Concurrent and lagged associations of prescription opioid use with pain and negative affect in the daily lives of chronic pain patients.

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Abstract

Objective: Prescribed opioids for chronic pain management contribute significantly to the opioid crisis. There is a need to understand the real-world benefits that, despite risks, lead chronic pain patients to persist in opioid use. Negative reinforcement models of addiction posit that individuals use substances to reduce aversive states, but have seldom been applied to prescribed opioids. Using ecological momentary assessment, we examined reciprocal associations between opioid use and physical pain, for which opioids are prescribed, and negative affect (NA), for which they are not. Method: Chronic low back pain patients on long-term opioid therapy (n = 34) without significant past-year opioid misuse reported multiple times daily via smartphone over two weeks ($n_{observations}$ = 2,285). We hypothesized that pain and NA would be positively associated with subsequent opioid use, and that use would be negatively associated with subsequent pain and NA. Results: Time-lagged multilevel models indicated that participants were more likely to use opioids and in larger doses following elevated pain and NA. There was also an interaction of concurrent pain and NA on opioid dose. In turn, participants reported reduced pain and NA following larger doses. Additionally, individuals at high risk for opioid misuse, compared to low risk, took larger doses following pain, but also experienced smaller subsequent pain and NA reductions. Conclusions: Opioid use was bidirectionally associated with pain and NA. Findings fit negative reinforcement models associated with risk of developing opioid use disorder. Educating patients and providers about negative reinforcement may help reduce opioid use and opioid-associated risks.

Keywords. Opioid use; ecological momentary assessment; chronic pain; negative affect; opioid crisis

Significance. This study suggests a need to educate chronic pain patients and providers about negative reinforcement principles and how they apply to prescribed opioid use for chronic pain management. Such education may reduce opioid risks in chronic pain patients.

Concurrent and lagged associations of prescription opioid use with pain and negative affect in the daily lives of chronic pain patients

The current opioid crisis in the United States (U.S.) is a significant public health concern, with more than 130 people dying after an opioid overdose every day (CDC, 2018). While the crisis has evolved over time, it has historical roots in the use of opioids for chronic pain management (Kolodny et al., 2015; Tompkins, Hobelmann, & Compton, 2017; Volkow, Benveniste, & McLellan, 2018). Reliance on opioid medication for chronic pain management has steadily increased since the 1990s, when regulatory barriers to opioid use for chronic pain management were reduced and long-acting opioid analgesics became available (Tompkins, Hobelmann, & Compton, 2017). As a result, the volume of opioid prescriptions grew enormously (Compton & Volkow, 2006; Levy, Paulozzi, Mack, & Jones, 2015). In part, opioid prescriptions increased as a result of a growing prioritization of adequate pain management in medical settings (Tompkins, Hobelmann, & Compton, 2017; World Health Organization, 1986). Additionally, early research suggested that the risk of prescription opioid misuse and addiction was low in individuals with clinical pain conditions (e.g., Portenoy, 1996). While some evidence suggests that prescription rates may have recently begun to decline (Jones, Lurie, & Throckmorton, 2016), opioids remain frequently prescribed for the management of chronic pain.

Chronic pain, typically defined as pain that persists longer than six months, is a serious medical issue affecting over 100 million U.S. adults at an annual cost above $550 billion (Comm. on Advancing Pain Research et al., 2011). Toblin et al. (2011) found that 18% of individuals with chronic pain were currently prescribed opioids, representing nearly half of those who used any prescription pain medication. Opioid use is especially common in individuals with chronic low back pain (CLBP), with as many as 66% being prescribed opioids (Martell et al.,

2007).

Although multiple factors are involved in the ongoing opioid crisis, particularly the recent rise of synthetic opioid (e.g., fentanyl) use, prescription opioid use for chronic pain remains an important contributor, with a significant subset of patients who take prescribed opioids experiencing use-related problems. These problems include transitioning to illicit use, developing opioid use disorder (OUD), and fatal overdose (Johnson et al., 2013; Von Korff, Kolodny, Deyo, & Chou, 2011). Vowles et al. (2015) found that 21% - 29% of chronic pain patients taking prescribed opioids misuse them, and 8% - 12% meet criteria for "addiction" (which they defined as use despite potential for or experience of harm). However, the prevalence of opioid use-related problems ranges dramatically across studies due to inconsistencies in definitions, making it difficult to know exactly how many chronic pain patients experience use-related problems (Voon, Karamouzian, & Kerr, 2017). Patients with chronic pain are also at risk for illicit opioid use, as 80% of heroin users report that their opioid use began with prescription opioid use (although this includes medical and nonmedical use; Muhuri, Gfroerer, & Davies, 2013).

In terms of overdose, while fentanyl was involved in the greatest number of overdose deaths in 2016, the rates of overdose deaths due to prescription opioids remain high and have not declined (Hedegaard et al., 2018). Using a conservative method that excluded all deaths involving synthetic opioids (e.g., fentanyl), Seth, Rudd, Noonan, and Haegerich (2018) similarly found that death rates of prescription opioids remained stable, with 17,000 deaths in 2016, representing a small increase from 2009 to 2016. It is also important to recognize that overdose does not require misuse and that higher prescribed opioid doses are associated with increased risk of overdose (Bohnert et al., 2011). Thus, there is a need both to reduce the number of

individuals regularly using prescribed opioids for chronic pain, and to improve the management of those who continue to use them. Current evidence suggests that such changes would reduce the number of individuals at risk for illicit opioid use, OUD, and overdose.

Achieving these goals, however, requires better understanding of why many chronic pain patients continue to use prescribed opioid analgesics, despite the risks for overdose and other use-related problems that opioids carry. It also requires understanding why they persist despite the fact that prolonged daily opioid use may be associated with opioid-induced hyperalgesia (OIH), a paradoxical increase in pain sensitivity (Arout, Edens, Pertrakis, & Sofuoglu, 2015), and tolerance, a reduction in sensitivity to opioids' effects (Volkow, Benveniste, & McLellan, 2018). In fact, the available evidence on the effectiveness of long-term opioid therapy is highly mixed (Manchikanti et al. 2011; Von Korff et al., 2011). Yet, the fact that many chronic pain patients persist in regular opioid use suggests they experience some benefits from use. Understanding these benefits may elucidate factors that contribute to persistence in use and, perhaps, the transition to problematic use. This, in turn, may suggest avenues for reducing opioid use and opioid-associated risks.

Negative reinforcement models of substance use (e.g., Baker et al., 2004; Koob & Le Moal, 2008; Sher & Levenson, 1982), may be relevant to understanding these benefits. These models posit that individuals use substances in order to remove an aversive stimulus. These models broadly involve three components. First, an individual experiences an unwanted aversive stimulus, following which they use a substance. Second, following use, the aversive stimulus is reduced or removed. Third, the next time they experience the aversive stimulus, the individual remembers and uses the substance again, repeating the cycle. This process is hypothesized to lead to increased use over time and, potentially, use-related problems. Specifically, over time, the

rewarding effects of the substance decrease (i.e., tolerance), while the potential for punishing effects if use is stopped (i.e., withdrawal) increase. In response to these effects, individuals may increase their use, and substance use disorder (SUD) can subsequently develop.

Past work on the negative reinforcement of substance use has primarily focused on negative affect (NA) or stress. However, these models apply to any aversive stimulus, and chronic pain may fit them particularly well, as pain is frequent, ongoing, and variable for most patients. This provides ample opportunities to develop a strong conditioned response between prescribed opioid use and pain stimuli. Moreover, opioids are explicitly prescribed in order to reduce pain. Negative reinforcement may thus, in part, explain why patients persist in opioid use despite the risks and lack of evidence for long-term effectiveness. Continued opioid use may not significantly improve pain long-term, but, directly following use, patients may experience short-term pain relief. The high immediacy and salience of this reduction may outweigh more long-term and hypothetical adverse consequences (Miltenberger, 2011). Unfortunately, the transient nature of these benefits means that pain will return and require additional opioid use. As use persists, dosages may escalate due to tolerance, and the result may be the eventual realization of negative consequences (e.g., OUD, overdose, death). However, and importantly, this conditioning process may emerge well prior to the experience of use-related problems.

Despite the applicability of basic negative reinforcement models, only a few studies have examined the role of negative reinforcement in prescription opioid use, particularly in the context of chronic pain management. Preclinical and human laboratory studies have found support for pain as a reinforcer of opioid administration (Comer et al., 2010; Ewan & Martin, 2013; Zhang et al., 2014). Multiple clinical studies not using intensive diary methodologies have found that greater trait-level NA, psychiatric comorbidity (potentially indicating elevated NA), and pain are

associated with greater opioid misuse and risk of misuse (Martel et al., 2014; Martel, Jamison, Wasan, & Edwards, 2014; Martel, Wasan, Jamison, & Edwards, 2013; Wasan et al., 2007; Wasan et al., 2015). In a daily diary study, Finan et al. (2017) found that greater daily pain and NA were associated with using greater dosages of short-acting and long-acting opioids, respectively, in a sample of patients with sickle cell disease. Fewer studies have examined the effect of opioid use on NA. In one laboratory study, Bruehl et al. (2015) found that, in chronic pain patients, high scores on an index of opioid misuse risk were associated with greater analgesia and fewer negative opioid effects ("feeling down" and "feeling bad") following controlled opioid administration. These findings might fit a negative reinforcement model. However, while Preston et al. (2018) found, using ecological momentary assessment (EMA), that participants with OUD on opioid-agonist treatment and not experiencing chronic pain reported increased NA prior to relapsing drug use, they found no effects of that drug use on NA. It is unknown whether results in this latter sample generalize to chronic pain patients not experiencing OUD. In sum, past work has examined parts, but not the whole of negative reinforcement in terms of prescription opioid use.

Specifically, to our knowledge, no studies have examined the *bidirectional* relationship of opioid use and aversive states (i.e., whether opioid use occurs in response to aversive states, and whether aversive states decrease following opioid use) in chronic pain patients taking prescribed opioids for pain management. Evidence of a bidirectional relationship in such patients would suggest that, as a result of negative reinforcement processes, they may be at risk for increasing their opioid use, and potential risk for illicit opioid use, OUD, and overdose, even in the absence of current opioid misuse and while following doctor's orders. This would have implications for the opioid crisis in terms of chronic pain patients, signaling the importance of

educating patients and physicians on negative reinforcement principles that may influence prescribed analgesic use patterns.

The present study used EMA (Shiffman, Stone, & Hufford, 2008) to examine, within a negative reinforcement framework, the bidirectional relationship of prescribed opioid use and aversive states over time in the lives of chronic pain patients. We examined a physical aversive state (pain) and an emotional aversive state (NA) in order to examine whether the benefits patients receive from opioid use are specific to a domain for which they are prescribed (i.e., pain) or also extend more broadly to other domains (NA). Additionally, NA is important in negative reinforcement models of substance use and is closely associated with pain (Gatchel et al., 2007).

EMA leverages mobile technology to capture dynamic phenomena as they occur in the moment in daily life. Thus, EMA makes it possible to examine whether chronic pain patients engage in negatively reinforcing use *under their own volition*. Volition is particularly relevant regarding implications. Opioids may have the potential to be negatively reinforcing, but this is less significant if patients in their natural environment are not actually using them in this manner. Additionally, if the benefits of opioid use are relatively short-term in nature, EMA offers the granularity necessary to detect associations that might otherwise be lost.

We thus examined opioid use, pain, and NA in daily life in a sample of chronic low back pain (CLBP) patients with no significant past-year opioid misuse who were on long-term opioid therapy. The primary goal of the study was to examine whether negative reinforcement processes influenced participants' prescribed opioid use. We hypothesized that there would be a bidirectional association of participants' opioid use and their self-reported pain and NA over time. In separate models, we evaluated whether patients used opioids and/or greater opioid dosages subsequent to elevations in pain and NA (i.e., pain $_{t-1}$/NA$_{t-1}$→use$_t$), and whether they

experienced reductions in pain and NA subsequent to opioid use and/or use of greater opioid dosages in the immediately preceding assessment period (i.e., $use_{t-1} \rightarrow pain_t/NA_t$).

An important aspect of negative reinforcement models of substance use, as alluded to above, is that the association of aversive stimuli and substance use is hypothesized to shift over time with continued use and the development of tolerance. This shift is important, as it potentially delineates between use of prescription opioids for pain relief and the possible beginning of problematic use that provides decreasing benefits. To examine the evidence for such a shift in our sample, we additionally examined exploratory models to determine whether observed associations differed by whether participants were at high, compared to low, risk of engaging in opioid misuse. Individuals at high risk of misuse should be more progressed than individuals at low risk in terms of negative reinforcement models, as these individuals are potentially closer to engaging in problematic use. These analyses were exploratory because cross-level interactions were not considered a priori in powering the original study hypotheses and data collection. We hypothesized that pain and NA would both be more strongly associated with subsequent opioid use in participants with high, compared to low, risk of opioid misuse. Conversely, we also hypothesized that participants at high risk would demonstrate increased tolerance, experiencing smaller reductions in pain and NA following opioid use.

Method

Participants

The sample consisted of 34 participants currently receiving opioid therapy for CLBP. This was a subset of a larger study examining alcohol and opioid use in the daily lives of CLBP patients. Participants either used alcohol less than once per month (n = 27) or were social drinkers (two or more times per week; n = 7). Participants were recruited from local pain

management clinics via flyers, and the general community via advertisements online.

Interested individuals completed an eligibility phone screening. Participants were required to meet the following criteria: a) taking prescribed opioid medication at least every-other-day, b) no significant past-year opioid misuse, defined as significant and frequent prescription deviations (e.g., regularly refilling prescriptions early), evidence of drug seeking behavior (e.g., prescriptions from multiple doctors), or significant concern from family members or physicians about their opioid use,[1] c) presence of CLBP for at least 6 months, with a past-month pain severity rating of at least 3 (out of 10) on a verbal numeric pain intensity scale, d) age between 18 and 60 years old, e) no current psychosis, intellectual disability, neurological dysfunction, or significant head trauma history, and f) not currently in treatment or interested in treatment for SUD. Participants using alcohol could not report past-year unsuccessful attempts to cut down/stop drinking or physiological withdrawal symptoms (indicators of severe alcohol use problems). Women could not report being pregnant or planning to become pregnant.

Mean age for the study was 45.3 (*SD* = 8.8) years. The majority of the sample was female (76.5%), white (94.1%), married/cohabitating (52.9%) or divorced/separated (26.5%), and had an annual income less than $25,000 (52.9%). While participants could not be actively misusing opioids, many were at elevated *risk* for misuse, as measured by the Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R; Butler et al., 2008). The majority of the sample (*n* = 22, 64.7%) was above the established SOAPP-R total score cutoff of 18 for opioid misuse risk (*M* = 27.61; *SD* = 14.29). Participants varied in terms of how long they had taken

[1] We screened out individuals who reported significant past-year misuse in order to increase the homogeneity of the sample. Negative reinforcement models of substance use predict that the relationship of opioid use and aversive stimuli would change as OUD develops. Thus, including individuals who were already engaging in significant misuse would potentially limit our ability to understand associations in individuals not already misusing opioids, who represent the majority of chronic pain patients and were the population that we were most interested in.

prescription opioids, with 8 (27.6%) prescribed opioids for 1 year or less, 6 (20.7%) prescribed for 1-3 years, 5 (17.2%) prescribed for 4-5 years, 8 (27.6%) prescribed for 5-10 years, and 2 (6.9%) prescribed for more than 10 years.[2] Most had regular interval opioid prescriptions, though often with some flexibility (e.g., 3-4 times per day). Most participants were also taking prescribed non-opioid medication, while 22 participants (64.7%) were prescribed antidepressant medication. See Table 1 for additional demographics, prevalence of current pain-related conditions other than CLBP, and prescription details.

Procedure

All procedures were approved by the Institutional Review Board, and participants provided informed consent. After completing the phone-screen, eligible participants completed an in-person interview regarding their medical/psychiatric history and medication use. They next completed an orientation session, consisting of self-report questionnaires, a brief experimental acute pain task, and in-depth training on the study-provided Android smartphone and EMA application. The current study was focused solely on the EMA portion of the project. Participants carried the smartphone for an average of 14 days. Staff checked-in with participants after the first two days of EMA by phone or email. Participants returned to the lab after one week. Data were downloaded from the phone and checked for compliance and anomalies. Participants finished after a second week of EMA and returned the smartphone. Participants were paid as they progressed through the study: $10 for the interview, $10 for the orientation, and $40 for each week of EMA data collection, provided compliance was above 80% (payment was reduced $10 for every 10% below 80%). Thus, maximum compensation was $100.

Ecological Momentary Assessment. The EMA protocol consisted of multiple reports.

[2] Information on length of opioid prescription was not available for 5 participants.

Items were the same regardless of prompt type (e.g., morning report versus a random prompt). *Morning reports* were made daily upon awakening. Participants taking opioids upon awakening reported this use in the morning report. *Random prompts* were scheduled to occur 6 times throughout the day. The phone set this schedule each day when the participant completed the morning report or at noon, whichever occurred first, and prompts were scheduled randomly within stratified time blocks from morning report/noon until midnight. Random prompts could not occur during a pain medication follow-up sequence (see below).

Participants made *user-initiated initial pain medication reports* after taking prescribed opioids. In case participants forgot to self-report opioid use, participants were also asked whether they had taken opioid medication since the previous prompt at all non-opioid centric reports. The specific opioids participants were currently prescribed were entered into the smartphone at orientation. When participants reported taking opioids, they indicated which opioid(s) they took, followed by the number of pills (allowing for half-pills), and how long ago they took them.

Pain medication follow-ups occurred at set intervals (30, 60, and 120 min.) following an initial opioid use report. If participants reported additional opioid use at 120 min., an additional follow-up prompt was scheduled 60 min. later. This continued if participants continued to report additional opioid use and allowed for intensive sampling of the period following opioid use. To minimize burden for participants who took opioid medications multiple times per day, a randomizer was built into the follow-up schedule, such that each scheduled prompt had an equal chance of being skipped. The randomizer created a 50%, or 75% chance of being skipped, or was turned off, depending on how often participants took opioid medication. As noted above, participants could not receive random prompts during the follow-up period.

Participants who consumed alcohol over the study period additionally completed initial

drink reports and drinking follow-ups, mimicking the protocol described above. If participants reported concurrent alcohol and opioid use, they completed dual use follow-ups. Concurrent use was rare and these reports (N = 64; 2.05% of total EMA reports) were not included in analyses.

For phone-initiated prompts (i.e., morning reports, random prompts, follow-ups), the phone sounded an audio alarm and vibrated for 30 seconds. It alarmed three times at 5 minute intervals until answered. Participants could suspend the phone if they knew they would not be able to answer prompts (e.g., at work, driving). Compliance for the study was high, with participants completing 90% of all phone-initiated prompts. Participants completed an average of 14 days (M = 13.88; SD = 1.32, *Range* = 8-16). Participants completed an average of 134.94 (SD = 24.87) prompts over the total study period and 9.21 (SD = 1.15) prompts per day.

Measures

Physical pain. At each prompt, participants rated their physical pain using a single item, which asked participants to rate their physical pain intensity over the previous 15 min. on a 0 (no pain) to 10 (worst possible pain) numeric rating scale.

Negative Affect. A shortened version of the Profile of Mood States (POMS; Lorr & McNair, 1971; Cranford et al., 2006) was used to assess affect at each prompt. Nine items assessing depression (sad, hopeless, discouraged), anxiety (anxious, on edge, uneasy), and anger (angry, resentful, annoyed) were aggregated to create a Negative Affect (NA) scale. Participants were asked to rate the extent to which they experienced each item over the previous 15 min. on a Likert-type scale from 1 (very slightly or not at all) to 5 (extremely). The scale composite exhibited excellent reliability for single-assessment (R_{1F} = 0.94), person-average (R_{KF} = 1.00), and change (R_C = 0.90) measures (Shrout & Lane, 2012).

Opioid use. Opioid use was examined dichotomously (i.e., occasions with no use = 0,

occasions with use = 1) and continuously (dosage taken). Opioid dosage was calculated for each occasion, based on the number of pills participants took (including half-pills) multiplied by the dosage per pill (collected at baseline). Occasion-level dosage was then converted to milligram morphine equivalents (MME; Von Korff et al., 2008), to adjust for the fact that participants in the study varied in terms of the specific opioid analgesics they were prescribed (see Table 1).

If participants reported using more than one prescribed opioid at a given occasion, the MME for each opioid was calculated and summed to provide one final value. The same conversion was made regardless of whether an opioid was short- or long-acting (9 participants were prescribed both long- and short-acting opioids, see Table 1). While limited, some evidence suggests that short and long-acting opioids differ primarily in terms of length of dosage effect, but not in terms of the immediate dosage effect (which we were primarily interested in in the current study; Argoff & Silvershein, 2009). To adjust for possible differences in effect of short versus long-acting opioids, an additional occasion-level dichotomous covariate was specified, indicating whether or not participants had taken a long-acting opioid.

Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R). At baseline, participants completed the SOAPP-R, a widely-used 24-item measure of risk for future opioid misuse in the context of pain management that has been shown to be predictive of future aberrant drug behaviors in prospective studies (Passik, Narayana, & Yang, 2014). The SOAPP-R was used to create an opioid misuse risk status indicator, using the established clinical total score cutoff of 18 or greater to identify high risk participants (Butler et al., 2008). While participants were not actively misusing opioids, 22 (64.7%) participants were above the cutoff for misuse risk.

Analytic plan

We used multilevel modeling (MLM) to evaluate our hypotheses. Logistic MLMs were fit for binary outcomes (i.e., dichotomous opioid use) in the statistical program R using the 'glmer' function and Laplace approximation in the 'lme4' package (Bates, Mächler, Bolker, & Walker, 2014), with results reported as Odds Ratios (OR). The PROC MIXED procedure in SAS® 9.4 (SAS Institute, 2014), using restricted maximum likelihood estimation, was used to model continuous outcomes (i.e., pain, NA, opioid dosage). Models accounted for the fact that occasion-level reports were nested within days, which were nested within person, and that reports were unevenly spaced across days and persons. Models had three levels (moment, day, and person) and included a person-level random intercept. Models where pain/NA were the outcome also included a day-level (nested within person) random intercept.[3] Degrees of freedom were calculated using the Kenward-Roger approximation.

All outcomes are reported in clinically interpretable metrics (e.g., change in pain, amount of opioids used), or as ORs. Models included the following covariates: Age (sample centered), gender, whether a long-acting opioid was reported,[4] the cumulative number of times opioids had been reported to that point (within day), hereafter referred to as opioid cycle, and variables to adjust for time (day of study, day of week, hour after wakeup, and time since the previous opioid report [in hours]). Time since the previous opioid report reset to zero at each opioid report.

To examine the bidirectional associations of opioid use with pain and NA over time, we conducted multiple sets of individual lagged MLMs. The first set examined whether pain and NA were associated with subsequent opioid use (i.e., pain $_{t-1}$/NA$_{t-1}$→use$_t$). In three separate models, we tested whether the main effect of pain, the main effect of NA, and the interaction of

[3] The day-level random intercept accounted for very minimal variance in the models examining the association of pain and NA with opioid use (i.e., pain $_{t-1}$/NA$_{t-1}$→use$_t$) and was dropped.
[4] Long-acting status was not included in models with dichotomous opioid use as the outcome due to collinearity (i.e., all moments where a long-acting opioid was used were necessarily moments where opioids were used).

pain x NA were associated with dichotomous opioid use and continuous opioid dosage. For these models, we included occasion-, day- (i.e., the day average of occasion-level estimates), and person-level (i.e., the person average of day-level estimates) estimates for pain/NA. Each estimate was centered on the cluster mean at the next-level, with person-level estimates centered within the sample mean. This centering disaggregated occasion-, day-, and person-level associations (Curran & Bauer, 2011). The second set of MLMs examined, in separate models, the association between opioid use and dosage with subsequent pain and NA (i.e., $use_{t-1} \rightarrow pain_t/NA_t$). We included occasion-, day-, and person-level estimates for opioid use[5] and dosage. Finally, we conducted exploratory analyses that repeated these two sets of MLMs, but additionally included interactions for indicators of primary interest with opioid misuse risk (based on SOAPP-R scores), a person-level dichotomous indicator.

For all models, lagged (i.e., from the previous prompt) and concurrent (i.e., from the same prompt) occasion-level indicators were included as predictors. This enabled us to test the associations of opioid use, pain, and NA intensively over time. Lagged indicators were created within-day (i.e., no carry-over from the previous night). Thus, the first observation for each day was not included in models, though it contributed lag information. For models examining opioid use/dosage as the outcome, we considered both the concurrent and lagged indicators of pain and NA to be temporally previous to any opioid effect. This is because participants were instructed to self-initiate a use report immediately after taking opioids and, thus, before significant absorption of the medication could have taken place. For reasons detailed in the results, we ultimately focused on concurrent pain and NA as the primary indicators of interest. In contrast, for models examining pain or NA as the outcome, we considered only the lagged indicators of dichotomous

[5] As opioid use was dichotomous, day- and person-level use represented the proportion of prompts for that day and person, respectively, where opioid use was reported.

opioid use and opioid dosage to be temporally previous to pain and NA, and concurrent indicators were included only to adjust for their effect. To ensure this sequence of prompts was reflected in the data, we excluded initial pain medication reports where the participant reported taking opioids more than 15 min. previously (n = 383, 12.24% of total EMA reports).

Results

Descriptives. Following exclusions for alcohol-related prompts and opioid prompts where use occurred more than 15 min. previously, there were 2,637 observations. Of these, use of at least one opioid was reported at 648 occasions (24.57% of prompts). Specifically, participants reported taking a short-acting opioid only at 570 (87.96%), a long-acting opioid only at 47 (7.25%), and both a short and long-acting opioid at 31 (4.78%) occasions. Of the opioid reports, 249 (38.43%) were made through a self-initiated initial opioid medication report, 195 (30.09%) through a random prompt, 138 (21.30%) through a morning report, and 66 (10.19%) through an opioid medication follow-up. In addition to prompts where opioid use was reported, participants completed 857 opioid follow-up prompts. The remaining 1,144 prompts did not involve opioid use and were morning reports or random prompts. Models included 2,285 prompts, as there were 351 first-of-the-day observations that did not include lagged information.

Mean pain for the sample was 5.84 (SD = 2.37) on a 0 to 10 numeric pain intensity rating scale. Mean NA was 1.83 (SD = 0.94) on a 1 to 5 scale. The mean occasion-level opioid dose was 21.82 MME (SD = 27.82 MME), with a minimum of 2.50 MME and a maximum of 225 MME. The majority of doses (85.49%) were 30 MME or less. The average daily opioid dose was 42.66 MME (SD = 59.85 MME, minimum = 0 MME, maximum = 405 MME). Participants reported taking opioids an average of 2.09 times per day (SD = 1.21), ranging from 0 to 6 reports. Participants used more than their prescribed dose on 22.38% of occasions (n = 145).

Are aversive states associated with opioid use (pain $_{t-1}$/NA$_{t-1}$→use$_t$)?

Physical pain. We first examined, in main effects models, whether pain was associated with the likelihood of opioid use and the opioid dosage used. Results are presented in Table 2. Lagged occasion pain was inversely associated with likelihood of subsequent opioid use (OR = 0.67, 95% CI = [0.59, 0.77], $p < .001$), indicating that greater pain at the occasion preceding opioid use was associated with decreased likelihood of current opioid use. While, on the surface, this may appear contrary to hypotheses, it is likely a combination of the fact that participants rarely reported opioid use across consecutive prompts and a strong association for concurrent occasion pain.[6] Therefore, we focused on concurrent occasion pain, which was positively associated with likelihood of opioid use (OR = 2.66, 95% CI = [2.26, 3.13], $p < .001$), indicating that greater pain in the past 15 min. was associated with increased odds of taking opioids. There was also a positive association for day-level pain (OR = 1.35, 95% CI = [1.10, 1.65], $p = .003$), indicating that participants were more likely to take opioids on days with more pain.

Examining amount of opioids taken, lagged occasion pain was negatively associated with subsequent opioid dosage used ($b = -0.32$, 95% CI = [-0.54, -0.10], $p = .005$). However, there was also a significant positive association of concurrent occasion pain with dosage ($b = 1.38$, 95% CI = [1.15, 1.62], $p < .001$), indicating that greater pain in the past 15 min. was associated with taking more opioids.

Negative affect. We next examined whether NA, in main effects models, was associated

[6] Specifically, participants reported opioid use across consecutive prompts on only 46 occasions. Therefore, the associations for lagged pain here and lagged NA below, combined with positive associations for concurrent pain and NA, may indicate that participants took opioids very soon after experiencing pain/NA and were unlikely to quickly do so again after their prior use. To examine this, we re-conducted models where use and dosage were the DVs and excluded all follow-up prompts (i.e., occasions most closely following use). In each model the lagged association became non-significant, while remaining associations did not change, except that the concurrent association for NA became a nonsignificant trend in the dichotomous use (but not dosage) model. Thus, as expected, the inverse lagged associations appear to depend upon prompts where opioid use was unlikely (i.e., immediately following prior use).

with opioid use (Table 2). Lagged occasion NA was inversely associated with likelihood of subsequent opioid use (OR = 0.54, 95% CI = [0.38, 0.76], $p < .001$). However, there was also a positive association for concurrent occasion NA with likelihood of opioid use (OR = 2.63, 95% CI = [1.88, 3.69], $p < .001$), indicating that greater NA in the past 15 min. was associated with increased odds of taking opioids. For opioid dosage used, lagged occasion NA was not associated with opioid dosage, whereas concurrent occasion NA was positively associated with opioid dosage used ($b = 1.69$, 95% CI = [1.09, 2.28], $p < .001$), indicating that greater NA in the past 15 min. was associated with taking more opioids.

Pain x negative affect. In addition to main effects of occasion-level pain and NA on opioid use, it is possible that the combination of both may exert interactive effects on opioid use. Therefore, we re-ran the models above adding in lagged and concurrent interactions at the occasion-level (i.e., lagged occasion pain x lagged occasion NA, and concurrent occasion pain x concurrent occasion NA; Table 3). For likelihood of use, and similar to the main effects model for pain, lagged occasion pain was inversely associated with the likelihood of taking opioids, while concurrent occasion pain was associated with greater likelihood of use. Day- and person-level pain were also positively associated with likelihood of use. Lagged and concurrent occasion NA were not associated with use, while day-level NA was negatively associated with likelihood of use. Neither the interaction of lagged occasion pain and NA, nor concurrent occasion pain and NA were significant. Note that the main effects should be understood in the context of the lagged and concurrent occasion pain x NA interactions.[7]

For opioid dosage, and again similar to the main effects model for pain, there was a significant negative association for lagged occasion pain and a significant positive association for

[7] Specifically, in models including interaction terms, the main effect of pain is the effect of pain when NA was at the mean for that person-day, and vice versa.

concurrent occasion pain. The interaction of lagged occasion pain and NA was not significant. There was, however, a significant interaction for concurrent occasion pain and NA (b = 0.72, 95% CI = [0.37, 1.07], $p < .001$). Figure 1 displays this interaction, displaying the association of concurrent occasion pain and opioid dosage at three levels of NA (i.e., the mean, the 20th percentile, and the 80th percentile of NA scores). As can be seen, experiencing both elevated pain and NA at the same occasion was associated with taking a larger opioid dose. In contrast, pain in the context of low NA was associated with taking a smaller dose than when NA was elevated or at the mean.

Is opioid use associated with aversive states (use$_{t-1}$→pain$_t$/NA$_t$)?

Physical pain. We next examined the associations of dichotomous opioid use and opioid dosage with subsequent pain. For these results, the lagged indicators of opioid use were of primary interest and concurrent indicators were included to adjust for their effect. Results are presented in Table 4. Lagged occasion dichotomous opioid use was not associated with subsequent pain. There was a positive association for day-level opioid use, indicating that participants reported more pain on days with more reports of opioid use (b = 1.33, CI = [0.56, 2.11], $p < .001$). There was a similar positive association for person-level opioid use, indicating that participants who took more opioids over the study reported more pain (b = 3.73, CI = [0.08, 7.38], p = .045). For opioid dosage, lagged occasion dosage was associated with decreased subsequent pain (b = -0.01, CI = [-0.01, -0.01], $p < .001$), indicating that taking more opioids was associated with reduced next-occasion pain. There was also again a positive association for day-level opioid use (b = 0.05, CI = [0.03, 0.07], $p < .001$), similar to that described above.

Negative affect. We next examined associations of opioid use with subsequent NA (Table 4). Lagged dichotomous occasion opioid use was not associated with subsequent NA. For

opioid dosage, lagged occasion opioid dosage was negatively associated with NA (b = -0.004, CI = [-0.01, -0.003], $p < .001$), indicating that greater opioid use was associated with reduced subsequent NA.

Exploratory analyses: Moderation by opioid misuse risk status

Finally, we examined whether the observed associations were moderated by opioid misuse risk, as indicated by the SOAPP-R. For these models, we only examined interactions between misuse risk and indicators of primary interest (e.g., concurrent occasion pain/NA for models with opioid use as the outcome), but results did not differ if interactions between opioid misuse risk and the other predictors were included in the models. For space considerations, we report here only the results for interactions with misuse risk, except where main effects changed. Full results from these models are presented in the Supplementary Materials.

There were no significant interactions with misuse risk for models predicting dichotomous use. For models predicting opioid dosage used (Table S1), there was an interaction of concurrent occasion pain and misuse risk was positively associated with opioid dosage used (b = 0.70, CI = [0.23, 1.18], $p = .004$). In the context of the significant main effect for concurrent occasion pain, this indicates that, while concurrent occasion pain was associated with opioid dosage used in both groups, the association was significantly stronger in the high risk group. For the association of NA with opioid use, there was no interaction with misuse risk.

Including both pain and NA as predictors of opioid dosage used (Table S2), the interaction of concurrent occasion pain and NA, the interaction of concurrent occasion pain and misuse risk, as well as the three-way interaction of concurrent occasion pain, NA, and misuse risk (b = -1.26, CI = [-1.98, -0.54], $p < .001$) were associated with opioid dosage used. As can be seen in Figure S1, this three-way interaction was driven by the fact that, for individuals at high

risk of opioid misuse, only pain, and not NA, was associated with opioid dosage used. For individuals at low risk, both pain and NA were associated with dosage used, with the association being strongest when pain and NA were both elevated. However, as can be seen in Figure S1, even this association was weaker than the omnibus (i.e., across NA) association of pain with opioid dosage in participants at high risk.

For the association of opioid use with pain (Table S3), there were significant associations for lagged dichotomous use, in separate models, with pain (b = -0.34, CI = [-0.54, -0.14], p < .001) and NA (b = -0.13, CI = [-0.22, -0.05], p = .003). These main effects were not significant in the original models (Table 3). Additionally, the interaction of lagged dichotomous use and misuse risk was positively associated with both pain (b = 0.41, CI = [0.17, 0.65], p < .001) and NA (b = 0.17, CI = [0.07, 0.28], p < .001). Similarly, the interaction of lagged occasion dosage and misuse risk was positively associated with pain (b = 0.02, CI = [0.01, 0.02], p < .001) and NA (b = 0.01, CI = [0.01, 0.01], p < .001). These findings suggest the acquisition of tolerance in participants at high misuse risk. While participants at low misuse risk experienced reductions in pain and NA following both opioid use and taking larger opioid doses, there was a reversal for participants at high misuse risk, who experienced significantly smaller reductions subsequent to opioid use.

Discussion

The present study examined the immediate benefits of prescribed opioid use in CLBP patients on regular long-term opioid therapy. Working within a negative reinforcement framework, we examined the bidirectional association of patients' opioid use and their pain and NA over time. Pain and NA (in the prior 15 min.) were separately and, in terms of dosage, interactively associated with greater opioid use. In turn, previous moment opioid dosage was

associated with greater subsequent reductions in pain and NA. Additionally, exploratory analyses indicated a shift in the association of pain and, to a lesser extent, NA, with the amount of opioids used in participants at high, compared to low, risk for opioid misuse. Pain, but not NA, was even more strongly associated with opioid dose in participants at elevated risk of misuse, yet these participants also experienced less relief of pain and NA following use, indicating tolerance. Thus, participants' prescribed opioid use generally followed patterns predicted by negative reinforcement models of substance use (e.g., Baker et al., 2004; Koob & Le Moal, 2008; Sher & Levenson, 1982). To our knowledge, no previous work has examined the momentary and bidirectional association of aversive stimuli and prescribed opioid use in chronic pain patients. The observed patterns suggest the potential for a conditioned association between opioid use and aversive states, and suggest that participants used opioids in their daily lives in a manner concordant with negative reinforcement models.

The present study offers potential insight into why chronic pain patients may persist in opioid use. Despite the potential for adverse consequences (e.g., OIH, OUD, overdose, death) patients do experience immediate desirable benefits (i.e., reduced pain and NA) when they use their medication. These effects may go far to obscure the fact that long-term opioid use may do little to decrease pain (Manchikanti et al. 2011; Von Korff et al., 2011). While speculative, these immediate and short-term benefits may place patients at elevated risk for increasing opioid use over time and, potentially, illicit use, OUD, and overdose. Negative reinforcement models of substance use would predict that, over time, as the body adapts to the presence of opioid analgesics, reductions in pain and NA become smaller as tolerance develops. According to these models, patients would then need to increase their use to compensate, either via increasing their prescribed opioid use or turning to illicit sources. This, combined with the fact that patients

would potentially face withdrawal (and increased pain and NA) if they stop taking opioids, could keep patients locked in a cycle of spiraling use, increasing their risk for adverse consequences. Thus, the short-term benefits of prescribed opioid use for chronic pain may have significant long-term costs for some patients.

Analyses comparing participants high and low on opioid misuse risk offer some initial support that the observed negative reinforcement patterns may potentially become problematic. Participants at high risk of misuse demonstrated indications of tolerance, with smaller reductions in pain and NA following both opioid use generally and, specifically, larger opioid doses. In fact, participants at high misuse risk experienced essentially no immediate reduction in pain or NA following use, as the size of the estimates for these interactions were as large or larger, in the opposite direction, than the estimates for the main effects in these models. Participants at high risk may also have attempted to compensate for this tolerance by taking stronger opioid doses when experiencing pain, as suggested by the interaction of pain and opioid misuse risk predicting subsequent opioid dose. It is not clear why participants at high risk did not also take stronger doses following NA than participants at low risk. It may be that participants at elevated misuse risk become focused on pain to the relative exclusion of other aversive stimuli. The three-way interaction of pain, NA, and opioid risk supports this, as NA did not moderate the association of pain and opioid dose in high misuse risk participants. However, it is important to note that, in main effects models NA remained associated with opioid dosage in both groups. Thus, while pain was more strongly associated with opioid dose in participants at elevated risk, NA was also elevated prior to opioid use, and, similar to pain, showed smaller reductions following use.

Despite these exploratory findings, however, it is important to emphasize that, while many in the sample were at risk for misuse, none of the participants in the current study reported

any significant past-year opioid misuse. Thus, while differences were already apparent between participants at high and low risk of misuse, additional longitudinal research is needed to fully understand to what degree using prescribed opioids in the context of their negatively reinforcing effects on pain and NA is associated with future illicit opioid use, OUD, and overdose.

A reasonable question is whether the behaviors observed in the current study are potentially risky and problematic or, in contrast, simply normative and expected. After all, it might be expected that participants would use opioids when in pain, and that taking opioids would reduce that pain. Indeed, the latter is the rationale for medical use of opioids for chronic pain management, as well as most other analgesics. Our position is that using opioids in a negatively reinforcing manner is both natural *and* potentially problematic. It is normative, and often appropriate, to take an analgesic medication when in pain, and to experience pain relief thereafter. However, the fact that negatively reinforcing use of analgesics is common-place may only magnify the potential risks of opioids. Opioids carry both a higher addiction potential and a greater risk of deleterious outcomes than other analgesics. Therefore, there is a greater risk of unintended negative consequences from taking them in a negatively reinforcing manner. It may be, then, that it is the very fact that negatively reinforcing use (i.e., taking an analgesic to relieve pain) is normative, combined with the high addiction potential of opioids, that is what makes negative reinforcement particularly significant for the development of problematic opioid use and OUD.

Thus, it is meaningful that the observed patterns in the current study epitomize negative reinforcement processes believed to contribute to increases in opioid use and the development of use-related problems. Moreover, individuals at high risk of opioid misuse demonstrated a shift in these patterns, taking stronger doses following pain and experiencing less pain and NA relief

following use, indicating that, in terms of negative reinforcement models, risk for misuse was associated with a progression in severity. The observed patterns, and their progression, may carry significant risks when repeated over and over, as typically occurs for chronic pain patients taking opioids regularly. Given the often unremitting nature of chronic pain, this pattern may be repeated without end, with the increasing potential for experiencing adverse consequences.

Nevertheless, most chronic pain patients taking prescribed opioids do not engage in illicit use, develop OUD, or overdose, and the current findings should not be taken as evidence that patients are doing something "wrong" in terms of their opioid use. In contrast, they suggest a need to effectively differentiate between opioid use that is and is not potentially problematic, and for interventions that target the former. While a definitive solution is beyond the scope of the current work, the findings suggest that there may be significant benefits from increased education regarding negative reinforcement processes in terms of both pain and NA. While a common topic in substance use treatment, most chronic pain patients and physicians may be unfamiliar with negative reinforcement principles, or unaware of their relevance to the maintenance and escalation of opioid use. Education on negative reinforcement may be an important prevention strategy, helping patients to slow, if not avoid, learned associations between pain, NA, and opioid use. While such associations, left unchecked, may not lead to use-related problems or OUD in most patients, such education may help prevent instances that would, while not preventing appropriate use for pain control. Similarly, such education may help physicians to prevent, identify, and address potentially problematic opioid use patterns among their patients.

For example, patients worried about becoming dependent on opioids may restrict use to when they "really need it." While intuitive on its face, this strategy may actually strengthen the

association between opioid use and pain relief. Indeed, physicians should potentially use caution regarding "as-needed" opioid prescriptions, as more flexible dosage schedules may encourage patients to take opioids in response to pain, thereby potentially strengthening conditioned opioid use. More research is needed on "as-needed" versus fixed-interval schedules, which little previous work has examined (Chou, Ballontyne, Fanciullo, Fine, & Miaskowski, 2009). Notably, only 12 (35.3%) participants in the current study took opioids with "as-needed" prescriptions, suggesting that negative reinforcement patterns may occur regardless of the prescribed schedule. Thus, it may also be important for providers to encourage patients to closely adhere to their prescribed dosage schedule. Given observed associations for NA, it is also possible that patients high in NA are prone to negatively reinforced opioid use and in need of safeguards to counteract this risk. This agrees with past work finding that elevated NA is associated with opioid use and misuse risk (Finan et al., 2017; Martel et al., 2014; Martel et al., 2014; Martel et al., 2013; Wasan et al., 2007; Wasan et al., 2015), though the current findings suggest that NA may be more significant in patients who are currently at low risk of misuse. Education on opioid-related reinforcement risks, potentially provided by clinical psychologists already integrated into medical settings, could thereby have significant positive effects on the opioid crisis in regard to prescribed opioid use for chronic pain.

A strength of the current study was that we were able to examine the bidirectional association of opioid use with pain and NA intensively over time. Although the current study design precludes statements about causality, the temporal ordering of events provides important information about the reciprocal nature of relationships between pain, NA, and opioid use and how they unfold over time. For analyses examining opioid use as the outcome, it is noteworthy that the observed significant positive associations noted were for concurrent, rather than lagged,

occasion pain and NA, while lagged occasion associations were largely negative. We consider concurrent occasion pain and NA in these models as temporally prior to opioid use given that participants' completed opioid use reports prior to the expected onset of the opioid pharmacologic effects. The findings for the concurrent indicators thus suggest that the influence of elevated pain and NA on opioid use was immediate in nature, illustrating how quickly these processes may unfold in real-time. This also may explain the observed negative associations for lagged occasion pain and NA. These lagged associations became nonsignificant when follow-up prompts were removed from the data (Footnote 6), suggesting that these associations were likely due to the fact that participants took their opioid medication immediately after pain and NA increases and were unlikely to do so again immediately thereafter.

Observed results, all of which were reported in clinically meaningful metrics or as ORs, were relatively small. For example, taking an additional 1 MME was associated with a 0.01 decrease in pain (thus, the average dose in the study, 21.82 MME, would reduce pain by about a fifth of a point). To some extent, this is to be expected when examining occasion-level associations. The observed changes occurred over a matter of minutes, and small changes can accumulate over the breadth of a day. At the same time, the finding of relatively small reductions in pain following opioid use is congruent with previous work that finds minimal evidence for the effectiveness of long-term opioids at the macro-level (Manchikanti et al. 2011). These momentary elevations and dips in aversive states, due to their close temporal relationship with use, may be highly reinforcing despite the fact that, overall, no large improvements are taking place. Baker et al. (2004) argued for a similar process for NA, stating that the association of substance use and NA may not enter the individual's awareness.

It is again important to note that participants in the current study did not report significant

past-year opioid misuse. Additionally, while length of prescription opioid use varied across the sample, most reported taking opioids for multiple years. Such long-term use in the absence of recent misuse raises the question of whether these participants would be likely to ever experience use-related problems or develop OUD, and, thus, to what degree the current findings are meaningful in terms of the development of opioid-related problems. While this is an important consideration, we are not aware of any studies that have examined the time course for the development of OUD or use-related problems in chronic pain patients. Even individuals with a long history of use in the absence of significant problems may be at risk of this in the future, a possibility supported by the fact that a small majority of the current sample was at elevated risk for opioid misuse. For example, patients with a strongly conditioned association between opioid use and pain and NA may be particularly vulnerable to transitioning to illicit opioid use should they lose access to their prescribed opioids. With increasing restrictions on opioid prescribing, this may be an increasingly likely event (Victor, Walker, Cole, & Logan, 2017). Additionally, while we would not categorize it as evidence of significant misuse, participants displayed evidence of use that was other-than-as-prescribed, using more opioids than prescribed on nearly a quarter of all opioid reports.

Observed associations were not specific to pain, but also extended to NA. Participants thus experienced benefits from opioid use in a domain for which they were not prescribed and which negative reinforcement models closely link to SUD (Baker et al., 2004; Koob & Le Moal, 2008). It should be noted, however, that analyses did not examine opioid use and NA in the absence of pain (or vice versa), and it would not be possible to separate their effects, especially given the close relationship of pain and NA (Gatchel et al., 2007). Findings for either should not be interpreted as being in the absence of the other. This is evidenced by the interaction of

concurrent pain and NA on opioid dosage. This suggests that both the pain that patients experience and their emotional state are important factors in determining their prescribed opioid use. However, the exploratory analyses suggest that this may be specific to individuals at lower risk of opioid misuse and that the importance of NA may be reduced in individuals at higher risk.

Associations were more consistent for opioid dosage than they were for dichotomous opioid use. This may have been because analyses were more powered to find associations for dosage, a continuous indicator with greater variability (MacCullum, Zhang, Preacher, & Rucker, 2002). Associations of dichotomous use on subsequent pain and NA were in the expected direction, but reduced statistical power may have played a role in the absence of significance.

To the best of our knowledge, this is the first occasion-level EMA study of chronic pain patients on clinically-indicated long-term opioid therapy (though see Finan et al., 2018 for an example of a daily diary study). Given that prescription opioid use for chronic pain remains an important contributor to the opioid crisis (Hedegaard et al., 2018; Seth et al., 2018), there is a need for additional research in this population. The current study offered multiple strengths in this regard. The use of EMA with an intensive longitudinal design enabled us to examine the bidirectional association of opioid use and pain/NA over time within-person with high external validity.

There were also multiple limitations. First, this was a quasi-experimental study and we were not able to establish causality. Second, despite collecting many assessments within person, the overall sample size was small, highlighting the need for replication in a larger sample. This, in particular, limited power for the exploratory cross-level interactions with opioid misuse risk. Third, the majority of participants were female and white, and all had CLBP, making it uncertain to what degree the observed effects generalize to the broader population or to other pain

conditions. Fourth, we specifically examined the effects of regular (i.e., at least every-other-day) opioid use, and it is unknown whether results would be similar in the context of less regular opioid use. Fifth, participants were not standardized regarding specific opioid medications prescribed, and 10 participants took both long and short-acting opioids. We adjusted for this by calculating MMEs and including a covariate for long-acting opioid use. Sixth, we relied upon participants to self-report their opioid pain medication use. Despite training, a substantial minority of opioid reports were made more than 15 min. after opioids were actually taken. These prompts were removed from analyses. It is also possible that some participants forgot to or otherwise did not make a report each time they took their opioids. Seventh, many participants were taking non-opioid pain medication, which may have had their own effects on pain and NA.

The present study also did not examine the third component of the negative reinforcement process. That is, whether reductions in pain or NA are associated with opioid use/increased use the next time pain or NA are encountered. Future research should collect longitudinal data to examine how the benefits of opioid use affect later use over more extended time periods. Another important future direction is to examine the moderating role of expectancies. Participants who expect opioids to reduce their pain (or NA) may be both more likely to use at moments of elevated pain and may experience greater reductions following use. A third future direction is to examine negative reinforcement processes in chronic pain patients who are actively misusing opioids. In particular, it would be valuable to directly compare pain patients who are and are not misusing opioids, or to longitudinally follow patients to examine whether the association of opioid use with pain and NA predicts transition to use-related problems and OUD. Future research should also seek to identify factors that may be protective in terms of preventing the transition to illicit use or OUD.

In conclusion, the present study used EMA to examine the real-world benefits that may lead chronic pain patients to persist in and increase their opioid use, despite both the significant risks of opioids and the mixed evidence for long-term opioid therapy's effectiveness. Working from a negative reinforcement framework, we found, in separate models, support for a bidirectional association of participants' opioid use and their self-reported pain and NA over time. Participants experienced desirable effects (i.e., pain and NA relief) following opioid use. These benefits were relatively small and transient in nature, thus leading to later return of pain and NA, and, potentially, continuation of the negative reinforcement cycle. While speculative, patients may persist in and, potentially, increase their opioid use in order to continue to experience benefits in the face of emerging opioid tolerance. Supporting this, participants at high risk of opioid misuse reported smaller benefits from use, indicating tolerance, and used larger amounts of opioids subsequent to pain. For some patients, this continued use may, over time, expose them to significant opioid-related risks and the development of OUD. There is, thus, a need for education on negative reinforcement among both patients and physicians. Greater awareness of negative reinforcement processes may be important for decreasing and better managing prescribed opioid use, potentially helping to reduce opioid use and opioid-related risks.

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Table 1. *Sample demographics (N=34).*

	n	%		*n*	%
Gender-Female	26	76.5	Prescribed Opioids		
Race			Hydromorphone	1	2.9
Black	2	94.1	Fentanyl (long-acting)	1	2.9
White	32	5.9	Hydrocodone	17	50.0
Marital Status			Morphine (long-acting)	4	11.8
Single, Never Married	5	14.7	Morphine (short-acting)	1	2.9
Married or Cohabitating	18	52.9	Oxycodone (short-acting)	10	29.4
Divorced or Separated	9	26.5	Oxycodone (long-acting)	4	11.8
Widowed	2	5.9	Tramadol	10	29.4
Annual Income			Prescribed Non-opioid Pain Medication		
$0 to $25,000	18	52.9	Acetaminophen[b]	16	47.1
$25,001 to $50,000	10	29.4	Muscle Relaxant	11	32.4
$50,001 to $75,000	2	5.9	Neuropathy-related[c]	19	55.9
Above $75,001	4	11.8	NSAID	11	32.4
Currently Employed	10	29.4	Number of opioid prescriptions		
On Disability	21	61.8	One	21	61.8
Other Current Pain-Related Conditions[a]			Two	12	35.3
Headaches	20	58.8	Three	1	2.9
Osteo or rheumatoid arthritis	24	70.6	Prescription dosage schedule		
Migraines	18	54.6	Regular interval only[d]	22	64.7
Irritable bowel syndrome	13	38.2	As-needed only	5	14.7
Fibromyalgia	14	41.2	Both	7	20.6
Neuropathy	11	33.3			
Carpal tunnel syndrome	10	29.4			

Note. [a]Current pain causing conditions (past six months) were self-reported by participants at baseline. [b]Includes participants taking opioid-acetaminophen combinations. [c]Gabapentin, neurotin, pregabalin. NSAID = nonsteroidal anti-inflammatory drug. [d]E.g., every four hours.

Table 2. *Association of concurrent and lagged pain and negative affect (NA), modeled separately, and dichotomous opioid use and opioid dosage in milligram morphine equivalents.*

	IV: Physical pain				**IV: Negative affect**			
	DV: Dichotomous use		**DV: Dosage**		**DV: Dichotomous use**		**DV: Dosage**	
Predictors	OR	95% CI	Est.	95% CI	OR	95% CI	Est.	95% CI
Intercept	0.03	[0.01, 0.16]***	1.92	[-0.16, 4.00]	0.04	[0.01, 0.16]***	1.97	[-0.09, 4.04]
Lagged occasion pain	0.67	[0.59, 0.77]***	-0.32	[-0.54, -0.10]**				
Concurrent occasion pain	2.66	[2.26, 3.13]***	1.38	[1.15, 1.62]***				
Day pain	1.35	[1.10, 1.65]**	0.21	[-0.12, 0.55]				
Person pain	1.35	[0.86, 2.11]	0.05	[-0.49, 0.59]				
Lagged occasion NA					0.54	[0.38, 0.76]***	-0.35	[-0.98, 0.28]
Concurrent occasion NA					2.63	[1.88, 3.69]***	1.69	[1.09, 2.28]***
Day NA					0.82	[0.53, 1.26]	0.23	[-0.63, 1.09]
Person NA					0.58	[0.24, 1.43]	-0.21	[-1.41, 0.99]
Covariates								
Time since last opioid (hr.)	0.19	[0.15, 0.23]***	-0.95	[-1.09, -0.81]***	0.17	[0.14, 0.21]***	-1.04	[-1.18, -0.89]***
Opioid cycle	2.69	[1.84, 3.94]***	1.51	[1.09, 1.93]***	2.40	[1.69, 3.40]***	1.60	[1.17, 2.03]***
Long-acting opioid[a]			43.90	[41.87, 45.93]***			44.14	[42.06, 46.21]***
Study day	0.98	[0.94, 1.02]	0.08	[0.004, 0.15]*	0.99	[0.95, 1.03]	0.07	[0.001, 0.15]*
Weekday (Saturday ref.)								
Sunday	1.32	[0.72, 2.43]	0.01	[-1.05, 1.08]	1.33	[0.77, 2.3]	-0.13	[-1.22, 0.96]
Monday	1.04	[0.58, 1.87]	0.16	[-0.90, 1.23]	1.01	[0.6, 1.72]	0.10	[-0.99, 1.19]
Tuesday	1.34	[0.74, 2.41]	0.29	[-0.80, 1.37]	1.37	[0.80, 2.35]	0.25	[-0.86, 1.36]
Wednesday	1.54	[0.85, 2.8]	-0.10	[-1.16, 0.96]	1.37	[0.79, 2.37]	-0.09	[-1.18, 0.99]
Thursday	0.74	[0.40, 1.36]	0.12	[-0.93, 1.16]	0.78	[0.45, 1.35]	0.12	[-0.95, 1.19]
Friday	1.34	[0.75, 2.41]	0.42	[-0.66, 1.49]	1.18	[0.70, 2.00]	0.28	[-0.82, 1.38]
Hour after wakeup	1.00	[0.93, 1.06]	-0.03	[-0.12, 0.06]	1.01	[0.95, 1.08]	-0.03	[-0.12, 0.07]
Age	1.04	[0.95, 1.13]	0.04	[-0.07, 0.15]	0.99	[0.92, 1.07]	0.03	[-0.07, 0.13]
Gender (male ref.)	1.12	[0.23, 5.54]	-0.13	[-2.12, 1.87]	1.29	[0.29, 5.65]	-0.12	[-2.11, 1.86]

Note. $N = 34$ individuals, 2,285 observations. OR = odds ratio, CI = confidence interval. [a]Whether opioids used were long-acting was not included as a covariate in dichotomous use models, due to collinearity. Degrees of freedom were calculated using the Kenward-Roger approximation. * $p < .05$. ** $p < .01$. *** $p < .001$.

Table 3. *Association of the interaction of concurrent and lagged pain and negative affect (NA) and dichotomous opioid use and opioid dosage in milligram morphine equivalents.*

	DV: Dichotomous use		DV: Dosage	
	OR	95% CI	Est.	95% CI
Predictors				
Intercept	0.02	[0.01, 0.12]***	1.58	[-0.52, 3.68]
Lagged occasion pain	0.70	[0.61, 0.8]***	-0.31	[-0.55, -0.07]*
Concurrent occasion pain	2.70	[2.26, 3.23]***	1.30	[1.04, 1.56]***
Day pain	1.58	[1.24, 2.01]***	0.29	[-0.10, 0.68]
Person pain	1.69	[1.04, 2.74]*	0.16	[-0.46, 0.77]
Lagged occasion NA	0.75	[0.5, 1.13]	-0.18	[-0.86, 0.50]
Concurrent occasion NA	0.85	[0.55, 1.31]	0.04	[-0.62, 0.70]
Day NA	0.55	[0.31, 0.96]*	-0.34	[-1.31, 0.63]
Person NA	0.36	[0.12, 1.02]	-0.45	[-1.83, 0.93]
Lagged occasion pain x NA	0.81	[0.62, 1.04]	-0.05	[-0.40, 0.31]
Concurrent occasion pain x NA	1.14	[0.93, 1.40]	0.72	[0.37, 1.07]***
Covariates				
Time since last opioid (hr.)	0.19	[0.15, 0.23]***	-0.95	[-1.09, -0.81]***
Opioid cycle	2.67	[1.82, 3.91]***	1.53	[1.11, 1.95]***
Long-acting opioid			43.61	[41.58, 45.65]***
Study day	0.99	[0.95, 1.03]	0.09	[0.01, 0.16]*
Weekday (Saturday ref.)				
Sunday	1.43	[0.77, 2.64]	0.07	[-1.00, 1.13]
Monday	1.08	[0.60, 1.96]	0.27	[-0.80, 1.34]
Tuesday	1.45	[0.80, 2.63]	0.32	[-0.77, 1.40]
Wednesday	1.64	[0.89, 3]	0.01	[-1.05, 1.07]
Thursday	0.76	[0.41, 1.4]	0.21	[-0.83, 1.26]
Friday	1.32	[0.73, 2.38]	0.46	[-0.61, 1.54]
Hour after wakeup	1.00	[0.94, 1.07]	-0.03	[-0.13, 0.06]
Age	1.03	[0.95, 1.12]	0.04	[-0.08, 0.15]
Gender (male ref.)	1.37	[0.29, 6.49]	-0.02	[-2.03, 2.00]

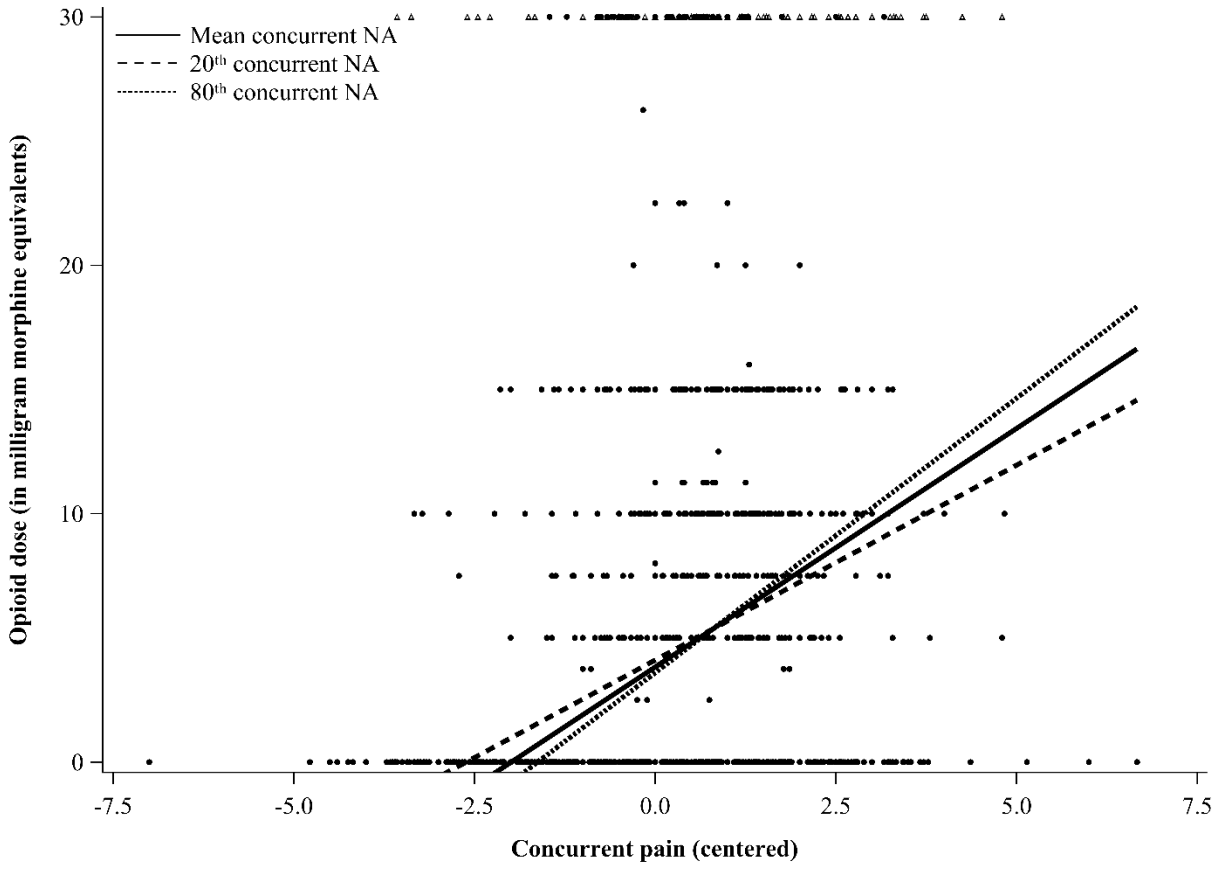
Note. $N = 34$ individuals, 2,285 observations. OR = odds ratio, CI = confidence interval.
[a]Whether opioids used were long-acting was not included as a covariate in the dichotomous use model, due to collinearity. Degrees of freedom were calculated using the Kenward-Roger approximation. * $p < .05$. ** $p < .01$. *** $p < .001$.

Table 4. *Association of concurrent and lagged dichotomous opioid use and opioid dosage with physical pain and negative affect over time.*

	DV: Physical pain				**DV: Negative affect**			
	IV: Dichotomous use		**IV: Dosage**		**IV: Dichotomous use**		**IV: Dosage**	
Predictors	Est.	95% CI	Est.	95% CI	Est.	95% CI	Est.	95% CI
Intercept	6.13	[4.77, 7.49]***	6.47	[5.09, 7.84]***	1.73	[1.12, 2.34]***	1.69	[1.09, 2.30]***
Lagged occasion opioid use	-0.08	[-0.22, 0.05]			-0.03	[-0.08, 0.03]		
Concurrent occasion opioid use	1.36	[1.18, 1.55]***			0.24	[0.16, 0.32]***		
Day opioid use	1.33	[0.56, 2.11]***			-0.06	[-0.37, 0.24]		
Person opioid use	3.73	[0.08, 7.38]*			-0.32	[-1.97, 1.33]		
Lagged occasion dosage			-0.01	[-0.01, -0.01]***			-0.004	[-0.01, -0.003]***
Concurrent occasion dosage			0.04	[0.03, 0.05]***			0.01	[0.004, 0.01]***
Day opioid use dosage			0.05	[0.03, 0.07]***			0.00	[-0.01, 0.01]
Person dosage			0.06	[-0.01, 0.12]			0.01	[-0.02, 0.04]
Covariates								
Time since last opioid (hr.)	0.03	[-0.004, 0.07]	-0.04	[-0.08, -0.01]**	0.03	[0.02, 0.05]***	0.02	[0.002, 0.03]*
Opioid cycle	-0.03	[-0.14, 0.09]	0.07	[-0.04, 0.18]	0.004	[-0.04, 0.05]	0.01	[-0.04, 0.05]
Long-acting opioid	-0.67	[-1.06, -0.27]***	-1.79	[-2.32, -1.26]***	-0.11	[-0.28, 0.06]	-0.34	[-0.56, -0.12]**
Study day	-0.001	[-0.02, 0.02]	-0.004	[-0.03, 0.02]	0.01	[-0.001, 0.02]	0.01	[-0.002, 0.02]
Weekday (Saturday ref.)								
Sunday	-0.43	[-0.76, -0.09]*	-0.39	[-0.74, -0.05]*	-0.14	[-0.28, -0.01]*	-0.14	[-0.28, -0.01]*
Monday	-0.21	[-0.54, 0.13]	-0.20	[-0.54, 0.14]	0.01	[-0.12, 0.15]	0.02	[-0.12, 0.15]
Tuesday	-0.12	[-0.46, 0.22]	-0.15	[-0.50, 0.19]	0.07	[-0.07, 0.2]	0.06	[-0.07, 0.20]
Wednesday	0.01	[-0.32, 0.35]	0.02	[-0.32, 0.36]	0.06	[-0.07, 0.19]	0.05	[-0.08, 0.18]
Thursday	0.14	[-0.20, 0.47]	0.11	[-0.23, 0.45]	0.08	[-0.05, 0.21]	0.07	[-0.06, 0.20]
Friday	-0.10	[-0.44, 0.23]	-0.11	[-0.45, 0.23]	0.08	[-0.05, 0.21]	0.07	[-0.06, 0.21]
Hour after wakeup	0.005	[-0.02, 0.03]	0.00	[-0.02, 0.02]	0.01	[-0.002, 0.02]	0.01	[-0.001, 0.02]
Age	-0.10	[-0.17, -0.03]**	-0.11	[-0.18, -0.03]**	-0.02	[-0.05, 0.01]	-0.02	[-0.06, 0.01]
Gender (male ref.)	0.14	[-1.24, 1.51]	0.19	[-1.29, 1.67]	0.17	[-0.45, 0.79]	0.20	[-0.45, 0.85]

Note. $N = 34$ individuals, 2,285 observations. CI = confidence interval. Degrees of freedom calculated using the Kenward-Roger approximation. * $p < .05$. ** $p < .01$. *** $p < .001$.

Figure 1. *Model fits for the interaction of concurrent occasion-level physical pain and negative affect (NA) for opioid dosage. Note: Solid lines represent the association of pain and opioid dosage at mean level NA and dotted lines at the 20th and 80th percentiles of NA. For presentation purposes, opioid dosage quantities greater than 30 milligram morphine equivalents (MME; N = 80) were winsorized to 30 MME. These observations are represented by triangles.*



Appendix

No previous work has been published from the dataset analyzed in the current manuscript.