Published in final edited form as:

Drug Alcohol Depend. 2015 August 1; 153: 286–292. doi:10.1016/j.drugalcdep.2015.05.011.

Hepatitis C virus infection and pain sensitivity in patients on methadone or buprenorphine maintenance therapy for opioid use disorders

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}, Jianren Mao^f, Robert R. Edwards^g, and Jeffrey H. Samet^{b,e,h}

^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

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.

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.

All authors must have materially participated in the research and/or article preparation. All authors have approved the final paper.

Authors' specific contributions are listed below:

Judith I. Tsui: study design, study procedures, data collection, analysis of data, interpretation of results, drafting of manuscript, revision of manuscript

Marlene C. Lira: study procedures, data collection, preparation and revision of manuscript

Debbie M. Cheng: study design, interpretation of results, revision of the manuscript

Michael R. Winter: analysis of data, interpretation of results, revision of the manuscript

Daniel P. Alford: study design, interpretation of results, revision of the manuscript

Jane M. Liebschutz: study design, interpretation of results, revision of the manuscript

Jianren Mao: study design, interpretation of results, revision of the manuscript

Robert R. Edwards: study design, interpretation of results, revision of the manuscript

Jeffrey H. Samet: study design, interpretation of results, revision of the manuscript

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute on Drug Abuse or the National Institutes of Health.

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.

^fDepartment of Anesthesia, Massachusetts General Hospital, 101 Merrimac Street, Boston, MA 02110

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

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

Abstract

Background—Patients with opioid use disorders on opioid agonist therapy (OAT) have lower pain tolerance compared to controls. While chronic viral infections such as HCV and HIV have been associated with chronic pain in this population, no studies have examined their impact on pain sensitivity.

Methods—We recruited 106 adults (41 uninfected controls; 40 HCV mono-infected; and 25 HCV/HIV co-infected) on buprenorphine or methadone to assess whether HCV infection (with or without HIV) was associated with increased experimental pain sensitivity and self-reported pain. The primary outcome was cold pain tolerance assessed by cold-press or test. Secondary outcomes were cold pain thresholds, wind-up ratios to repetitive mechanical stimulation (i.e., temporal summation) and acute and chronic pain. Multivariable regression models evaluated associations between viral infection status and outcomes, adjusting for other factors.

Results—No significant differences were detected across groups for primary or secondary outcomes. Adjusted mean cold pain tolerance was 25.7 (uninfected controls) vs. 26.8 (HCV mono-infection) vs. 25.3 (HCV/HIV co-infection) seconds (global p -value=0.93). Current pain appeared more prevalent among HCV mono-infected (93%) compared to HCV/HIV co-infected participants (76%) and uninfected controls (80%), as did chronic pain (77% v. 64% v. 61% respectively). However, differences were not statistically significant in multivariable models.

Conclusion—This study did not detect an association between HCV infection and increased sensitivity to pain among adults with and without HIV who were treated with buprenorphine or methadone for opioid use disorders. Results reinforce that pain and hyperalgesia are common problems in this population.

Keywords

Opioid use disorder; pain; chronic pain; opioid agonist therapy; methadone; buprenorphine; hepatitis C; HIV

1. INTRODUCTION

Chronic pain is a global problem (Blyth et al., 2001; Gureje et al., 1998) and a frequent cause for seeking medical care (Andersson et al., 1999; Kroenke and Mangelsdorff, 1989; Mantyselka et al., 2001). Patients with a history of opioid use disorders appear to be particularly vulnerable to pain (Karasz et al., 2004; Rosenblum et al., 2003; Sheu et al., 2008). The prevalence of chronic pain among persons with opioid use disorders treated with opioid agonist therapy (OAT) ranges from 36 to 61% (Barry et al., 2009, 2013; Jamison et al., 2000; Rosenblum et al., 2003). Chronic pain is problematic for patients with substance

use disorders as it has been associated with risk for persistent heroin use (Potter et al., 2010; Tsui et al., 2013) and relapse to use of drugs and alcohol (Larson et al., 2007). However, treatment for opioid use disorders with OAT can lead to alterations in pain sensitivity leading to hyperalgesia. Studies using the cold-pressor test have demonstrated lower pain tolerance among individuals with opioid use disorders on OAT compared to controls (Compton et al., 2012, 2000; Doherty et al., 2001). Treating chronic pain in this population is a clinical challenge as patients with a history of substance use disorders are more likely to misuse prescription opioids (Turk et al., 2008), and the risks and benefits of their long-term use are in question (Noble et al., 2010). It is important to understand the root causes for pain among patients with opioid use disorders in order to effectively address pain in this population.

Hepatitis C virus (HCV) may be a factor contributing to risk for pain among persons with a history of opioid use disorders. The majority (67–96%) of patients with opioid use disorders on OAT have chronic HCV infection (Novick and Kreek, 2008). Extra-hepatic effects of HCV infection include painful conditions such as arthralgias and peripheral neuropathy (Cacoub et al., 2000, 2005; Vassilopoulos and Calabrese, 2005). Investigators have hypothesized that cytokines could also provide a link between chronic pain and HCV (Thompson and Barkhuizen, 2003). HCV infection causes a complex immune response leading to enhanced production of pro-inflammatory cytokines such as TNF- α (Blackard et al., 2007; Knobler et al., 2003; Nelson et al., 1997; Zylberberg et al., 1999), IL-6 (Malaguarnera et al., 1997; Migita et al., 2006; Oyanagi et al., 1999) and IL-1 β (Loftis et al., 2008). These cytokines are neuroimmune mediators that can generate “sickness-behavior” in animals (Watkins and Maier, 2005). Furthermore, HCV is neuroinvasive and can infect glial cells (Laskus et al., 2005), which when activated release inflammatory cytokine that promote excitatory impulses and enhance pain sensitivity (Kim et al., 2007; Tanga et al., 2005).

Some observational studies suggest that patients with HCV are more likely to experience pain. A high prevalence of chronic pain has been observed among HCV-infected veterans (Silberbogen et al., 2007; Whitehead et al., 2008) and HCV was associated with pain among HIV-infected persons, even after adjustment for psychiatric co-morbidities and socio-demographics (Tsui et al., 2012). A study of persons with opioid use disorders seeking treatment with buprenorphine found that patients with HCV were more likely to report intolerance to physical discomfort (Tsui et al., 2011). Prior studies of experimental pain tolerance comparing participants on methadone and buprenorphine to controls have not explored the contributions of HCV even though this infection is highly prevalent in the OAT treated population. Persons with opioid use disorders who have injected drugs are also at risk for infection with HIV, a condition which is also associated with chronic pain (Macfarlane et al., 2001).

This study was undertaken to explore whether infection with HCV, with or without HIV co-infection, was associated with greater experimental pain sensitivity and self-reported chronic pain compared to uninfected controls in a sample of patients on buprenorphine or methadone maintenance for opioid use disorders.

2. MATERIALS AND METHODS

2.1 Objective and Study Design

We conducted a cross-sectional study to assess the effect of HCV on pain sensitivity among patients on methadone or buprenorphine. Participants were grouped into three exposure categories: uninfected controls (HCV−/HIV−), HCV mono-infected (HCV+/HIV−), or HCV/HIV co-infected (HIV+/HCV+). We hypothesized that HCV infection, both with and without HIV, would be associated with lower cold pain tolerance and self-reported chronic pain. We did not include an HIV-only infected group as our study aim was to test the hypothesis that HCV was associated with increased pain sensitivity. In addition, HCV is much more prevalent among persons who inject drugs compared to HIV (Mathers et al., 2008; Nelson et al., 2011), such that most persons with opioid use disorders who have acquired HIV through injection drug use will commonly also be co-infected with HCV (Pilon et al., 2011; Vickerman et al., 2010). Therefore we believed it would be difficult to recruit an HIV-only infected group of patients with opioid use disorders. The primary aim of this study was to test whether HCV mono-infection was associated with increased pain sensitivity compared to uninfected controls. An exploratory aim was to compare HCV/HIV co-infected subjects compared to uninfected controls.

2.2 Participants

Study participants were recruited from January, 2012 through December, 2013 from the Boston Medical Center (BMC) Office Based Opioid Treatment (OBOT) Program, (a buprenorphine program in adult primary care clinic), the BMC Center for Infectious Diseases (HIV primary care site), and a Boston Public Health Commission (BPHC) Opioid Treatment Program (methadone clinic). Flyers advertising the study 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. In addition, each participant needed to have testing consistent with one of the following three groups documented in the medical record: 1) uninfected control, 2) HCV mono-infected, or 3) HCV/HIV co-infected. Negative serology tests were required to have been conducted within three months of the in-person screening visit. Persons infected with HCV were required to have had a confirmatory HCV RNA viral load that was detectable. Persons who had spontaneously cleared HCV (i.e., were HCV antibody positive but viral load undetectable without treatment) and were also not infected with HIV were categorized as controls along with the HCV antibody negative individuals. Persons infected with HIV were required to have documentation in the electronic medical record of at least one of the following: positive HIV screening antibody test, detectable HIV viral load, or have HIV included in medical history/problem list. Exclusion criteria included: current pregnancy, numbness in hands that would prevent sensation of pain or movement in response to pain, current opioid

use for the treatment of chronic pain, current or past successful treatment for HCV, 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

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, urine toxicology testing, and pain testing procedures. Participants were asked to take their normal dose of buprenorphine or methadone but to refrain from taking over-the-counter and prescribed pain medications 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 past week pain (Cleeland, 2009), lifetime and past-30 day alcohol and drug use (ASI; McLellan et al., 1992), state trait anxiety (STAI; Spielberger et al., 1983, 1995), depression (PHQ-9; Kroenke et al., 2001), and pain catastrophizing (Sullivan et al., 1995). A medical chart review was performed (e.g., HCV and HIV serology, liver function and current medications). Urine toxicology tests (enzyme immunoassay) were conducted to assess recent use of opiates, cocaine, amphetamines, benzodiazepines and barbiturates.

2.4 Main Independent Variable

The main independent variable of interest was HIV/HCV status categorized into three groups: HCV mono-infection; HCV/HIV co-infection; and uninfected controls. The comparisons of interest were between each HCV group (mono-infected and co-infected with HIV) vs. uninfected controls, however, the primary study aim was to compare HCV mono-infected to controls.

2.5 Primary Outcome

The primary outcome was cold pain tolerance, defined as the number of seconds until hand withdrawal during the cold-pressor test. Cold-pressor procedures were similar to those used by Edwards et al. (2004). The test consisted of a 7-L ThermoScientific refrigerator bath, continually circulated by a submerged pump to maintain a constant temperature of 3 °C. Subjects were instructed to place their dominant arm in the tank so that ice water covered the hand past the wrist. They were instructed to keep their hand in the water for as long as possible and to remove their arm from the water when they could no longer tolerate the ice bath. The cold-pressor test was truncated at 300 seconds (only 1 subject had test truncated) to avoid any lasting injury. The time from submersion to hand withdrawal (i.e., cold tolerance) was measured in seconds using a stopwatch.

2.6 Secondary Outcomes

Secondary outcomes included: cold pain threshold, wind-up ratio, self-reported chronic pain and current (past week) pain. Cold pain threshold was measured as number of seconds to the initial perception of pain (expressed verbally), but not hand withdrawal. Wind-up ratio was assessed with mechanical punctate stimulators using the quantitative sensory protocol previously described by Rolke et al. (2006), and adapted by other researchers (Edwards et al., 2011). Seven weighted punctate stimulators with flat contact area of 0.2mm diameter and weights from 8–512mN were applied to the middle finger of the non-dominant hand at a rate of 2 seconds on, 2 seconds off in an ascending order of weights. Subjects rated each stimulus on a scale from 0–100, with 0 meaning “no pain” and 100 meaning “the worst pain imaginable”. Using the weighted probe that was first associated with discomfort, participants were asked to rate their pain on the first and tenth stimuli. This test was conducted twice. Wind-up ratio was defined as the ratio of means of rated discomfort comparing the tenth and the first stimulus, reflecting the magnitude of increase in perceived pain.

Current pain was defined by a positive response to the first question in the BPI: “Throughout our lives, most of us have had pain from time to time (such as minor headache, sprains and toothaches)....have you had pain other than these everyday kinds of pain in the past week?”. Chronic pain was defined as current pain that had been present for at least 3 months assessed by a subsequent question about pain duration.

2.7 Confounders

Potential confounders included demographics (i.e., age, sex and non-white race), education (high school graduate versus non-graduate), disability status, OAT type (i.e., buprenorphine versus methadone), duration of OAT, depressive symptoms (PHQ-9), pain catastrophizing (PCS score), anxiety (STAI), and use of gabapentin. These variables were selected a priori as factors that could influence pain and pain perception based on literature and clinical experience (Edwards et al., 2004, 2005; Macfarlane et al., 2001).

2.8 Statistical Analysis

Preliminary analyses were conducted using descriptive statistics to compare characteristics and outcomes of the study subjects across the three exposure groups 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 linear regression models to assess whether group status (i.e., HCV mono-infected and HCV/HIV co-infected versus controls) was associated with lower mean withdrawal latency (i.e., tolerance), after adjustment for the potential confounders of age, sex, race, education, disability status, type and duration of OAT, depression, pain catastrophizing, anxiety, and use of gabapentin. Similar approaches were used for the secondary outcomes of pain threshold and wind-ratio (i.e., temporal summation). All three continuous outcomes were natural log transformed due to their skewed distributions, and results were back-transformed for ease of interpretation. The dichotomous outcomes of chronic pain and any past week pain were analyzed using multivariable logistic regression and controlled for the same covariates. Sensitivity analyses for the primary outcome were conducted restricting the control group to participants who

had never been exposed to HCV and were antibody negative (i.e., excluding those who were antibody positive but RNA negative, demonstrating they had spontaneously cleared infection). Analyses were conducted using 2-sided tests; a p-value < 0.05 was considered statistically significant. To minimize multiple testing, pairwise comparisons were not made unless the global p-value for HIV/HCV group status was statistically significant. The study was designed to have 80% power to detect a mean difference as small as 23 seconds in the primary outcome withdrawal latency between either HCV infected group and controls using a two sample t-test, assuming the standard deviation for withdrawal latency was 36.7 seconds (Pud et al., 2006) and an alpha level of 0.05. The primary aim of the study was to compare HCV mono-infected subjects to uninfected controls and the target recruitment was achieved for both of these groups. Comparison of HCV/HIV co-infected subjects versus uninfected controls was an exploratory aim and recruitment of the HCV/HIV co-infected subjects stopped after 25 of the planned 40 were enrolled. Based on the assumptions used in the original calculations, a sample size of 25 for the co-infected subjects would result in 68% power for the exploratory comparison of withdrawal latency between the co-infected and uninfected groups. All analyses were conducted using SAS version 9.3.

3. RESULTS

Of the 124 people screened, 106 were eligible and enrolled. Reasons for not being eligible were: HIV/HCV status unconfirmed (n=8), HIV+ only (n=8), having a bleeding problem that precluded blood draw (n=1), and taking methadone for pain not opioid use disorders (n=1). The final sample included 41 uninfected controls, 40 HCV mono-infected and 25 HCV/HIV co-infected. The majority of patients (67/106) were recruited from the BMC Office-Based Opioid Treatment Program; 20/106 were recruited from the Boston Public Health Commission (BPHC) Opioid Treatment Program, and 19/106 were recruited from the BMC Center for Infectious Diseases. Characteristics of the sample overall and by group status are listed in Table 1. Median age was 45 (IQR: 37–51) years, 48% were female, 32% non-white. Median duration on OAT was 2.5 years and most participants (81%) were treated with buprenorphine.

The majority (96%) of HIV infected participants were on anti-retroviral therapy, and the median (IQR) CD 4 cell count and HIV viral loads were 593.0 (416.0, 768.0) and 36.5 (10.0, 130.0) respectively (Table 1). The majority (83%) in both the HCV mono-infected and HCV/HIV co-infected groups had genotype 1 HCV infection, and the median HCV viral load was similar in both groups (Table 1).

HCV mono-infected and HCV/HIV co-infected patients were older than uninfected participants, reported higher rates of disability and lifetime injection drug use (Table 1). Urine toxicology was positive for opiates in 16% of all samples (indicating illicit opioid use), and there was no statistically significant difference in the proportions that were positive across the three groups (global p=0.32). The majority of the sample (84%) reported pain in the past week, and 68% reported chronic pain that had lasted at least 3 months. The prevalence of current and chronic pain was highest among individuals with HCV only, although there was no statistically significant difference among the three groups. Among participants who endorsed current pain (n=89), there was no difference in median pain

severity or interference between the 3 groups (Table 1). Among all 3 groups, the most often reported location of the pain was the back; the second most reported was the knees.

Overall, there were no significant differences detected across groups for primary or secondary outcomes in the unadjusted or adjusted models. The adjusted means for the primary outcome cold pain tolerance were: 25.7 seconds in uninfected controls vs. 26.8 in HCV mono-infected patients vs. 25.3 seconds in HCV/HIV co-infected patients (global $p=0.93$; Table 2). The adjusted ratio of means was 1.04, (95% CI: 0.78, 1.38) for HCV mono-infection vs. controls; 0.98 (95% CI: 0.69, 1.40) for HCV/HIV co-infection vs. controls. Likewise, there were no significant differences in cold thresholds and wind-up ratios after adjustment for other factors (Table 2). Similarly, there were no significant differences in the relative odds for reporting chronic pain (aOR=2.13, 95% CI: 0.69, 6.58 for HCV mono-infection vs. controls; aOR=0.58, 95% CI: 0.14, 2.39 for HCV/HIV co-infected vs. controls; global p -value=0.15) or current pain (aOR=2.45, 95% CI: 0.53, 11.21 for mono-infection vs. controls; aOR=0.56, 95% CI: 0.11, 2.80 for HCV/HIV co-infected vs. controls; global p -value=0.25) (Table 3). Of note, there were no factors that were significantly associated with chronic pain and any past week pain in the models (Table 3).

When we performed sensitivity analyses restricting controls to only those who were HCV antibody negative ($n=28$) we did not see any substantive differences. The adjusted means for the primary outcome cold pain tolerance were: 24.2 seconds in uninfected controls vs. 27.2 in HCV mono-infected patients vs. 27.2 in HCV/HIV co-infected seconds (global $p=0.75$).

4. DISCUSSION

In this study of adults maintained on methadone or buprenorphine for treatment of opioid use disorders, we found no evidence that infection with HCV, with or without HIV, was associated with lower cold pain tolerance or thresholds. We also did not observe any significant differences in wind-up ratios to mechanical stimulation (i.e., temporal summation) among HCV-infected persons compared to uninfected controls.

This is the first study to report whether pain sensitivity differs among patients with and without HCV. Researchers have previously hypothesized that HCV may lead to central sensitization and central pain conditions such as fibromyalgia (Thompson and Barkhuizen, 2003), but there has been no evidence to date to link HCV with hyperalgesia and temporal summation. Although we did not find evidence that infection with HCV, with or without HIV, alters pain sensitivity among these participants on OAT, we did observe uniformly low pain tolerance (<50 seconds) which is consistent with other studies using cold pressor test in opioid-maintained subjects (Compton et al., 2012, 2000; Doherty et al., 2001). Interestingly, a recent study suggested that cold pain tolerance may improve after opioid maintenance cessation (Wachholtz and Gonzalez, 2014). Also, with 68% of the total sample reporting chronic pain, this study reinforces that pain continues to be a pervasive problem for patients on OAT, even in the era of buprenorphine treatment.

It is perhaps unexpected that we should find no differences in pain sensitivity among persons with and without HCV. In a prior study of persons with opioid use disorders seeking treatment with buprenorphine, it was observed that patients with HCV were more likely to

report intolerance to physical discomfort (Tsui et al., 2011). The fact that all our participants were maintained on OAT could contribute to our findings, as it is possible that opioid-related hyperalgesia might overwhelm any differences caused by HCV. Therefore, it may be a consideration to repeat this study among patients with a history of opioid use disorders who are not on maintenance OAT, or to perform additional studies to examine the effects of HCV treatment and viral eradication on pain.

4.1 Limitations

There were a number of limitations to this study. First, we did not adjust for duration of infection with HCV as most patients were unaware of the timing of exposure/infection since patients are typically asymptomatic with acute infection. Given that most complications of HCV, both hepatic and extra-hepatic, occur after decades of infection, it is possible that central nervous system changes leading to hyperalgesia would follow the same natural history and our sample contained too many individuals who were recently infected. Another potential limitation is that our control group included individuals who spontaneously cleared their infection (n=23). Again, based on knowledge of the natural history of HCV-related complications, it seems unlikely that brief acute exposure would cause any long-lasting effects on pain sensitivity. Nonetheless, we conducted sensitivity analyses restricting controls to participants who had never been exposed (i.e., were HCV antibody negative) and our results were not appreciably changed. The fact that all our participants were on OAT might be perceived as a limitation, although an advantage is that “controls” more closely resembled other groups aside from infection status. It is possible that opioid-related hyperalgesia could overwhelm any differences caused by HCV. Therefore, it may be a consideration to repeat this study among patients with a history of opioid use disorders who are not on maintenance OAT, or to perform additional studies to examine the effects of HCV treatment and viral eradication on pain. An additional limitation is that we performed limited quantitative sensory testing of pain in this study. However, the cold-pressor test has most consistently demonstrated alterations in pain sensitivity in studies of patients on OAT, while other methods of pain testing (e.g. electrical stimulation) have not yielded consistent differences (Chen et al., 2009; Compton et al., 2012; Doherty et al., 2001). Finally, our modest sample size limited the power of this study to detect differences of the observed magnitude, such as for the self-reported pain outcomes (the study was powered to detect an OR 3.6 for chronic pain but the observed OR was 2.13). However, for our primary outcome of cold pressor test response the observed differences were so small in magnitude (i.e., a few seconds) as not to be considered of clinical importance.

4.2 Conclusions

This study of persons with opioid use disorders maintained on OAT (i.e., buprenorphine or methadone) found no significant differences in pain sensitivity or temporal summation among persons with HCV mono-infection and HCV/HIV co-infection compared to uninfected controls. Results do not suggest that chronic viral infections like HCV and HIV contribute to hyperalgesia among persons maintained on methadone or buprenorphine for opioid use disorders. However, this study did observe a high prevalence of current and chronic pain among participants, and also confirmed prior studies demonstrating low pain tolerance among persons on opioid maintenance therapy. Additional research is needed to

understand to the root causes of pain among persons with opioid use disorders and frequent co-morbidities such as HCV and HIV, in order to more effectively prevent and treat pain in this population.

Acknowledgments

Funding Source: This study was supported by grant K23DA027367 from the National Institute on Drug Abuse, and through BU-CTSI Grant Number KL2 TR000158.

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

References

- Andersson HI, Ejlertsson G, Leden I, Schersten B. Impact of chronic pain on health care seeking, self care, and medication. Results from a population-based Swedish study. *J Epidemiol Community Health*. 1999; 53:503–509. [PubMed: 10562870]
- 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*. 2009; 70:1213–1218. [PubMed: 19607760]
- 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]
- Blackard JT, Kang M, St Clair JB, Lin W, Kamegaya Y, Sherman KE, Koziel MJ, Peters MG, Andersen J, Chung RT. Aids Clinical Trials Group, A.S.T. Viral factors associated with cytokine expression during HCV/HIV co-infection. *J Interferon Cytokine Res*. 2007; 27:263–269. [PubMed: 17477814]
- Blyth FM, March LM, Brnabic AJ, Jorm LR, Williamson M, Cousins MJ. Chronic pain in Australia: a prevalence study. *Pain*. 2001; 89:127–134. [PubMed: 11166468]
- Cacoub P, Renou C, Rosenthal E, Cohen P, Loury I, Loustaud-Ratti V, Yamamoto AM, Camproux AC, Hausfater P, Musset L, Veyssier P, Raguin G, Piette JC. Extrahepatic manifestations associated with hepatitis C virus infection: a prospective multicenter study of 321 patients. *Medicine (Baltimore)*. 2000; 79:47–56. [PubMed: 10670409]
- Cacoub P, Saadoun D, Limal N, Leger JM, Maisonnobe T. Hepatitis C virus infection and mixed cryoglobulinaemia vasculitis: a review of neurological complications. *AIDS*. 2005; 19(Suppl 3):S128–134. [PubMed: 16251808]
- Chen L, Malarick C, Seefeld L, Wang S, Houghton M, Mao J. Altered quantitative sensory testing outcome in subjects with opioid therapy. *Pain*. 2009; 143:65–70. [PubMed: 19237249]
- Cleeland, CS. [accessed on Mar 17 2015] The Brief Pain Inventory User Guide. 2009. http://www.mdanderson.org/education-and-research/departments-programs-and-labs/departments-and-divisions/symptom-research/symptom-assessment-tools/BPI_UserGuide.pdf
- Compton P, Canamar CP, Hillhouse M, Ling W. Hyperalgesia in heroin dependent patients and the effects of opioid substitution therapy. *J Pain*. 2012; 13:401–409. [PubMed: 22424799]
- Compton P, Charuvastra VC, Kintaudi K, Ling W. Pain responses in methadone-maintained opioid abusers. *J Pain Symptom Manage*. 2000; 20:237–245. [PubMed: 11027904]
- Doverly M, White JM, Somogyi AA, Bochner F, Ali R, Ling W. Hyperalgesic responses in methadone maintenance patients. *Pain*. 2001; 90:91–96. [PubMed: 11166974]
- Edwards RR, Haythornthwaite JA, Sullivan MJ, Fillingim RB. Catastrophizing as a mediator of sex differences in pain: differential effects for daily pain versus laboratory-induced pain. *Pain*. 2004; 111:335–341. [PubMed: 15363877]
- 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]

- Edwards RR, Wasan AD, Michna E, Greenbaum S, Ross E, Jamison RN. Elevated pain sensitivity in chronic pain patients at risk for opioid misuse. *J Pain*. 2011; 12:953–963. [PubMed: 21680252]
- Gureje O, Von Korff M, Simon GE, Gater R. Persistent pain and well-being: a World Health Organization Study in Primary Care. *JAMA*. 1998; 280:147–151. [PubMed: 9669787]
- Jamison RN, Kauffman J, Katz NP. Characteristics of methadone maintenance patients with chronic pain. *J Pain Symptom Manage*. 2000; 19:53–62. [PubMed: 10687327]
- Karasz A, Zallman L, Berg K, Gourevitch M, Selwyn P, Arnsten JH. The experience of chronic severe pain in patients undergoing methadone maintenance treatment. *J Pain Symptom Manage*. 2004; 28:517–525. [PubMed: 15504628]
- Kim D, Kim MA, Cho IH, Kim MS, Lee S, Jo EK, Choi SY, Park K, Kim JS, Akira S, Na HS, Oh SB, Lee SJ. A critical role of toll-like receptor 2 in nerve injury-induced spinal cord glial cell activation and pain hypersensitivity. *J Biol Chem*. 2007; 282:14975–14983. [PubMed: 17355971]
- Knobler H, Zhornicky T, Sandler A, Haran N, Ashur Y, Schattner A. Tumor necrosis factor- α -induced insulin resistance may mediate the hepatitis C virus-diabetes association. *Am J Gastroenterol*. 2003; 98:2751–2756. [PubMed: 14687828]
- Kroenke K, Mangelsdorff AD. Common symptoms in ambulatory care: incidence, evaluation, therapy, and outcome. *Am J Med*. 1989; 86:262–266. [PubMed: 2919607]
- 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]
- Laskus T, Radkowski M, Adair DM, Wilkinson J, Scheck AC, Rakela J. Emerging evidence of hepatitis C virus neuroinvasion. *AIDS*. 2005; 19(Suppl 3):S140–144. [PubMed: 16251811]
- Loftis JM, Huckans M, Ruimy S, Hinrichs DJ, Hauser P. Depressive symptoms in patients with chronic hepatitis C are correlated with elevated plasma levels of interleukin-1 β and tumor necrosis factor- α . *Neurosci Lett*. 2008; 430:264–268. [PubMed: 18063307]
- Macfarlane GJ, McBeth J, Silman AJ. Widespread body pain and mortality: prospective population based study. *BMJ*. 2001; 323:662–665. [PubMed: 11566829]
- Malaguarnera M, Di Fazio I, Romeo MA, Restuccia S, Laurino A, Trovato BA. Elevation of interleukin 6 levels in patients with chronic hepatitis due to hepatitis C virus. *J Gastroenterol*. 1997; 32:211–215. [PubMed: 9085170]
- Mantyselka P, Kumpusalo E, Ahonen R, Kumpusalo A, Kauhanen J, Viinamaki H, Halonen P, Takala J. Pain as a reason to visit the doctor: a study in Finnish primary health care. *Pain*. 2001; 89:175–180. [PubMed: 11166473]
- Mathers BM, Degenhardt L, Phillips B, Wiessing L, Hickman M, Strathdee SA, Wodak A, Panda S, Tyndall M, Toufik A, Mattick RP. Reference Group to the U.N. on H.I.V and Injecting Drug Use. Global epidemiology of injecting drug use and HIV among people who inject drugs: a systematic review. *Lancet*. 2008; 372:1733–1745. [PubMed: 18817968]
- McLellan AT, Kushner H, Metzger D, Peters R, Smith I, Grissom G, Pettinati H, Argeriou M. The Fifth Edition of the Addiction Severity Index. *J Subst Abuse Treat*. 1992; 9:199–213. [PubMed: 1334156]
- Migita K, Abiru S, Maeda Y, Daikoku M, Ohata K, Nakamura M, Komori A, Yano K, Yatsuhashi H, Eguchi K, Ishibashi H. Serum levels of interleukin-6 and its soluble receptors in patients with hepatitis C virus infection. *Hum Immunol*. 2006; 67:27–32. [PubMed: 16698422]
- Nelson DR, Lim HL, Marousis CG, Fang JW, Davis GL, Shen L, Urdea MS, Kolberg JA, Lau JY. Activation of tumor necrosis factor- α system in chronic hepatitis C virus infection. *Dig Dis Sci*. 1997; 42:2487–2494. [PubMed: 9440625]
- Nelson PK, Mathers BM, Cowie B, Hagan H, Des Jarlais D, Horyniak D, Degenhardt L. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. *Lancet*. 2011; 378:571–583. [PubMed: 21802134]
- Noble M, Treadwell JR, Tregear SJ, Coates VH, Wiffen PJ, Akafomo C, Schoelles KM. Long-term opioid management for chronic noncancer pain. *Cochrane Database Syst Rev*. 2010:CD006605. [PubMed: 20091598]

- Novick DM, Kreek MJ. Critical issues in the treatment of hepatitis C virus infection in methadone maintenance patients. *Addiction*. 2008; 103:905–918. [PubMed: 18422827]
- Oyanagi Y, Takahashi T, Matsui S, Takahashi S, Boku S, Takahashi K, Furukawa K, Arai F, Asakura H. Enhanced expression of interleukin-6 in chronic hepatitis C. *Liver*. 1999; 19:464–472. [PubMed: 10661679]
- Pilon R, Leonard L, Kim J, Vallee D, De Rubeis E, Jolly AM, Wylie J, Pelude L, Sandstrom P. Transmission patterns of HIV and hepatitis C virus among networks of people who inject drugs. *PLoS One*. 2011; 6:e22245. [PubMed: 21799802]
- 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):S80–86. [PubMed: 20307799]
- 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]
- Rolke R, Magerl W, Campbell KA, Schalber C, Caspari S, Birklein F, Treede RD. Quantitative sensory testing: a comprehensive protocol for clinical trials. *Eur J Pain*. 2006; 10:77–88. [PubMed: 16291301]
- 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]
- 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]
- Silverbogen AK, Janke EA, Hebenstreit C. A closer look at pain and hepatitis C: preliminary data from a veteran population. *J Rehabil Res Dev*. 2007; 44:231–244. [PubMed: 17551875]
- Spielberger, CD.; Gorsuch, RL.; Lushene, R.; Vagg, PR.; Jacobs, GA. *Manual for the State-Trait Anxiety Inventory*. Consulting Psychologists Press, Inc; Palo Alto, CA: 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*. Oxford University Press; New York: 1995.
- Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: development and validation. *Psychol Assess*. 1995; 7:524–532.
- Tanga FY, Natile-McMenemy N, DeLeo JA. The CNS role of Toll-like receptor 4 in innate neuroimmunity and painful neuropathy. *Proc Natl Acad Sci U S A*. 2005; 102:5856–5861. [PubMed: 15809417]
- Thompson ME, Barkhuizen A. Fibromyalgia, hepatitis C infection, and the cytokine connection. *Curr Pain Headache Rep*. 2003; 7:342–347. [PubMed: 12946286]
- Tsui JI, Cheng DM, Coleman SM, Blokhina E, Briden 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, Cheng DM, Libman H, Briden C, Samet J. Hepatitis C virus infection is associated with painful symptoms in HIV-infected adults. *AIDS Care*. 2012; 24:820–827. [PubMed: 22272656]
- Tsui JI, Herman DS, Kettavong M, Anderson BJ, Stein MD. Chronic pain and hepatitis C virus infection in opioid dependent injection drug users. *J Addict Dis*. 2011; 30:91–97. [PubMed: 21491290]
- Turk DC, Swanson KS, Gatchel RJ. Predicting opioid misuse by chronic pain patients: a systematic review and literature synthesis. *Clin J Pain*. 2008; 24:497–508. [PubMed: 18574359]
- Vassilopoulos D, Calabrese LH. Extrahepatic immunological complications of hepatitis C virus infection. *AIDS*. 2005; 19(Suppl 3):S123–127. [PubMed: 16251807]
- Vickerman P, Hickman M, May M, Kretzschmar M, Wiessing L. Can hepatitis C virus prevalence be used as a measure of injection-related human immunodeficiency virus risk in populations of injecting drug users? An ecological analysis *Addiction*. 2010; 105:311–318. [PubMed: 19922515]

- Wachholtz A, Gonzalez G. Co-morbid pain and opioid addiction: long term effect of opioid maintenance on acute pain. *Drug Alcohol Depend.* 2014; 145:143–149. [PubMed: 25456326]
- Watkins LR, Maier SF. Immune regulation of central nervous system functions: from sickness responses to pathological pain. *J Intern Med.* 2005; 257:139–155. [PubMed: 15656873]
- Whitehead AJ, Dobscha SK, Morasco BJ, Ruimy S, Bussell C, Hauser P. Pain, substance use disorders and opioid analgesic prescription patterns in veterans with hepatitis C. *J Pain Symptom Manage.* 2008; 36:39–45. [PubMed: 18358690]
- Zylberberg H, Rimaniol AC, Pol S, Masson A, De Groote D, Berthelot P, Bach JF, Brechot C, Zavala F. Soluble tumor necrosis factor receptors in chronic hepatitis C: a correlation with histological fibrosis and activity. *J Hepatol.* 1999; 30:185–191. [PubMed: 10068094]

Highlights

Among persons on opioid agonist therapy, hepatitis C virus (HCV) status did not affect tolerance to pain.

There was a high prevalence of chronic pain overall in the sample (68%).

All persons, regardless of HCV status, demonstrated low pain tolerance.

Table 1

Characteristics of Study Sample by Group Status

	Overall	Uninfected Controls	HCV Mono- infected	HCV/HIV Co- infected
	n=106 (%)	n=41 (%)	n=40 (%)	n=25 (%)
Median Age (IQR)	45 (37, 51)	42 (33, 49)	44 (36, 52)	50 (44, 53)
Female	51 (48.1)	23 (56.1)	18 (45.0)	10 (40.0)
Non-white race	34 (32.1)	11 (26.8)	12 (30.0)	11 (44.0)
High school graduate	84 (79.2)	34 (82.9)	31 (77.5)	19 (76.0)
Married/Partnered	65 (61.3)	23 (56.1)	23 (57.5)	19 (76.0)
On disability	47 (44.3)	11 (26.8)	16 (40.0)	20 (80.0)
1 night homeless, past 3 months	22 (20.8)	7 (17.1)	7 (17.5)	8 (32.0)
Smoker	88 (83.0)	31 (75.6)	35 (87.5)	22 (88.0)
Methadone (vs. buprenorphine)	20 (18.9)	4 (9.8)	10 (25.0)	6 (24.0)
Years on OAT, median (IQR)	2.0 (1.0, 3.0)	2.0 (1.5, 4.0)	1.5 (0.8, 3.0)	1.5 (0.7, 3.0)
Dose of OAT (mg), median (IQR)				
Methadone (n=20)	60 (41.5, 89)	41.5 (30, 69)	69.5 (45, 96)	56.3 (50, 75)
Buprenorphine (n=86)	16 (16, 16)	16 (16, 16)	16 (12, 16)	16 (16, 16)
Current gabapentin use	33 (31.1)	13 (31.7)	14 (35.0)	6 (24.0)
Heroin use, ever	102 (96.2)	37 (90.2)	40 (100)	25 (100)
IDU, ever	82 (77.4)	19 (46.3)	38 (95.0)	25 (100)
STAI Anxiety score, median (IQR)	31.5 (25.0, 48.0)	31.0 (25.0, 50.0)	32.0 (25.0, 46.0)	32.0 (25.0, 43.0)
Pain catastrophizing score, Median (IQR)	32.0 (18.0, 39.0)	31.0 (18.0, 38.0)	33.0 (17.0, 39.5)	32.0 (23.0, 43.0)
PHQ-9 Depression score, median (IQR)	10.0 (6.0, 17.0)	10.0 (7.0, 17.0)	12.0 (4.5, 17.0)	9.0 (4.0, 15.0)
Recent amphetamine use, urine drug test	3 (2.8)	1 (2.4)	1 (2.5)	1 (4.0)
Recent cocaine use, urine drug test	11 (10.4)	2 (4.9)	6 (15.0)	3 (12.0)
Recent opiate use, urine drug test	17 (16.0)	7 (17.1)	4 (10.0)	6 (24.0)

	Overall	Uninfected Controls	HCV Mono- infected	HCV/HIV Co- infected
	n=106 (%)	n=41 (%)	n=40 (%)	n=25 (%)
Recent benzodiazepine use, urine drug test	8 (7.5)	2 (4.9)	4 (10.0)	2 (8.0)
Current pain (pain past week)	89 (84)	33 (80)	37 (93)	19 (76)
Chronic pain (3 months)	71 (68)	25 (61)	30 (77)	16 (64)
Pain severity, median (IQR) (n=89)	4.0 (3.0, 5.8)	3.8 (3.0, 5.8)	4.0 (3.0, 5.0)	4.0 (2.5, 6.0)
Pain interference, median (IQR) (n=89)	4.6 (2.6, 6.3)	4.4 (3.3, 7.0)	4.4 (2.4, 6.1)	5.0 (2.3, 6.1)
HIV viral load, median (IQR) (n=20) copies/mL	36.5 (10.0, 130.0)			36.5 (10.0, 130.0)
CD4 count, median (IQR) (n=25) cells/ μ L	593.0 (416.0, 768.0)			593.0 (416.0, 768.0)
CD4 count (<200 cells/ μ L) (n=25)	2 (8)			2 (8)
Currently taking medications for HIV (n=25)	24 (96)			24 (96)
HCV viral load, median (IQR) (n=65) IU/mL	674902.0 (200001.0, 2345110.0)		694904.5 (91501.5, 2293055.5)	671796.0 (436000.0, 2663965.0)
HCV genotype (n=53)				
1	44 (83)		25 (83)	19 (83)
2	2 (4)		1 (3)	1 (4)
3	3 (6)		2 (7)	1 (4)
4	4 (7)		2 (7)	2 (9)

Table 2

Results from multiple linear regression models: adjusted means and ratio of means*

	Adjusted Means**	Adjusted Ratio of Means (95% CI)	$p^{\dagger}$
Cold tolerance			
Uninfected Controls	25.7	ref	0.93
HCV Mono-infected	26.8	1.04 (0.78, 1.38)	
HCV/HIV Co-infected	25.3	0.98 (0.69, 1.40)	
Cold threshold			
Uninfected Controls	8.9	ref	0.49
HCV Mono-infected	10.0	1.13 (0.92, 1.38)	
HCV/HIV Co-infected	9.6	1.08 (0.84, 1.38)	
Windup Ratio			
Uninfected Controls	2.5	ref	0.79
HCV Mono-infected	2.5	1.01 (0.71, 1.43)	
HCV/HIV Co-infected	2.8	1.15 (0.74, 1.78)	

* Means for cold tolerance, cold threshold, and windup ratio outcomes were back-transformed to original units after regression analyses of log-transformed values

** Adjusted for demographics, plus education, disability, type and duration of opioid agonist therapy, depression (PHQ-9), pain catastrophizing, state trait anxiety (STAI), and gabapentin use

† Represents global p-value, pairwise comparison conducted only if global p-value significant at $\alpha=0.05$

Table 3
Fully Adjusted Logistic Regression Results, Relative Odds for Current or Chronic Pain

	Current Pain		Chronic Pain	
	OR (95% CI)	p	OR (95% CI)	p
Uninfected Controls	ref	0.25	ref	0.15
HCV Mono-infected	2.45 (0.53, 11.21)		2.13 (0.69, 6.58)	
HCV/HIV Co-infected	0.56 (0.11, 2.80)		0.58 (0.14, 2.39)	
Age	1.04 (0.95, 1.13)	0.39	0.98 (0.92, 1.04)	0.44
Female	1.72 (0.48, 6.15)	0.41	0.45 (0.17, 1.20)	0.11
Non-white race	0.46 (0.11, 2.05)	0.31	0.99 (0.32, 3.13)	0.99
High school graduate	1.15 (0.25, 5.35)	0.86	2.20 (0.67, 7.22)	0.19
On disability	0.84 (0.20, 3.59)	0.81	5.12 (1.42, 18.44)	0.01
Methadone (v. buprenorphine)	2.77 (0.37, 20.67)	0.32	1.39 (0.35, 5.56)	0.64
OAT years	ref	0.50	ref	0.82
1 st quartile	5.92 (0.50, 70.07)		0.72 (0.18, 2.87)	
2 nd quartile	1.05 (0.21, 5.23)		1.37 (0.35, 5.46)	
3 rd quartile	1.09 (0.21, 5.56)		1.13 (0.28, 4.57)	
4 th quartile				
PHQ-9	1.05 (0.93, 1.19)	0.44	1.06 (0.97, 1.16)	0.22
PCS	1.03 (0.98, 1.08)	0.33	1.00 (0.97, 1.04)	0.87
STAI	1.03 (0.96, 1.10)	0.40	1.00 (0.96, 1.05)	0.99