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Day-to-day pain symptoms are only weakly associated with opioid craving among patients with chronic pain prescribed opioid therapy

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Abstract

Background—Over the past decade, there has been a substantial rise in the use of opioids for the treatment of chronic noncancer pain. Despite the potential benefits of opioid therapy, the rise in the use of opioids has been accompanied by escalating rates of prescription opioid misuse and addiction. There is now a growing body of evidence indicating that opioid craving (i.e., the subjective desire to consume opioids) is one of the strongest determinants of opioid misuse among patients with chronic pain prescribed opioids. Although research has elucidated some of the factors associated with opioid craving, the contribution of patients' levels of pain to opioid craving remains unclear.

Objective—The main objective of this study was to examine the day-to-day association between pain and opioid craving. Methods: In this longitudinal cohort study, patients with chronic pain prescribed opioid therapy completed baseline measures and were then asked to provide daily reports of pain intensity and opioid craving for a period of 14 days.

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Contributors

Drs. Jamison, Wasan, and Edwards designed the study. Drs. Martel and Finan conducted the statistical analyses, and all authors contributed to data interpretation. Dr. Martel wrote the first draft of the manuscript, and all co-authors (Finan, McHugh, Issa, Edwards, Jamison, Wasan) provided feedback and contributed to a subsequent version of the manuscript. All authors approved the final version of the manuscript.

Conflict of interest

Dr. Wasan is a consultant for Analgesic Solutions and Zogenix. Dr. Jamison has investigator-initiated grants from Pfizer and Mallinckrodt. Drs. Jamison, Wasan, Edwards, Finan, and McHugh have grants from the National Institutes of Health (NIH). Dr. Martel receives funding from the Canadian Institutes of Health Research. Funding agencies were neither involved in the writing of the manuscript, nor in the decision to submit the manuscript for publication. The authors have no financial interests in the results of this research, and all authors declare that they have no conflicts of interest.

Results—Multilevel analyses indicated that day-to-day elevations in patients' levels of pain were associated with heightened opioid craving. That is, on more painful days, patients reported higher levels of craving. Within-person changes in pain intensity, however, explained less than 5% of the variance in patients' reports of craving.

Conclusion—Findings from this study suggest that patients with chronic pain do not crave their opioid medications simply because they experience high levels of pain. The theoretical and clinical implications of our findings are discussed.

Keywords

Chronic pain; Opioid therapy; Opioid craving

1. Introduction

Over the past few years, there has been a growing interest in examining the factors that contribute to prescription opioid misuse among patients with chronic pain. Although a number of factors may lead to opioid misuse, research indicates that opioid craving (i.e., the subjective desire to consume opioids) is one of the strongest determinants of prescription opioid misuse. Among patients with chronic pain prescribed long-term opioid therapy, opioid craving has been found to be associated with various indices of prescription opioid misuse, including patient reports of opioid misuse (Martel et al., 2014a; Wasan et al., 2009), physician ratings of opioid misuse behaviors (Wasan et al., 2012), and abnormal urine toxicology screens (Butler et al., 2008; Wasan et al., 2012).

While considerable research has been conducted on the determinants of craving among illicit drug users (for a review, see Drummond, 2001; Tiffany and Wray, 2012), our understanding of craving among patients with pain who are medically prescribed opioids has lagged behind, and little is known about the factors that influence prescription opioid craving. The handful of studies conducted in this area have indicated that opioid craving may be influenced by patient-specific variables such as sex (Wasan et al., 2009), negative affect (Martel et al., 2014a,b; Wasan et al., 2012), and past history of substance use problems (Rosenblum et al., 2003). A few studies have also indicated that opioid craving can be influenced by the level of pain experienced by chronic pain patients (Martel et al., 2014a,b), but the association between pain and craving has surprisingly been found to be modest, at best. For instance, in previous cross-sectional analyses, correlations between measures of pain intensity and opioid craving ranged from .04 to .13 (Garland et al., 2016; Martel et al., 2014a,b), which suggests that patients' symptoms of pain contribute only minimally to opioid craving. Given that opioids are prescribed to pain patients for the specific medical purpose of relieving pain, one would expect that opioid craving is driven, at least in part, by patients' symptoms of pain and/or the potential pain relief that may be experienced from opioid use. In previous research, the weak association that has been observed between patients' reports of pain and opioid craving has been somewhat counterintuitive, and additional research is needed to further elucidate the nature of the association between these two variables among patients with pain.

One of the major caveats of previous studies that have examined the association between pain and craving among patients with chronic pain is the reliance on cross-sectional study designs in which patients made ratings of craving based on past opioid craving experiences (Garland et al., 2016; Martel et al., 2014a,b; Wasan et al., 2009). The potential biases associated with retrospective reports have been well-documented (Shiffman, 2009; Stone and Broderick, 2007), which places limits on the accuracy of previous opioid craving assessments among patients with pain. Moreover, given that patients' levels of pain and craving are likely to fluctuate over time (e.g., from day to day), previous cross-sectional studies could not capture the potentially dynamic association between pain and craving, which raises the possibility that the magnitude of this association may have been artificially underestimated. A method of choice to circumvent these issues is the use of longitudinal study designs in which repeated (e.g., daily) assessments enable to investigate the day-to-day fluctuations in pain and craving as well as the daily covariation between these variables. Among patients with pain prescribed opioids, the day-to-day association between pain and opioid craving has yet to be systematically investigated.

In this longitudinal cohort study, patients with chronic pain prescribed long-term opioid therapy were asked to provide reports of pain intensity and opioid craving once a day for a period of 14 days. The primary objective of this study was to examine the day-to-day association between pain and opioid craving. Of particular interest was the extent to which day-to-day changes in pain intensity contributed to opioid craving. Analyses also examined whether patient sex, negative affect, or past history of SUD moderated the association between pain intensity and craving.

2. Methods

2.1. Participants

The Human Subjects Committee of Brigham and Women's Hospital (BWH) approved study procedures and written informed consent was obtained from every participant. Patients included in the present 14-day diary study were recruited through the BWH Pain Center, and were part of a larger 6-month randomized clinical trial of a behavioral intervention designed to improve prescription opioid compliance. However, none of the patients included in the present study underwent any form of experimental treatment; patients included this study served as controls, and were part of the "usual" treatment control condition (for methods of the trial, see Jamison et al., 2010). Although some data from the broader parent study have been previously published (Jamison et al., 2010; Wasan et al., 2012), this is our first report examining the diary data using a daily process approach (i.e., examining variables and associations of interest from a day-to-day, within-person perspective).

The study eligibility criteria for the present study were identical to those of the broader parent study. Patients met the following inclusion criteria: (1) chronic back or neck pain for more than 6 months, (2) able to speak and understand English, and (3) at "high" risk of prescription opioid misuse based on responses on the Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R; Butler et al., 2008), past records of abnormal urine screens, and physician ratings of opioid misuse. As depicted in Fig. 1 from the supplementary file, a subgroup of patients at "low" risk for opioid misuse was also included.

(4) Use of opioids on a daily basis for the past 6 months or more. Opioid types and doses were verified by a research assistant using the electronic medical record system, and opioid conversion tables were used to convert daily opioid doses into morphine equivalents. In order to be included in the study, patients had to remain on a stable dose of opioids throughout the study period. All other adjuvant medications also remained constant throughout the study.

Patients were excluded from participation if they met any of the following criteria: (1) current diagnosis of cancer, (2) acute osteomyelitis or acute bone disease, (3) DSM-IV diagnosis of any psychotic disorder, or (4) current substance use disorder (SUD) of any kind within the past year (i.e., positive on the Mini International Neuropsychiatric Interview (M.I.N.I. v.5.0; Sheehan et al., 1998). At the BWH Pain Center, patients with an active SUD are generally not prescribed opioid analgesics; they are referred to a local addiction treatment facility before undergoing pain treatment and before being eligible for study participation.

2.2. Measures and procedures

2.2.1. Baseline session—Upon arrival at the BWH Pain Center, patients provided informed consent and completed a demographic questionnaire. Patients were then asked to report any past history of SUD that involved either alcohol or illicit drugs. Patients' reports of past history of SUD were subsequently corroborated using the Prescription Drug Use Questionnaire interview (PDUQ; (Compton et al., 1998)), a 20-min structured interview during which patients were queried about any personal history of substance abuse and/or treatment (e.g., AA: Alcoholics Anonymous; NA: Narcotics Anonymous). Patients' reports were also verified against electronic medical records.

Prior to beginning the take-home diary period, patients received a personal digital assistant (PDA; Hewlett Packard) and were familiarized with its use in the presence of a research assistant. Patients were then asked to rate their level of anxiety, depression, and irritability on a VAS that ranged from 0 (not much) to 100 (very much). Previous studies conducted among patients with chronic pain have supported the reliability and validity of these PDA measures (Jamison et al., 2009, 2010; Marceau et al., 2007; Martel et al., 2014a).

2.2.2. Daily ratings of pain intensity and opioid craving—During the 14-day study period, patients provided ratings of pain intensity and opioid craving, once a day, using a PDA. A built-in alarm was scheduled to prompt patients at a fixed time during the day to remind them to enter PDA data. The alarm was set based on patients' reports of their typical sleep/wake schedule and other practical considerations. This was determined when patients were given the PDA by the research assistant following their baseline visit at BWH. PDA entries were date- and time-stamped to ensure validity, to record specific times when PDA ratings were made, and to monitor patients' compliance over the 14-day period. A sampling period of 14 days was chosen in order to limit the burden placed on patients, to maximize compliance with the diary protocol, and to minimize the likelihood of attrition.

2.2.2.1. Daily ratings of pain intensity: Using the PDA, patients were asked to rate the average level of pain they experienced over the past 24 h on a 0–10 VAS that ranged from 0

(no pain) to 10 (worst pain possible). These ratings were then automatically converted and stored on a 0–100 scale. This measure is an adaptation of the standard visual analog scale commonly used in the Brief Pain Inventory (Tan et al., 2004) to assess pain intensity levels among patients with chronic pain.

2.2.2.2. Daily ratings of opioid craving: Patients were asked to rate the level of opioid craving they experienced over the past 24 h using 3 different items: (1) How much have you craved your opioid medication? (2) How often have you found yourself thinking about the next opioid dose? (3) How strong was your urge to take more opioid medication than prescribed? These items were rated on a 0–100 VAS and were based on the Cocaine Craving Scale validated by Weiss et al. (Weiss et al., 2003). These items were used in our previous studies to assess craving among patients with chronic pain prescribed opioid therapy (Martel et al., 2014a; Wasan et al., 2012).

2.3. Data reduction and analysis

All analyses were conducted using IBM-SPSS v.21. Descriptive data for continuous variables were presented as means and standard deviations, and data for categorical variables were presented as percentages.

Consistent with previous research, an index of craving was computed by averaging patients' ratings on the 3 craving items. An index of negative affect was also computed by averaging patients' baseline ratings of anxiety, depression, and irritability. Cronbach's alphas for the craving and negative affect indices were .96 and .87, respectively.

Primary analyses were conducted using multilevel modeling given the hierarchical data structure of the present study, in which repeated daily assessments (Level 1 units) were nested within participants (Level 2 units). Multilevel modeling was also well-suited to handle the unequal number of data points across participants due to missing data. Given that multilevel modeling can account for unbalanced data set and/or missing data (Peugh, 2010; Singer and Willett, 2003), all 67 participants could be included in multilevel analyses without using any data imputation procedure. In our study, 66% of patients (n = 44/67) completed the 14 diary days, and 88% completed a minimum of 10 diary days. As in most diary studies, some patients completed more diary days than required, which led to an average of 14.7 diary days completed across all participants. Results indicated that those who completed the 14 diary days did not differ significantly from those who did not on any of the main study variables, such as pain ($t = 0.71$, ns) or craving ($t = 1.5$, ns). Also, these patients did not differ significantly in terms of age ($t = -0.86$, ns), gender ($X2 = .12$, ns), or in any other demographic variable (all ps > .05).

We first conducted a series of multilevel analyses examining the potential confounding influence of patient demographics (i.e., age, ethnicity, education, marital status, employment status) and opioid regimen characteristics (i.e., number of opioid prescriptions, opioid type/dose) on daily craving levels. The influence of psychological/psychiatric variables (i.e., baseline negative affect, past history of SUD) on opioid craving was also examined. Consistent with recommendations (Snijders and Bosker, 1999; West et al., 2007), variables

that were significantly associated with craving were retained as covariates in the multilevel models described below.

The subsequent multilevel analysis that was conducted examined the within-person association between pain intensity and opioid craving. Given that we were interested in examining the influence of day-to-day changes in pain intensity on craving, Level 1 pain intensity scores were centered within participants, a procedure that has been referred to as group-mean centering (Enders and Tofighi, 2007; Nezlek, 2001). This was done by computing, for each participant, the mean of Level 1 pain scores across assessment time points. Mean scores were then subtracted from daily scores, resulting in a set of "deviation scores". These scores represent the extent to which a patient, on a given day, deviated from his/her own mean in terms of pain intensity (Enders and Tofighi, 2007; Kreft and De Leeuw, 1998). Deviation scores allowed us to examine, using multilevel modeling, whether day-to-day elevations in pain intensity were associated with patients' levels of craving. In order to examine the association between pain intensity and craving, a multilevel model was built using the craving index as the dependent variable. In this model, relevant Level 2 variables were first added to the model as covariates. Pain intensity was then added to the model as a Level 1 independent variable, which permitted examination of the within-person association between pain intensity and craving after controlling for potential confounders.

In order to examine the potential moderators of the association between pain intensity and opioid craving, 3 distinct multilevel models were built using the craving index as the dependent variable. We were particularly interested in examining whether the association between pain intensity and craving was moderated by patient gender (Level 2), negative affect (Level 2), or past history of SUD (Level 2). In all these models, 2-way interaction terms between Level 1 pain intensity scores and each of these variables were specified after the inclusion of appropriate main effects. Any significant 2-way interaction effect would suggest that the association between daily pain intensity and craving is moderated by patient gender, negative affect, or past history of SUD.

All the multilevel models that were built in this study followed a sequential procedure (Kopala-Sibley et al., 2012; Russell et al., 2011; Wallace and Green, 2002), which first involved specifying a random intercept and fixed effects for independent variables. When significant fixed effects emerged, slopes were then treated as random effects, and model fit was re-evaluated using the likelihood ratio test. Random parameters were dropped if they resulted in a significantly worse model fit (Schwartz and Stone, 1998; Singer, 1998; Singer and Willett, 2003). All models were carried out using maximum-likelihood estimation and included a first-order autoregressive variance covariance matrix (AR1) in order to account for autocorrelations between repeated assessments. As recommended (Hayes, 2007; Peugh, 2010), effect sizes were estimated by calculating the percentage reduction in unexplained variance at both the between- and within-person level, relative to the unexplained variance of the null model. This measure of explained variance is analogous to the R^2 value traditionally reported when conducting linear regression (Hayes, 2007; Heck et al., 2014; Peugh, 2010).

3. Results

3.1. Descriptive statistics

Descriptive statistics for study measures are presented in Table 1, and the different types of medications that were used by patients included in our study are presented in Table 2. The average baseline negative affect score was 44.0 (SD = 25.3). Data aggregated across diary days indicated that the average daily level of pain reported by patients was 64.4 (SD = 15.71), and that the average daily level of opioid craving was 18.3 (SD = 18.1). Medication regimens included the prescription of long-acting (LA) opioids for 54.7% of patients, and the prescription of short-acting (SA) opioids for breakthrough pain for 75% of patients. As typically seen in tertiary care centers, up to 29.7% of patients were taking both types of opioid formulations. The average morphine equivalent daily opioid dose used by patients was 137.2 mg/day (SD = 104.9).

3.2. Influence of baseline variables on daily levels of opioid craving

We first conducted a series of multilevel analyses examining the influence of patient demographics and opioid regimen characteristics on opioid craving levels. Results indicated that none of these variables were significantly associated with craving (all p's > .05). Multilevel models then examined the influence of psychological (i.e., baseline negative affect, past history of SUD) variables on daily levels of craving. Results indicated that higher levels of baseline negative affect were associated with heightened levels of craving, B = .26, SE = .09, $p < .01$. Results also indicated that patients with a history of SUD reported higher daily levels of craving than patients without a history of SUD, $F(1, 66) = 6.10$, $p < .05$. The between-person pseudo R^2 for the effects of baseline negative affect and history of SUD were .11 and .09, respectively. Consistent with recommendations (Snijders and Bosker, 1999; West et al., 2007), baseline negative affect and SUD history were thus the only Level 2 variables retained as covariates in subsequent multilevel models.

3.3. Influence of day-to-day changes in pain intensity on opioid craving

The next multilevel model examined whether within-person changes in pain intensity, from day-to-day, influenced levels of opioid craving. As can been seen in Table 3, the multilevel model was built using the craving index as the dependent variable. In this model, baseline negative affect (Level 2) and past history of SUD (Level 2) were first added simultaneously to the model as independent variables. Pain intensity was then subsequently added to the model as a Level 1 independent variable. A likelihood ratio test indicated that inclusion of pain intensity as a random effect resulted in a significantly worse model fit, $\chi^2(1) = 364$, $p < .001$; this random parameter was thus dropped from the final model. Results from fixed effects indicated that day-to-day elevations in pain were associated with heightened ratings of craving, B = .16, SE = .02, $p < .001$. The within-person pseudo R^2 for the effect of pain intensity on craving was .037 when adjusting for Level 2 covariates, and.04 when these covariates were removed from the model.[1]

1Given that the specific time of the day when patients made their PDA entries varied over the course of the 14-day period, "time of the day" was modeled based on PDA time stamps. Results of a multilevel model using the craving index as the dependent variable revealed that the main effect of "time of day" was not significant (p = .656). This indicates that patients' craving ratings did not vary significantly as a function of the time of the day when PDA entries were made. For exploratory purposes, we also examined whether

3.4. Moderators of the association between pain intensity and craving

Three distinct multilevel models were built in order to examine whether patient gender, negative affect, or past history of SUD moderated the association between daily pain intensity and opioid craving. In all these models, two-way interaction terms between Level 1 pain scores and each of the other independent variables were specified. Results indicated that two-way interaction effects between pain intensity and gender (B = .06, SE = .04, ns), negative affect (B = .00, SE = .001, ns), and past history of SUD (B = .03, SE = .04, ns) were not significant. Taken together, results from these models indicated that the association between pain intensity and opioid craving was not moderated by any of these variables.

4. Discussion

In this longitudinal cohort study, patients with chronic pain prescribed long-term opioid therapy were asked to provide self-reports of pain intensity and opioid craving over a period of 14 days. The primary objective of this study was to examine the day-to-day association between pain and opioid craving. Analyses also examined whether patient sex, negative affect, or past history of SUD moderated the association between pain intensity and craving.

In the present study, multilevel analyses indicated that day-to-day elevations in patients' levels of pain were associated with heightened opioid craving. That is, on more painful days, patients reported higher levels of craving. Interestingly, results indicated that patients' average levels of pain intensity (i.e., aggregated across diary days) were not significantly associated with craving, which suggests that within-person changes in pain occurring from day to day are likely to exert a greater influence on craving than the "average" or "typical " levels of pain experienced by patients. It is worth pointing out, however, that within-person changes in pain intensity explained less than 5% of the variance in patients' reports of craving. The relatively weak influence of pain on craving observed at both the within- and between-person levels is consistent with previous work (Garland et al., 2016; Martel et al., 2014a,b; Wasan et al., 2012), and suggests that patients do not crave opioids simply because they experience high levels of pain.

Some patient characteristics were found to influence average daily levels of opioid craving. For example, we found that higher baseline levels of negative affect were associated with heightened daily levels of opioid craving. Results also indicated that patients with a past history of SUD reported, on average, higher levels of craving than patients without a history of SUD. Taken together, this set of findings is consistent with previous studies showing that negative affect and past history of SUD are associated with heightened opioid craving among patients with chronic pain prescribed opioid therapy (Garland et al., 2016; Martel et al., 2014a; Rosenblum et al., 2003; Wasan et al., 2012).

Analyses were conducted to examine the variables that might moderate the association between daily levels of pain intensity and craving. Results of multilevel moderation analyses revealed that the association between daily pain intensity and craving was not moderated by

patients' average daily levels of pain (i.e., pain ratings aggregated across diary days) were associated with craving. Results indicated that average daily pain was not significantly associated with craving, B = .27, SE = .14, R^2 = .042, ns.

any of the potential moderators of interest. That is, the magnitude of the association between daily pain intensity and opioid craving did not vary as a function of patient gender, negative affect, or past history of SUD. Additional research will be needed to determine whether other patient characteristics might moderate the association between pain intensity and opioid craving among patients with chronic pain prescribed opioid therapy.

The findings of the present study have both theoretical and clinical implications. From a theoretical standpoint, our findings advance our understanding of the determinants of prescription opioid craving among patients with chronic pain. Importantly, our findings challenge some intuitive assumptions with regards to the influence of pain on prescription opioid craving, and suggest that patients' levels of pain intensity contribute only minimally to opioid craving states. Although there is intuitive appeal to the notion that patients crave their opioid medications due to pain and the potential pain relief that may be experienced from opioid use, our findings provide compelling evidence that opioid craving states are likely to be driven by factors other than patients' pain symptoms. This set of findings raises questions concerning the wide array of other factors that might be responsible for prescription opioid craving in this population, and could have particularly important implications for emerging conceptual models that aim to address the link between craving and prescription opioid misuse among patients with chronic pain (Garland et al., 2013).

The present findings also have implications for clinicians involved in the management of patients with pain who are prescribed opioids. As noted earlier, craving has been associated with elevated rates of prescription opioid misuse among patients with pain prescribed opioid therapy (Butler et al., 2008; Garland et al., 2016; Martel et al., 2014a; Wasan et al., 2009), suggesting that clinical interventions designed to alter opioid craving could potentially contribute to decreasing problematic opioid use and improving opioid treatment outcomes. The findings here suggest that opioid craving states are likely to persist regardless of fluctuations in patients' levels of pain over time and/or the degree of analgesia provided by their opioid medication. In order to prevent or reduce opioid craving, it might become necessary to use interventions specifically aimed at targeting opioid craving or the factors underlying craving. For example, in the treatment of opioid use disorders, craving represents a core target symptom of both pharmacological and behavioral interventions. Among patients with chronic pain, interventions that aim to alter the association between craving and opioid use may be particularly promising. In the substance use literature, some of these interventions have been described, including drug cue exposure interventions (Drummond et al., 1995), mindfulness-based therapies (Garland et al., 2014), and cognitive-behavioral interventions designed to alter the mal-adaptive cognitive and affective processes that may contribute to craving (Marlatt and George, 1984; Monti et al., 1989). Although longitudinal treatment studies among patients with pain will be needed to determine the most effective ways to reduce craving over the course of opioid therapy, such interventions could possibly yield clinically meaningful reductions in prescription opioid craving.

There are limitations to the present study that must be considered when interpreting our findings. First, patients included in this study were recruited from a tertiary pain center and were taking relatively high doses of opioids. It thus remains unclear whether the nature of our findings on craving would be comparable among patients taking lower doses of opioids.

Second, patients neither underwent urine screens nor blood testing during the 14-day study period. Before being enrolled in the parent study, patients did submit a urine sample that was analyzed using gas chromatography/mass spectrometry (GC/MS) as a baseline measure of substance use, but this was more than 2 months before the start of the 14-day diary period. Patients submitted a second urine sample as part of their enrollment in the parent study, but this was more than 3 months after the end of the 14-day diary period. Given the relatively short detection window of GC/MS for most illicit and prescription drugs, urine data could not be used reliably for analyses or data interpretation purposes. Future longitudinal studies on craving should consider conducting urine or blood screens at some point during the diary protocol to more stringently account for all substances ingested by participants. Third, although we assessed patients' baseline levels of negative affect, we did not specifically evaluated whether patients met diagnostic criteria for a diagnosis of depressive or anxiety disorder. These disorders are known to be quite prevalent among patients with pain prescribed opioids (Dennis et al., 2015; Edlund et al., 2007; Sullivan et al., 2005) and might exert a particularly strong influence on the day-to-day association between pain and craving. Fourth, the PDA alarm was scheduled to prompt patients at a fixed time during the day to remind them to enter PDA data. Although this is a commonly used diary method, it is characterized by some degree of predictability, which may have influenced the nature of patients' ratings. Future studies should consider employing diary protocols involving random prompts occurring during prespecified time periods in order to minimize rating bias while simultaneously maximizing compliance (Moskowitz et al., 2009; Shiffman et al., 2008; Stone and Shiffman, 2002). Finally, despite the use of a longitudinal study design that allowed us to examine the extent to which day-to-day changes in patients' levels of pain contributed to craving, our primary study outcome (i.e., craving) was assessed only once daily. Future studies should consider collecting multiple within-day ratings of craving in order to capture the potentially rapid within-day fluctuations in craving among patients using opioids. In addition to multiple daily time-based assessments of craving, future studies should consider allowing patients to initiate craving reports, by themselves, whenever craving is being experienced. This type of diary protocol, termed "event-based sampling", has previously been used to study craving among patients with other types of substance use problems, such as smoking, heavy drinking, and illicit drug use (for a review, see (Shiffman, 2009)). The potential combination of event-and time-based sampling protocols should also be considered in order to strengthen inferences about prescription opioid craving and its determinants among patients with pain.

In spite of these limitations, our findings provide valuable new insights into our understanding of the link between pain and opioid craving among patients with chronic pain prescribed opioid therapy. One of the key strengths of this study was to examine the influence of day-to-day changes in pain on opioid craving from a longitudinal, within-person perspective. In the present study, the weak association between pain and craving that was observed across the 14-day diary period provides further evidence that chronic pain patients do not crave their prescription opioids simply because they experience high levels of pain. Additional longitudinal studies will be needed to explore the potential contribution of biological, psychological, and social/contextual factors to opioid craving among patients prescribed long-term opioid therapy. Advances in this domain might not only enhance our

understanding of opioid craving, but might also ultimately help to prevent or reduce the alarming rates of prescription opioid misuse among patients with chronic pain.

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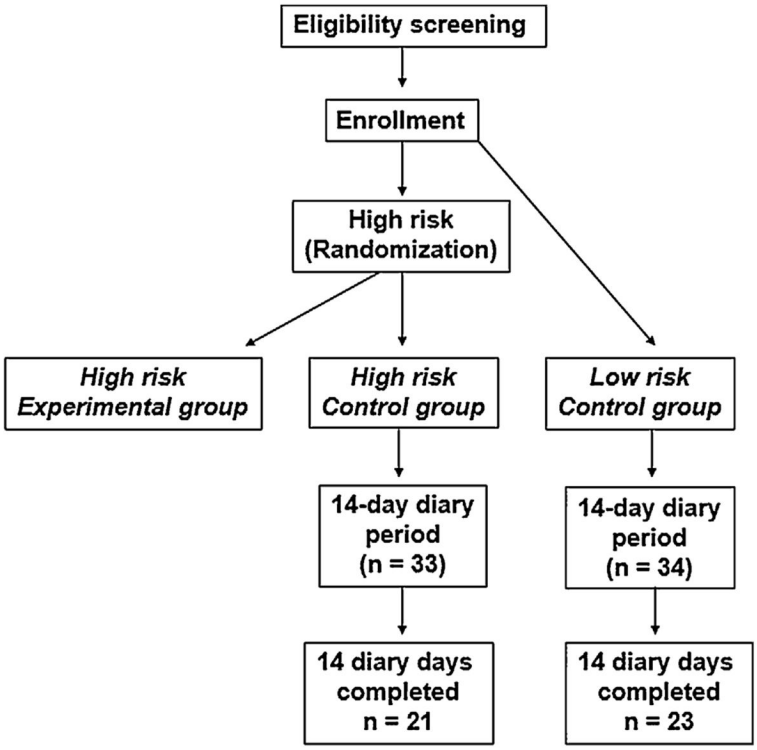

Fig. 1.
Study flow diagram.

Table 1

Sample characteristics and descriptive data for main study variables.

Baseline measures	
Ethnicity (% white)	74.6%
Marital status (% married/relationship)	49.3%
Employment (% unemployed)	71.6%
Education (≥high school)	70.1%
Sex (% women)	49.3%
Past history of substance use disorder (% yes)	52.2%
Negative affect	44.0 (25.3)
Daily diary measures	
Average daily pain intensity	64.4 (15.7)
Average daily opioid craving	18.3 (18.1)

Note. Values in parentheses are standard deviations. Average daily pain intensity and opioid craving represent aggregated scores across the 14-day diary period.

Table 2

Types of medications used by patients during the 14-day study period.

Opioids	100%
Opioid type	
Short-acting	75.0%
Long-acting	54.7%
Both types	29.7%
Opioid dose (ME; mg/day)	137.2 ± 104.9
Antidepressants	45.5%
Anxiolytics/sedatives	27.3%
Anticonvulsants	33.3%
Muscle relaxants	24.2%
Acetaminophen	22.3%
NSAIDs	19.7%

Note. Values in parentheses are standard deviations. Opioid dose represents the average daily morphine equivalent (ME; mg/day).

Table 3

Multilevel model examining the within-person association between pain intensity and opioid craving while controlling for Level 2 variables.

Fixed effects	**β**	**SE**	**df**	**t**	***p***
Intercept	13.99	5.22	66	2.68	<0.05
Level 2					
Past history of SUD	8.5	4.50	66	1.91	.061
Baseline negative affect	.21	.09	66	2.29	<0.05
Level 1					
Pain intensity	.16	.02	924	7.21	<0.001
Random effects: Covariance parameters	Subject	β	SE	z	*p*
Intercept	ID	296.51	54.27	5.46	<0.001
AR (1)	ID	.44	.03	12.53	<0.001
Residuals	ID	92.11	5.79	15.91	<0.001

Note. Values are from the final model. Level 1 pain intensity is within-person centered. Level 2 negative affect is centered around the grand-mean. β = unstandardized regression coefficient; SE = Standard error.