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Associations among Pain, Non-Medical Prescription Opioid Use, and Drug Overdose History

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Background and Objective: Recently, use of prescription opioids (POs) has increased; non-medical PO (NMPO) use is linked to overdose. NMPO use is common among individuals prescribed opioids for pain, and those in substance use disorder (SUD) treatment with pain could be at increased risk for unintentional overdose due to NMPO use. We examined associations between pain, NMPO use, and overdose among SUD treatment patients.
Methods: Among 342 patients at a residential SUD treatment center, logistic regression examined the association of overdose with pain, adjusting for substance use, suicide attempts, and demographics.
Results: Pain was positively related to NMPO use. Heroin use, suicide attempts, pain, and NMPO use were positively associated with overdose; but NMPO use attenuated the pain-overdose relationship.
Conclusions: The relationship between pain and overdose among substance users may be, in part, explained by the association between pain and heavy NMPO use. (Am J Addict 2014;23:41–47)

BACKGROUND AND OBJECTIVES

Overdose in Substance Using Individuals

Individuals with substance use disorders (SUDs) are at elevated risk for overdose.[1–8] Among SUD treatment patients, history of non-fatal overdose is relatively common with the prevalence of prior overdose ranging from 24% to 61%[1,9–12] and research regarding unintentional overdose decedents suggests that most have a history of substance abuse.[13] Patients completing SUD treatment are at particularly elevated risk for post-treatment overdose, potentially due to decreased tolerance.[14,15] Thus, it is important to identify potential modifiable risk factors for unintentional overdose among SUD patients.

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Pain and Prescription Opioid Use as Risk Factors for Overdose

Prior work regarding risk factors for post-treatment overdose found that higher self-reported pain levels during the year before treatment predicted a greater likelihood of post-treatment overdose, even after controlling for history of overdose, sexual abuse, suicide attempts, and demographics.[9] Chronic pain may increase overdose risk because those with pain may use higher levels of prescription opioid (PO) pain medications due to analgesic effects. Thus, overdoses among individuals using POs may have occurred in part due to increasing use of their prescribed pain medications, and prior research supports increased overdose risk at higher prescribed doses of POs.[16,17] This notion is consistent with evidence that SUD treatment patients with chronic pain report more use of heroin and other opioids than those without pain,[18,19] potentially as an attempt to self-medicate. This is also consistent with Ballantyne and Mao's[20] framework for understanding adverse outcomes of opioid therapy. Specifically, they theorize that prolonged use of opioids results in cellular and intracellular changes that lead to pharmacologic tolerance and hypersensitivity to pain (ie, hyperalgesia). Tolerance and hyperalgesia then contribute to the patient's perception that the current dose of POs is not sufficient for pain relief, which results in dose escalation, thereby increasing risk for adverse outcomes such as overdose.

In contrast to the theorized model, in analyses conducted by Britton et al.[9] with SUD treatment patients, opioid use was only associated with post-treatment overdose at the bivariate level and was not significant when adjusting for other factors. However, the measure of opioid use in this study did not distinguish between heroin and POs, and only assessed whether opioids were a participant's "preferred substance of use," which may not identify patients with pain conditions who are prescribed opioids but use them non-medically. A previous investigation also demonstrated that a single-item measure of non-medical PO (NMPO) use identifies fewer non-medical users compared to several items designed to assess various

types of non-medical use (eg, taking more than prescribed, "borrowing" medications).[21]

Although prior research indicates a link between heroin use and overdose,[22,23] less is known about risks for overdose due to use of POs, which are pharmacologically similar to heroin. However, the increase in medical use of POs has been tied to overdose trends in that POs surpassed heroin (and cocaine) as the leading cause of fatal overdose as PO prescribing increased.[24–26] Among non-treatment samples[5,13,27] investigations have also demonstrated links between NMPO use and non-fatal overdose. Within SUD treatment, NMPO use is relatively common among patients prescribed opioids for pain.[28–32]

Similar to other definitions,[33–35] we define NMPO use as any use of POs in excess of how they were prescribed (eg, using more than prescribed or longer than prescribed) and/or use for reasons other than medical care (eg, to get high, relax, or sleep). Given the prevalence of NMPO use among pain patients and the relationship between POs and overdose[5,24,25,27] it is possible that, among those in SUD treatment, NMPO use could account for the relationship between pain and non-fatal overdose. Further, those who engage in frequent (ie, heavier) NMPO use may be at a higher overdose risk than those who only occasionally use POs.

The Present Study

Considering the previous research establishing relationships between pain and opioid use with overdose and Ballantyne and Mao's[20] model, the present study adds to current understanding by utilizing data from a SUD treatment sample to explore relationships between pain, NMPO use, and overdose. Specifically, because pain may lead to NMPO use, we were interested in evaluating *heavy* (ie, more frequent) NMPO use in relation to pain and overdose. Furthermore, because prior work[9] did not find a significant relationship between opioid *preference* and overdose when controlling for other factors, we explored the association of *heavy* NMPO use with overdose; such use may be a stronger correlate of overdose given how common NMPO use is among individuals in SUD treatment. Therefore, among adults in SUD treatment, we examined the hypotheses that pain and NMPO use would be associated with increased likelihood of lifetime overdose. Because prior research has demonstrated relationships between suicide and depressive symptoms with overdose,[1,9] we also evaluated the relationships between suicide attempt history and overdose history.

METHODS

Procedure and Study Setting

We examined data from a pilot data collection used in the formation of a randomized control trial examining the impact of a pain-related cognitive-behavioral intervention for substance users. Men and women age 18 or older were recruited over 1 year (2008–2009) from a large residential SUD treatment center serving the Detroit and Flint, Michigan areas. This center provides separate residential services to approximately 420 men and 210 women per year who stay for approximately 60 days; approximately 77% complete their course of treatment.

On recruitment days, research staff made announcements about the research study at the study site's morning meeting for all patients. Patients were encouraged to attend screening sessions during their daily free time. This process allowed us to screen a large number of patients without interfering with their treatment; however, it does not allow comparison between participants and non-participants/refusals on various characteristics, nor does it allow for assessing reasons for not participating. Individuals who attended a screening session were given information about the protocol, gave written informed consent, and completed self-administered screening questionnaires in 45–60 minutes. Exclusion criteria included: inability to speak or understand English, inability to provide written consent, or the research staff's observation of acute psychotic symptoms. No potential participants were excluded at screening. Participants were compensated with a $10 gift card. Approval for this study was provided by the Institutional Review Board at the University of Michigan.

Measures

The screening questionnaire consisted of self-administered surveys measuring demographics, pain, mental and physical health functioning, and substance use history. The following measures were utilized in the present analyses:

Pain

Participants' average pain level during the previous week was assessed using the 11-point Numeric Rating Scale of pain intensity[36] (PI-NRS) which read: "On a scale of 0–10, with 0 being no pain at all and 10 being the worst possible pain, how would you rate your pain on the average during the last week?" This measure has external validity and can detect clinically meaningful changes in subjective pain intensity.[36]

Non-Medical Prescription Opioid Use

Participants completed the 17-item Current Opioid Misuse Measure[37] (COMM) which assesses self-reported frequency of thoughts and behaviors pertaining to aberrant PO use in the 30 days prior to SUD treatment. Response choices range from 0 (never) to 4 (very often). The COMM has demonstrated internal consistency and test–retest reliability.[37,38] As described by Price et al.,[21] we created a variable measuring NMPO use relevant to individuals in SUD treatment using the six items assessing: going to someone other than one's prescribing physician, taking medications differently than prescribed, taking medications belonging to someone else, taking more than prescribed, borrowing from someone else, and using pain medicine for symptoms other than pain. Internal consistency reliability among these items was .93.

In previous work with this sample, Price et al.[21] used any positive response (ie, 1–4) on any of these six items to denote non-medical use and found that use of this criterion is more sensitive to detection of NMPO use than a single-item measure. Because we were evaluating *heavy* NMPO use, we created a new metric for this measure by defining *heavy* use as a response of "very often" (ie, 4) on any one of these six questions. Thus, for our analyses, participants' responses were dichotomized into presence or absence of past 30-day *heavy* NMPO use.

Substance Use and Overdose History

We used items from the self-report Addiction Severity Index[39,40] (ASI) to assess substance use history. Participants reported the number of years in their lifetimes they had used several substances, including alcohol, heroin, and cocaine. In addition to including years of alcohol use in our analyses, we included lifetime heroin and cocaine use because, aside from prescription opioids, these two substances have been repeatedly related to increased risk for overdose.[2,6,25,41] Although not validated in the self-report version of the ASI, we also included an item from the interviewer–administered ASI[42] asking, "How many times have you overdosed on drugs?" for which participants wrote in the number of times they had overdosed. Participants' responses on the heroin, cocaine, and overdose items were dichotomized (yes/no) for a history of any lifetime overdose or use of heroin or cocaine.

Suicide Attempts

To assess suicide attempt history, we used a single item from the Beck Scale for Suicide Ideation–Self-Report.[43,44] Participants indicated if they had attempted suicide never, once, or at least twice. For the present analyses, participants' responses were dichotomized into ever/never attempting suicide.

Data Analysis

Chi-square analyses and independent samples *t*-tests were used to evaluate bivariate associations between independent variables (ie, age, gender, race, education, alcohol use, heroin use, cocaine use, pain, suicide attempts, and NMPO use) and overdose history. We utilized Holmbeck's[45] three-step method to assess relationships among heavy NMPO use, pain, and overdose: (1) using logistic regression with simultaneous entry of independent variables, we evaluated the association of pain ratings, gender, age, education (high school/less than high school), race (Caucasian/non-Caucasian), years of regular alcohol use, lifetime heroin use (ever/never), lifetime cocaine use (ever/never), and lifetime suicide attempts (ever/never) with heavy NMPO use (present/absent); (2) controlling for the same demographic and substance use variables, we evaluated the association of pain ratings with non-fatal overdose (ever/never); and (3) we separately assessed for a potential mediating effect of heavy NMPO use by utilizing the same model described in Step 2 with the addition of heavy NMPO use as an independent variable.

RESULTS

Patient Characteristics

Participants were 326 patients enrolled at the study site who provided complete data on all study variables (351 were screened; 25 had missing data on relevant variables and were not included in analyses). The sample of 326 was 75.5% male with a mean age of 35.1 years (SD = 10.6). Most were Caucasian (65.3%); African Americans (26.7%), Hispanic/Latinos (1.5%), and other races/ethnicities (6.5%) were also represented. Participants had an average of 11.8 years of education (SD = 2.1), most were unemployed (72.8%), and 17.0% were currently married or living with a partner. Other sample characteristics are provided in prior publications.[21,46]

Ninety-four (28.8%) participants reported a lifetime history of overdose and 74 (22.4%) reported *heavy* NMPO use in the month preceding treatment. Figure 1 depicts the proportion of individuals, by overdose history, who endorsed "very often" engaging in each of six items assessing NMPO use (a full summary of item responses among this sample is available in a prior publication[20]). Overdose history differed across groups based on gender, race, heroin use, cocaine use, suicide attempts, and presence/absence of past 30-day heavy NMPO misuse (Table 1). Age, education, pain, and years of alcohol use did not significantly differ by overdose history.

Multivariable Analyses

Following Step 1 in the analysis plan, the logistic regression model testing the association between pain ratings and heavy NMPO use was statistically significant ($p < .001$; Table 2, Model 1). Those who had ever used heroin (OR = 5.07; 95% CI = 2.53–10.14) and those with a history of at least one suicide attempt (OR = 2.59; 95% CI = 1.40–4.78) were more likely to have reported heavy NMPO use. Higher pain ratings were also associated with increased odds of heavy NMPO use (OR = 1.31; 95% CI = 1.16–1.48).

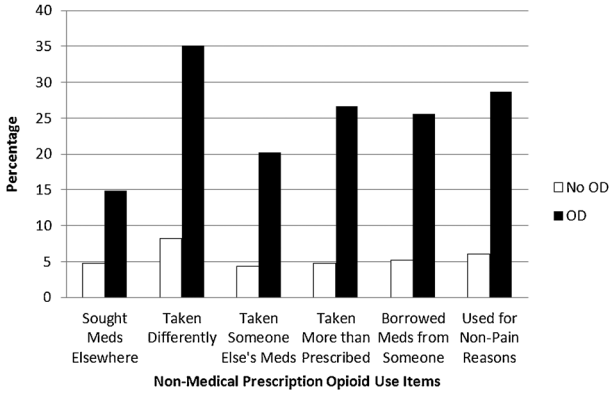

FIGURE 1. Percent of participants, by overdose (OD) history, who reported "very often" to items assessing non-medical prescription opioid use.

TABLE 1. Associations of demographics, substance use, and pain ratings with lifetime history of overdose

	Lifetime history of overdose		
	No ($n = 232$)	Yes ($n = 94$)	
Characteristic	N(%) or M (SD)	N(%) or M (SD)	Test statistic and significance level
Age	35.8 (10.2)	33.5 (11.2)	$t(324) = 1.78$, $p = .08$
Years of regular alcohol use	11.0 (10.1)	11.4 (11.0)	$t(324) = -0.31$, $p = .75$
Gender			
Males	184 (74.8%)	62 (25.2%)	$\chi^2(1) = 6.44$, $p < .05$
Females	48 (60.0%)	32 (40.0%)	
Race			
Caucasian	136 (63.9%)	77 (36.2%)	$\chi^2(1) = 16.03$, $p < .001$
Non-Caucasian	96 (85.0%)	17 (15.0%)	
Education			
High school	157 (73.7%)	56 (26.3%)	$\chi^2(1) = 1.94$, $p = .16$
Less than high school	75 (66.4%)	38 (33.6%)	
Lifetime suicide attempt			
Yes	48 (52.2%)	44 (47.8%)	$\chi^2(1) = 22.53$, $p < .001$
No	184 (78.6%)	50 (21.4%)	
Lifetime heroin use			
Yes	42 (41.6%)	59 (58.4%)	$\chi^2(1) = 62.40$, $p < .001$
No	190 (84.4%)	35 (15.6%)	
Lifetime cocaine use			
Yes	129 (63.6%)	74 (36.5%)	$\chi^2(1) = 15.22$, $p < .001$
No	103 (83.7%)	20 (16.3%)	
Past 30-day heavy non-medical use of prescription opioids			
Yes	29 (39.7%)	44 (60.3%)	$\chi^2(1) = 45.31$, $p < .001$
No	203 (80.2%)	50 (19.8%)	
Past-week pain level	3.7 (3.0)	4.3 (2.8)	$t(324) = -1.71$, $p = .09$

TABLE 2. Summary of logistic regression analyses evaluating associations of pain and heavy non-medical opioid use with overdose ($N = 326$)

	Model 1: Predicting heavy non-medical prescription opioid use	Model 2: Predicting lifetime overdose	Model 3: Predicting lifetime overdose
Independent variables	OR (95% CI)	OR (95% CI)	OR (95% CI)
Female	1.42 (0.74–2.73)	0.93 (0.48–1.80)	0.90 (0.46–1.77)
Caucasian	1.24 (0.59–2.61)	**2.19 (1.09–4.40)***	**2.25 (1.09–4.63)***
Age	0.98 (0.94–1.01)	1.00 (0.96–1.03)	1.00 (0.96–1.04)
High school education	0.64 (0.34–1.22)	**0.52 (0.28–0.96)***	0.55 (0.29–1.04)
Lifetime suicide attempt	**2.59 (1.40–4.78)****	**2.58 (1.43–4.67)****	**2.23 (1.20–4.12)***
Years of regular alcohol use	1.00 (0.96–1.04)	1.03 (0.99–1.06)	1.03 (0.99–1.06)
Lifetime heroin use	**5.07 (2.53–10.14)*****	**6.93 (3.61–13.32)*****	**5.42 (2.76–10.64)*****
Lifetime cocaine use	1.19 (0.60–2.36)	1.72 (0.89–3.32)	1.72 (0.88–3.36)
Past week pain rating	**1.31 (1.16–1.48)*****	**1.11 (1.00–1.23)***	1.07 (0.96–1.19)
Past 30-day heavy non-medical prescription opioid use	—	—	**2.99 (1.53–5.84)****
	Model $\chi^2(9) = 76.61^{***}$	Model $\chi^2(9) = 92.34^{***}$	Model $\chi^2(10) = 102.67^{***}$

$^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$; Boldface type indicates statistically significant results during the review process.

In Step 2 of the analysis, the logistic regression model evaluating associations of demographic variables, cocaine and heroin use, and pain with overdose was also significant ($p < .001$; Table 2, Model 2). In this model, heroin use (OR = 6.93; 95% CI = 3.61–13.32) and higher pain ratings (OR = 1.11; 95% CI = 1.00–1.23) both increased the odds of participants reporting an overdose. In addition, having a high school education or greater was associated with decreased odds of reporting an overdose (OR = 0.52; 95% CI = 0.28–0.96), whereas Caucasian race (OR = 2.19; 95% CI = 1.09–4.40) and history of suicide attempt (OR = 2.58; 95% CI = 1.43–4.67) were both associated with increased odds of prior overdose.

In Step 3, when heavy NMPO use was added as a dependent variable and a separate analysis was conducted, the model was also significant ($p < .001$; Table 2, Model 3). However, the association of pain with overdose was no longer significant (OR = 1.07; 95% CI = 0.96–1.19) with the inclusion of PO use in the model, which was associated with increased odds of prior overdose (OR = 2.99; 95% CI = 1.53–5.84). In this model, heroin use (OR = 5.42; 95% CI = 2.76–10.64), suicide attempts (OR = 2.23; 95% CI = 1.20–4.12), and Caucasian race (OR = 2.25; 95% CI = 1.09–4.63) also continued to be significantly associated with overdose.

DISCUSSION

Prior overdoses were relatively common in these SUD treatment patients. Over 28% reported at least one lifetime overdose, which is within the range of 24–61% reported in other SUD treatment samples.[1,9–12] Consistent with prior research and theory,[5,20,24–27] *heavy* NMPO use was associated with overdose when accounting for demographics, history of suicide attempts, and other substance use. Those with higher pain ratings were also more likely to report an overdose; however, this association was reduced when heavy NMPO use was included in our model.

That pain was associated with NMPO use is consistent with prior work evaluating substance users' non-medical use of POs and benzodiazepines.[47] The observed relationship between pain and overdose was also consistent with a prior prospective study of patients who completed SUD treatment.[9] Our results differ from those of Britton et al.[9] because they only found a bivariate association between opioid preference and overdose risk, which became non-significant in multivariate analyses. Using an expanded measure of NMPO use, the current results suggest that such use could help explain why individuals with pain are at elevated overdose risk. Although prior research has identified that males have a higher likelihood of non-fatal overdose,[5,9] in our sample, gender was significantly related to overdose in bivariate analyses, but not in multivariable models. This inconsistency may be due to the relatively small proportion of females in our sample.

The present investigation addresses a gap in the literature by assessing multiple behaviors characteristic of NMPO use, and these results have implications for assessment, intervention, and overdose prevention. These findings highlight the need for assessing overdose history, including specific substances used prior to overdose, at SUD treatment entry, given the notable prevalence of overdose among individuals in SUD treatment and that prior overdose is the strongest predictor of future overdoses.[48] In evaluating overdose risk among SUD treatment patients, assessors may benefit from asking not only about recent frequency of or lifetime history of opioid use, but also about pain levels, pain treatment, and the several types of NMPO use included in this study's measure of NMPO use.

Like individuals who reported heavy NMPO use, participants who used heroin were at increased risk for overdose. Together, these findings likely reflect the heightened risk of respiratory depression associated with opioids broadly compared to other substances[49] and those who use both POs and heroin could be at a particularly heightened risk. Furthermore, individuals with a history of suicide attempts had increased odds of reporting an overdose. Our data does not allow for determining intentionality, such as if the overdoses were attempted suicides; however, this observed relationship also supports the importance of assessing suicide history in relation to overdose risk. Future research on overdose should include thorough assessments of causal substances and intentionality.

Although these findings are exploratory and cross-sectional, they suggest that the relationship between pain and overdose history among substance users may be, at least in part, explained by the association between pain and heavy PO use. Among individuals in SUD treatment, those with chronic pain may have greater access to POs due to the prescribing of POs for pain treatment. The hyperalgesia and tolerance that can be caused by long-term use of opioids[20] could increase the frequency of heavy NMPO use. Obtaining pain ratings from individuals entering SUD treatment may help identify those in need of further assessment, including a more detailed evaluation of PO use, and who may benefit from targeted interventions designed to reduce overdose risk and improve pain management through non-pharmaceutical treatments. Results also suggest that coordination between SUD clinicians and pain care providers may be important for overdose risk assessment, careful monitoring of PO use, and prevention interventions. However, future research is needed to understand the contexts surrounding overdose when opioids are prescribed versus obtained from other sources.

Despite these implications, this exploratory investigation has several limitations. First, this study was cross-sectional, with key variables measured over different time periods (eg, past-week pain, 30-day NMPO use, lifetime overdose), and we cannot infer causality. We also cannot distinguish the circumstances of overdoses reported, and whether variables such as pain, PO use, and/or suicide attempts were causes of the reported overdoses. While pain and PO misuse may be ongoing, their patterns could fluctuate over time and it is not known whether the variables used in this study represent pain and substance use proximal to the reported overdoses. Further, this study is limited in that it could not examine the relationships of pain and NMPO use with *fatal* overdose. In

addition to geographic limitations, participants came from a single residential SUD treatment program and the reported associations may differ for individuals in other settings. Our recruitment procedures could also be subject to a volunteer bias. Because participants completed measures at treatment entry, pain ratings could have been influenced by recent withdrawal symptoms and may not be a sole reflection of a chronic pain level. Inclusion of comprehensive pain measures in future research may clarify these relationships.

Furthermore, this investigation is limited in that participants were asked to report their number of prior drug overdoses, and not about the causal substance, route of administration, or co-ingestion of drugs and alcohol. Thus it is possible that substances other than POs (eg, benzodiazepines), or co-ingestion of substances are responsible for the reported overdoses. It is also possible that, if analyses were able to be restricted to overdoses that were only PO-related, the associations reported in this investigation could be stronger. We also did not assess intentionality of the reported overdoses. However, we were able to include lifetime suicide attempts in our analyses, and although this variable was related to overdose history, the associations between overdose, pain, and NMPO use persisted after this adjustment. Our measure of *heavy* NMPO use has not been previously validated and additional research examining whether this is associated with other key domains, such as persistence of use and experiencing other adverse consequences of use, would help to establish the validity of this measure.

The present results, coupled with those of Britton et al.,[9] begin to address a gap in the literature by providing an initial understanding of the inter-relationships between pain, overdose, and NMPO use among SUD treatment patients. These results can inform longitudinal evaluations that can directly assess the causal mechanisms of overdose. Specifically, longitudinal data utilizing a larger sample would allow for examining mediation and bi-directionality through a structural equation modeling approach with reciprocal, cross-lagged longitudinal paths. Measures designed to capture more information regarding the duration of NMPO use could provide a more complete picture of how these variables are associated over time. Future research should also address additional factors that could influence overdose, such as route of drug administration, co-ingestion with other substances, psychiatric distress, and intentionality. In addition, future research should evaluate variables which may be associated with pain, such as chronicity, condition, and treatment history, in relation to risk of overdose among individuals in SUD treatment. Finally, research is needed to evaluate whether overdose risk among this population can be reduced through targeted prevention and intervention.

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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