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REGULAR ARTICLE

A Preliminary Investigation of the Underlying Mechanism Associating Daily Sleep Continuity Disturbance and Prescription Opioid Use Among Individuals With Sickle Cell Disease

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Abstract

Background There are emerging data indicating that sleep disturbance may be linked with an increase in opioid use. The majority of sickle cell disease (SCD) patients experience sleep disturbances, which can elevate pain severity and pain catastrophizing, both of which are important predictors of opioid consumption.

Purpose We conducted a preliminary investigation on the association between previous night sleep disturbance and short-acting opioid use, as well as the potential mediating roles of pain severity and pain catastrophizing. Because sex is associated with sleep disturbance, pain-related experiences, and opioid use, we also explored the potential moderating role of sex.

Methods Participants were 45 SCD patients who were prescribed opioids. For 3 months, sleep diaries were collected immediately upon participants' awakening. Daily pain severity, pain catastrophizing, and prescription opioid use measures were collected before bedtime.

Results Multilevel structural equation modeling revealed that wake time after sleep onset (WASO) during the previous night (Time 1) predicted greater short-acting opioid use during the next day (Time 2). Pain severity and pain catastrophizing measured during the next day (Time 2) also mediated the association between the two. Sex moderation analysis showed that the positive association between WASO and pain severity was largely driven by women.

Conclusion These findings provide some preliminary evidence as to the mechanism linking sleep continuity disturbance and opioid requirement in SCD patients. Future studies should replicate and extend these findings with clearer temporal information and employing more refined measures of sleep continuity and prescription opioid use in a larger sample.

Keywords: Sickle cell disease · Sleep disturbance · Opioid use · Pain severity · Pain catastrophizing

Introduction

Sickle cell disease (SCD) is a common and disabling inherited blood disorder. There are more than 100,000 individuals with SCD in the USA, and the number of patients is expected to increase by about 30% in the next 30 years [1]. Pain management is central to SCD patient care, as patients with SCD often experience acute pain (e.g., vaso-occlusive crisis) and chronic pain [2, 3]. The mainstay for pain management among many patients with SCD is long-term opioid therapy [4, 5]. However, there are numerous safety concerns in long-term opioid therapy such as dependence, elevated risk for respiratory depression, and opioid-induced hyperalgesia [6–8]. Identifying modifiable factors that can help patients attenuate their experience of pain and lower their opioid requirement, therefore, is an important goal for successful SCD management.

Investigating the effects of sleep disturbance on prescription opioid use is particularly relevant to addressing this goal for a number of reasons. First, the

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majority of SCD patients report experiencing significant sleep disturbances, including chronic insomnia [9, 10]. Second, there is growing evidence that sleep plays an important role in modulating pain sensitivity and inhibition in both healthy adults and individuals with chronic pain [11, 12]. Third, sleep disturbance is recognized as an important risk factor for the development, maintenance, and exacerbation of problematic substance use [13, 14]. Lastly, many sleep problems can be effectively treated through evidence-based interventions, such as cognitive–behavioral therapy for insomnia [15] and positive airway pressure (PAP) treatments [16]. Hence, examining the role of sleep disturbance in prescription opioid use may shed further light on helping patients with SCD better manage their pain with a lower need for opioids.

One previous study found that greater sleep continuity disturbance during the previous night was associated with higher doses of analgesic medication during the next day among adults hospitalized for burn injuries [17]. However, the underlying mechanisms of this association are unclear. The present study not only seeks to replicate this previous finding in a different clinical sample, but also extends the literature by examining factors that may help better understand the underlying mechanisms associating sleep disturbance and prescription opioid use.

Pain severity is a plausible mediator of this association. Sleep disturbance elevates both laboratory assessed pain sensitivity and clinical pain [11, 18, 19]. Greater pain, in turn, can elevate individuals' daily use of prescription opioids [20]. In fact, in our previous study using daily diary data from SCD patients, we found that sleep continuity disturbance (i.e., the duration of wakefulness after sleep onset) predicts next-day increases in clinical pain severity [21]. We also found in this same study that higher daily pain severity is associated with greater short-acting opioid use [22]. However, whether daily pain severity significantly mediates the association between the two, and whether sleep disturbance directly predicts daily prescription opioid use over and above the effect of pain severity has not been examined.

Pain catastrophizing, a maladaptive cognitive-affective reaction to actual or anticipated pain [23, 24], is another promising candidate mediator of the association between sleep disturbance and opioid use. Previous studies showed that individuals with lower subjective sleep quality tend to report higher pain catastrophizing [25–27]. More recently, a daily diary study of fibromyalgia patients demonstrated that greater previous night nonrestorative sleep was associated with higher next morning pain catastrophizing, which in turn, predicted higher levels of pain and activity interference during the day [28]. Furthermore, pain catastrophizing also predicts postoperative opioid use and is an important risk factor for prescription opioid misuse [29–31]. Combined, these previous findings suggest that the effect of sleep disturbance on prescription opioid use may also be mediated by pain catastrophizing.

Emerging evidence supports the importance of investigating sex differences in associations among sleep disturbance, pain-related experiences, and opioid use. Women in general tend to have a greater predisposition to developing insomnia [32], are more susceptible to pain-related outcomes [33, 34], and report higher pain catastrophizing [35, 36]. On the other hand, men with chronic pain are at greater risk than women in progressing to high-dose opioid therapy and death due to opioid overdose [37]. In the present study, we explored the potential moderating role of sex in our proposed mediation model.

In sum, in the present study, we examined whether previous night sleep disturbance is associated with next day prescription opioid use through elevation of pain severity and pain catastrophizing among individuals with SCD. As an exploratory aim, we also tested the sex moderation effects of this mediation model.

Methods

Overview

The present study is a secondary data analysis of 3-month daily diary data previously collected from patients with SCD. Two papers were published using this data set from our research group. Moscou-Jackson et al. [21] investigated how sleep continuity variables are associated with daily experiences of pain in SCD. However, they did not examine the role of sleep in pain catastrophizing nor prescription opioid use, nor the moderating effects of sex. Finan et al. [22] examined how daily opioid use in SCD varies as a function of daily pain severity, pain catastrophizing, and affective states, but did not examine the role of sleep in daily prescription opioid use nor sex differences. The present study seeks to bridge these questions and differs from these two studies in that we are (i) testing the direct association between sleep continuity disturbance and short-acting opioid use during the next day; (ii) evaluating the potential mediating roles of pain severity and pain catastrophizing in the association between sleep disturbance and prescription opioid use; (iii) exploring sex moderation effects in the mediation model; and (iv) employing a more advanced analytic technique—multilevel structural equation modeling (MSEM)—that allows for testing multiple mediators simultaneously in a single model.

Participants

Participants were recruited from the community in Baltimore and Washington D.C. region using flyers

and advertisements, as well as referrals from local SCD clinics. Inclusion criteria for the study were: (i) 18 years of age or older, (ii) diagnosis of a SCD hemoglobinopathy genotype (i.e., HbSS, HbSC, HbS/β-thalassemia), (iii) currently receiving a stable dose of pain medication including opioids, nonsteroidal anti-inflammatory drugs, or acetaminophen, and (iv) no experience of vaso-occlusive crisis within the past 3 weeks. Exclusion criteria were: (i) report of on-going substance abuse issues, (ii) a significant cognitive impairment or psychiatric disorder, (iii) current infection (including HIV with a neuropathy), (iv) diagnosis of an autoimmune disorder, or (v) currently pregnant or plan to become pregnant in the next 6 months of the study. Note that individuals on chronic transfusion were also allowed to participate in the current study.

As previously described [22], among a total of 84 SCD participants available from the parent study, the present study included only the 45 participants who were prescribed and using opioids. A flow chart that describes the selection process of this final sample used in our study is presented in Electronic Supplementary Fig. 1. A series of χ^2 and *t*-tests revealed that there were no significant socio-demographic differences (i.e., age, sex, race, education level, and marital status) between the included vs. excluded sample (*p*-values ranging from .21 to .65). Not surprisingly, the included sample reported significantly higher mean diary pain severity (0–100 numerical rating scale) compared to the excluded sample (M_{included} = 32.9 vs. M_{excluded} = 9.7, $p < .05$).

Procedure

An initial telephone screening was conducted to ensure that interested participants met the eligibility criteria presented above. Those who passed the phone screening were invited for an in-person visit. Each participant provided written informed consent prior to the start of the baseline study session which included self-report questionnaires, a medical and psychiatric history, and a series of laboratory assessments of pain sensitivity (see [38] for more details). At the end of the baseline session, a research coordinator trained each participant to use an electronic PDA (Palm personal electronic organizer, Palm, Inc., U.S. Robotics, Sunnyvale, CA) for a 90-day diary assessment. Diaries were completed two times per day; one in the morning and the other in the evening. The morning assessment took place immediately upon participants' awakening, and the evening assessment was measured just before the participants' bedtime. Although participants did not receive any daily reminders to complete the diary, they were tracked by the research coordinator and helped with any technical issues that arose. All participants were provided with financial incentives based upon completion of their diary. All study procedures were approved by an institutional review board at Johns Hopkins School of Medicine.

Measures

Predictor variables

Daily sleep parameters. Immediately upon awakening, participants were instructed to record their last night's bedtime, how long it took to fall asleep, the total amount of time they were awake during the night, final wake up time, and time they got out of bed. These sleep diary items were used to calculate total sleep time (TST; duration from bedtime to final wake time), sleep onset latency (SOL; the amount of time it takes one to go from being awake to sleep), and wake after sleep onset (WASO; duration of wakefulness after sleep onset).

Mediators

Daily pain severity. Participants rated their average pain level for the day before going to bed each night using an electronic slider on the PDA screen between 0 ("no pain") and 100 ("pain as bad as you can imagine").

Daily pain catastrophizing. Using the evening diary, participants reported the average intensity of pain catastrophizing throughout the day. Three items were adapted from the Pain Catastrophizing Scale (PCS; [39]): (i) "I could not seem to keep the pain out of my mind," (ii) "I thought the pain was never going to get better," and (iii) "I kept thinking about how much it was going to hurt." Each item represented one of the three main constructs (i.e., rumination, helplessness, and magnification) of PCS. Items were rated on a 0 ("not at all") to 100 ("very much") scale using the PDA electronic slider. By averaging these three items, we created a composite of daily pain catastrophizing. A number of previous studies have used this composite of daily pain catastrophizing scale [22, 40, 41]. The composite showed excellent internal consistency (Cronbach α = .99).

Outcome variable

Daily short-acting opioid use. As previously described by Finan et al. [22], at the baseline session prior to diary assessment, participants who reported using opioids provided detailed information about their opioid prescriptions (e.g., generic name, dose, and frequency). If their prescription and/or dose changed during the study, participants were instructed to inform the research coordinator immediately so that the change in prescription opioid information is logged into our database. For the daily diary, participants were asked to indicate how many pills of their prescribed opioid/s they had consumed that day. At baseline, participants provided the

name and dosage of each prescribed opioid medication. This information was used to compute morphine equivalent daily dosage (MEDD) separately for short- and long-acting opioids in order to standardize opioid intake across different prescription opioids. The total MEDD was defined as the product of the number of pills reported by daily diary and the morphine equivalent dose of each pill. The oral morphine equivalents (ME) conversion was based upon standard equianalgesic conversion calculation methods [42–44]. Details on ME conversion are available as Supplementary material. In the present study, we only used the short-acting opioid use variable based upon our previous study, which revealed extremely low within-person variability in daily long-acting opioid use [22].

Data Analytic Strategy

All main analyses were conducted using SPSS Version 26 and Mplus version 8.0 [45]. First, using SPSS, preliminary analyses examined diary completion rates, and descriptive statistics and intraclass correlations (ICCs) of study variables. Second, a multilevel structural equation model (MSEM) was conducted using Mplus in order to effectively test a model with multiple mediators [46] that included both pain severity and pain catastrophizing ratings. When conducting MSEM, Mplus in default automatically partitions the within- and between-person level variances using person-mean centering that is the conventional centering method in multilevel modeling [47]. Hence, regression (path) coefficients are directly interpreted at the corresponding levels of analysis [46]. The person-centered scores indicate day-to-day deviations from a participant's own mean score over the entire diary period (e.g., 90 days) for that variable.

To systematically investigate the role of sleep disturbance in prescription opioid use, we tested three different MSEM models. The first model only included previous night's sleep continuity parameters (i.e., TST, WASO, and SOL) predicting next day short-acting opioid use. Then, we conducted a second model which tested the potential mediation effects of pain severity and pain catastrophizing. The last model examined sex moderation effects employing multiple group analysis. Multiple group analysis compares the model fits of two models using a chi-square difference test: (i) a *configurable* model that allows regression paths to be freely estimated across sex, and (ii) a *constrained* model that constrains regression paths to be equal across sex. If the result of the χ^2 difference test is significant (i.e., constrained model has a significantly worse model fit than the configurable model), it is assumed that there is an overall sex difference in the model. Then, each regression path is examined to see if there are any significant sex differences using the MODEL CONSTRAINT command from Mplus. To balance the chances of Type I and Type II errors, we set the alpha level at .01 for exploring sex moderation effects.

We only interpret and report the results of the within-person level (day level) model because (i) our research questions and hypotheses focus on the within-person level, and (ii) the associations among study variables at the between-person level are all cross-sectional because each variable in this level represents a person mean (i.e., average of daily diary assessments). Thus, the findings of the between-person level analyses cannot provide any directionality of regression results.

MSEM in Mplus uses the restricted maximum likelihood estimator, which can effectively handle non-normally distributed outcomes (e.g., short-acting opioid use). Missing data were handled by full information maximum likelihood (FIML) under the commonly used missing at random assumption [48]. The Rmediation software [49] was used to test the significance of the mediated effects of pain severity and pain catastrophizing in the association between sleep parameters and short-acting opioid use. Rmediation computes asymmetric confidence limits for the distribution of the product of *a* path and *b* path. This method for testing mediation has substantially better control of Type I error rates and has higher statistical power than traditional mediation analyses, such as the Sobel test. The statistical significance of mediated effects from Rmediation was determined by a 95% confidence interval, which is the preferable method for determining the statistical significance of mediated effects. It is assumed that there is a significant mediating effect if the confidence interval does not include zero.

Results

Preliminary findings

We investigated compliance with the daily diary protocol by calculating the diary completion ratio (i.e., the number of diaries completed out of the total number of days that the participant possessed the PDA). The average diary completion ratio was 72.3% (i.e., 2,386 days of 3,300 days) for the morning diary and 75.5% (i.e., 2,493 days out of 3,300 days) for the evening diary. Table 1 summarizes the demographic and clinical characteristics of our sample. Participants' average age was 37.5 years and the majority self-identified themselves as Black. Approximately 71% (n = 32) of the participants were females, and most of them had the HbSS hemoglobinopathy genotype, were currently not living with a romantic partner, and had at least some college or technical school experience. A series of t-tests and χ^2 tests revealed that there were

Table 1. Sample characteristics ($N = 45$)

	Mean (SD) or %			
Variables	Female (n =32)	Male (n = 13)	Total	p
Age (years)	35.88 (10.97)	41.46 (11.33)	37.49 (11.24)	.13
Race				
African American	93.8%	100%	95.5%	.38
More than one race	6.3%	0%	4.5%	
Hemoglobinopathy genotype				.68
SS	67.7%	69.2%	68.2%	
S-Beta0 thalassemia	6.5%	7.7%	6.8%	
S-Beta+ thalassemia	9.7%	0%	6.8%	
SC	16.1%	23.1%	18.2%	
Hemoglobin level	9.27 (1.98)	8.78 (1.86)	9.12 (1.93)	.45
White blood cell count	10273.55 (3572.41)	10723.85 (6862.02)	10406.59 (4699.75)	.78
Taking hydroxyurea				.98
Yes	31.3%	31.3%	31.1%	
Average short-acting opioid use (ME)	23.88 (46.20)	23.56 (33.20)	23.79 (42.48)	.98
Average long-acting opioid use (ME)	74.81 (142.51)	38.81 (77.55)	64.43 (127.37)	.40
Body mass index (BMI)	27.23 (6.10)	24.64 (6.34)	26.50 (6.20)	.22
Education				.33
Some high school	0%	7.7%	2.2%	
High school graduate/GED	15.6%	23.1%	17.8%	
Technical school graduate	12.5%	7.7%	11.1%	
Some college	43.8%	23.1%	37.8%	
College graduate	25.0%	23.1%	24.4%	
Master's/doctoral degree	3.1%	15.4%	6.6%	
Marital status				.20
Married/partnered	25.0%	25.0%	25.0%	
Single	62.5%	50.0%	59.1%	
Divorced/separated	12.5%	25.0%	15.9%	

Note. ME, morphine equivalents.

no significant sex differences in demographic and clinical characteristics, including the proportion of hemoglobinopathy genotype, hemoglobin levels, the number of white blood cells, use of hydroxyurea, morphine equivalents of short- and long-acting opioid use that were averaged across diary study periods, and body mass index level.

Table 2 displays descriptive statistics and ICCs of all study variables. On average participants reported approximately 7 hr of TST. Participants' reported average WASO and SOL were all slightly longer than 30 min which are comparable to those with clinical insomnia disorder [50]. Overall, participants reported a moderate level of daily pain severity and pain catastrophizing. ICCs ranged from .30 (WASO) to .69 (short-acting opioid use), indicating the use of multilevel modeling was appropriate given that there was substantial within-person variation across days. For instance, only 30% of the variation was explained by between-person differences in WASO and the rest of the variation was explained by within-person changes. In terms of bivariate correlations, most of the study variables were correlated in expected directions. For instance, WASO was positively and significantly associated with daily pain severity ($r = .15$, $p < .001$) and pain catastrophizing ($r = .07$, $p < .001$).

Associations between sleep parameters and daily short-acting opioid use

Models examined were fully saturated, and thus, the model fit indices were not generated. Fig. 1 presents a summary of the first model which included only the sleep parameters as predictors. On days following greater than usual WASO, participants reported using more short-acting opioids. Specifically, for every 10-min increase of WASO, daily short-acting opioid use increased

Table 2. Descriptive statistics and bi-variate within-person correlations of study variables

Variables	1	2	3	4	5	6
1.Total sleep time (TST)	–	–.32***	–.23***	–.07***	–.09***	–.05**
2.Wake after sleep onset (WASO)		–	.15***	.13***	.15***	.07***
3.Sleep onset latency (SOL)			–	.03	.03	.02
4.Daily pain severity				–	.56***	.22***
5.Daily pain catastrophizing					–	.22***
6.Daily short-acting opioid use						–
Mean	7.16	35.13	38.38	30.26	18.73	36.25
SD	2.62	61.18	51.19	24.88	25.76	68.31
ICC	.39	.30	.47	.60	.56	.69

Note. *p < .05, **p < .01, *** p < .001. In order to examine pure level-1 (within-person) correlations, all variables were person-mean centered. As a result, some descriptive statistics are slightly different from Finan et al.'s [22] study which were based upon between-person means (i.e., level-1 variables averaged across days).

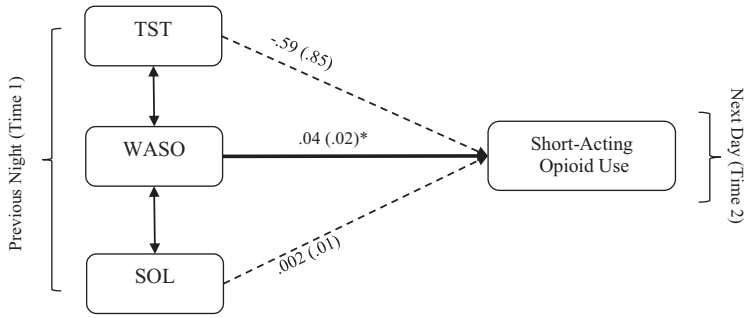

Fig. 1. A multi-level path model that excludes mediators. *Note*. All path estimates are unstandardized regression coefficients. Values in brackets are standard error estimates. Single-headed arrows indicate regression paths. Double-headed arrows indicate correlations. Bold lines indicate statistically significant paths. *p < .05.

by 0.4 ME. The rest of the sleep parameters (TST and SOL) did not significantly predict short-acting opioid use during the next day.

Mediating effects of daily pain severity and pain catastrophizing

Fig. 2 summarizes findings of the second model which expanded the first model by including two mediators. Greater previous night WASO was associated with a higher level of daily pain severity (p = .011) and pain catastrophizing (p = .002). Daily pain severity (p = .008) and pain catastrophizing (p = .001), in turn, were significantly related to greater use of short-acting opioids. For instance, for every 10 unit increase of pain severity (from a 0–100 numerical rating scale), daily short-acting opioid use increased by 3.8 ME. Table 3 shows detailed point estimates and confidence intervals of each mediated effect that was tested in this model. Both pain severity (95% CI: .002, .025) and pain catastrophizing (95% CI: .003, .039) significantly mediated the relation between WASO and short-acting opioid use. The effects of TST and SOL on short-acting opioid use were not significantly mediated by pain severity or pain catastrophizing (see Table 3). However, a trend was observed in the association between TST and pain catastrophizing (p = .075), such that greater previous night TST was related to lower pain catastrophizing reported during the next day. It is also noteworthy that the direct effect of WASO on short-acting opioid use trended toward significance (p = .072), even when controlling for the effects of two mediators.

Sex moderation effects

The result of the Satorra-Bentler scaled χ^2 difference test showed that there was a statistically significant model fit difference between the constrained and configurable (freely estimated) models [$\chi^2(32) = 99.00$, $p < .001$], indicating significant sex differences in the mediation model. We further explored which regression paths were significantly different between men and women. There was a significant sex moderation effect in the association between WASO and pain severity (p = .009, 95% CI: –.099, –.014). Specifically, while there was a positive and significant association between WASO and pain severity among women (B = .05, SE = .02, p = .003), there was no significant association between the two among men (B = –.01, SE = .02, p = .596). As a result of this sex

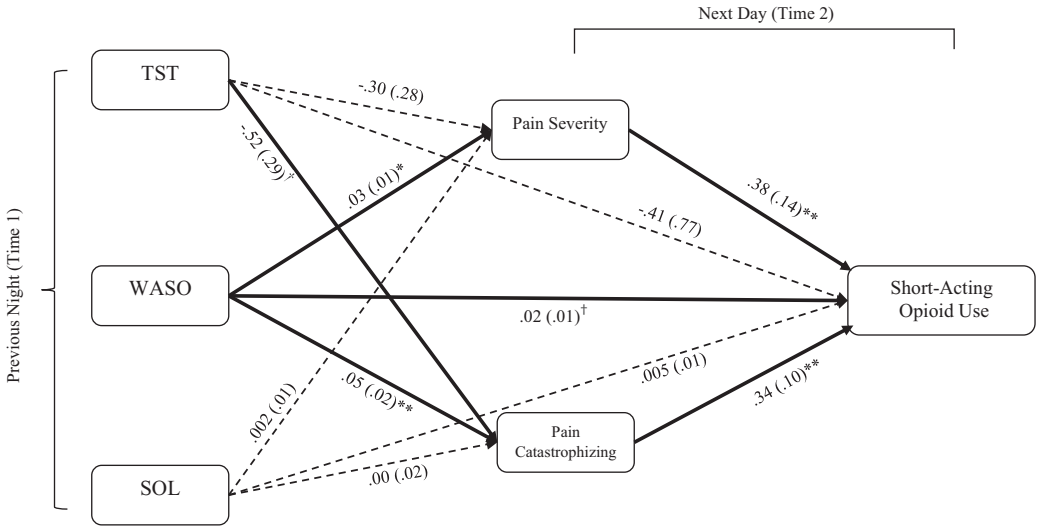

Fig. 2. A multi-level path model that includes mediators. *Note*. All path estimates are unstandardized regression coefficients. Values in brackets are standard error estimates. Single-headed arrows indicate regression paths. Double-headed arrows indicate correlations. Bold lines indicate statistically significant paths. $^{\dagger}p < .10$, $*p < .05$, $**p < .01$.

Table 3. Mediated effects of daily pain severity and pain catastrophizing and 95% asymmetric confidence interval (CI)

Predictors	Mediators	*a* Path ß (SE)	*b* Path ß (SE)	*ab* correlation	Point estimate	95% Asymmetric CI	
						Lower	Upper
TST		–.30 (.28)	.38 (.14)	–.003	–.1141	–.388	.095
WASO	Pain severity	.03 (.01)	.38 (.14)	.029	.0114*	.002	.025
SOL		.002 (.01)	.38 (.14)	.028	.0008	–.007	.010
TST		–.52 (.29)	.34 (.10)	.089	–.1742	–.420	.016
WASO	Pain catastrophizing	.05 (.02)	.34 (.10)	.186	.0174*	.003	.039
SOL		.00 (.02)	.34 (.10)	.153	.0003	–.013	.016

Note. TST, total sleep time; WASO, wake after sleep onset; SOL, sleep onset latency; *, statistically significant mediated effect.

moderation effect, the WASO → pain severity → short-acting opioid Use mediation was statistically significant among women (point estimate = .019, 95% CI: .003, .040), but not among men (point estimate = –0.004, 95% CI: –0.021, 0.012). The rest of the regression paths did not significantly differ between men and women.

Findings of Post-hoc Analyses

Many SCD patients experience vaso-occlusive crises (VOC), which is commonly characterized by extreme acute pain, and prescription opioids are frequently used to manage VOC. Thus, VOC can be an important factor to consider in examining the association between daily pain severity and prescription short-acting opioid use. We conducted a post-hoc analysis to examine whether the association of daily pain severity and short-acting opioid use remains statistically significant after controlling for the experience of VOC. As expected, we found that daily VOC significantly predicted short-acting opioid use ($B = 12.92$, $SE = 5.45$, $p = .018$). Additionally, with VOC as a covariate in the model, both daily pain severity ($B = .27$, $SE = .12$, $p = .029$) and pain catastrophizing ($B = .27$, $SE = .09$, $p = .002$) remained significant predictors of short-acting opioid use.

Previous studies have shown that daily levels of negative affect are closely associated with pain catastrophizing and pain severity [51]. In order to test the robustness of the mediated effects of daily pain severity and pain catastrophizing, we included negative affect as an additional covariate, which was measured by a composite of six items (i.e., feeling anxious, nervous, sad, alone, tired, and blue) derived from the Positive and Negative Affect Schedule and Profile of Mood State [52, 53]. Results showed that even after controlling for daily negative affect, both daily pain severity ($B = .39$, $SE = .16$, $p = .012$) and pain catastrophizing ($B = .37$, $SE = .13$, $p = .004$) significantly predicted short-acting opioid use.

As indicated by ICC, short-acting opioid use has substantial between-person level variability. We explored whether person-mean of sleep continuity variables, pain severity, and pain catastrophizing can significantly account for the between-person variability of short-acting opioid use. We controlled for some between-person factors (i.e., use of hydroxyurea, ethnicity, age, and BMI) that can potentially confound the associations among our study variables. Partial correlation analysis revealed that in controlling for these covariates, only average pain severity had a significant association with average short-acting opioid use (r = .34, p = .046).

Discussion

The present study conducted a preliminary investigation of whether pain severity and pain catastrophizing mediate the daily association between sleep disturbance and prescription opioid use among individuals with SCD. We also explored whether sex differences moderate the mediating effects of pain severity and pain catastrophizing in the relationship between sleep disturbance and short-acting opioid use. Although these findings require replication, our study suggests that WASO and short-acting opioid use are quite robustly associated, and both pain severity and pain catastrophizing also partially mediate the association between WASO and short-acting opioid use. In addition, we found that sex significantly moderated the association between WASO and pain severity, such that the association between the two was significant among women but not among men.

Prior to including mediators in the model, we found that longer WASO during the previous night was significantly associated with greater short-acting opioid use during the next day (see Fig. 1). This is consistent with findings of Raymond et al.'s [17] study which demonstrated that greater WASO is associated with more opioid intake during the same night and during the next day among hospitalized burn injury patients. Even after including daily pain severity and pain catastrophizing, which are potent predictors of prescription opioid use [20, 29, 54] as mediators in the model, the direct association between WASO and short-acting opioid use still trended toward significance, potentially indicating its robustness. We also found some preliminary evidence that the association of sleep disturbance and daily opioid use in SCD could also be explained through daily changes in pain severity and pain catastrophizing. Post-hoc analyses revealed that these mediated effects remained significant, even after controlling for the experience of vaso-occlusive crisis and daily negative affect. As demonstrated in previous longitudinal studies which displayed significant predictive effects of pain severity and pain catastrophizing on prescription opioid use among individuals with chronic pain [20, 29–31], targeting the reduction of pain severity and pain catastrophizing, in addition to sleep continuity disturbance, appears to be an important clinical target in helping individuals with SCD to lower their opioid requirement. It is important to note, however, that pain severity, pain catastrophizing, and short-acting opioid use were all measured at the same assessment time point. Future studies should measure these variables more frequently during the day to delineate temporal differences among them.

Interestingly, among various sleep parameters, we found that only WASO was significantly associated with daily pain severity and pain catastrophizing. Although speculative, one possibility is that compared to total sleep time and sleep onset latency, WASO (i.e., the duration of wakefulness after sleep onset) appears to more directly capture disruptions in slow wave and rapid eye moment (REM) sleep, which are associated with one's pain perception and inhibition [11, 55]. In fact, a recent experimental sleep disruption study found that forced awakening after sleep onset, which targeted increasing WASO, produced a significantly larger reduction in slow wave sleep and increase in REM latency than the restricted sleep onset condition which targeted increasing sleep onset latency [56]. Furthermore, findings indicate that prolonged middle of the night awakenings are the most common sleep disturbance associated with a variety of chronic pain conditions [11]. Some recent findings from experimental and intervention studies further provide support for the unique effects of WASO on pain and pain catastrophizing. For instance, using a healthy female sample, Smith et al. [57] demonstrated that experimentally disrupting sleep continuity significantly decreased endogenous pain inhibition and increased spontaneous pain severity. However, these effects were not exhibited in the delayed sleep onset group or the control group that did not experience any sleep disturbances [57]. Another study by Lerman et al. [41] found that improvement of WASO in an early treatment phase of cognitive behavioral therapy for insomnia among individuals with knee osteoarthritis was associated with reduced trait and nocturnal pain catastrophizing in a later treatment phase. Future studies which employ experimental sleep disruption will be needed to determine the mechanisms through which sleep disruption during the sleep period, relative to other sleep continuity deficits such as delayed onset of sleep, leads to higher pain severity, and pain catastrophizing.

Notably, the path from WASO to pain severity was moderated by sex such that there was a positive and statistically significant association between the two among women, but not among men. As a result, while only pain catastrophizing mediated the association between WASO

and short-acting opioid use among men, both pain severity and pain catastrophizing emerged as significant mediators in this association among women. A recent laboratory study [58] supports this divergent sex effect in the association between WASO and pain severity. The authors found that temporal summation, a common feature observed in many chronic pain disorders, is significantly elevated by 2 days of laboratory-induced sleep continuity disturbance only in healthy women [58]. Our findings suggest that decreasing sleep continuity disturbance may be particularly important for female SCD patients in improving pain severity, which in turn, may also lower their requirements for short-acting opioids.

Observing small effect associations at the within-person level using daily diary or ecological momentary assessment methods is quite common (e.g., [59–61]), and the effect sizes in our study were also quite small overall. However, these small effects may still have some clinically meaningful implications. For instance, we found that for every 10-min increase of WASO, daily short-acting opioid use increased by 0.4 ME. However, it should be noted that sleep continuity disturbance is quite common among individuals with SCD. If an SCD patient had a bad night and had 2 hr of WASO, which is approximately a 1.5 SD above our sample mean of WASO (see Table 2), daily short-acting opioid use can be increased by nearly 5 ME, which may no longer be trivial. To further ascertain this possibility, we suggest that future studies examine growth trajectories over longer periods of time to determine whether the small mediated and direct effects of WASO on daily short-acting opioid use accumulate over time and exert a clinically meaningful risk of dose escalation of opioids over longer periods of time, or even increase risk of opioid misuse or abuse, as has been observed in other groups [13, 14].

We are also mindful that our findings are specifically based upon patients with SCD prescribed opioids. Although a large proportion of patients with SCD experience chronic pain, they exhibit disease characteristics that are substantially different from other chronic pain conditions (e.g., chronic low back pain, fibromyalgia, arthritis, temporomandibular disorders, etc.). For instance, the vast majority of patients with SCD are of African or Hispanic heritage and they often experience vaso-occlusive crises that cause severe pain. In addition, SCD is a congenital blood disorder, whereas most chronic pain conditions are acquired over long periods of time. Thus, the extent to which findings from our study are generalizable to patients with other chronic pain conditions is an open question. Given that sleep disturbance, pain severity, pain catastrophizing, and opioid use are regarded as important factors for the management of chronic pain, evaluating the present model in other non-SCD chronic pain populations would be important in future studies.

Although our findings are preliminary, we believe that it is important to help patients with SCD to adequately manage their sleep and pain in order to help them lower their opioid requirement and improve their quality of life. Indeed, there are a number of evidence-based psychosocial interventions, such as cognitive-behavioral therapy (CBT) and mindfulness-based intervention (MBI), which can effectively improve sleep disturbance, as well as pain severity and catastrophic thinking patterns [62–65]. However, the accessibility of these interventions among patients with chronic pain is a major issue [66], especially in light of the current COVID-19 pandemic [67]. Utilizing an online version of these interventions may be particularly helpful in reducing this important clinical gap in helping patients with SCD to improve their sleep, pain severity, pain catastrophizing, and opioid use. Online CBT and MBIs are not only more accessible, but also have shown effect sizes comparable to those found in interventions delivered in person [68, 69].

Limitations

There are a number of limitations in the present study. First, although participants provided quite extensive daily diary data (i.e., assessed up to 90 days), the sample size (N=45) was fairly small, particularly for the moderation analysis. In addition, we had a much smaller number of male participants than female participants. Thus, some other important sex differences may have not been detected due to suboptimal statistical power. Despite this limitation, exploring sex effects is still an important endeavor in research and clinical care. Second, our sleep measures were based upon subjective sleep diary reports. Although sleep diary is the gold standard for measuring various sleep parameters in behavioral sleep treatments, more objective sleep continuity data through actigraphy or an ambulatory sleep monitoring device should be collected in future studies. Third, our diary data was measured only twice per day (i.e., morning and at the end of the day). Multiple daily assessments of our study variables could further expand our nascent understanding of the dynamic associations among pain severity, pain catastrophizing, and prescription opioid use, as these were measured at a single point in time at the end of the day. Fourth, our measure of daily prescription opioid use did not provide information as to whether participants engaged in problematic opioid use (e.g., misuse). Future studies should expand upon the present analyses by assessing opioid use intention and deviation from specific prescription guidelines in order to capture participants' potential problematic opioid use. Lastly, daily prescription opioid use was also dependent upon participants' self-report of daily

use. To increase the precision of this measure, future studies should consider using an electronic medication packaging device or monitor that can more objectively record dosing events and store these records electronically [70].

Conclusion

We found preliminary evidence that an increase in time awake during the previous night's sleep period was associated with greater pain severity and pain catastrophizing the next day, which in turn, related to greater short-acting opioid use. Women, compared to men, were more likely to report greater pain severity when they had higher WASO during the previous night. Replication and extension of the current findings through future studies that employ enhanced methods in a large sample are needed. Such methods should include more frequent diary or ecological momentary assessment to improve temporal resolution and more objective measures of sleep continuity and prescription opioid use. If consistently replicated, we may be able to further improve our existing nonpharmacological pain management strategies for SCD, reduce sex disparities, and also lower requirements of prescription opioids.

Supplementary Material

Supplementary material is available at *Annals of Behavioral Medicine* online.

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Compliance with Ethical Standards

Authors' Statement of Conflict of Interest and Adherence to Ethical Standards The authors declare that they have no conflict of interest.

Authors' Contributions C.M.C., and J.A.H. designed and conducted the study with contribution from P.H.F., M.T.S., C.P.C., J.M.S., and S.M.L. C.J.M. analyzed data. C.J.M., and P.H.F. wrote the manuscript. All authors critically reviewed the manuscript.

Ethnical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study. These procedures were approved by an institutional review board at Johns Hopkins School of Medicine.

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