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Daily Opioid Use Fluctuates as a Function of Pain, Catastrophizing, and Affect in Patients With Sickle Cell Disease: An Electronic Daily Diary Analysis

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Abstract

Chronic opioid therapy is a common treatment regimen for patients with sickle cell disease (SCD), a chronically painful recessive hemoglobinopathy. The collective risk profile of chronic opioid therapy necessitates an understanding of which pain-related factors, such as affect and pain catastrophizing, are associated with the ebbs and flows of opioid use in daily life, a topic that has received very little attention among patients with any type of chronically painful condition, including SCD. We therefore investigated the variability of day-to-day patterns of short- and long-acting opioid use and their associations with pain and pain-related cognitive and affective processes in daily life among patients with SCD using a nightly electronic diary (N = 45). Opioid use was self-reported and converted into oral morphine equivalents for analysis, which was conducted with mixed effects modeling. Results indicated that greater pain and pain catastrophizing were associated with greater use of short-acting opioids, and negative affect was associated with greater use of long-acting opioids. Additionally, the association of pain and short-acting opioid use was moderated by pain catastrophizing, showing that opioid use was elevated when patients catastrophized about their pain, even if they reported low levels of pain. These findings suggest that monitoring pain-related cognitive and affective variables may be a useful approach to understanding risk for problematic opioid use in patients with daily pain.

Keywords

Opioid use; pain; catastrophizing; affect; sickle cell disease

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Supplementary Data

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Sickle cell disease (SCD) is an autosomal recessive hemoglobinopathy primarily affecting African American individuals in the United States. It is characterized by anemia, fatigue, severely painful vaso-occlusive crises,² and daily pain.⁴¹ Chronic opioid therapy is a consensus-recommended, common pain management strategy for SCD patients with chronic pain, although there is limited evidence to support its efficacy in this population.⁵² Treating chronic pain with chronic opioid therapy presents numerous risks, including opioid-induced hyperalgesia, central sensitization, opioid-induced headaches, problematic opioid use (ie, misuse, abuse, and/or addiction),^{5,7,10,11,32} and opioid overdose.⁹ People of lower socioeconomic status and with lower educational achievement, who comprise most of the SCD population,^{14,24} are among the most vulnerable to these risks.⁴²

These potential downstream consequences of chronic opioid therapy present challenges to patients as well as providers, who must balance the risks against the clear need for acute opioid therapy in the context of extremely painful vaso-occlusive crises. Short- as well as long-acting opioids are prescribed for patients with SCD.²³ Short-acting opioids are commonly prescribed for the treatment of acute elevations in pain,¹ raising the possibility that their use in daily life may be influenced by individually specific pain-related factors that covary with daily variation in pain. Long-acting opioids, in contrast, are typically prescribed to be used stably, irrespective of current pain level, and therefore their use may be less influenced by day-to-day changes in pain and psychosocial function.¹ The collective risk profile of opioid therapy for chronic pain necessitates an understanding of which pain-related factors are associated with the ebbs and flows of opioid use in daily life, a topic that has received very little attention in the literature on opioid use among patients with any type of chronically painful condition, including SCD. To that end, the present study investigated the variability of day-to-day patterns of short- and long-acting opioid use and their associations with pain and pain-related cognitive and affective processes in daily life among patients with SCD.

Because of the persistent stress associated with the unpredictability of SCD pain, affective well-being has long been a focus of research and treatment efforts in this population.^{6,51} Positive affect (PA) has been linked with lower levels of pain, less health care utilization, and less opioid use in adults with SCD,^{22,39} a pattern similar to findings from the broader literature on PA and chronic pain.¹⁹ Outside of SCD, negative affect (NA) is significantly associated with craving for and misuse of opioids among patients with chronic musculoskeletal pain.^{30,49} Patients with chronic pain and comorbid depression, which is characterized by high NA, low PA, or both, are more likely to misuse prescription opioids than those without depression.^{28,37,48} Even more relevant to the management of pain, the links between affect and prescription opioid use appear to be malleable, and may change from day to day. For example, increases in daily PA over the course of a mindfulness intervention were associated with reduced problematic opioid use behaviors in patients with chronic low back pain receiving chronic opioid therapy.²¹

Pain catastrophizing is a maladaptive cognitive coping strategy that amplifies the experience of pain through rumination, magnification, and/or an appraisal of helplessness.^{27,45} Situational pain catastrophizing is associated with elevated reports of clinical pain across a wide range of chronic pain conditions^{12,45} and increased laboratory pain sensitivity.³³ Pain

catastrophizing is associated with increased risk for opioid misuse,^{29,31} a finding that holds even when controlling for depression and anxiety symptoms.²⁹ Because SCD sufferers report levels of pain catastrophizing that surpass those observed in other chronic pain conditions, including rheumatoid arthritis, osteoarthritis, and back pain,⁸ daily catastrophizing may be associated with the ebbs and flows of opioid use in daily life.

The relationship between cognitive affective states and opioid use patterns is relevant to our understanding of how problematic opioid use develops in patients with chronic pain. In the present study, we analyzed daily self-report prescription opioid use data from a longitudinal cohort study of patients with SCD. These analyses make no assumption about the intent of use, and therefore do not speak to problematic opioid use per se. Rather, they address the following questions: 1) are daily levels of pain severity associated with daily levels of opioid use? 2) Are daily levels of cognitive (pain catastrophizing) and affective (PA and NA) states associated with daily levels of opioid use? 3) Do daily pain catastrophizing, NA, and/or PA moderate the association of daily pain and daily opioid use? and 4) do these associations differ with long-acting versus short-acting opioids? We hypothesized that daily pain, affect, and catastrophizing would be associated with daily opioid use; that affect and catastrophizing would moderate the association of pain and opioid use; and that the associations would be stronger for short-acting relative to long-acting opioids.

Methods

Participants

Participants were part of a larger study (N = 84) investigating pain and inflammation among individuals with SCD.^{4,36} Participants were recruited through local SCD clinics as well as posted flyers and advertisements, and were eligible to participate if they were: 1) 18 years of age or older, 2) diagnosed with a SCD hemoglobinopathy genotype (HbSS, HbSC, HbS/β-thalassemia), 3) receiving a stable dose of nonsteroidal anti-inflammatory drugs, acetaminophen, or opioids, 4) without a vaso-occlusive crisis (ie, an acute, severely painful hematologic episode prompted by the disruption of blood flow by sickle red blood cells, often within capillary venules) within the past 3 weeks, and 5) willing to provide informed consent. Exclusion criteria included: 1) active substance abuse, 2) a significant cognitive impairment or unstable psychiatric disorder, 3) current infection, 4) diagnosis of an autoimmune disorder, 5) HIV infection with a neuropathy, or 6) current pregnancy or plan to become pregnant in the subsequent 6 months of the study.

Participants were instructed to complete an electronic diary each day for 90 days, although the total number of diary days varied between participants. Of the 84 participants in the parent study, we excluded 9 participants from the present analyses who completed <1 week (<7 days) of diary entries and/or had a diary completion ratio (ie, the proportion of days the participant carried the personal digital assistant [PDA] with completed diary entries) of 25%. We previously used these criteria in a separate article that reported on other diary measures in this study.³⁶ Of the remaining participants, 55 reported being prescribed an opioid medication. Participants who were prescribed an opioid but reported taking 0 pills over the entire diary reporting period (n = 10) were excluded from analyses because of measurement invariance. Therefore, the final sample included for analyses in the present

study was $N = 45$. Of that total, 27 reported taking short- as well as long-acting opioids, 14 reported taking only short-acting opioids, and 4 reported taking only long-acting opioids. Daily oral morphine equivalents (ME) were calculated separately for short- and long-acting opioids.

The investigators, including a physician experienced in the management of pain in SCD (C.P.C.), visually inspected the daily self-reported opioid use with spaghetti plots to identify clinically anomalous daily reports. There were instances in which participants reported going from high daily doses of opioids to no opioid use, and at later occasions again reporting high daily doses. We operationalized day-to-day changes from >100 mg ME on day t to 0 mg ME on day $t + 1$ as unreliably reported data, on the basis of the expectation that such a shift in dose would induce withdrawal symptoms and would be highly atypical in reality. Data from the 0-mg days that either preceded or followed a >100 mg day were treated as missing, but the rest of the participant's data were preserved for analysis.

Procedure

An institutional review board approved all study procedures. Written informed consent was obtained from each study participant at the baseline study session. Questionnaires and a medical and psychiatric history were collected at the baseline session. After completion of a laboratory assessment of pain (see Campbell et al⁴), participants were trained to use a study-issued electronic PDA. The PDA included 2 daily reporting periods (morning for sleep and evening for pain, catastrophizing, affect, and opioid use) and was used to record daily experiences over the 90-day period (see Moscou-Jackson et al³⁶).

Measures

Daily Measures—The PDA (Palm personal electronic organizer, Palm, Inc., U.S. Robotics, Sunnyvale, CA) protocol was delivered using a customized application. Responses to each item were logged into customized menus and data entry screens with the use of a stylus pen. Participants received financial incentives on the basis of completion of the diary. All primary measures (pain, catastrophizing, affect, and opioid use) were assessed in the evening diary only. Pain, catastrophizing, and affect items were all assessed with electronic sliders anchored between 0 and 10, which were converted to 0 to 100 scores for analysis. We previously reported that participants in the parent study had a 78% adherence rate for the completion of evening diary entries.³⁶ In this subsample, the adherence rate was 74%.

Daily opioid use: At baseline, participants reported all current opioid prescriptions and their accompanying doses. If a prescription and/or dose changed over the course of the study, participants were asked to inform study staff and the change was logged into our database, and accounted for in our present analyses. Each night before bed, participants reported how many “pills” they took that day, where “pill” was defined as the full prescribed dose.

From the reported data, we calculated daily ME to normalize opioid intake across medications. Daily ME was calculated separately for short- and long-acting opioids. Total daily dose of each opioid was defined as the product of the number of “pills” of each medication taken per day and the strength of each “pill.” The total daily dose of each

medication was multiplied by standard equianalgesic conversion factors derived from empirical guidelines^{20,46,47} to produce the oral ME dose. Most opioid analgesics have a standard ME conversion factor that is invariant across published guidelines. However, the conversion of fentanyl and methadone to oral ME differs across studies. For the present study, the total daily fentanyl dose ($n = 5$) was calculated by multiplying the patch strength (25 $\mu\text{g/h}$) by 24 hours and treating it as a parenteral infusion; the conversion factor used was the equianalgesic oral ME dose for parenteral fentanyl. Conversion of methadone to equianalgesic doses is complex, because there is little published information on conversion from methadone to other opioids, and conversion of other opioids to methadone appears to be nonlinear with methadone acting as relatively more potent at higher starting doses of the opioid being converted. There is also tremendous interindividual variability in the metabolism of methadone,¹⁵ further complicating the standardization of equianalgesic dosing. Because the methadone doses involved in this study were modest, a conversion factor of 4 mg oral morphine per 1 mg oral methadone was chosen ($n = 4$).

Clinical Pain Severity: Each night before bed, participants were instructed to record their average pain level for the day. Participants manipulated an electronic slider on the screen between 0 (“no pain”) and 10 (“pain as bad as you can imagine”), which was converted to 0 to 100 for analysis. Participants were also asked, “Are you in a sickle cell crisis today?” This enabled us to control for percent of days spent in crisis, an individual difference factor in SCD that accounts for variance in pain ratings.³⁸

PA and NA: Each night before bed, participants were instructed to report on the average intensity of a series of positive and negative emotions throughout the day. Emotion adjectives covering high as well as low activation affective states, and that appear on commonly used affect scales (eg, Positive and Negative Affect Schedule [PANAS]⁵⁰; Profile of Mood States³⁴) were used. Positive emotion items included happy, calm, and cheerful. Negative emotion items included alone, sad, nervous, anxious, tired, and blue. Items were rated on a 0 to 10 scale using an electronic slider, where 0 = not at all and 10 = very much, and converted to 0 to 100 for analysis. Positive and negative emotion items were averaged separately to create daily composite measures of PA and NA, respectively. Internal consistency was strong for the aggregated PA (Cronbach $\alpha = .90$) as well as NA (Cronbach $\alpha = .86$) scales in the full sample. The moderate correlations between PA and NA aggregated across days ($r = -.55$), as well as the moderate correlations between baseline depressive symptoms and aggregated daily PA and NA ($r = -.41$ and $.56$, respectively) indicated adequate discriminant and convergent validity.

Pain Catastrophizing: Each night before bed, participants reported on the average intensity of the following catastrophizing cognitions: 1) I could not seem to keep the pain out of my mind, 2) I thought the pain was never going to get better, 3) I kept thinking about how much it was going to hurt. The items were adapted from those on the Pain Catastrophizing Scale⁴⁴ and were chosen as exemplars from each of the 3 primary constructs of catastrophizing: rumination, helplessness, and magnification. Items were rated on a 0 to 100 scale using an electronic slider, where 0 = not at all and 100 = very much. Items were averaged to create a

composite pain catastrophizing scale. Internal consistency for the measure aggregated across days was very strong (Cronbach $\alpha = .99$).

Data Analytic Strategy

The data were hierarchically structured such that observations were nested within subjects. We preliminarily inspected the longitudinal data and verified that there was substantial autocorrelation between pain on day t and pain at day $t + 1$ ($r = .77$), that slightly declined at each subsequent lag ($t + 2$: $r = .73$; $t + 3$: $r = .72$; $t + 4$: $r = .70$). Opioid use reports evidenced similar patterns of autocorrelation across lags ($t + 1$: $r = .93$; $t + 2$: $r = .93$; $t + 3$: $r = .90$; $t + 4$: $r = .87$). These observations led us to evaluate study hypotheses with mixed effects modeling, which is ideally suited for analyzing nested data structures with longitudinal autocorrelation. Because of the high, but exponentially declining correlations across measurements, we modeled an autoregressive 1 variance-covariance matrix.

In this subsample of the larger study, 904 observations of a possible 3,473 observations (ie, total number of days participants had the PDA) were missing (26%). Missing data were assumed to be missing at random, which is common in intensive microlongitudinal data sets.³ In support of this assumption, a generalized estimating equation showed that missingness in opioid use reports was not significantly predicted by previous day pain scores ($P = .40$). Additionally, the distribution of missing short-acting (skewness = .66; kurtosis = $-.11$) and long-acting (skewness = .89, kurtosis = $-.31$) opioid use data was normal. Therefore, missing data were handled by restricted maximum likelihood, permitting an analysis of all available data without biasing estimates under the assumption that data were missing at random.²⁵ Random intercepts were included in all models. All level 1 variables (daily pain, catastrophizing, PA, and NA) were centered within person by subtracting each subject's mean from each observation, as recommended by Enders and Tofighi.¹³

Mixed effects models evaluated daily contingencies between: 1) pain severity and opioid use, 2) PA and opioid use, 3) NA and opioid use, and 4) pain catastrophizing and opioid use. The opioid use outcomes were found to be non-normal because of a high frequency of reports of 0 opioid doses (32% of days for short-acting, and 20% of days for long-acting opioids). However, the robustness of mixed effects models using maximum likelihood estimation is more strongly influenced by the distribution of the residuals than the raw outcome data.⁴³ We evaluated the distribution of the random effects residuals, as well as several alternative models to better understand the appropriateness of mixed effects modeling for our primary analyses. A thorough description of these steps is provided in the Supplementary Material. In brief, we observed that the random effects residuals were symmetrical, and the effects observed in our primary analyses were generally supported in mixed effects models that removed participants with abnormal residuals, mixed effects models that excluded "0" opioid days (thereby correcting the skewness and kurtosis of the outcome distribution), as well as in discrete choice probit models that predicted the binary outcome of any opioid use versus nonuse from each of the primary independent variables (daily pain, NA, PA, and catastrophizing). On the basis of these supplemental analyses, we decided that mixed effects modeling was the best option for our data, and that all participants with opioid use data should be included.

Separate models were fit to test those relationships for short-acting and long-acting opioid use. Within opioid class, PA and NA coefficients were estimated simultaneously to control for overlapping variance in the opposing affective valences.

Both primary models included main effects for person-mean centered pain, PA, NA, and catastrophizing, as well as interactions between person-mean centered pain and PA, NA, and catastrophizing. Both models controlled for the following covariates: age, sex, average daily pain severity (across diary days), and an indicator for vaso-occlusive crisis. Age and sex were covaried because they are common sources of individual differences in chronic pain.^{17,18} Pain catastrophizing and NA were included simultaneously to partial out shared variance between those constructs.^{33,40}

Main effects and interactions of primary predictors were deemed statistically significant at $P < .05$. Analyses were performed using SPSS, version 22.0 (IBM Corp, Armonk, NY).

Results

Sample Characteristics

Participant characteristics are reported in Table 1. Table 2 shows correlations, means, and SDs of the independent variables examined in this study.

Opioid Use Characteristics

Table 3 shows the short- and long-acting opioid medications reported by participants in the present study with accompanying dose ranges. Among short-acting opioid users ($n = 41$), short-acting opioids were used on 53% of diary days; pain was reported (>0 of 100) on 97% of those days, and clinically significant pain (≥ 30 of 100) was reported on 70% of those days. Among long-acting users ($n = 31$), long-acting opioids were used on 69% of diary days; pain was reported on 95% of those days, and clinically significant pain (≥ 30 of 100) was reported on 72% of those days. To evaluate the variance in short- and long-acting opioid use, we calculated the intraclass correlation coefficient (ICC) from the intercept and residual variance components. For short-acting opioid use, $ICC = .69$, indicating that 69% of the variance was between-person and 31% of the variance was within-person (ie, day-to-day). For long-acting opioid use, $ICC = .91$, indicating that 91% of the variance was between-person and 9% of the variance was within-person. These data show that short as well as long-acting opioid use evidenced day-to-day variability (albeit substantially less for long-acting relative to short-acting opioid use) and were therefore reasonable targets for an analysis of day-to-day variation.

Associations of Daily Levels of Pain, Affect, and Catastrophizing With Short-Acting Opioid Use

Fig 1 shows spaghetti plots visualizing the extent to which short-acting (Fig 1A) and long-acting (Fig 1B) opioids covaried with pain severity reports from day to day. We selected 6 exemplar cases for each opioid type for visual display: 2 with a weak within-person correlation between pain and opioid use, 2 with a medium-sized correlation, and 2 with a larger correlation. The ‘within-person’ correlations were obtained by correlating the person-

centered variables with each other. A full panel of spaghetti plots for the effects of pain, NA, PA, and catastrophizing for short-acting as well as long-acting opioid use for all participants is showing in Supplementary Figs 1,2, 3, and 4.

Our linear mixed-effects model for short-acting opioids (full results in Table 4) showed that daily levels of pain ($P = .006$) and catastrophizing ($P < .001$), were significantly associated with daily levels of short-acting opioid use. PA ($P = .78$) and NA ($P = .65$), in contrast, were not associated with short-acting opioid use. The magnitude of the effects was small; short-acting opioid use increased by 1.8 mg ME for pain and 2.5 mg ME for catastrophizing for every 10-point increase in each (on the 101-point scale). However, interpretation of these effect magnitudes should be qualified by the fact that they were derived from a multifactorial mixed effects model, and so the extent to which they reflect real-time opioid consumption is not certain. In addition to the main effects, there was a significant interaction between daily pain and daily catastrophizing ($P = .001$). The continuous interaction is shown graphically in Fig 2 as discrete lines representing differences in the model-adjusted means of short-acting opioid use in ME units from low pain days to high pain days for low, medium, and high levels of daily catastrophizing. The figure shows that the relationship of pain and short-acting opioid use was attenuated as daily catastrophizing increased. Put differently, when pain was low, SCD patients reported higher opioid use if they were catastrophizing about their pain than if they were not catastrophizing. In contrast, when pain was high, the relative level of catastrophizing was less influential on opioid use.

In contrast to catastrophizing, neither PA nor NA significantly interacted with daily pain in the prediction of short-acting opioid use.

Associations of Daily Levels of Pain, Affect, and Catastrophizing With Long-Acting Opioid Use

Daily levels of NA ($P = .001$) were significantly associated with daily levels of long-acting opioid use. The magnitude of the effect was small; long-acting opioid use increased by 3.4 mg ME for every 10-point increase (on a 101-point scale) in NA. In contrast, daily pain, PA, and catastrophizing were not associated with long-acting opioid use, and there were no significant interactions between any psychological measure and pain in the prediction of long-acting opioid use. Table 5 shows the statistics from the long-acting mixed effects model.

Discussion

We found that short- and long-acting opioid use among patients with daily pain due to SCD significantly varied from day to day. Short-acting opioid use varied as a function of daily pain, and daily pain catastrophizing, and long-acting opioid use varied as a function of daily NA, over and above between-person differences in average pain severity across diary days. Perhaps the most interesting finding was that the association of daily pain and daily short-acting opioid use was moderated by daily pain catastrophizing. When pain catastrophizing was elevated, short-acting opioid use was higher, even if pain levels were lower than average.

The primary strength of the present study is the daily tracking of pain, affect, catastrophizing, and opioid use using an electronic diary. This allowed detailed tracking of daily opioid use in a sample of patients with chronic SCD pain. Although opioid therapy is strongly recommended to treat acute crisis pain, the evidence for chronic opioid therapy for chronic SCD pain is limited. An expert panel recently released a consensus report on the management of SCD pain that adapted conservative recommendations regarding the use of chronic opioid therapy for SCD.⁵² Therefore, our findings address a critical issue in the clinical management of SCD pain by reporting the daily opioid use patterns of SCD patients and the extent to which they covary with pain and pain-related cognitive and affective measures. We observed that days characterized by elevated pain and catastrophizing were associated with increased daily use of short-acting opioids, and days of elevated NA were associated with increased daily use of long-acting opioids. The association of short-acting opioid use and daily pain reflects the possibility of appropriate opioid use behavior in our sample, because short-acting opioids are typically prescribed as needed, giving patients license to adjust dosing to their level of pain. However, daily levels of catastrophizing explained some of the day-to-day variability in short-acting opioid use, even after partialing out the expected contribution of pain.

Notably, daily pain catastrophizing moderated the association between daily pain and short-acting opioid use. Opioid use was greater on low pain days when individuals catastrophized at high levels. Additionally, whereas higher pain levels predicted greater opioid use when catastrophizing was low, as catastrophizing increased within-person, the strength of the association between pain and opioid use diminished. Patients are often encouraged to increase use of short-acting opioids in the event of a pain flare. However, these data introduce the possibility that maladaptive cognitive appraisals of the meaning of pain, over and above the pain level itself, may influence the decision to increase their prescribed doses. Such a possibility should be tested in temporally sequential designs, such as ecological momentary assessment with multiple within-day measures. Previous studies have reported that pain catastrophizing is associated with elevated risk for opioid misuse.^{16,26,29,35} Although we cannot determine if the increased opioid use patterns we observed across days were instances of misuse (ie, use in a manner other than how the medications were prescribed), we showed for the first time, to our knowledge, that daily pain catastrophizing is associated with self-reported opioid use behavior, particularly when pain is lowest. Furthermore, our findings reveal that the associations of daily levels of pain and catastrophizing with short-acting opioid use are robust to the significant contributions of between-person differences in the frequency of vaso-occlusive crisis (VOCs) and average pain levels, suggesting that pain management strategies may be optimally informed by the assessment of intra- as well as interindividual differences.

The fact that long-acting opioid use varied daily as a function of NA suggests that patients were self-adjusting use of an opioid medication that is typically prescribed at a constant daily dose in relation to an affective state. It is noteworthy that daily pain was not independently associated with long-acting opioid use in our model. However, pain and NA were highly correlated, and the within-person variance in long-acting opioid use was small. These may have contributed to the findings observed in our relatively small sample. We cannot conclude that these patterns reflect opioid misuse because we did not collect the

prescriber data needed to determine whether this variability in use of long-acting opioids was consistent with the patients' treatment plans. However, the present findings highlight the need for such an investigation in future studies.

One possible clinical application of these findings is to integrate the use of daily diaries in the early stage of treatment planning for chronic pain management. Assessment of these cognitive-affective states with a focus on pain catastrophizing patterns from day to day, for example, could inform clinicians of which patients tend to catastrophize on low pain days, which may trigger closer scrutiny of opioid use patterns and consideration of adjunct psychosocial interventions (eg, to target pain catastrophizing) to complement pharmacological pain management strategies.

This study has several limitations of note. First, the once-daily tracking of opioid use limited our ability to evaluate temporal sequences of pain and opioid use within-day. Furthermore, there was relatively little within-person variance in opioid use, particularly for long-acting opioids, which limited our ability to capture strong associations between the affective and cognitive measures and opioid use on a daily basis. This problem may be mitigated in several ways in future studies. Ecological momentary assessment could be used to evaluate random within-day sampling of pain as well as opioid use as well as event-contingent (eg, pain flares) assessments of these measures. This approach would permit the testing of sequential associations between temporally proximal psychosocial variables of interest and opioid use. For example, influential positive and negative interpersonal events may powerfully augment PA and NA in a manner that may reveal stronger associations with opioid use. Importantly, such an approach may help clarify whether the relatively small daily associations between affective and cognitive measures and opioid use observed in this study become more clinically meaningful when associated with activating life events, such as an argument with a family member. In addition to focusing on the more proximal within-person predictors of opioid use, future studies should identify between-person factors that interact with within-person factors, particularly because most of the variance in daily opioid use in our study was between-person. It is possible, for example, that between-person variation in genetic traits would moderate the daily associations between affect, catastrophizing, pain, and opioid use.

This study also relied on self-reported use and lacked objective verification of opioid use. Future studies could use medication adherence tracking devices, such as MEMS Caps (WestRock Company, Sion, Switzerland), to achieve greater accuracy in actual opioid dose from day to day. The use of an electronic medication monitoring system would address concerns about reporting biases and provide exact timing data on medication use. Morphine equivalence calculations introduced another limitation, although one that is unavoidable in clinical cohort studies such as this; indexing daily opioid dose through a common ME metric cannot control for individual differences in drug metabolism, cross-tolerance, and half-life, and therefore is an imperfect measure. Another limitation was that patients in this sample reported relatively low levels of pain on average, which may limit the generalizability of the findings to patients with more severe chronic pain. Finally, the diary lacked direct measures of opioid abuse liability, such as drug-liking and -craving, precluding our ability to evaluate the contribution of reward-related mechanisms to the observed associations.

Conclusions

Our findings show the influence of cognitive and affective variables on daily opioid use patterns in patients with daily SCD-related pain. Our sample exhibited day-to-day variability in short-acting opioid use that was associated with variability in pain level and pain catastrophizing, whereas day-to-day variability in long-acting opioid use was associated with elevated NA. These psychological measures are commonly associated with pain, but the present study introduces the possibility that maladaptive day-to-day regulation of pain-related cognition and emotion may influence short- and long-acting opioid use. These data argue for greater patient-prescriber communication regarding opioid use. For example, it may be helpful to increase education to patients on how each opioid medication should be taken from day to day in an effort to reduce the variability associated with cognitive and affective states. These insights may help to inform risk management and additional clinical intervention approaches.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Perspective

The present study shows that pain and pain-related cognitive and affective variables are associated with daily variation in prescription opioid use in SCD. The findings may have broad implications for tracking and defining risk for prescription opioid misuse in patients with daily pain.

Figure 1.

(A) Exemplars of daily trajectories of pain and short-acting opioid use. (B) Exemplars of daily trajectories of pain and long-acting opioid use. Plots of covariation of daily pain (red bars) with short-acting opioid use (green lines, A) and long-acting opioid use (blue lines, B) are presented across diary days for exemplar participants with weak, medium, and strong within-person correlations between pain and opioid use. The Y-axis is normalized for each participant on the basis of their individual minimum (.00) and maximum (1.00) values for pain and opioid use across days. Vaso-occlusive crisis events (green bars) are superimposed on each plot, if and when they occurred for each participant, to contextualize the pain and opioid use data.

Figure 2. Catastrophizing moderates the association of daily pain and short-acting opioid use. Model-adjusted means of daily short-acting opioid use are shown in oral ME milligrams. Low, average, and high pain catastrophizing lines represent that bottom, middle, and top third, respectively, of the sample distribution of catastrophizing days. Low and high daily pain markers on the X-axis represent the bottom and top half of the sample distribution, respectively.

Table 1

Participant (N = 45) Demographic Characteristics

	Total
Mean age, years	37.49 (11.24)
Female sex	71.10
Race	
African American	93.35
Other (not reported)	6.65
Education	
High school or tech school	31.10
Some college	37.8
College graduate	31.00
Marital status	
Single/separated/divorced	72.3
Married/cohabitating	24.20
Not reported	3.5

NOTE. Data are presented as % except where otherwise noted.

Table 2

Correlations, Means, and SDs of Measures

Variable	1	2	3	4
1. Average pain	–	–.31 [*]	.69 ^{**}	.80 ^{**}
2. PA		–	–.51 ^{**}	–.33 [*]
3. NA			–	.77 ^{**}
4. Pain catastrophizing				–
Mean (SD)	32.93 (20.22)	58.53 (16.00)	29.32 (15.88)	21.68 (20.92)

^{*}
 $P < .05$.

^{**}
 $P < .001$.

Table 3**Long- and Short-Acting Opioid Medications**

	N	Average Prescribed Dose	Average Total Daily ME Consumed	Average Pain On Opioid Use Days
Long-acting				
Morphine	17	30.88 (23.40)	82.13 (105.22)	39.09 (16.34)
Oxycodone	5	81.00 (57.71)	185.45 (195.27)	44.23 (17.18)
Methadone	4	80.00 (32.66)	515.81 (199.10)	44.93 (19.48)
Fentanyl Patch	5	110.00 (41.83)	122.69 (42.94)	46.07 (10.60)
Short-acting				
Oxycodone	17	11.02 (5.36)	30.58 (32.74)	33.98 (15.69)
Hydromorphone	26	16.12 (7.72)	66.04 (68.34)	42.20 (16.78)
Meperidine	1	5.00 (0)	21.07 (0)	62.79 (0)
Tramadol	2	10.00 (0)	21.82 (2.57)	53.37 (9.76)
Hydrocodone	1	10.00 (0)	50.00 (0)	48.52 (0)

NOTE. Means (and SDs) of prescribed and consumed doses are provided for each medication in oral ME. Average daily pain reports were aggregated across diary days, and separately on days of self-reported opioid use, as a function of medication. The number of participants taking each medication (n) exceeds the total sample size (N = 45) because some participants were prescribed multiple opioid medications.

Table 4

Full Results From Short-Acting Opioid Linear Mixed Effects Model

<i>Parameter</i>	<i>B (SE)</i>	<i>t</i>	<i>P</i>
Fixed effects			
Intercept	−9.40 (32.73)	−.29	.78
Sex	18.92 (21.28)	.89	.38
VOC	−11.93 (2.77)	−4.31	< .001
Age	.12 (.87)	.14	.89
Average pain	1.45 (.47)	3.05	.004
Daily pain	.18 (.07)	2.75	.006
Daily PA	.02 (.06)	.34	.74
Daily NA	.03 (.07)	.40	.69
Daily catastrophizing	.25 (.07)	3.74	< .001
PA × Pain	.005 (.003)	1.51	.13
NA × Pain	.0002 (.004)	.07	.95
Catastrophizing × Pain	.007 (.002)	3.33	.001
<i>Wald Z</i>			
Random effects			
Intercept	3,192.79 (800.79)	4.00	< .001
AR1	1,914.93 (79.64)	24.04	< .001

Abbreviations: AR1, autoregressive 1; VOC, vaso-occlusive crisis.

Statistically significant results ($P < .05$) are shown in bold.

Values in parentheses are standard error (SE), as indicated in the column header.

Table 5

Full Results From Long-Acting Opioid Linear Mixed Effects Model

<i>Parameter</i>	<i>B (SE)</i>	<i>t</i>	<i>P</i>
Fixed effects			
Intercept	−34.27 (164.75)	−.21	.84
Sex	5.25 (87.16)	.06	.95
VOC	−9.15 (4.00)	−2.29	.02
Age	.13 (3.60)	.04	.97
Average pain	4.68 (1.89)	2.48	.02
Daily pain	.09 (.10)	.88	.38
Daily PA	.09 (.08)	1.11	.27
Daily NA	.34 (.10)	3.24	.001
Daily catastrophizing	.09 (.08)	1.10	.27
PA × Pain	.001 (.005)	.28	.78
NA × Pain	−.008 (.005)	−1.42	.16
Catastrophizing × Pain	.006 (.004)	1.57	.12
<i>Wald Z</i>			
Random effects			
Intercept	33,826.44 (9,333.80)	3.62	< .001
AR1	5,505.37 (357.78)	15.34	< .001

Abbreviations: AR1, autoregressive 1; VOC.