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Predictors of pain-related functional impairment among people living with HIV on long-term opioid therapy

David P. Serota, MD, MSc[1],[2], **Christine Capozzi, MPH**[3], **Sara Lodi, PhD**[4], **Jonathan A. Colasanti, MD, MSPH**[1], **Leah S. Forman, MPH**[5], **Judith I. Tsui, MD, MPH**[6], **Alexander Y. Walley, MD, MSc**[3],[7], **Marlene C. Lira, BA**[3], **Jeffrey Samet, MD, MA, MPH**[3],[7], **Carlos del Rio, MD**[1], **Jessica S. Merlin, MD, PhD, MBA**[8]

[1]Division of Infectious Diseases, Department of Medicine, Emory University, Atlanta, Georgia

[2]Division of Infectious Diseases, Department of Medicine, University of Miami Miller School of Medicine, Miami, Florida

[3]Clinical Addiction Research and Education (CARE) Unit, Section of General Internal Medicine, Department of Medicine, Boston Medical Center, Boston, Massachusetts

[4]Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts

[5]Biostatistics and Epidemiology Data Analytics Center (BEDAC), Boston University School of Public Health, Boston, Massachusetts

[6]Department of Medicine, University of Washington, Seattle, Washington

[7]Department of Community Health Sciences, Boston University School of Public Health, Boston, Massachusetts

[8]Division of General Internal Medicine, Center for Research on Healthcare, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Abstract

People living with HIV (PLWH) have high levels of functional impairment due to pain, also called pain interference. Long-term opioid therapy (LTOT) is commonly prescribed for chronic pain among PLWH. We sought to better understand the predictors of pain interference, measured with the Brief Pain Inventory Interference subscale (BPI-I), among PLWH with chronic pain on LTOT. Using a prospective cohort of PLWH on LTOT we developed a model to identify predictors of increased pain interference over 1 year of follow up. Participants (n=166) were 34% female, 72% African American with a median age of 55 years, and 40% had severe pain interference (BPI-I ≥7). In multivariable models, substance use disorder, depressive symptoms, PTSD symptoms, financial instability, and higher opioid doses were associated with increased pain interference.

Corresponding Author: David P. Serota, MD, MSc, Division of Infectious Diseases, Department of Medicine, University of Miami Miller School of Medicine, 1120 NW 14th Street, Suite 851, Miami, Florida 33136, United States, Phone: 305-243-6331, Fax: 888-246-4258, dserota@med.miami.edu.

Conflict of Interest

The authors report no conflicts of interest

Data sharing

These data are not publicly available

Measures of behavioral health and socioeconomic status had the most consistent association with pain interference. In contrast, the biomedical aspects of chronic pain and LTOT—comorbidities, duration of pain—were not predictive of pain interference. PLWH with chronic pain on LTOT with lower socioeconomic status and behavioral health symptoms have higher risk of pain interference. Addressing the social determinants of health and providing access to behavioral health services could improve patients' pain-related functional status.

Keywords

chronic pain; opioid use; social determinants of health

Introduction

Chronic pain is an important public health concern (Sogomonian et al., 2016), especially for people living with HIV (PLWH) (Bruce et al., 2017). Over 20% of the United States population reports chronic pain, while 8% of Americans suffer from high-impact chronic pain interfering with life or work activities (Dahlhamer et al., 2018). Although the reported prevalence of chronic pain among PLWH varies widely, between 39% and 85%, it is universally high, and often severe (Bruce, et al., 2017; Miaskowski et al., 2011; Parker, Stein, & Jelsma, 2014). Chronic pain is associated with negative HIV outcomes, including increased healthcare utilization, decreased quality of life, retention in care, and viral suppression (Merlin et al., 2018; Merlin, Westfall, et al., 2012; Sabin et al., 2018).

PLWH also have high levels of functional impairment due to pain, called pain interference. Pain interference is often measured with the Brief Pain Inventory Interference scale (BPI-I), and describes how pain impacts one's ability to work, maintain relationships, and enjoy life (Cleeland, 2009). In a cohort of 156 PLWH, 28% reported moderate to severe pain interference (Merlin, Cen, et al., 2012). The reasons for such high levels of functional impairment are not clear. However, one possibility is that PLWH have a higher prevalence of substance use disorders (SUD), mental health disorders, and multimorbidity-related disability than the general population, all of which are also more common among people with chronic pain (Bair, Robinson, Katon, & Kroenke, 2003; Do et al., 2014; Johs et al., 2017; Morasco et al., 2011; Uebelacker et al., 2015; Wong et al., 2018). Therefore, the presence and activity of chronic pain risk factors among PLWH might explain their higher levels of pain interference.

Identifying modifiable factors associated with pain interference in PLWH is important to help guide clinical resources and to design interventions aimed at the drivers of pain interference. Because there is evidence suggesting that long-term opioid therapy (LTOT) may be prescribed more commonly and at higher doses among PLWH (Becker et al., 2016; Silverberg et al., 2012), we focused on a group frequently encountered in HIV primary care —PLWH with chronic pain and receiving LTOT (Becker, et al., 2016; Edelman et al., 2013; Silverberg, et al., 2012). The biopsychosocial model of chronic pain in PLWH suggests that biological, psychological, and social factors are all important contributors to the experience of pain among PLWH, who face unique challenges in each of those domains (Merlin et al.,

2014). Our objective was to investigate the association between factors from the biopsychosocial model and pain interference among a group of PLWH on LTOT. Based on this model, we hypothesized that psychological factors—including depressive symptoms and SUD—would be associated with higher levels of pain interference rather than biomedical or social variables (Barry, Pilver, Potenza, & Desai, 2012; Morasco, Corson, Turk, & Dobscha, 2011; Morasco et al., 2013).

Methods

Study design and population

We used data collected as part of a prospective observational cohort study of PLWH on long-term opioid therapy in two HIV clinics in Atlanta, Georgia and Boston, Massachusetts. Both clinics are housed within their respective city's largest safety-net healthcare systems and care for underserved populations. The Atlanta-based clinic is a Ryan White HIV/AIDS Program–funded clinic, serving >6000 patients who are predominantly African American. The Boston-based clinic serves 1400 patients from a variety of communities including low-income families, minorities, and immigrants. The primary study was the Targeting Effective Analgesia in Clinics for HIV (TEACH) study, a randomized controlled trial (RCT) of an intervention to improve opioid prescribing in HIV clinics (NCT02564341). The patient cohort (NCT02525731) was created in part to study self-reported outcomes of PLWH on LTOT. In the RCT, clinic providers caring for PLWH on LTOT were randomized along with their patients to a collaborative care intervention or a control condition to evaluate for changes in guideline-concordant opioid prescribing. Detailed description of the study population and design has been published previously (Colasanti et al., 2019; Lira et al., 2019). Participant enrollment began in July 2015 with follow up through February 2018.

Patients included in the cohort, and the current analyses, met the following criteria: ≥18 years; living with HIV, fluent in English, and receiving LTOT (≥3 opioid prescriptions written at least 21 days apart during the preceding 6 months) (Starrels et al., 2010). Potential participants were identified using the electronic medical record and those who consented into the study completed a 60- to 90-minute survey, administered verbally by a research assistant. Participants were contacted approximately 12 months later to complete the same survey. At both sites, data from the medical record were extracted by dedicated personnel (Clinical Data Warehouse at Boston Medical Center and Center for AIDS Research at Emory University). Study staff then conducted audits on 10% of the data to ensure accuracy. Study participants received compensation for their two visits. Research staff entered survey responses electronically directly using REDCap (Harris et al., 2009).

The TEACH study was approved by the institutional review boards at the Boston University Medical Campus, Emory University School of Medicine, and the Grady Health System Research Oversight Committee.

Outcome definition

The primary outcome variable for this study was the Brief Pain Inventory (BPI) interference subscale (BPI-I), measured at baseline and at 12 months, collected verbally by a research

assistant during the survey. This subscale has been validated as a measure of pain-related functional status and includes questions about the degree to which pain interferes with multiple domains (general activity, mood, walking ability, work, relationships, sleep, and enjoyment of life) over the preceding week, rated from 0 to 10 (0-does not interfere at all, 10-completely interferes) (Cleeland, 2009; Keller et al., 2004; Krebs et al., 2018). The BPI-I subscale score is computed as the average score of these questions. For descriptive analyses, we used a cutoff of ≥7/10 to define severe pain interference in order to characterize the subset of participants with the highest levels of impairment due to pain (Castel et al., 2007; Zelman, Dukes, Brandenburg, Bostrom, & Gore, 2005), while the outcome for inferential statistics was BPI-I as a continuous variable.

Predictors of Interest

Potential predictors of pain interference were chosen *a priori* based on literature review and expert knowledge (Barry, Pilver, Hoff, & Potenza, 2013; Merlin, Cen, et al., 2012; Morasco, Corson, et al., 2011; Morasco, et al., 2013; Mun et al., 2019; Uebelacker, et al., 2015; Wong, et al., 2018). All measures were self-reported or taken from medical record review. We organized our evaluation around the biopsychosocial framework. (Blake et al., 1995). Biomedical and health-related variables included comorbidity level (Charlson Comorbidity Index [CCI]) (Charlson, Pompei, Ales, & MacKenzie, 1987), pain location and duration, presence of multiple pain sites, and opioid dose in the prior 30 days as measured by milligrams of morphine equivalent daily dose (MEDD), HIV viral load, and CD4 cell count. Psychological variables included SUD (Texas Christian University Drug Screen II, 2007), depressive symptoms (Center for Epidemiologic Studies Depression Scale [CESD]) (Lewinsohn, Seeley, Roberts, & Allen, 1997), anxiety symptoms (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), and post-traumatic stress disorder (PTSD) symptoms, all collected by survey. Social variables included education level, income, and housing and food insecurity (Kim et al., 2017; Vogenthaler et al., 2010). Financial security was assessed by asking if participants had run out of money for basic needs.

Statistical Analysis

Descriptive statistics were used to characterize the study sample at baseline, overall and stratified by baseline BPI-I score (≥7 versus <7). A covariance matrix was created for the independent variables. There was high covariance between measures of depression, PTSD, and anxiety. Cross-sectional data was used from baseline and the follow-up visit to increase the sample size, but was then adjusted for within-subject correlation over the two time points. To identify predictors of BPI-I, a series of mixed linear regression models with random intercepts and slopes were fit using data from both visits. First, unadjusted models for each potential predictor of interest were estimated. Second, a stepwise selection procedure was performed in order to maximize the Bayesian Interference Criterion (BIC), a measure of model fit statistic. Age and gender were forced into the final multivariable model. We were interested in the association between both depression and PTSD with pain interference (Barry, et al., 2012; Morasco, et al., 2013), however, due to the high covariance between the mental health variables, we created two separate multivariable models using each as these variables as the representative candidate. BIC was chosen to maximize use of

the available data while minimizing overfitting of the model to our data, which could decrease external validity. Analyses were performed using SAS 9.4 (Cary, North Carolina).

Results

Baseline characteristics for the 166 study participants, all of whom were PLWH on LTOT, are shown in Table 1 stratified by pain interference severity. The median age of participants was 55 years (IQR 49-59), 66% were male, and 72% were African American. Participants faced challenges including disability, low education, and food and financial insecurity. Depressive symptoms were common (41% with CESD ≥16) as were symptoms of PTSD (23%); 10% had a SUD and 10% an alcohol use disorder. The median dose of opioids was 15 mg MEDD (IQR 4-36) with a range from 0 to 260 mg. Forty percent of participants reported severe pain interference at baseline, with median BPI-I score of 6.1 (IQR 4.1-7.7).

Bivariate associations between exposures and pain interference are shown in Table 2. In the primary multivariable model (Model 1), depression (beta=0.9, 95% CI 0.3-1.5) and SUD (beta=1.1, 95% CI 0.1-2.0) were independently associated with higher pain interference (Table 2). Being female (beta=0.8, 95% CI 0.1-1.6) and experiencing financial insecurity (beta=1.0, 95% CI 0.4-1.7) were also associated with higher average BPI-I. Participants with joint pain as their primary pain etiology had higher pain interference (beta= 0.9, 95% CI 0.2-1.7). For every 10 MEDD increase, the expected BPI-I score was 0.1 (95% CI 0.0-0.1) higher. When depression was replaced with PTSD symptoms in the analyses (Model 2), PTSD symptoms were associated with an average increase in BPI-I of 1.6 (95% CI 0.9-2.3).

Discussion

In this cohort of PLWH with chronic pain on LTOT, severe pain interference was common, with more than a third reporting severe functional impairment from their pain. We found that behavioral health symptoms (depression and PTSD), SUD, and a measure of socioeconomic status (financial instability) predicted higher BPI-I scores. Pain-related factors associated with higher pain interference included joint pain and higher opioid dose. Factors from social, psychological, and biomedical domains all contributed significantly to pain interference over the study period, especially depression, PTSD, and SUD, which are potential targets for interventions (Merlin, et al., 2014). While some of these associations have been observed in prior research, these data confirm the importance of mental health and social factors for pain interference among PLWH with chronic pain.

In our study, depressive symptoms were associated with increased pain interference (Barry, et al., 2012; Uebelacker, et al., 2015). The relationship between pain and depressive symptoms is bidirectional: depression is associated with decreased pain tolerance and more distress from painful stimuli (Hassett et al., 2018) and conversely, people with chronic pain have an increased rate of developing incident depression (Hilderink, Burger, Deeg, Beekman, & Oude Voshaar, 2012). When compared to isolated pain or depression, the combination of chronic pain and depression is associated with a synergistic negative effect on functional impairment (Dhanju et al., 2019). This relationship is further complicated by the fact that initiation of LTOT is associated with the development of depression, and

patients with depression are more likely to receive opioids for chronic pain (Mazereeuw, Sullivan, & Juurlink, 2018). For PLWH who have higher rates of depression and chronic pain, the relationship between depression and pain interference is likely magnified (Do, et al., 2014). The results of this study extend research identifying an association between depressive symptoms and pain interference to PLWH. Our findings reinforce the importance of the co-management of depression in patients with chronic pain (Uebelacker et al., 2016).

Based on our model, PTSD symptoms had a strong association with pain interference. Similar to depression, prior studies have shown that people with PTSD are more likely to have pain interference and are also more likely to receive LTOT (Phifer et al., 2011). PTSD leads to maladaptive illness-focused pain coping strategies, such as guarding, activity avoidance, and deferring tasks to others (Morasco, et al., 2013). Higher pain interference among those with PTSD is mediated by higher rates and severity of depression. PLWH have higher rates of PTSD (McLean & Fitzgerald, 2016), which in turn contributes to the higher pain interference among PLWH compared to the general population. These data highlight the need to assess for symptoms of depression and PTSD in PLWH with chronic pain and suggest that intervention on both pain and psychiatric conditions may improve pain-related functional status.

Substance use disorder was associated with increased pain interference independent of depression. SUDs are associated with negative coping strategies, such as excessive focus on pain and feelings of helplessness, which may lead to greater pain interference (Kneeland, Griffin, Taghian, Weiss, & McHugh, 2019; Zale, Maisto, & Ditre, 2015). At the same time, pain is associated with increased substance use and craving among PLWH (Tsui et al., 2013; Tsui et al., 2014; Tsui et al., 2016). In a trial of patients with chronic pain, Morasco and colleagues showed that implementation of a collaborative care intervention attenuated the negative effect of SUDs on pain interference, indicating that clinic-based behavioral interventions have potential to make improvements often not achieved by pain medications (Morasco, Corson, et al., 2011). Once identified, patients with SUD should be counseled and referred for treatment, ideally in a behavioral health program integrated into primary care.

We identified a history of “running out of money for basic needs often” as being associated with an average of 1 point more interference on the BPI-I. A prior study in a similar cohort of urban, low SES, PLWH showed that lower educational attainment was associated with worse pain severity (Miaskowski, et al., 2011). A lower SES environment and financial strain leads to lower perceived control, lower self-esteem, and a more pessimistic outlook, which contribute to negative health outcomes including lower functional status, depression, and anxiety (Gallo, de Los Monteros, & Shivpuri, 2009; Kahn & Pearlin, 2006; Mun, et al., 2019). Although not directly modifiable in the clinical setting, provider understanding of how SES impacts a patient’s function and coping can be helpful to delivering optimal care. Ideally, HIV care should be multidisciplinary and include access to a social work or case manager team in addition to counselors and mental health providers.

Over one third of the PLWH in this cohort suffered from severe pain interference at baseline despite access to comprehensive medical care and receipt of LTOT. The efficacy of LTOT for the management of chronic pain has not been demonstrated (Busse et al., 2018; Krebs, et

al., 2018) and novel approaches to improving pain-related function are needed in HIV primary care clinics. Clinical care for HIV in this cohort was successful, with virologic suppression for 89%, despite chronic pain and other comorbidities. As aging PLWH become more clinically complex beyond management of HIV itself, these results help to prioritize modifiable risk factors for poor functional outcomes due to pain: financial instability, SUD, and behavioral health conditions.

We found that increased daily opioid dose was associated with increased pain interference. Based on the observational nature of this study, we cannot determine whether high opioid dose caused higher pain interference or if it represents the fact that patients with more severe pain might receive higher doses of opioids. The SPACE trial compared opioid vs non-opioid approaches for chronic musculoskeletal pain and found no difference in pain interference between groups, but higher pain severity in those randomized to receive opioids, which supports the idea that opioids may have negative consequences on pain (Krebs, et al., 2018). Furthermore, studies of opioid dose-reduction have demonstrated improvements in function and quality of life with decreasing MEDD (Frank et al., 2017). However, both the CDC and the FDA released warnings to prescribers and patients about the risks of rapidly tapering opioids or abruptly stopping them (Dowell, Haegerich, & Chou, 2019; “FDA identifies harm reported from sudden discontinuation of opioid pain medicines and requires label changes to guide prescribers on gradual, individualized tapering,” 2019). While MEDD was used as a continuous variable in this study, the relationship between MEDD and pain interference may not be linear and could have been more prominent among those with the highest opioid doses.

This study has several limitations. As an observational study, unmeasured confounding could explain the association between the exposures and pain interference. While we have identified variables with statistically significant associations with pain interference, these data should not be taken as proof of causality and are instead exploratory and hypothesis generating. We cannot conclude that addressing these variables will improve pain-related function, but these observations provide hypotheses for future interventions and inform clinical practice. Although the magnitude of association for many of the predictors (about 1 point on the BPI-I) is considered clinically meaningful in pain intervention trials (Krebs, et al., 2018), it is not as easily interpretable in an observational study. Finally, because we used a predictive modeling approach and had limited power based on sample size, we did not assess for interaction and conclusions about the synergistic effect of multiple variables cannot be drawn.

Conclusion

Using data from a prospective cohort of PLWH on LTOT we evaluated how biomedical, psychological, and social variables impact pain interference. We found that depressive symptoms, PTSD symptoms, substance use disorders, financial stress, and higher opioid doses were predictive of higher pain interference as measured by the BPI-I. In contrast, age, race, comorbidity level, and pain duration were not associated with the level of pain-related functional status. Overall, these findings highlight patient characteristics that should warn clinicians of an elevated risk of future pain-related impairment. These results also help

identify future areas of potential intervention—especially financial insecurity and mental health—to mitigate pain interference among PLWH with chronic pain.

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Table 1.

Baseline characteristics in a cohort of people living with HIV on long-term opioid therapy

Variable	Overall (N=166), n (%)	BPI interference ≥7 (N=66), n (%)	BPI interference <7 (N=100), n (%)
Age, median (IQR)	55 (49-59)	54 (49-59)	55 (49-59)
Female	57 (34)	25 (38)	32 (32)
Race			
White	31 (19)	12 (18)	19 (19)
Black/African American	120 (72)	48 (73)	72 (72)
Other	15 (9)	6 (9)	9 (9)
Hispanic	15 (9)	8 (12)	7 (7)
Employment			
Working full or part time	33 (20)	9 (14)	24 (24)
Disabled	119 (72)	52 (79)	67 (67)
Other	14 (8)	5 (8)	9 (9)
Did not graduate high school	55 (33)	23 (35)	32 (32)
Ran out of money for basic necessities, past 12 months			
Often (monthly or more often)	48 (29)	21 (32)	27 (27)
Occasionally	55 (33)	25 (38)	30 (30)
Never	63 (38)	20 (30)	43 (43)
Did not eat for ≥2 days in the past 30 days for financial reasons	21 (13)	11 (17)	10 (10)
No health insurance	13 (8)	4 (6)	9 (9)
CD4 T-cell count (cells/mm^3), median (IQR)	449 (305-695)	439 (317-636)	476 (303-720)
Undetectable HIV viral load (<200 copies/mL)	147 (89)	62 (94)	85 (86)
HCV antibody positive	45 (27)	20 (30)	25 (25)
Charlson comorbidity index score, median (IQR)	7 (6-9)	7 (6-8)	7 (6-9)
Years of chronic pain, median (IQR)	8 (2-11)	6 (2-12)	8 (3-11)
Years of LTOT, median (IQR)	5 (2-10)	5 (2-10)	5 (2-10)
MEDD 30 days before baseline (mg), median (IQR)	15 (4-36)	15 (4-34)	15 (4-37)
Site of worse pain			
Joint pain	53 (32)	26 (39)	27 (27)
Back pain	53 (32)	23 (35)	30 (30)
Feet pain	21 (13)	8 (12)	13 (13)
Other pain	35 (21)	9 (14)	26 (26)
No pain	4 (2)	0 (0)	4 (4)
Multisite pain	24 (15)	12 (18)	12 (12)
Depression screen positive	76 (46)	28 (42)	48 (48)
PTSD screen positive	29 (18)	15 (23)	14 (14)
Anxiety screen score, median (IQR)	28 (24-38)	32 (26-41)	27 (24-34)

Variable	Overall (N=166), n (%)	BPI interference ≥7 (N=66), n (%)	BPI interference <7 (N=100), n (%)
Alcohol use disorder (TCA II)	17 (10)	7 (11)	10 (10)
Substance use disorder (TCA II) *	16 (10)	8 (12)	8 (8)

BPI, Brief Pain Inventory; IQR, interquartile range; LTOT, long-term opioid therapy; MEDD, morphine equivalent daily dose

* There were 23 SUD overall, 6 had multiple SUDs. Only the primary substance used is represented in the table (N=16). Frequencies were cocaine (N=12), cannabis (N=6), opioid (N=3), stimulant (N=1), and clonidine (N=1)

Table 2.

Predictors of higher pain interference among people living with HIV on long-term opioid therapy over 1 year

Variable	Unadjusted Beta (95% CI)	P-value	Model 1: Adjusted Beta (95% CI)	Model 1: P-value	Model 2: Adjusted Beta (95% CI)	Model 2: P-value
Age (per 10 years)	0.09 (−0.41, 0.58)	0.73	−0.02 (−0.47, 0.43)	0.93	−0.06 (−0.51, 0.38)	0.78
Gender						
Female	1.10 (0.32, 1.89)	<0.01	0.84 (0.12, 1.56)	0.02	0.66 (−0.06, 1.39)	0.07
Male	Ref		Ref		Ref	
Race						
African American	−0.10 (−1.10, 0.90)	0.97				
Other	0.00 (−1.56, 1.55)	0.97				
White	Ref					
High school graduate	0.45 (−1.26, 0.36)	0.27				
Run out of money for needs (1)						
Often	1.24 (0.51, 1.98)	<0.01	1.04 (0.35, 1.74)	0.01	0.93 (0.23, 1.62)	0.03
Occasionally	0.69 (−0.05, 1.42)	<0.01	0.54 (−0.16, 1.23)	0.01	0.49 (−0.21, 1.18)	0.03
Never	Ref		Ref		Ref	
Depression screen positive (2)	1.09 (0.46, 1.72)	<0.01	0.89 (0.29, 1.48)	<0.01		
PTSD screen positive (3)	1.86 (1.14, 2.58)	<0.01			1.56 (0.86, 2.26)	<0.01
Substance use disorder (4)	1.38 (0.39, 2.36)	<0.01	1.08 (0.14, 2.01)	0.02		
Alcohol use disorder (4)	1.06 (−0.06, 2.19)	0.06				
CCI (per 1 point)	0.01 (−0.18, 0.19)	0.95				
Worst pain site						
Joint	1.02 (0.24, 1.80)	<0.01	0.92 (0.16, 1.67)	<0.01	0.96 (0.20, 1.72)	<0.01
Feet	−0.12 (−1.17, 0.92)	<0.01	−0.08 (−1.08, 0.93)	<0.01	−0.12 (−1.12, 0.88)	<0.01
Other/none	−1.06 (−1.84, −0.27)	<0.01	−1.01 (−1.77, −0.26)	<0.01	−0.91 (−1.67, −0.16)	<0.01
Back	Ref		Ref		Ref	
Multisite pain	0.62 (−0.38, 1.62)	0.22				
Opioid dose (per 10 mg MEDD)	0.06 (−0.01, 0.13)	0.09	0.07 (0.01, 0.13)	0.03	0.07 (0.01, 0.13)	0.02
Pain duration (years)						
10+	−0.40 (−1.25, 0.46)	0.54				
5-10	0.10 (−0.93, 1.14)	0.54				
<5	Ref					

Model 1: Depression used as the candidate mental health condition

Model 2: PTSD used as the candidate mental health condition

CCI, Charlson Comorbidity Index; MEDD, morphine equivalent daily dose

1. "How often in the past 12 months did you run out of money for basic needs?" Occasionally=less than monthly, often=monthly or more

2. Center for Epidemiologic Studies Depression Scale

3. PTSD Check List – Civilian Version (PCL-C)

4. Texas Christian University Drug Screen V