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Pain Intensity as a Moderator of the Association between Opioid Use and Insomnia Symptoms among Adults with Chronic Pain

Mary Beth Miller¹, Wai Sze Chan², Ashley F. Curtis¹, Jeff Boissoneault³, Michael Robinson³, Roland Staud⁴, Richard B. Berry⁴, and Christina S. McCrae¹

¹Department of Psychiatry, University of Missouri School of Medicine, Columbia, MO, USA

²Department of Psychiatry, Geisel School of Medicine at Dartmouth, Lebanon, NH, USA

³Department of Clinical and Health Psychology, University of Florida, Gainesville, FL, USA

⁴Department of Medicine, University of Florida, Gainesville, FL, USA

Abstract

Objective: Research documenting the impact of opioid use on sleep among individuals with chronic pain has been mixed. This study aimed to determine if pain intensity moderates the association between opioid use and insomnia symptoms among adults with comorbid symptoms of insomnia and chronic widespread pain.

Methods: Participants ($N=144$; 95% female; mean age=51.6, $SD=11.4$) completed assessments of insomnia symptoms, pain, and use of sleep/pain medication. Multiple regression was used to determine if pain intensity moderates the association between opioid use (yes/no) and sleep onset latency (SOL), wake after sleep onset (WASO), sleep quality, or time in bed. Analyses controlled for gender, symptoms of sleep apnea, symptoms of depression, use of sleep medication (yes/no), and use of non-opioid pain medication (yes/no).

Results: Stronger pain intensity was associated with longer self-reported WASO and worse sleep quality, independent of opioid use. Conversely, opioid use was associated with longer time in bed, independent of pain intensity. Opioid use and pain intensity interacted in the prediction of SOL, such that opioid use (vs. non-use) was associated with longer SOL in the context of mild but not moderate to severe pain intensity.

Conclusions: Opioid use was associated with more difficulty falling asleep among adults with chronic pain; however, this cross-sectional effect was only significant among those reporting lower pain intensity. Authors speculate that this effect is masked among those with severe pain because the pain-related sleep debt they acquire throughout the night then facilitates sleep onset the next day.

Corresponding Author: Christina S. McCrae, Ph.D., One Hospital Drive DC067.00, Columbia, MO 65211, Phone: 1-573-882-0982, Fax: 1-573-884-1070, mccraec@health.missouri.edu.

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Keywords

sleep; insomnia; pain medication; opioid use; fibromyalgia

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1. Introduction

Two out of three adults with chronic pain suffer from insomnia (Marshansky et al., 2018). Insomnia symptoms, including difficulty initiating/maintaining sleep and poor sleep quality (Edinger et al., 2004), are prospective predictors of fibromyalgia and chronic widespread pain (Nitter, Pripp, & Forseth, 2012); and resolution of insomnia symptoms has been associated with improvements in these conditions (Koffel et al., 2016). While the association between sleep and pain is bidirectional, sleep disturbance seems to be a stronger predictor of pain than vice versa (Finan, Goodin, & Smith, 2013; Koffel et al., 2016). Thus, identification of factors that influence insomnia symptoms among adults with chronic pain may inform prevention and treatment efforts for both disorders.

Opioids are among the most widely prescribed pharmacological treatments for individuals with chronic pain (Rasu, Sohraby, Cunningham, & Knell, 2013). While multiple studies have documented a positive association between opioid use and sleep-disordered breathing (Davis, Behm, & Balachandran, 2017; Filiatrault et al., 2016), the association between opioid use and insomnia symptoms is poorly understood. Among individuals with chronic pain, opioid use is associated with improved sleep in some studies (Webster, Smith, Mackin, & Iverson, 2015; Yarlal et al., 2016), is linked to worse insomnia symptoms in other studies (Morasco, O'Hearn, Turk, & Dobscha, 2014), and is not associated with sleep impairment in others (Chapman, Lehman, Elliott, & Clark, 2006; Lintzeris et al., 2016). Indeed, recent reviews noted the paucity of research in this area and concluded that further research is needed to understand the impact of opioids on insomnia symptoms among adults with chronic pain (Cheatle & Webster, 2015; Mystakidou et al., 2011).

One potential contributor to the discrepancy in these findings is individual variation in pain intensity. Greater bodily pain is a prospective predictor of new-onset insomnia in the general population (LeBlanc et al., 2009). Similarly, more intense pain is a unique predictor of insomnia symptoms among those with chronic pain, even when accounting for anxiety and depression (Dragioti, Levin, Bernfort, Larsson, & Gerdle, 2017). Given the negative impact of pain on insomnia symptoms within this population, opioid use may be more helpful in relieving nighttime pain, thereby facilitating sleep, among those experiencing more severe pain.

This study aimed to extend previous research by determining if pain moderates the association between opioid use and insomnia symptoms among individuals with comorbid symptoms of insomnia and chronic pain. Based on data indicating that more severe pain is associated with worse insomnia symptoms (Dragioti et al., 2017; LeBlanc et al., 2009) and opioid use may alleviate pain in some samples (Webster et al., 2015; Yarlal et al., 2016), we hypothesized that opioid use would be associated with shorter sleep onset latency, shorter wake after sleep onset, and better sleep quality among those experiencing more (versus less) intense pain. Time in bed was also identified as an outcome of interest, since extended time

in bed may contribute to symptoms of insomnia (Borbely, Daan, Wirz-Justice, & Deboer, 2016). Collectively, findings are expected to extend previous research by documenting the direct and potentially moderating effects of opioid use and pain intensity on insomnia symptoms among individuals with comorbid symptoms of insomnia and chronic pain.

2. Materials and Methods

2.1. Participants and Procedure

Adults reporting symptoms of insomnia and fibromyalgia were recruited to participate in a randomized controlled trial examining the efficacy of Cognitive Behavioral Therapy for Insomnia among patients with comorbid chronic insomnia and fibromyalgia (McCrae et al., 2018). As part of the baseline screening protocol, participants ($N = 235$) completed one night of ambulatory (at-home) polysomnography (Grass Technologies 25-channel AURA Portable Recording System), two weeks of daily sleep diaries, and two weeks of actigraphy (Phillips Respironics Actiwatch 2). These baseline data were the focus of current analyses. Baseline participants were considered for inclusion in the current data analysis plan ($N = 168$) if they reported (a) an average SOL or WASO >30 minutes across the 14 days of baseline assessment, consistent with diagnosis of insomnia (Lichstein, Durrence, Taylor, Bush, & Riedel, 2003); and an average pain intensity $\geq 10/100$ across the 14 days of baseline, consistent with a rating of at least mild chronic pain (Boonstra et al., 2016). Of those who were considered for inclusion, 144 participants provided sufficient data for inclusion in the data analytic sample (see Data Screening and Analysis Plan). All procedures were approved by the University of Florida's institutional review board.

2.2. Measures

2.2.1. Insomnia symptoms—Participants completed written sleep diaries each day for 14 days. Each morning upon waking, they estimated what time they got into bed; what time they tried to go to sleep; how long it took them to fall asleep (SOL); how many times they woke up during the night and the total duration of these awakenings (WASO); the time of their final awakening; and what time they got out of bed. Participants also rated their sleep quality on a scale from 1 (*very poor*) to 5 (*very good*). Time in bed was calculated as the time elapsed between trying to go to sleep and getting out of bed. Daily estimates were averaged over the 14 days.

Participants also wore wrist actigraphy for the 14 days of baseline assessment. Self-reported (daily diary) outcomes were identified as the primary outcomes of interest because self-report is the recommended method of assessment for insomnia (Schutte-Rodin, Broch, Buysse, Dorsey, & Sateia, 2008). However, actigraphy estimates of SOL and WASO were also examined to determine the extent to which findings generalize to objective measures of insomnia.

2.2.2. Opioid use—On daily sleep diaries, participants indicated (*yes/no*) if they used an opioid pain medication. If yes, they also reported the type and milligrams consumed. For descriptive purposes, milligrams of opioid medication were converted to lowest recommended dosage units (e.g., for codeine, 15mg = 1 and 30mg = 2) and averaged across

the 14 days of baseline assessment. Given the relatively low incidence of opioid use in this sample (35%), analyses focused on the impact of any use (yes/no), rather than the impact of opioid dose.

2.2.3. Pain intensity—Participants rated current pain intensity on a scale from 0 (*no pain*) to 100 (*most intense pain imaginable*) each evening before bed on a visual analogue scale. Daily scores were averaged.

2.2.4. Demographics—Participants provided information regarding their age, gender, race, and ethnicity. On the daily sleep diaries, participants indicated (*yes/no*) if they had taken a sleep medication each day. They also completed one night of ambulatory polysomnography, which was used to calculate each participant's apnea-hypopnea index (AHI), or number of complete or partial pauses in breathing per hour of sleep.

2.3. Data Screening and Analysis Plan

Data were screened for missing values and normality prior to analysis. Of the 168 participants who met inclusion criteria, 24 were missing data on predictor, outcome, or potential confounding variables and, therefore, were excluded from the data analytic sample. Descriptive statistics are depicted in Table 1, and correlations among study variables are depicted in Table 2. Skewness and kurtosis estimates for all variables fell within the acceptable range (Tabachnick & Fidell, 2007).

Analyses were conducted in IBM SPSS Statistics 24. For primary analyses, hierarchical multiple regression was used to examine pain intensity as a moderator of the association between opioid use and self-reported insomnia symptoms (SOL, WASO, and sleep quality). In secondary analyses, the SOL and WASO models were replicated using actigraphy (as opposed to self-reported) outcomes. Gender, baseline symptoms of sleep apnea (measured using AHI), symptoms of depression, use of sleep medication, use of non-opioid pain medication, use of opioid pain medication, and pain intensity were modeled as predictors of insomnia symptoms in Step 1. The two-way interaction between pain intensity and opioid use was added in Step 2. Unstandardized regression coefficients (see Table 3), which indicate the change in the dependent variable associated with one unit increase in the independent variable, were used as indicators of effect size (Baguley, 2009).

Follow-up tests of simple slopes were conducted to determine the significance of the association between opioid use and insomnia symptoms at high, average, and low levels of pain intensity (Cohen, Cohen, West, & Aiken, 2003). High and low values of pain intensity were specified as one standard deviation above and below the mean, respectively. Predictor variables were mean centered to calculate the regression slopes depicted in Figure 1.

3. Results

3.1. Descriptive statistics

Participants ($N=144$; 95% female) were adults reporting comorbid symptoms of insomnia and chronic pain (see Table 1). One in three (35%) reported opioid use over the two weeks of daily diary assessment, while half (55%) reported use of non-opioid pain medication.

3.2. Primary analyses

Main effects and interaction terms are presented in Table 3. Step 1 predictors accounted for a significant amount of variance in sleep onset latency [$F(7, 136) = 3.18, p = .004, \text{Adj. } R^2 = .10$], sleep quality [$F(7, 136) = 4.75, p < .001, \text{Adj. } R^2 = .16$], and time in bed [$F(7, 136) = 4.21, p < .001, \text{Adj. } R^2 = .14$], but not wake after sleep onset [$F(7, 136) = 1.91, p = .07, \text{Adj. } R^2 = .04$]. In Step 2 of the model, the interaction between pain intensity and opioid use predicted a significant amount of unique variance in sleep onset latency, [$F(8, 135) = 3.36, p = .002; R^2 = .03, p = .045$], but not sleep quality [$F(8, 135) = 1.94, p = .06; R^2 = .01, p = .16$], time in bed [$F(8, 135) = 3.79, p < .001; R^2 = .01, p = .35$], or wake after sleep onset [$F(8, 135) = 1.94, p = .06; R^2 = .01, p = .16$]. Follow-up tests of simple slopes indicated that opioid use was associated with longer time to sleep onset in the context of low ($\beta = 27.71, SE = 11.21, p = .02$) but not average ($\beta = 12.88, SE = 7.26, p = .08$) to high ($\beta = -1.95, SE = 9.34, p = .84$) pain intensity (see Figure 1).

3.3 Secondary Analyses

To determine the extent to which findings may generalize to objective measures of insomnia symptoms, regression models were replicated using actigraphy (as opposed to self-report) estimates of SOL and WASO as outcomes (see Table 3). Again, Step 1 predictors accounted for a significant amount of variance in sleep onset latency [$F(7, 132) = 3.63, p = .001, \text{Adj. } R^2 = .12$] but not wake after sleep onset [$F(7, 132) = 1.75, p = .10, \text{Adj. } R^2 = .03$]. In Step 2 of both models, the interaction between pain intensity and opioid use was not significant (see Table 3).

4. Discussion

Opioids are widely prescribed for individuals with chronic pain (Rasu et al., 2013), the majority of whom indicate distress related to sleep (Finan et al., 2013). Yet the association between opioid use and insomnia symptoms in this population is poorly understood. This study builds on previous research by documenting that the association between opioid use and insomnia symptoms differs as a function of pain. In contrast to hypotheses, opioid use was not associated with improvements in insomnia symptoms, regardless of pain intensity; however, it was associated with more difficulty falling asleep in the context of mild pain. The exacerbating effect of opioid use on insomnia symptoms is consistent with some previous research (Morasco et al., 2014; Robertson et al., 2016). Previous studies attributed this association to higher rates of sleep apnea among those on opioid medications (Morasco et al., 2014; Robertson et al., 2016). However, this explanation is unlikely to account entirely for this association, as opioid use remained a significant predictor of insomnia symptoms when controlling for sleep apnea and sleep apnea was not a significant predictor of insomnia symptoms in this sample.

One potential explanation for the isolated effect of opioid use on sleep onset latency among those with less severe pain relates to time spent awake in bed. It is typical for individuals with insomnia to spend more time in bed in order to compensate for inadequate or disrupted sleep; however, this extended time in bed reduces the build-up of 'sleep debt' (sleep drive or 'Process S') that facilitates sleep onset the following night (Borbely et al., 2016). In this

sample, individuals experiencing more severe pain reported more time awake in bed at night (likely due in part to elevations in pain), but similar (if not shorter) amounts of time in bed. In this case, the negative influence of opioids on sleep onset may be masked among those with more severe pain because pain-related insomnia symptoms build 'sleep debt' that then facilitates sleep onset the next day. In support of this hypothesis, opioid use was a marginally significant predictor of increased sleep onset latency and wake after sleep onset measured using actigraphy.

4.1. Clinical Implications

Opioid use was not associated with improvements in insomnia symptoms across any level of pain intensity, and was associated with worse insomnia symptoms among those reporting less intense pain. Clinically, data suggest that individuals on opioid treatment regimens should be instructed to maintain sleep habits that support healthy circadian rhythms (e.g., consistent wake-times), particularly if they are experiencing milder levels of pain. Cognitive Behavioral Therapy for Insomnia (CBT-I) is an ideal treatment to promote healthy sleep patterns within these individuals and is recommended for treatment of insomnia, even if short-term hypnotic treatment is used (Schutte-Rodin et al., 2008; Siebern & Manber, 2011). Given the potentially dangerous drug interactions associated with combined use of opioid and hypnotic medications (Kandel, Hu, Griesler, & Wall, 2017), CBT-I is likely a better alternative to use of hypnotic medications among individuals with comorbid symptoms of insomnia and chronic pain.

4.2. Limitations

This study clarifies the association between opioid use and insomnia symptoms in a population at high risk of problems related to both disorders; however, it had limitations. First, women comprised the majority of the sample. This sample is consistent with higher rates of insomnia and pain among women (Fillingim, King, Ribeiro-Dasilva, Rahim-Williams, & Riley, 2009; Ford, Cunningham, Giles, & Croft, 2015); however, it indicates a need to determine if findings would generalize to men. Second, although participants were strongly encouraged to complete diaries each morning, sleep diaries were completed via paper forms; therefore, the timeliness of reporting cannot be guaranteed. Analyses were also limited to cross-sectional associations that do not represent causal associations among variables. Future studies are needed to establish the temporal precedence of associations between variables and to determine if this effect persists over time.

4.3. Conclusion

Opioid use was associated with longer time to sleep onset among adults with insomnia and chronic pain, but only among those reporting mild symptoms of pain. This association may have been masked among individuals with more severe pain due to pain-related sleep debt. Clinically, findings suggest that it may be important to advise patients reporting symptoms of insomnia about the risks of extending time in bed when providing them with opioid pain medication and that use of behavioral or cognitive-behavioral treatment for insomnia may be recommended. Studies examining the longitudinal associations between opioid use and insomnia symptoms while accounting for individual differences in pain are encouraged.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- One in three individuals with chronic pain reported use of opioid pain medication.
- Opioid use was associated with longer sleep onset latency.
- This association was only significant in the context of less severe pain.

Figure 1.
Pain intensity by opioid use interaction on sleep onset latency.

Table 1. Descriptive statistics for individuals reporting comorbid symptoms of insomnia and chronic pain ($N = 144$).

	<i>N (%) or Mean (SD)</i>
Age	51.6 (11.4)
Female gender	137 (95%)
Race	---
White	112 (78%)
Black	28 (19%)
Native Hawaiian/Pacific Islander	0 (0%)
Asian	0 (0%)
American Indian/Alaska Native	2 (1%)
Bi/Multiracial	2 (1%)
Hispanic/Latino	6 (6%)
Apnea-hypopnea index (AHI)	4.3 (6.4)
AHI < 5	97 (67%)
AHI 5 – 14.9	38 (26%)
AHI ≥ 15	9 (6%)
Symptoms of depression (BDI-II)	17.2 (11.6)
Sleep medication	57 (40%)
Antihistamine	20/57 (35%)
Benzodiazepine or hypnotic	24/57 (42%)
Antidepressant	25/57 (44%)
Days of use out of 14 days (<i>SD</i>)	7.4 (5.1)
Non-opioid pain medication	79 (55%)
Over-the-counter	70 (88%)
Non-steroidal anti-inflammatory	9 (11%)
Days of use out of 14 days (<i>SD</i>)	5.8 (4.6)
Opioid pain medication	51 (35%)
Days of use out of 14 days (<i>SD</i>)	9.1 (4.9)
Pain intensity	52.4 (18.2)
Sleep onset latency	---
Self-report	58.2 (41.0)
Actigraphy	46.0 (37.7)
Wake after sleep onset	---
Self-report	51.8 (37.0)
Actigraphy	54.4 (24.1)
Sleep quality	2.6 (0.6)
Time in bed	522.7 (76.4)

Note. BDI-II = Beck Depression Inventory.

Table 2

Zero-order correlations among study variables ($N = 144$).

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.
1. Opioids	--											
2. Female	-0.10	--										
3. AHI	0.20*	-0.13	--									
4. BDI-II	0.17*	0.04	-0.13	--								
5. Sleep meds	0.14	-0.02	0.15	0.12	--							
6. Non-opioids	-0.10	0.12	-0.03	-0.08	0.01	--						
7. Pain	0.22**	-0.17*	-0.02	0.39***	-0.08	-0.24**	--					
8. SOL self-report	0.19*	-0.04	0.14	0.24**	0.24**	-0.02	0.01	--				
9. SOL actigraphy	0.25**	-0.15	0.04	0.29**	0.10	-0.16	0.24**	0.48***	--			
10. WASO self-report	0.03	0.11	-0.09	0.23	-0.12	-0.11	0.22**	0.08	-0.01	--		
11. WASO actigraphy	0.21*	0.07	0.13	0.06	0.07	-0.01	0.11	0.19*	0.24**	0.28**	--	
12. Quality	-0.14	0.02	0.09	-0.14	0.17*	0.23	-0.38***	-0.06	-0.06	-0.30***	-0.05	--
13. Time in bed	0.22**	-0.02	0.08	0.24**	0.31***	-0.05	-0.03	0.42***	0.36***	0.11***	0.50***	0.10

* *Note.* $p < .05$.** $p < .01$.*** $p < .001$.

AHI = apnea hypopnea index. BDI-II = Beck Depression Inventory. Sleep meds = yes/no use of sleep medication. Non-opioids = yes/no use of non-opioid medication. Opioids = yes/no use of opioid medication. Pain = average pain intensity (visual analogue scale). Quality = sleep quality. SOL = sleep onset latency. TIB = time in bed. WASO = wake after sleep onset.

Table 3. Main effects and interactions in the prediction of concurrent insomnia symptoms ($N = 144$).

Self-Report Outcomes	Sleep Onset Latency (minutes)			Wake after Sleep Onset (minutes)			Sleep Quality			Time in Bed (minutes)		
	B	SE	p	B	SE	p	B	SE	p	B	SE	p
Step 1: Main Effects												
Intercept	55.47	34.26	.11	-15.21	31.84	.63	3.23	0.45	<.001	526.95	62.47	<.001
Female gender	-6.71	15.62	.67	26.27	14.51	.07	-0.13	0.21	.54	-9.25	28.48	.75
AHI	0.95	0.67	.16	-0.39	0.62	.53	0.01	0.01	.34	0.47	1.21	.70
BDI-II	0.93	0.32	.004	0.02	0.30	.94	<.001	.004	.94	1.61	0.58	.01
Sleep med use	13.29	6.91	.06	-7.09	6.42	.27	0.16	0.09	.08	37.10	12.59	.004
Non-opioid use	-0.29	6.77	.97	-5.73	6.29	.36	0.17	0.09	.06	-8.37	12.34	0.50
Opioid use	10.22	7.22	.16	1.30	6.71	.85	-0.11	0.10	.26	25.82	13.17	0.05
Pain	-0.24	0.21	.24	0.43	0.19	.03	-0.01	.003	<.001	-0.67	0.38	0.08
Step 2: Interaction												
Pain × opioid dose	-0.81	0.40	.045	0.53	0.37	.16	-0.01	0.01	.30	-0.68	0.73	.35
Actigraphy Outcomes												
Step 1: Main Effects												
Intercept	66.84	33.58	.049	15.94	22.46	.48	N/A			±		
Female gender	-22.44	15.39	.15	12.27	10.29	.24						
AHI	0.16	0.61	.79	0.58	0.41	.16						
BDI-II	0.73	0.29	.01	0.23	0.20	.24						
Sleep med use	4.40	6.36	.49	0.67	4.26	.88						
Non-opioid use	-7.07	6.23	.26	1.23	4.17	.77						
Opioid use	12.17	6.73	.07	8.62	4.50	.06						
Pain	0.15	0.19	.44	0.08	0.13	.53						
Step 2: Interaction												
Pain × opioid dose	-0.21	0.37	.57	-0.08	0.25	.76						

[±]Note. Actigraphy time in bed was calculated using a combination of actigraphy and self-report data, resulting in self-report and actigraphy estimates that were highly correlated, $r(143) = 0.91$, $p < .001$; for this reason, analyses were not replicated. AHI = apnea hypopnea index. BDI-II = Beck Depression Inventory. N/A = not applicable. Sleep med use = yes/no use of sleep medication over the 14 days of sleep diaries.