Drug and Alcohol Dependence 204 (2019) 107456

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Pain severity and prescription opioid misuse among individuals with chronic pain: The moderating role of alcohol use severity

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ARTICLE INFO

Keywords:
Pain
Chronic pain
Alcohol
Opioids
Comorbidity

ABSTRACT

Background: Chronic pain is a public health problem associated with opioid misuse. Yet, it is important to understand factors underlying opioid misuse in the context of pain. Alcohol use is one factor to consider given past work documenting use of alcohol to manage pain. However, it is unknown whether alcohol use severity exacerbates the relation between pain and opioid misuse. This study sought to examine relations between pain and prescription opioid misuse and the moderating role of alcohol use severity in two online survey studies of individuals with chronic pain.

Method: Individuals with chronic pain (study 1, $n = 364$; study 2, $n = 437$) were administered measures of pain, alcohol use, and opioid misuse.

Results: In study 1, there was a significant interaction of pain severity and alcohol use ($b = 0.16$, $p < 0.001$). Pain was significantly related to opioid misuse among those with higher ($b = 1.50$, $p < 0.001$), but not lower ($b = -0.26$, $p = 0.430$) alcohol use. In study 2, there was a significant interaction of pain severity and alcohol use ($b = 0.03$, $p < 0.001$). Pain was significantly related to opioid misuse among those with higher ($b = 0.74$, $p < 0.001$), but not lower ($b = 0.07$, $p = 0.620$) alcohol use.

Conclusions: In two online samples, there was evidence of a novel interaction of pain severity and alcohol use severity in relation to opioid misuse. Although cross-sectional, results replicated in two studies. Pain severity was related to opioid misuse among those with higher but not lower alcohol use. Those who use alcohol, even below suggested cut-offs, may be more likely to misuse opioids when in pain.

1. Introduction

The misuse of prescription opioids (e.g., taking in a manner/dose other than as prescribed; taking non-prescribed medications) is a significant problem in the United States (U.S.; Brady et al., 2015), constituting the ongoing 'opioid epidemic'. Yet, opioids are still widely prescribed in the U.S. (Fuentes et al., 2018; Kuehn, 2007). Although there was a decrease in the amount of opioids prescribed in the U.S. each year (2011–2015), rates in 2015 were nearly four times greater than in Europe (Guy et al., 2017). Opioid prescription rates in the US have decreased, yet they remained almost 300% higher in 2016 than in 1991 (Center for Disease Control, 2017; Volkow, 2014). In 2015, more than one third of the U.S. population used prescription opioids and among those prescribed, 12.5% reported misuse (Han et al., 2017). The prevalence rates of prescription opioid misuse and opioid use disorder (OUD) have each more than doubled from 2001 to 2002 to 2012–2013 (Saha et al., 2016). Alarmingly, death rates from opioid overdoses have tripled (Rudd et al., 2016) or quadrupled (Calcaterra et al., 2013) over the past 10–15 years. Although overdoses are largely associated with heroin use, rates of heroin and synthetic opioid (e.g., fentanyl) use are escalating among those using prescription opioids (Compton et al., 2016). Furthermore, death rates from synthetic opioids have increased, with a 22-fold increase from 2002 to 2017 (National Institute on Drug Abuse, 2018). These rates have continued to increase yearly and fatal opioid overdose continues to increase (Scholl et al., 2019).These statistics necessitate increased attention towards factors underlying

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https://doi.org/10.1016/j.drugalcdep.2019.02.036
Received 21 October 2018; Received in revised form 22 February 2019; Accepted 28 February 2019
Available online 22 August 2019
0376-8716/

prescription opioid misuse.

Not surprisingly, pain is a central factor related to prescription opioid (mis)use (Price et al., 2011). Pain complaints represent a substantial public health crisis, as a significant number (19%) of adults in the U.S. report, chronic, persistent pain, and 11% report daily pain (Kennedy et al., 2014; Nahin, 2015). A large national study found that pain relief was the most commonly reported motivation for misuse of opioids (Han et al., 2017). Indeed, chronic pain is one of the most common reasons for medical care in the U.S. and prescription opioids are frequently prescribed to manage pain (Daubresse et al., 2013; Gostin et al., 2017) despite the Centers for Disease Control and Prevention guidelines recommending non-opioid therapies as the preferred treatment for chronic pain (Dowell et al., 2016). Although prescribed opioids have been considered efficacious for short term use (i.e., 12 weeks or less; American Pain Society and American Academy of Pain Medicine, 2009), the effectiveness and long-term outcome for opioid use (e.g., for chronic pain) is understudied and associated with serious risks, including abuse, overdose, and numerous health problems (e.g., myocardial infarction; Chou et al., 2014). Opioid misuse is common among individuals with chronic pain, with the estimated prevalence of opioid misuse between 21% and 29% among those with chronic pain (for review, see Vowles et al., 2015).

Although it has been difficult to identify consistent predictors of prescription opioid misuse among those with chronic pain, history of drug/alcohol abuse is one of the strongest (Turk et al., 2008). Furthermore, alcohol use is one of the leading causes of preventable death in the U.S. (Stahre, 2014) and rates of use, high-risk drinking, and alcohol use disorder (AUD) are rising (Grant et al., 2017). Alcohol use is significantly related to increased prescription drug misuse (Hughes et al., 2016). Furthermore, AUD is related to nonmedical use of prescription opioid medications (Schepis and Hakes, 2013) as well as OUD (Hartzler et al., 2010, 2011). Individuals with AUD are also more likely to begin misusing prescription opioids and they more quickly transition from opioid misuse to OUD than those without AUD (Schepis and Hakes, 2017). Among those with OUD, a comorbid AUD diagnosis is related to increased risk for mortality (Bogdanowicz et al., 2015). Both opioids and alcohol act upon reward centers (e.g., dopaminergic neurons; Spanagel and Weiss, 1999). Moreover, the use of alcohol is linked to more opioid-related deaths which may occur as alcohol and opioids mutually reinforce one another to increase the risk of respiratory depression or as alcohol lowers the tolerance for opioids, resulting in greater risk for overdose (Hill et al., 2016).

Greater alcohol use may also exacerbate the relation between pain and opioid misuse. The simultaneous misuse of alcohol and opioids is common (Witkiewitz and Vowles, 2018), particularly among those with chronic pain (Vowles et al., 2018). There is a high co-occurrence of pain and alcohol use (Boissoneault et al., 2019; Brennan et al., 2005) as well as the use of alcohol to cope with pain (Zale et al., 2015). Alcohol (mis) use is common among individuals using opioids for pain management (Kim et al., 2013; Lawton and Simpson, 2009; Serdarevic et al., 2018), which is particularly relevant given alcohol use is contraindicated for pain/opioid treatment (Ives et al., 2006). Alcohol has well-documented pain-dampening effects (Horn-Hofmann et al., 2015) and is commonly involved in emergency room visits for opioid-based pain relief and opioid-related overdose deaths (Gomes et al., 2017; Jones et al., 2014). In one study of chronic pain patients using prescribed opioids, those who drank at risky levels reported greater pain relative to those drinking at moderate levels (Larance et al., 2016). Among those with chronic pain in long-term opioid treatment, the presence of AUD was associated with greater rates of opioid overdose and higher health care costs relative to those without AUD (Landsman-Blumberg et al., 2017).

Despite this past work documenting relations of alcohol use among opioid users with chronic pain, no study has evaluated the moderating role of alcohol use severity on the relation between pain and opioid misuse. Theoretically, individuals with chronic pain who are experiencing more severe pain may misuse opioids to a greater degree. Past work has documented synergistic effects of pain and alcohol use severity in relation to emotion outcomes (e.g., depression; Paulus et al., 2017) but not prescription opioid misuse. Additionally, greater alcohol use may exacerbate this pain-opioid misuse relation such that for individuals who drink more, pain severity may be more strongly related to opioid misuse relative to individuals who drink less. Given alcohol is associated with greater use of other substances such as opioids (Hughes et al., 2016) coupled with evidence that withdrawal from alcohol has hyperalgesic effects (Jochum et al., 2012) those with more severe alcohol use may experience greater pain (Larance et al., 2016), be more sensitive to pain sensations, and misuse opioids to a greater degree to manage pain, relative to those with less severe alcohol use.

The current investigation sought to examine relations between pain and prescription opioid misuse and the moderating role of alcohol use severity using data from two online samples of individuals with chronic pain. Study 1 evaluated this moderation model among individuals with chronic pain (many of whom were using prescription opioids). It was hypothesized that those with more severe alcohol use would evidence a stronger positive relationship between pain and opioid misuse relative to those with less severe alcohol use. It was expected that the interaction would be evident after accounting for statistically and theoretically relevant factors of age, sex, level of education, and depressive symptoms (Back et al., 2011; Campbell et al., 2010; Grattan et al., 2012; Kelly et al., 2008). These findings were expected to replicate in a second sample. Study 2 evaluated the same model among individuals with chronic pain, all of whom were using prescription opioids.

2. Study 1 methods

2.1. Study 1 participants

Participants residing in the U.S. were recruited online from Amazon Mechanical Turk (MTurk), a method of collecting online survey data. The MTurk system is secure and allows for participant confidentiality, as researchers only have access to an MTurk "worker ID" that is not linked to any protected health information. Participants who completed the survey were paid $3.00 for their time. This study was approved by the University of New Mexico's Human Subjects Institutional Review Board.

2.2. Study 1 measures

2.2.1. Pain severity

Pain was assessed continuously with one item: average pain severity over the preceding week (0 no pain – 10 maximal pain).

2.2.2. British Columbia major depression inventory (BCMDI; Iverson and Remick, 2004)

The BCMDI is a 16-item self-report measure assessing depressive symptoms over the preceding two weeks. Items (e.g. "I feel sad, down in the dumps, and/or blue (nearly every day)" are rated from 0 (Not a problem) to 5 (A very severe problem) and summed to a continuous total score. The BCMDI has been reliably used among chronic pain patients (McCracken and Gutiérrez-Martínez, 2011; Vowles et al., 2007). Internal consistency in the present sample was excellent (Cronbach's $\alpha = .90$).

2.2.3. Current opioid misuse measure (COMM; Butler et al., 2007)

The COMM is a 17-item self-report measure of problematic prescription opioid use in the context of chronic pain over the preceding 30 days. Items (e.g. "how often have you taken your medications differently from how they are prescribed") are rated from 0 (Never) to 4 (Very often) and summed to a continuous total score. The COMM has good psychometric properties among chronic pain patients (Butler et al., 2007). In the present sample, internal consistency was good (Cronbach's $\alpha = .88$).

2.2.4. Alcohol use disorders identification test (AUDIT; Saunders et al., 1993)

The AUDIT is a 10-item (e.g. "How often do you have six or more drinks on one occasion") self-report measure of alcohol consumption and problems (i.e., alcohol use severity). Items are summed to a continuous total score. It has strong psychometric properties among clinical and non-clinical samples (Reinert and Allen, 2002). In the current sample, internal consistency was excellent (Cronbach's α = .90).

2.3. Study 1 procedure

Potential participants were screened for eligibility, consisting of pain: (1) on most days of the week (i.e., 4 or more days per week), (2) at an average weekly severity of 3 or greater on a 0–10 numerical rating scale, and (3) for at least three months in duration. Those who experienced only chronic headache pain were not eligible. Information regarding prescription opioid use was collected, but not a requirement for study entry.

2.4. Study 1 data analytic plan

The interactive effect of average pain severity and alcohol use severity (AUDIT) on opioid misuse (COMM) was examined with hierarchical regression in SPSS 24. Step 1 included covariates alone (age, sex, years of education, depressive symptoms [BCMDI]), step 2 added the unique effects of average pain severity and alcohol use severity, and step 3 added the interaction term (average pain severity x alcohol use severity). The PROCESS macro for SPSS (Hayes, 2012) determined the simple slopes for the relationship between average pain severity and opioid misuse for +1 SD and -1 SD values of alcohol use severity. Additionally, the Johnson-Neyman (JN; Johnson and Fay, 1950) technique was used (via PROCESS macro) to determine the value(s) of the moderator (alcohol use severity) where the relationship between average pain severity and opioid misuse transitions from statistically non-significant to statistically significant (Preacher et al., 2006). This approach can theoretically provide more precision than in simple slope analysis, which only estimate associations at "high" and "low" values.

3. Study 1 results

Data from 364 individuals with chronic pain (55.3% female; Mage = 36.6) was available for analysis. Individuals reported average pain severity (M = 5.1) represents moderate/distressing pain on a 0–10 scale. Average AUDIT scores (M = 4.5) were in the low risk range (i.e., below 7). Average COMM scores (M = 12.3) were above the suggested cut-off (9+). See Table 1 for additional study participant characteristics. Correlations among study variables are in Table 2.

Covariates in step 1 accounted for significant variance in opioid misuse (F (4359) = 33.49, $p < .001$, $R^2 = .27$). Depression was significantly associated with opioid misuse (see Table 3). Step 2 accounted for significantly more variance in opioid misuse (F (6357) = 30.39, $p < .001$, $\Delta R^2 = .07$), where alcohol use ($B = .39$, $SE = .07$, $p < .001$) was a significant predictor, and pain was not ($B = .47$, $SE = .27$, $p = .081$). Including the interaction term of average pain severity and alcohol use in step 3 significantly improved model fit (F (7356) = 29.00, $p < .001$, $\Delta R^2 = .03$), and the interaction term was a significant predictor ($B = .16$, $SE = .04$, $p < .001$). Examining the simple slopes revealed that those with high AUDIT total scores (+1SD; $B = 1.50$, $SE = .38$, $p = .001$), but not low (-1 SD; $B = -.26$, $SE = .33$, $p = .430$; see Fig. 1 for simple slopes) evidenced a statistically significant association between average pain severity and opioid misuse. The JN technique revealed that the effect of pain severity on opioid misuse was significant only for those with an AUDIT of 4.84 or greater (34.34% of the current sample).[1]

Table 1
Participant Demographic Characteristics.

	Study 1 (n = 364)	Study 2 (n = 437)
Gender (female)	55.3%	74.1%
Age	36.60 (11.17)	38.49 (11.14)
Average pain severity	5.05/10	21.87/30 (7.29/10)
Average pain duration	6.85 (7.09) years	–
Pain medication use		–
Any	83.7%	–
Prescribed Non-Opioid	56.6%	–
Prescribed Opioid	24.7%	100%
Race		
White/Non-Hispanic	77.7%	77.8%
Asian/Pacific Islander	8.7%	0.9%
Black	6.7%	8.7%
Hispanic	5.2%	13.3%
Native American/Alaskan Native	0.8%	3.4%
Other	1.1%	3.8%
Middle Eastern	0.8%	–
Education		
Some college	35.1%	–
Bachelor's degree/trade school	44.3%	40.7%
Post-graduate degree	14.9%	–
High School	5.4%	30.9%
Did not complete high school	0.3%	5.7%
Employment		
Full time	38.2%	41.0%
Reduced hours or retired due to pain	26.5%	19.7%
AUDIT Total	4.52 (6.06)	–
ASSIST Alcohol	–	8.73 (10.73)
COMM Total	12.27 (9.37)	17.82 (17.02)

4. Study 2 methods

4.1. Study 2 participants

Participants were recruited from individuals residing in the U.S. through Qualtrics, an online survey management system. Adults with a Qualtrics Panels account that endorsed moderate to severe chronic pain and current use of prescription opioid pain medication were sent a survey advertisement.

4.2. Study 2 measures

4.2.1. Patient health Questionnaire-2 (PHQ-2; Kroenke et al., 2003)

The PHQ-2 is a 2-item self-report measure of depression. Items (e.g., "feeling down, depressed, or hopeless") are rated from 0 (*not at all*) to 4 (*nearly every day*) and summed to a continuous total score. The PHQ-2 is a valid screen for depression (Kroenke et al., 2003). Internal consistency was good in the present sample (Cronbach's α = .89).

4.2.2. Alcohol, smoking, and substance involvement screening test (ASSIST-alcohol subscale; WHO ASSIST working group, 2002)

The ASSIST-alcohol is an 8-item self-report of alcohol use severity within the past three months. Items are summed to a continuous total score. It has strong psychometric properties (Humeniuk et al., 2008). In the current study, the ASSIST-alcohol showed excellent internal consistency (Cronbach's α = .90).

4.2.3. Graded chronic pain scale (GCPS; Von Korff et al., 1992)

The current study used the three-item pain severity (intensity) scale. Items are rated from 0 (*No pain*) to 10 (*Pain as bad as could be*) and

[1] Analyses on the study 1 sample were also run covarying for prescription opioid use vs. not. The pattern of findings did not change. There was a statistically significant interaction of pain and alcohol use severity; pain was significantly related to opioid misuse scores for those with high but not low alcohol use severity.

Table 2
Bivariate correlations.

	1.	2.	3.	4.	5.	6.	7.
1.Age	–	.068	-.040	-.177**	.156**	-.260**	-.277**
2.Sex	.098*	–	-.057	-.129**	.028	-.259**	-.179**
3.Education	.065	-.040	–	.125**	−0.045	.123**	.145**
4.Depression	-.062	.078	-.008	–	.119*	.436**	.616**
5.Pain	-.060	.105*	-.055	.275**	–	.033	.165**
6.Alcohol Use Severity	-.050	.046	-.001	.062	-.148**	–	.582**
7.Opioid Misuse	-.048	.058	-.060	.524**	.182**	.286**	–

Note: Correlations for Study 1 in the shaded grey, and for Study 2 in the unshaded section. For Study 1, the BCMDI was used as a measure of depression, and for Study 2, the PHQ-2 was used. The pain measure for study 1 was a measure of average pain severity, and for Study 2, was the GCPS pain severity subscale. Finally, Study 1 utilized the AUDIT total score for alcohol use severity, and Study 2 utilized the ASSIST alcohol score. Both studies used the COMM-Total for opioid misuse. * $p < .05$ **$p < .01$.

Table 3
Hierarchical Regression Results For Study 1 and Study 2.

Study 1						Study 2					
Step		**B**	**SE**	**t**	**p-value**	**Step**		**B**	**SE**	**t**	**p-value**
1	Constant	7.62	3.091	2.465	0.014	1	Constant	18.26	3.19	5.73	< 0.001
	Age	−0.033	0.038	−0.874	0.383		Age	−0.27	0.06	−4.70	< 0.001
	Sex	0.185	0.847	0.218	0.827		Sex	−3.64	1.40	−2.60	0.010
	Education	−0.144	0.175	−0.823	0.411		Education	0.71	0.41	1.74	0.080
	BCMDI Total	0.318	0.028	11.32	< 0.001		PHQ-2 Depression	4.59	0.31	15.01	< 0.001
2	Constant	2.632	3.365	0.782	0.435	2	Constant	3.84	3.53	1.09	0.280
	Age	−0.015	0.036	−0.407	0.685		Age	−0.21	0.05	−3.85	< 0.001
	Sex	−0.214	0.815	−0.263	0.793		Sex	−1.04	1.30	−0.80	0.420
	Education	−0.085	0.168	−0.504	0.614		Education	0.52	0.37	1.41	0.160
	BCMDI Total	0.295	0.028	10.556	< 0.001		PHQ-2 Depression	3.37	0.30	11.14	< 0.001
	Average Pain	0.469	0.268	1.747	0.081		GCPS Pain Severity	0.39	0.11	3.68	< 0.001
	AUDIT Total	0.392	0.066	5.952	< 0.001		ASSIST Alcohol	0.56	0.06	9.13	< 0.001
3	Constant	5.948	3.421	1.739	0.083	3	Constant	11.77	3.98	2.96	< 0.001
	Age	−0.008	0.036	−0.222	0.824		Age	−0.22	0.05	−4.15	< 0.001
	Sex	−0.262	0.801	−0.327	0.744		Sex	−0.60	1.28	−0.47	0.640
	Education	−0.1	0.165	−0.607	0.544		Education	0.58	0.36	1.59	0.110
	BCMDI Total	0.308	0.028	11.12	< 0.001		PHQ-2 Depression	3.43	0.30	11.54	< 0.001
	Average Pain	−0.259	0.328	−0.791	0.429		GCPS Pain Severity	0.02	0.14	0.16	0.870
	AUDIT Total	−0.354	0.21	−1.69	0.092		ASSIST Alcohol	−0.25	0.21	−1.22	0.220
	Interaction	0.161	0.043	3.744	< 0.001		Interaction	0.04	0.01	4.06	< 0.001

Note: Hierarchical regression for study 1 (left) and study 2 (right). The first step contains covariates only (age, sex, education, depression). The second step includes the main effects of pain (study 1, average pain; study 2, GCPS pain severity) and alcohol use severity (study 1, AUDIT; study 2, ASSIST). The third step includes the pain by alcohol use severity interaction term. Opioid misuse (COMM) is the outcome in both studies.

summed to a continuous total score; however, scores were also transformed to a 0–10 scale for descriptive purposes (Table 1). The GCPS pain severity showed good internal consistency in the current study (Cronbach's α = .85).

4.2.4. Current opioid misuse measure (COMM; Butler et al., 2007)

See study 1 (above) for COMM description. Internal consistency was excellent in the current study (Cronbach's α = .97).

4.3. Study 2 procedure

Respondents were screened for eligibility and directed to the online anonymous survey. Inclusion criteria included being between the ages of 18–64, reporting chronic pain that persisted at least three months (moderate to severe pain over the previous four weeks), and current use of opioid pain medication. Exclusion criteria included being younger than the age of 18, a non-English speaker, and inability to give informed, voluntary, written participation consent. The survey took approximately 30 min to complete. Participants could opt to receive their compensation in varying forms (e.g., cash-based incentives [i.e., gift cards], rewards miles, rewards points, etc.). The study protocol was approved by the Institutional Review Board at the University of Houston.

4.4. Study 2 data analytic plan

Statistical analyses were identical to those in study 1. The interaction of pain severity (GCPS) and alcohol use severity (ASSIST) in relation to opioid misuse (COMM) was examined. Covariates included age, sex, years of education, and depressive symptoms (PHQ-2).

5. Study 2 results

Data from 437 individuals with chronic pain and opioid use (74.1%

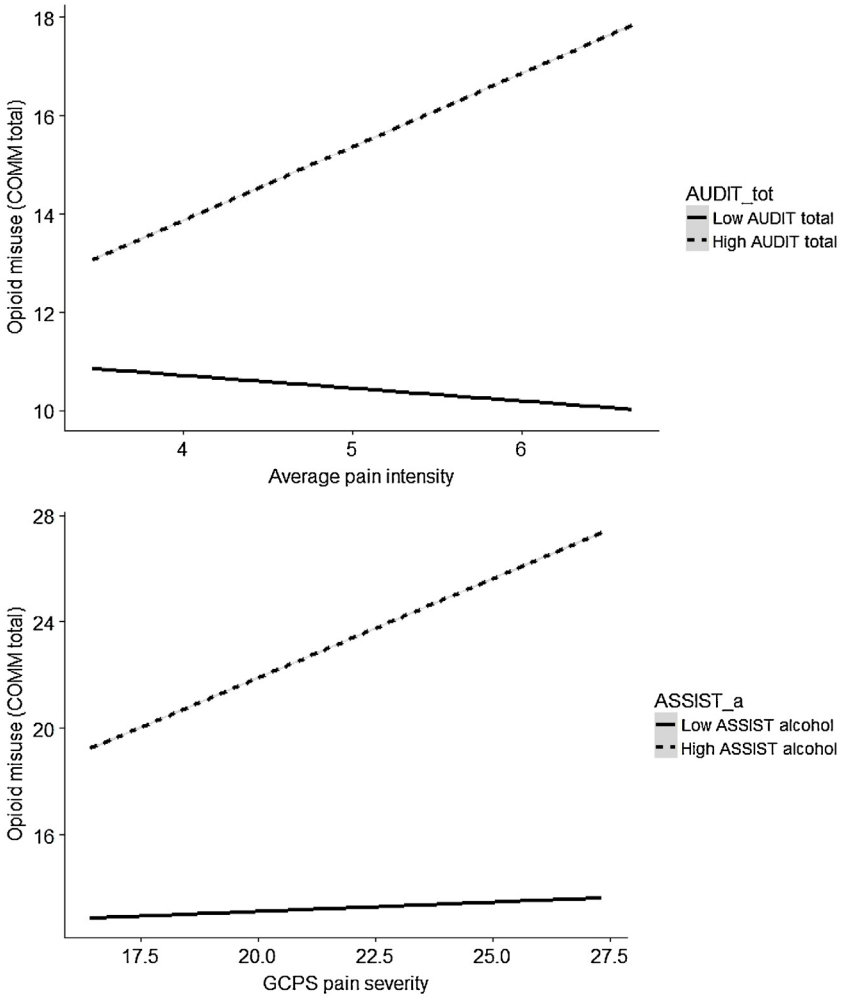

Fig. 1. Simple Slopes Demonstrating the Effect of Pain Severity on Opioid Misuse among Individuals with High and Low Alcohol Use Severity.
Note: Top – Study 1 (n = 364). Low AUDIT total = -1SD from mean (B = -.26, SE = .33, p = .430); high AUDIT total = +1 SD from mean (B = 1.50, SE = .38, p = .001). Bottom – Study 2 (n = 437). Low ASSIST alcohol = -1SD from mean (B = .07, SE = .14, p = .620); high ASSIST alcohol = +1 SD from mean (B = .74, SE = .13, $p < .001$).

female; Mage = 38.5) was available for analysis. Individuals reported average pain severity (M = 7.3) represents severe/intense pain on a 0–10 scale. Average ASSIST scores (M = 8.7) were in the moderate range (i.e., between 11–26). Average COMM scores (M = 17.8) were above the suggested cut-off (9+). See Table 1 for additional study participant characteristics. Correlations among study variables are in Table 2 (above the diagonal).

Including all covariates (age, sex, education, depression) in step 1 accounted significant variance in opioid misuse (F (4432) = 83.80, $p < .001$, R^2 = .44). Examining the individual predictors revealed that age, sex, and depression were each significantly associated with opioid misuse (Table 3). Step 2 of the model, adding the main effects of pain severity and alcohol use accounted for significantly more variance in opioid misuse (F (6430) = 84.21, $p < .001$, ΔR^2 = .10), where both pain severity (B = .42, SE = .11, $p < .001$) and alcohol use (B = .53, SE = .06, $p < .001$) were significant predictors of opioid misuse. Including the interaction term of pain severity and alcohol use in step 3 of the model indicated significantly improved model fit (F (7429) = 76.70, $p < .001$, ΔR^2 = .02), and the interaction term was a significant predictor of opioid misuse (B = .03, SE = .01, $p < .001$). Examining simple slopes revealed that the association between pain severity and opioid misuse was significant for those with high (+1SD) alcohol use scores (B = .74, SE = .13, $p < .001$), but not low (-1 SD; B = .07, SE = .14, p = .620; see Fig. 1 for simple slopes) alcohol use scores. The JN technique revealed a critical value of 4.60, indicating that the slope of pain severity predicting opioid misuse was significant for those with an ASSIST score of greater than 4.60 (49.89% of the current sample).

6. Discussion

The current two studies demonstrated a consistent pattern of findings regarding the association between average pain severity and prescription opioid misuse as a function of alcohol use severity among a sample of adults with chronic pain. In two independent samples of individuals with chronic pain, pain severity was statistically significantly related to opioid misuse among those with relatively greater alcohol use; however, pain severity was unexpectedly not statistically significantly related to opioid misuse among those with lower alcohol use. These findings were evident after controlling for age, sex, education, and depressive symptoms. Study 1 was limited insofar as participants were not all opioid users (although a significant portion were), whereas study 2 replicated findings and extended them in a sample where all individuals were opioid users. Thus, there is converging support across two samples that pain-opioid misuse relations may be concentrated among those with relatively greater alcohol use. These findings are important in the effort to better understand opioid misuse in the ongoing crisis as well as the increasing alcohol use problem in the U.S.

(Gostin et al., 2017; Grant et al., 2017).

Regarding the interactive effects, the JN procedure revealed that pain severity was positively associated with opioid misuse for approximately one third of the first sample (AUDIT total scores of 4.84 or higher) and approximately half of the second sample (ASSIST Alcohol scores of 4.59 or higher). It is unclear whether these differences in percentages may be impacted by the different alcohol measures used or sample characteristics. Importantly, both values are below suggested cut-offs on the AUDIT (7+ for women and 8+ for men represent "hazardous drinking"; Saunders et al., 1993) and ASSIST (0–10 represent "low risk" drinking; Humeniuk et al., 2008) and may represent "normative" drinking. Nevertheless, such drinking may still be associated with consequences and, in this case, greater opioid misuse in the context of greater pain. It is important to note that even moderate drinking may still pose serious health consequences. Indeed, recent multinational work has found that there is no safe level of drinking, contradicting popular cut-offs (Griswold et al., 2018). Furthermore, it is important to note that AUDIT and ASSIST cut-offs have been determined for general samples. We are unaware of any studies to evaluate cut-offs for hazardous/risky alcohol use specifically among individuals with chronic pain, specifically. Future work should establish drinking cut-offs among chronic pain patients, as it is possible that lower cut-offs on standard measures may be needed to identify individuals at risk for health/substance use consequences relative to general/healthy samples.

Across studies, the size of interaction was consistent (2–3% of additional variance) which is notable (Abelson, 1985) given that a substantial portion of variance in opioid misuse was accounted for by covariates and main effects in the first two steps (Table 3). Based on Cohen's f^2 ($R^2/1\text{-}R^2$), the interaction effects observed here would be considered large for both study 1 (f^2 = .03) and study 2 (f^2 = .02; Kenny, 2015). Furthermore, these effects are meaningful given evidence that the median observed f^2 for interactions has been estimated at .002 (Aguinis et al., 2005). In general, many studies are generally underpowered to identify statistically significant interactions (e.g., Fairchild and MacKinnon, 2009). Taken together, the pattern and size of interactions was similar across studies despite sample differences, adding confidence to the findings that greater pain is associated with greater opioid misuse among those with higher but not lower alcohol use.

In addition to the interactive effects noted, there are several other findings worthy of mention. Greater depressive symptoms related significantly and strongly to greater opioid misuse in both samples, after controlling for variance due to age, sex, and education, consistent with past work (Grattan et al., 2012). Education level was not significantly related opioid misuse after accounting for all other covariates, although there was a significant bivariate correlation of education with opioid misuse (Table 2). Younger age was associated with greater opioid misuse, yet these relations were only statistically significant in the second sample. Regarding bivariate correlations, older age was significantly associated only with female sex in study 1 whereas older age was associated with greater pain and, surprisingly, lower depression, less severe alcohol use, and lower opioid misuse in study 2. After accounting for covariates, there was a consistent main effect of alcohol use severity in both samples with greater alcohol use relating to greater opioid misuse. Pain severity evidenced a main effect on opioid misuse in sample 2 with a trending association for sample 1; greater pain was associated with greater opioid misuse, after controlling for alcohol use severity and covariates. However, it is important to note that this main effect should be interpreted with caution given the significant moderating relationship of alcohol use severity.

These studies represent preliminary work in an understudied area, although the findings could have important clinical implications if replicated and extended. The major finding across these two studies is that individuals with relatively greater alcohol use may represent a vulnerable subgroup among individuals with chronic pain. Thus, screening and intervention for alcohol use/problems among those with chronic pain is warranted, particularly among individuals with opioid-based pain treatment. Such screenings (Henihan et al., 2016) and interventions (Watkins et al., 2017) have been considered feasible among people using opioids in primary care settings and should be evaluated among those with chronic pain, specifically. Although many clinicians may already screen for alcohol use, the current results suggest that lower alcohol cut-offs could be considered for individuals to receive intervention, given the potential for greater pain-opioid relations. As noted, the minimum scores associated with significant pain-opioid misuse relations were below established cut-offs on two well-validated measures of alcohol use (Humeniuk et al., 2008; Saunders et al., 1993). Furthermore, past work suggests that less than one fifth of adults in the U.S. have discussed alcohol consumption with a health professional (McKnight-Eily et al., 2014). Practitioners have a tendency to focus on the most severe patients (e.g., those with substance use disorders) rather than those with 'at-risk' or problematic use of substances (Venner et al., 2018). This issue is relevant given the growing movement to shift focus from substance use disorders (e.g., AUD) to more encompassing forms of use, such as misuse (e.g., Reid et al., 1999) which are more common and may be more responsive to intervention (Institute of Medicine, 1990; Saunders and Conigrave, 1990). Indeed, there is a need for more focus on alcohol problems, broadly, among patients being treated for opioid misuse (Hall and Strang, 2017; Harris et al., 2010).

Additional work is also needed to understand other factors that may impact opioid use, particularly among those with relatively low alcohol use. Considering the finding that pain was not statistically significantly associated with opioid misuse among those with relatively lower alcohol use in either sample, it will be important for research to identify factors underlying opioid misuse among chronic pain patients who either abstain or drink quite little.

Although these two studies converged upon a novel finding that individuals with chronic pain with greater alcohol use may misuse opioids more in the context of more severe pain, there are several limitations. First, the study 1 sample was selected based on chronic pain, not opioid use, specifically. As such, not all participants were using opioids (though a substantial portion were). In study 2, all participants were experiencing chronic pain and were opioid users. Study 2 is limited in that information regarding prescription/non-prescription use and dosages was not available. Thus, future work will need to carefully evaluate how factors related to use (e.g., dosage, length of time of use, prescription vs. non-prescription use) impact the associations documented here. Second, this study focused on prescription opioid misuse; although use of other opioids (e.g., heroine) was possible, it was not the focus of the current study. Third, both studies are limited by self-report. When dealing with substance use, particularly misuse or illicit use, it is possible that some individuals underreported or neglected to report such activity, especially amounts. Thus, conclusions drawn from the findings must be tempered. For example, the COMM although a gold-standard measure of prescription opioid misuse contains items related to mood and may be associated with false-positives for opioid misuse. However, analyses did control for depression to partially account for this limitation. Additionally, the measure of pain, although commonly used (Hawker et al., 2011), was limited to a screening single item relating to severity in study 1; however, study 2 utilized a well-validated and psychometrically sound measure of pain. Fourth, both studies utilized cross-sectional designs and findings here represent associations at one time-point rather than effects over time. Thus, we are unable to model more complex associations (e.g., comparing individuals using alcohol before vs. after developing chronic pain). Given the dearth of research on alcohol and opioid use among those with chronic pain (Vowles et al., 2018), this study represents a novel first step in this area. However, these associations should be evaluated longitudinally to evaluate how alcohol use over time (and history of alcohol use) impacts pain-opioid relations. Fifth, the current studies also did not evaluate the impact of other substances in the

relation between pain and opioid use. For example, co-use of benzodiazepines or cannabis in combination with opioids and/or alcohol is associated with negative outcomes (Day, 2013; Rogers et al., 2018) and the use of tobacco is elevated among opioid users with chronic pain (Ekholm et al., 2009). Polysubstance use is common, particularly among people using opioids (Winkelman et al., 2018) and co-use of substances is difficult to fully account for. These studies document one piece of a complicated puzzle and demonstrate that individuals with chronic pain who use alcohol to a greater degree may engage in opioid misuse in the context of greater pain relative to those who use alcohol less. Future work should attempt to build off these findings to evaluate how use of other substances impacts pain-opioid relations. Sixth, these studies did not measure motives for use. Thus, although pain is associated with use, it is unknown whether the pain prompted or directly caused the use. Although both samples were primarily White and this may be a limitation to generalizability to diverse samples, it is important to note that opioid users are more likely to be White (Winkelman et al., 2018). Insofar as generalizability refers to how a sample can be applied to a population, the large percentage of White participants might not be as big a limitation, given demographic breakdown of opioid users in the U.S. Nevertheless, future work should evaluate factors underlying opioid use in diverse samples.

In sum, the present studies demonstrated the important role that alcohol use plays in the association between pain severity and opioid misuse among individuals with chronic pain. Despite differences in measurement and samples, the pattern of findings and effect sizes across studies were highly concordant. Findings suggest that alcohol use severity exacerbates the pain-opioid association such that pain is positively associated with opioid misuse only among those with relatively greater alcohol use. Importantly, the levels of alcohol use associated with greater pain-opioid misuse relations documented here were below established cut-offs suggesting that even moderate or "low risk" alcohol use among individuals with chronic pain may be associated with negative consequences. Given these findings, clinicians should consider regularly screening and providing resources for alcohol use among individual with chronic pain, and perhaps consider lowering the threshold for what may be considered problematic drinking among chronic pain patients, particularly those who may be using opioids.

Contributors

KEV and MJZ designed the main study/data collection and provided edits on the manuscript. DJP and AHR conducted statistical analyses and drafted manuscript. JB supervised data collection for study 2 and provided edits on the manuscript. All authors have approved the final article.

Declaration of Competing Interest

None.

Acknowledgements

Dr. Zvolensky sponsored this research though his endowment from the University of Houston.

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