Nicholson KL. Characterization of the antinociceptive effects of the individual isomers of methadone after acute and chronic administrations. *Behav Pharmacol.* 2011; 22:548–557.
- Pud D, Cohen D, Lawental E, Eisenberg E. Opioids and abnormal pain perception: new evidence from a study of chronic opioid addicts and healthy subjects. *Drug Alcohol Depend.* 2006; 82:218–223. [PubMed: 16229972]
- Raehal KM, Bohn LM. The role of beta-arrestin2 in the severity of antinociceptive tolerance and physical dependence induced by different opioid pain therapeutics. *Neuropharmacology.* 2011; 60:58–65. [PubMed: 20713067]
- Reiger DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, Goodwin FK. Comorbidity of mental disorders with alcohol and other drug abuse. *JAMA.* 1990; 19:2511–2518.
- 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]
- Savage SR, Joranson DE, Covington EC, Schnoll SH, Heit HA, Gilson AM. Definitions related to the medical use of opioids: evolution towards universal agreement. *J Pain Symptom Manage.* 2003; 26:655–667. [PubMed: 12850648]
- Tsang A, Von Korff S, Lee J, Alonso E, Karam M, Angermeyer G, Borges GL, Bromet EJ, Demyttenaere K, de Girolamo G, de Graaf R, Gureje O, et al. Common chronic pain conditions in

developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. *J Pain*. 2008; 9:883–891. [PubMed: 18602869]

Wachholtz A, Gonzalez G, Boyer E, Rosenbaum C, Ziedonis D. The intersection of chronic pain treatment and opioid analgesic misuse: a review of the causes, treatments, and policy strategies. *Subst Abuse Rehabil Rev*. 2011a; 2:145–162.

Wachholtz A, Pearce M. Does spirituality as a coping mechanism help or hinder coping with chronic pain? *Curr Pain Headache Rep*. 2009; 13:127–132. [PubMed: 19272278]

Wachholtz A, Ziedonis D, Gonzalez G. Co-morbid pain and opioid addiction: psycho-social and pharmacological treatments. *Subst Use Misuse*. 2011b; 46:1536–1552. [PubMed: 21756033]

Yekkirala AS, Banks ML, Lunzer MM, Negus SS, Rice KC, Portoghese PS. Clinically employed opioid analgesics produce antinociception via μ - δ opioid receptor heteromers in Rhesus monkeys. *ACS Chem Neurosci*. 2012; 3:720–727. [PubMed: 23019498]

Zimmerman, M. Interview Guide for Evaluating DSM-IV Psychiatric Disorders and the Mental Status Examination. Psych Products Press; East Greenwich, RI: 1994.

Highlights

- Individuals with comorbid pain and opioid addiction have different psychophysiological pain response compared to opioid-naïve individuals with chronic pain.
- 4 groups with chronic pain were assessed: 1-methadone maintenance for addiction, 2-buprenorphine maintenance for addiction; 3-history of opioid maintenance for addiction but with prolonged abstinence; and 4-opioid naïve controls
- Among those with co-morbid pain and opioid addiction, there appears to be long-term differences in pain sensitivity that do not resolve with discontinuation of opioid maintenance treatment compared to opioid naïve controls.
- Pain tolerance was better among those with prolonged abstinence compared to those on active opioid maintenance
- Pain tolerance may improve after prolonged opioid abstinence as length of time from last use increases

Figure 1.
Time to first pain (sensitivity) report by group.
Log rank (df=3) $\chi^2=15.50$ $p<.001$

Figure 2.
Duration of contact with the water (pain tolerance) during the pain task.
Log Rank χ^2 (df=3), 20.11 $p < .001$.

Figure 3.
Correlation between pain tolerance and number of weeks since last opioid use.

Table 1

Demographics

	All N=120	Methadone N=30	Buprenorphine N=30	Prolonged Abstinent N=30	Opioid Naïve Control N=30
Gender					
Male	47 (40%)	17 (57%)	11 (37%)	10 (33%)	9 (30%)
Female	73 (60%)	13 (43%)	19 (63%)	20 (67%)	21 (70%)
Racial Descent					
Caucasian	101 (84%)	26 (87%)	25 (83.3%)	25 (83.3%)	25 (83.3%)
African	5 (4%)	2 (7%)	3 (10%)	0	0
Native Am	7 (6%)	1 (3%)	1 (3.3%)	4 (13.3%)	1 (3.3%)
Multi	7 (6%)	1 (3%)	1 (3.3%)	1 (3.3%)	4 (13.3%)
Ethnicity					
Latino	17 (14.2%)	4 (13%)	3 (10%)	6 (20%)	4 (13%)
Age M (SE)	42 (1.04)	39.9 (1.90)	42.7 (1.85)	46.4 (2.13)	39 (2.28)
Pain Type					
Muscular-Skeletal	96 (80%)	21 (70%)	23 (77%)	26 (87%)	26 (86%)
Neuropathic	5 (4%)	2 (7%)	2 (6%)	1 (3%)	0 (0%)
Mixed	19 (16%)	7 (23%)	5 (17%)	3 (10%)	4 (14%)
Pain Severity SF-36 M(SE)	54.3 (0.91)	55.6 (2.10)	52.4 (1.85)	54.2(1.76)	55.0 (1.61)

Table 2

Intervention group comparisons

	All N=120	Metadone N=30	Buprenorphine N=30	Prolonged Abstinence N=30	Opioid Naïve Control N=30	F
	<i>Mean (SE)</i>	<i>Mean (SE)</i>	<i>Mean (SE)</i>	<i>Mean (SE)</i>	<i>Mean (SE)</i>	
Sensitivity (sec) ¹	31.3 (3.41)	27.3 ^a (2.33)	21.13 ^b (1.48)	28.2 ^c (5.27)	54.4 ^{abc} (11.39)	F(3,119) = 6.04; p<.001
Tolerance (sec) ²	76.7 (6.95)	56.0 ^a (7.63)	52.2 ^b (5.35)	61.4 ^c (10.5)	137.1 ^{abc} (20.62)	F(3,119) = 10.53; p<.001
Pain Rating (0–100) ³	63.8 (2.29)	67.4 (4.41)	61.9 (5.03)	66.3 (4.36)	59.8 (4.58)	F(3,119)=0.61; p = ns
Craving Rating (0–100) ⁴	10.4 (2.09)	15.5 ^a (2.61)	10.0 (2.34)	15.2 ^b (5.24)	1.0 ^{ab} (.99)	F(3,119)=2.73; p<.05
Craving Rating (0–100) ⁵		15.5 (2.61)	10.0 (2.34)	15.2 (5.24)	N/A	F(2, 89)=.44; p= ns
DDQ- Desire	11.2 (.64)	14.5 ^a (1.75)	11.2 ^b (.99)	11.9 ^c (1.33)	7.3 ^{abc} (.64)	F(3,119)=5.91; p=.001
DDQ- Desire ⁵		14.5 (1.75)	11.2 (.99)	11.9 (1.33)	NA	F(2,89)=1.49, p= ns
DDQ-Neg Reinforce	8.3 (.60)	10.4 ^a (1.41)	10.4 ^b (1.34)	8.1 ^c (1.13)	4.4 ^{abc} (.30)	F(3,119)=6.19; P=.001
DDQ-Neg Reinforce ⁵		10.4 (1.41)	10.4 (1.34)	8.1 (1.13)	NA	F(2,89)=1.09, p=ns
DDQ-Control	8.1 (.46)	7.6 ^b (.83)	5.3 ^{ac} (.57)	10.4 ^{bc} (1.0)	9.2 ^a (.95)	F(3,119)=6.65; p<.001
DDQ-Control ⁵		7.6 ^a (.83)	5.3 ^b (.57)	10.4 ^{ab} (1.0)	NA	F(2,89)=9.81; p<.001

¹Time to 1st Pain

²Duration of contact until hand removed from cold water because “it is too painful”.

³Overall pain rating of cold pressor task

⁴Opioid craving level induced by the cold pressor pain task

⁵Comparing only the active or historical opioid treatment groups

Letters indicate significant difference (p<.05) between the groups with the same letter

Table 3

Cox Time to Event Analysis on group differences in pain sensitivity.

	Methadone		Buprenorphine		Prolonged Abstinence		Opioid Naïve Control	
	χ^2	p	χ^2	p	χ^2	p	χ^2	p
Methadone	.104	.747	.104	.747	.540	.462	11.166	.001
Buprenorphine					1.021	.312	11.193	.001
Prolonged Abstinence	.540	.462	1.021	.312			6.406	.011

Table 4

Cox Time to Event Analysis on group differences in pain tolerance.

	Methadone		Buprenorphine		Prolonged Abstinence		Opioid Naïve Control	
	χ^2	p	χ^2	p	χ^2	p	χ^2	p
Methadone	.013	.909	.013	.909	.061	.805	13.465	.000
Buprenorphine					.120	.729	13.708	.000
Prolonged Abstinence	.061	.805	.120	.729			11.853	.001

Table 5

Pearson R correlations examining duration of opioid abstinence among the prolonged abstinence group and pain sensitivity and tolerance.

	Pain Tolerance	Pain Rating
Abstinence (weeks)		
<i>R</i>	.366	-.079
<i>p</i>	.023	.339
Pain Tolerance (sec)		
<i>R</i>	1	-.183
<i>p</i>		.166