Pain Intensity And Anxiety Sensitivity In Relation To Opioid Misuse And Dependence Among Individuals With Chronic Pain

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A thesis submitted to the Department of Psychology,
College of Liberal Arts and Social Sciences
in partial fulfillment of the requirements for the degree of

Master of Arts

in Clinical Psychology

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University of Houston
August 2020

ABSTRACT

The United States (US) population consumes an estimated 68% of the world's prescribed opioids each year, and over 2 million adults in the US suffer from an opioid use disorder. Although chronic pain populations are among the highest risk segments of the general population for opioid misuse and dependence, there is little understanding of individual risk characteristics that may be related to greater risk for these outcomes among this group. The present investigation explored the concurrent role of anxiety sensitivity and pain intensity and their interaction in relation to opioid misuse and dependence among 429 adults with chronic pain (73.9% female, M_{age} = 38.32 years, *SD* = 11.07). Results revealed that both anxiety sensitivity and pain intensity were associated with opioid misuse and dependence. Pain intensity and anxiety sensitivity interacted such that for individuals with higher anxiety sensitivity, but not lower anxiety sensitivity, higher pain interference was related to more severe opioid dependence. There was no evidence of an interaction for opioid misuse. Post-hoc analyses indicated that of the lower-order anxiety sensitivity facets, physical and mental incapacitation concerns significantly contributed to variance in opioid misuse and only mental incapacitation concerns significantly contributed to variance in opioid dependence. Overall, the current findings provide support for the importance of assessing anxiety sensitivity in screening for opioid-related problems among persons with chronic pain, as it may represent a distinct pathway to poorer opioid-related outcomes among this group.

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The United States (US) Department of Health and Human Services (HHS) declared a public health emergency in 2017 to address the national opioid crisis, commonly referred to as the opioid crisis or epidemic (HSS, 2017). This position was motivated by the high rate of opioid consumption and opioid-related death in the US. Specifically, the US prescribes opioids more than any other country and consumes an estimated 68% of the world's prescribed opioids on a yearly basis (Degenhardt et al., 2019). Each year an estimated 1.68 million deaths are attributed to opioid misuse in the US (Gomes et al., 2018), and two thirds of drug overdose deaths in the US involve an opioid (Hedegaard et al., 2017).

Despite efforts to change opioid prescribing practices (Bohnert et al., 2011; Macintyre et al., 2014), 17% of Americans are prescribed an opioid each year (Nelson & Perrone, 2012). Most persons are prescribed opioids for the treatment of chronic pain (Vowles et al., 2015), defined as persistent or frequent pain (i.e., pain every day or most days) that lasts 3 months or more (Johannes et al., 2010; Kennedy et al., 2014). Indeed, as many as 1 in 4 chronic pain patients receive long-term opioid therapy (Dowell et al., 2016). Extensive evidence highlights that opioids are generally ineffective for managing chronic pain in the long-term and warrant increased use as tolerance develops (Ballantyne & Shin, 2008; Kalso et al., 2004; Kissin, 2013). The need for increased dose or frequency of use place individuals who use opioids for chronic pain management at increased risk for opioid misuse (i.e., using opioids in a manner different than prescribed; Butler et al., 2007) and dependence (i.e., continued

use of opioids despite experiencing difficulties that they know or believe to be caused by their opioid use; Ward et al., 1999), and other adverse negative health consequences (e.g., death; Bohnert et al., 2011, 2016).

One determinant of opioid misuse and dependence in a multitude of studies and across a wide range of populations is pain intensity (Coloma-Carmona et al., 2018; Voon et al., 2015; Weiss et al., 2014). Indeed, individuals with and without chronic pain report using opioids to relieve pain and report more frequent use with more severe pain (Weiss et al., 2014). Moreover, opioid-dependent persons have greater pain intensity and interference than those without opioid dependence (Coloma-Carmona et al., 2018). Among individuals receiving treatment for opioid-use disorder, greater pain intensity is associated with self-managing of pain with opioids and the perception that methadone dosage is too low (Voon et al., 2015). Further, individuals who experience flare-ups of pain during treatment are more prone to relapse to opioid use (Griffin et al., 2016). Despite significant work documenting pain relief as a primary motivator for initial opioid use as well as the relationship between increasing pain intensity and opioid problems, some work has suggested that pain intensity itself may not be the best metric to understand the opioid epidemic (Ballantyne & Sullivan, 2015). In fact, some emerging research has implicated psychological factors as more important to understand the opioid epidemic than pain intensity (McHugh et al., 2016; Rogers et al., 2018). Yet, relatively little research has focused on the relative explanatory value of pain intensity compared to other psychologically based individual difference factors linked to substance use problems.

A construct that has been receiving increased attention for its role in substance use problems is anxiety sensitivity (DeHaas et al., 2001; McHugh et al., 2017; Stewart et al., 1999). Anxiety sensitivity refers to the fear of the negative expected consequences of anxiety and anxiety-related sensations (Reiss et al., 1986a). Anxiety sensitivity has three lower-order factors that all load on a single higher-order factor (Jardin et al., 2018). The lower-order factors represent physical concerns, mental incapacitation concerns, and social concerns, and the higher-order factor represents the global anxiety sensitivity construct (Allan et al., 2015). A person higher in anxiety sensitivity would endorse believing that heart palpitations are a sign of a heart attack whereas a person lower in anxiety sensitivity would believe that such sensations are relatively harmless bodily sensations. Thus, individuals with higher anxiety sensitivity theoretically may be more likely to use substances to attenuate the fear that comes with their physiological responses that they interpret as being catastrophic. Anxiety sensitivity is a relatively stable individual difference factor (Kotov et al., 2007), but malleable in response to clinical intervention (i.e., it can be reduced) or life stress (i.e., it can be increased; Worden et al., 2015). Work has implicated anxiety sensitivity in opioid misuse among chronic pain patients. For example, anxiety sensitivity is associated with opioid misuse, more severe opioid dependence, and using more opioids to get high (i.e., intoxication) among this vulnerable group (Hearon et al., 2011; McHugh et al., 2017; Rogers, Kauffman, et al., 2019). Additionally, among opioid dependent persons, higher levels of anxiety sensitivity are associated with greater opioid craving in response to experiencing (Stathopoulou et al., 2018) and

greater fear of withdrawal symptoms (Baxley et al., 2019; Rogers et al., 2020; Rogers, Shepherd, et al., 2019; Zvolensky et al., 2020).

Although past work has demonstrated independent promise for both anxiety sensitivity and pain intensity on opioid use problems, a key gap in the existing literature pertains to whether anxiety sensitivity and pain intensity both are related to the risk of opioid misuse and dependence among persons with chronic pain when considered concurrently. That is, the effects of anxiety sensitivity and pain intensity when controlling for the other have not been directly explored among persons with chronic pain. Because both anxiety sensitivity and pain intensity invoke mechanisms designed to account for increased affective disturbance (Allan et al., 2018; Gerrits et al., 2015), it is important to determine the unique explanatory validity of these constructs relative to one another in a single model. Further, it is possible that pain intensity and anxiety sensitivity interact to confer greater risk for opioid misuse and dependence. Consequently, the associations between pain intensity and opioid misuse and dependence may be stronger among individuals who are more anxious about aversive bodily sensations. Answering these types of questions may enhance our understanding of important individual difference influences on opioid misuse and dependence among adults with chronic pain and help stimulate more precise treatment strategies for this underserved group. This work would be especially useful in a model that examines the incremental validity of these two constructs relative to other well-established factors associated with opioid misuse and dependence among this group, such as age (Cleland et al., 2011), gender (Serdarevic et al., 2017), anxious/depressive

symptoms (Martel et al., 2014), income (Clarke et al., 2014), education (Rogers et al., 2019a), and drug use (Sehgal et al., 2012; Turk et al., 2011).

Present Study: Aim and Hypothesis

The present investigation sought to explore the main and interactive effects of anxiety sensitivity and pain intensity in relation to opioid misuse and dependence among adults with chronic pain. It was hypothesized that anxiety sensitivity and pain intensity would each explain clinically significant and unique variance in opioid misuse and dependence after accounting for the shared variance between one another and other factors (e.g., age; Baxley et al., 2019) correlated with opioid-related problems among this health disparities group. However, it also was predicted that anxiety sensitivity would account for a greater proportion of variance in the criterion variables than pain intensity. Additionally, we hypothesized that adults with chronic pain with elevated pain intensity and anxiety sensitivity would experience greater opioid misuse and dependence.

Method

Procedure

Participants were recruited nationally through Qualtrics, an online survey management system, a validated and representative methodology used in past substance use research (Rogers, Kauffman, et al., 2019; Rogers, Shepherd, et al., 2019; Szabo et al., 2018). Adults with a Qualtrics Panels account who endorsed moderate to severe chronic pain ("Have you had chronic pain (pain that is present most days or every day) over the past 3 months?": none, very mild, mild, moderate, severe) as well as current use of opioid pain medication ("Are you using opioid pain

medication?") in a Qualtrics pre-screen were directed to the online survey. Participants provided informed consent prior to completing the 30-minute survey. Participants could opt to receive their payment in varying forms (e.g., cash-based incentives [i.e., gift cards], rewards miles, rewards points, etc.). Although the forms were different, the level of compensation remained consistent across respondents ($4.20). The study protocol was approved by the Institutional Review Board at the sponsoring institution and was performed in accordance with the ethical standards in the 1964 Declaration of Helsinki and its later amendments.

Participants

Participants were 429 adults (73.9% female, M_{age} = 38.32 years, SD = 11.07) self-reporting current moderate to severe chronic pain and opioid use for chronic pain, who were recruited via online survey. Eligible participants were between 18-64 years of age, reported persistent (at least three months) current moderate to severe chronic pain, and current use of opioid pain medication. Participants were excluded if they were younger than 18 years, a non-English speaker (to ensure comprehension of the study questions), or were unable to provide informed, voluntary, written consent to participate.

Most of the sample was White (77.9%), with 13.3% identifying as Hispanic/Latino, 8.4% Black/African American, 3.3% Native American/Alaska Native, 2.8% multiracial, 0.9% Asian/Pacific Islander, and 0.9% other. In terms of education, 41.6% of participants reported completing an associate degree or higher. Over a quarter of the sample (30.3%) reported attaining a high school diploma, 22.4% reported "some college," and the remaining 5.8% reported having not completed high

school. The median income bracket fell within the range of $25,000 - $34,999. Regarding substance use in the past 3 months, in addition to using opioids, 59.9% of the sample reported using tobacco, 56.4% reported alcohol use, 38.9% reported using cannabis, 14.4% reported using cocaine, 20.7% reported using amphetamine, 12.1% reported using amphetamine, 13.1% reported using inhalants, 45.7% reported using sedatives, 12.6% reported using hallucinogens (see Table 3).

Measures

Demographics Questionnaire. Demographics information including, gender, race, age, education level, and income was collected. These variables were used as covariates in our models.

Drug Use. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST 2.0; Ali et al., 2002) is an 8-item questionnaire that assesses lifetime use and use in the past 3 months of 10 substances, including tobacco, alcohol, cannabis, cocaine, amphetamine-type stimulants, inhalants, sedatives, hallucinogens, opioids, and 'other drugs'. The ASSIST yields a substance risk score, wherein lower risk is indicated by a score between 0 and 10 for alcohol and between 0 and 3 for all other substances, moderate risk is indicated by a score from 11-26 for alcohol and 4-26 for all other substances, and higher risk is indicated by score 27 or higher for all substances. The ASSIST has demonstrated good concurrent, construct, and discriminative validity (Humeniuk et al., 2008). Drug use was included as a covariate in this study and ASSIST items were used to describe substance use patterns of the sample (see Table 3).

Patient Health Questionnaire-4. The Patient Health Questionnaire (Löwe et al., 2010) is a 4-item measure that consists of a 2-item depression scale (PHQ-2; (Kroenke et al., 2003) and a 2-item anxiety scale (GAD-2; Kroenke, Spitzer, Williams, Monahan, & Löwe, 2007). Respondents are asked to rate how often each of the symptoms of anxiety (e.g., "Feeling nervous, anxious, or on edge") and depression (e.g., "Feeling down, depressed, or hopeless") have bothered them on a scale from 0 (*not at* all) to 4 (*nearly every day*). The PHQ-4 has demonstrated sound psychometric properties in past work (Löwe et al., 2010). The PHQ-4 total score was utilized in the current study as a measure of anxious and depressive symptoms ($\alpha = .91$).

Anxiety Sensitivity Index-3. The Anxiety Sensitivity Index-3 (ASI-3; Taylor et al., 2007) is an 18-item measure derived from the original Anxiety Sensitivity Index designed to assess fear of anxiety-related physical sensations (Reiss et al., 1986b). Respondents are asked to evaluate on a scale from 0 (*Very little*) to 4 (*Very much*) the extent they feel concerned regarding the possibility of adverse effects relating to their anxiety symptoms. The ASI-3 is comprised of three subscales including physical concerns, mental incapacitation concerns, and social concerns. The ASI-3 has been successfully used with opioid users (Rogers, Kauffman, et al., 2019). The current study utilized the total score ($\alpha = .97$) and subscale scores (physical concerns: $\alpha = .92$; mental incapacitation concerns: $\alpha = .95$; social concerns: $\alpha = .92$).

Graded Chronic Pain Scale. The Graded Chronic Pain Scale (GCPS) is an 8-item measure of self-reported pain intensity and disability (Von Korff et al., 1992). Pain intensity items (3) are rated on an 11-point scale from 0 (*No pain*) to 10 (*Pain as*

bad as could be). For the current study, the total pain intensity score was utilized (α = .85).

Current Opioid Misuse Measure. The Current Opioid Misuse Measure (COMM) is a 17-item questionnaire designed to detect opioid misuse, as well as assess gradation of opioid misuse, among chronic pain patients on opioid therapy (Butler et al., 2007). Past work has demonstrated that the COMM is a highly reliable measure of opioid misuse that has been used in numerous studies (Rogers et al., in press; Rogers, Kauffman, et al., 2019; Wasan et al., 2007). The COMM total score was used as a criterion variable (α = .97).

Severity of Dependence Scale. The Severity of Dependence Scale (SDS) is a 5-item measure of gradations of substance dependence (e.g., heroin, cocaine, amphetamine). The SDS has also been validated for opioid use (Gossop et al., 1995) and responses for the current study are anchored to problems associated specifically with opioid use. The SDS total score was used as a criterion variable in the current study (α = .87).

Data Analytic Plan

Using SPSS Version 26, first, sample descriptive statistics and zero-order correlations among study variables were examined. Second, two 4-step hierarchical regression analyses were conducted for current opioid misuse and severity of opioid dependence. In each model, the first step included the following covariates: age (Cleland et al., 2011), gender (Serdarevic et al., 2017), income (Clarke et al., 2014), education (Rogers et al., 2019a), and drug use (Sehgal et al., 2012). Income and education were dichotomized according to median values in this sample (Mdn_{income} =

"$35,000 - $49,000"; $Mdn_{education}$ = "some undergraduate college") to create reference groups. Income was coded such that a value of 0 indicated less than $35,000, and a value of 1 indicated greater than $35,000. Education was coded such that a value of 0 indicated high school education or less, while a value of 1 indicated some college or higher. Anxious/depressive symptoms was then entered in the second step to adjust for the generalized role of anxious/depressive symptoms in the model (Haller & Acosta, 2010; Martel et al., 2014). At the third step, pain intensity and anxiety sensitivity were entered simultaneously. At the fourth step, the interaction effect of pain intensity and anxiety sensitivity was entered. Variables were centered prior to computing the interaction term. Model fit for each of the steps was evaluated with the *F* statistic and increase in variance accounted for (change in R^2). Squared semi-partial correlations (sr^2) were used as measures of effect size for each of the individual predictors and are interpreted as small (.04), medium (.24), and large (.64) (Ferguson, 2009). Planned follow-up tests in the form of simple slope analyses were conducted for significant interactions using the PROCESS macro (Hayes, 2013) to examine associations between pain intensity and the dependent variables across anxiety sensitivity.

Results

Bivariate Correlations

Descriptive statistics and zero-order correlations among study variables are presented in Table 1. Pain intensity was modestly but statistically significantly related with age (r = .16), education (r = -.10), opioid misuse (r = .16), severity of opioid dependence (r = .20), anxious/depressive symptoms (r = .14), and anxiety sensitivity (r = .18). Anxiety sensitivity was statistically significantly and modestly related with

age (r = -.24), gender (r = .10), and drug use (r = .23) and strongly related to opioid misuse (r = .66), severity of opioid dependence (r = .54), and anxious/depressive symptoms (r = 67).

Primary Analyses

Current Opioid Misuse. Covariates entered in the first step accounted for a statistically significant amount of variance (R^2 = .23, F[5, 423] = 25.66, p < .001) and age, gender, and drug use emerged as significant predictors (see Table 2). At step two, a statistically significant main effect emerged for anxious/depressive symptoms (ΔR^2 = .26, F[1, 422] = 69.49, p < .001), accounting for an additional 26% of variance. In the third step, the addition of pain intensity and anxiety sensitivity accounted for statistically significantly more variance in current opioid misuse (ΔR^2 = .08, F[2, 420] = 71.35, p < .001). Pain intensity (B = .26, SE = .11, p = .02) accounted for an additional 1.0% of variance, and the addition of anxiety sensitivity (B = .29, SE = .04, p < .001) accounted for an additional 7.0% of variance after accounting for the shared covariance of each and the effect of covariates. In the fourth step, the interaction of pain intensity and anxiety sensitivity was not statistically significant (ΔR^2 = .004, F[1, 419] = 64.25, p = .054).

Severity of Opioid Dependence. Covariates entered in the first step accounted for a statistically significant amount of variance (R^2 = .14, F[5, 423] = 14.026, p < .001), and age, gender, and drug use emerged as statistically significant predictors (see Table 2). At step two, a statistically significant main effect emerged for anxious/depressive symptoms (ΔR^2 = .17, F[1, 422] = 31.31, p < .001), accounting for an additional 17.0% of variance. In the third step, In the third step, the addition of pain

intensity and anxiety sensitivity accounted for statistically significantly more variance in current opioid dependence (ΔR^2 = .07, F[2, 420 = 32.22, p < .001). Pain intensity (B = .09, SE = .03, p = .002) accounted for an additional 1.0% of variance and anxiety sensitivity accounted for an additional 5.0% of variance (B = .06, SE = .01, p = <.001) after accounting for the shared covariance of each and the effect of covariates. The interaction of pain intensity and anxiety sensitivity in the fourth step was significant (ΔR^2 = .01, F[1, 419] = 29.30, p = .05) and accounted for an additional 1.0% of variance in current opioid dependence. Inspection of the form of the interaction indicated that greater pain intensity was related to more severe opioid dependence among individuals with higher anxiety sensitivity (b = .15, SE = .04, p < .001) but not individuals with lower anxiety sensitivity (b = .04, SE = .04, p = .21; see Figure 1).

Post-hoc Analyses

Post-hoc analyses were conducted to determine which lower order factors of anxiety sensitivity (i.e., physical concerns, mental incapacitation concerns, and social concerns) statistically significantly contribute to variance in the outcomes. Specifically, we conducted two additional three-step hierarchical regression analyses for opioid use and dependence where covariates (i.e., age, gender, education, income, and drug use) were entered in the first step, anxious/depressive symptoms was entered in the second step, and pain intensity and physical concerns, mental incapacitation concerns, and social concerns, were simultaneously entered in the third step.

Current Opioid Misuse. For current opioid misuse, the first two steps of the hierarchical regression analyses were the same as for our primary analyses. The addition of pain intensity and physical concerns, mental incapacitation concerns, and

social concerns in the third step accounted for statistically significantly more variance in current opioid misuse ($\Delta R^2 = .08$, $F[4, 418] = 57.70$, $p < .001$). After controlling for the shared covariance of each and the effect of covariates, the addition of physical concerns ($B = .38$, $SE = .16$, $p = .02$) and the addition of mental incapacitation concerns ($B = .49$, $SE = .17$, $p = .01$) each accounted for an additional 1.0% of variance in current opioid misuse.

Severity of Opioid Dependence. For severity of opioid dependence, the first two steps of the hierarchical regression analyses were the same as for our primary analyses. The addition of pain intensity and physical concerns, mental incapacitation concerns, and social concerns in the third step accounted for statistically significantly more variance in opioid dependence ($\Delta R^2 = .07$, $F[4, 418] = 25.82$, $p < .001$). After controlling for the shared covariance of each and the effect of covariates, mental incapacitation concerns ($B = .09$, $SE = .05$, $p = .04$) accounted for an additional 1.0% of variance in severity of opioid dependence.

Discussion

Adults with chronic pain are a high-risk segment of the population in terms of opioid misuse and dependence (Coloma-Carmona et al., 2018; Voon et al., 2015; Weiss et al., 2014). Emerging evidence suggests better understanding individual difference factors that are related to opioid misuse and dependence among adults with chronic pain is a clinically important matter from a public health perspective (McHugh et al., 2016; Rogers et al., 2018). Therefore, the current investigation sought to concurrently evaluate pain intensity and anxiety sensitivity in terms of opioid misuse and dependence among adults with chronic pain.

Results of the investigation revealed novel findings in relation to opioid misuse and dependence among adults with chronic pain. Specifically, as hypothesized, both anxiety sensitivity and pain intensity were associated with opioid misuse and dependence. Thus, after accounting for their shared variance, anxiety sensitivity and pain intensity were each independently related to opioid misuse and dependence. Across models, inspection of the size of the observed effects indicated that anxiety sensitivity consistently explained a relatively greater percentage of variance in the dependent measures compared to pain intensity. Indeed, anxiety sensitivity explained a statistically significant variance (7.0% for opioid misuse; 5.0% for severity of opioid dependence) whereas pain intensity explained less variance (1.0% for opioid misuse; 1.0% for severity of opioid dependence). Further, all of the observed effects were evident after accounting for the variance that was explained (49% and 31% for the studied models) by variables age (Cleland et al., 2011), gender (Serdarevic et al., 2017), income (Clarke et al., 2014), education (Rogers et al., 2019a), anxious/depressive symptoms (Martel et al., 2014), and drug use. These data make clear that anxiety sensitivity may be an important, yet underrecognized, individual difference variable among adults with chronic pain that may be more important to opioid misuse and dependence than pain intensity itself.

Consistent with prediction, anxiety sensitivity and pain intensity interacted to explain variance in opioid dependence. Results suggested that among individuals with higher anxiety sensitivity, relative to those with lower anxiety sensitivity, increased pain intensity is related to more severe opioid dependence. This finding provides evidence that opioid users who are more anxious about aversive bodily sensations may

be more likely to be dependent on opioids. However, contrary to prediction, there was no evidence that anxiety sensitivity and pain intensity interacted to explain variance in opioid misuse after adjusting for other relevant variables. It may be that opioid dependence represents a specific subset of opioid-related cognitions that are especially relevant to anxiety sensitivity and pain intensity. Indeed, the SDS explicitly taps into psychological components of substance dependence (Gossop et al., 1995)), while the COMM taps into aberrant substance-related behaviors (Butler et al., 2007). The absence of a statistically significant interaction for opioid misuse casts some doubt on the perspective that the association between pain intensity and opioid misuse is stronger among individuals who are more anxious about aversive bodily sensations. It may be that anxiety sensitivity moderates other aspects of the pain experience, such as interference or disability from pain, in terms of opioid misuse and dependence. Future research is needed to explore possible anxiety sensitivity moderating effect for opioid misuse and dependence among adults with chronic pain. Moreover, there is a need to develop a comprehensive model of anxiety sensitivity in terms of other variables for opioid misuse and dependence. Such a perspective could offer a clearer model that could be used to systematically guide research in this context.

Post-hoc analyses focused on which lower-order anxiety sensitivity facets were related to opioid misuse and dependence. This work offers a further degree of analysis in terms of lower-order dimensions account for the global score effect. Mental incapacitation concerns were the most consistent predictor and offered unique variance for both opioid misuse and dependence. Physical concerns were a statistically significant contributor for only opioid misuse. No significant effects were evident for

social concerns. Although post hoc in nature, these findings point to mental incapacitation and physical concerns as being relatively more relevant than social concerns for opioid misuse and dependence. It may be that the perception of losing cognitive control in response to aversive interoceptive sensations triggers a desire to use opioids, placing persons at greater risk for misuse and dependence. The lack of association between anxiety sensitivity physical concerns and opioid dependence may be due to power, as the zero-order relation was strong (r = .50). Future research is needed to evaluate whether coping motives or opioid craving mediate the association between mental incapacitation (and possibly physical concerns) in terms of opioid misuse and dependence using longitudinal methodology among adults with chronic pain.

Although not a primary study aim, an additional observation warrants comment. Specifically, despite anxious/depressive symptoms tapping, at least in part, into aspects of aversive interoceptive experience, this construct shared a range of 2% with pain intensity and 44% of variance with anxiety sensitivity. Such data help make clear that the unique variance of anxiety sensitivity and pain intensity can be separated from anxious/depressive symptoms. That said, the amount of variance explained by anxious/depressive symptoms was large for both criterion variables (i.e., 20% for opioid dependence and 31% for opioid misuse). Such data highlight the prominent association between the broad-based tendency to experience anxious/depressive symptoms states and opioid-related problems. These data underscore the need for further research to explicate the etiologic and maintaining role of anxious/depressive symptoms in opioid misuse and dependence.

Clinically, the results of the present study could help guide the development of specialized intervention strategies for adults with chronic pain for opioid misuse and dependence. For example, there may be clinical utility in developing a targeted integrated psychosocial intervention that prioritizes anxiety sensitivity, and specifically and mental incapacitation concerns, as a clinical target for opioid misuse and dependence among adults with chronic pain (Raines et al., 2020). By focusing on anxiety sensitivity as a vulnerability factor, such an intervention could theoretically offer advancements in precision medicine. For example, opioid users with elevated levels of anxiety sensitivity may benefit from cognitive-behavioral strategies, such as psychoeducation about anxiety, interoceptive exposure training, and skills development focused on increasing emotional acceptance and tolerance delivered prior to engaging in an opioid quit attempt. Indeed, such strategies may act to increase tolerance of negative affect and craving and may facilitate greater rates of successful quit attempts. Although some work has sought to address anxiety sensitivity in opioid treatment (Tull et al., 2007), such interventions represent an area that warrants further investigation.

There are study limitations that deserve comment. First, the sample primarily consisted of White/Caucasian individuals. Past work has found differences in pain outcomes (e.g. pain intensity, pain-related disability, and pain frequency; (Meints et al., 2019; Portenoy et al., 2004) as well as opioid use outcomes (e.g. opioid withdrawal and craving; Brown et al., 2010) across Caucasian/White adults and non-white adults and thus, these findings may not generalize to racial/ethnic minority groups. Additionally, the racial/ethnic breakdown of the sample did not allow us

sufficient power to conduct tests of the potential moderating effect of race/ethnicity, but future work with a more diverse sample would benefit from doing this. We did, however conduct simple tests of mean differences across White/Caucasian (n = 334) and non-White/Caucasian (n = 95) individuals and did not find significant differences across these groups among our variables of interest (i.e., pain intensity, opioid misuse, opioid dependence, anxiety sensitivity, and anxious/depressive symptoms; see Table 4). Second, because the findings were based upon a cross-sectional study design, the findings cannot address causal relations. Thus, future research could explore concurrent relations among anxiety sensitivity and pain intensity using prospective designs or laboratory methodologies. Such work would uniquely extend the present research to novel methodological contexts. Third, the sample only included adults and was primarily female. Consequently, there is a need to replicate and extend the present findings to samples that include a greater percentage of males and younger individuals (LeResche et al., 2015; Rogers et al., 2020). Fourth, data were collected via self-report. Future research using multi-dimensional approaches to measuring constructs (e.g., urine drug screens) could improve confidence in observed results. Fourth, the facets of anxiety sensitivity were highly correlated with the anxiety sensitivity total score. Although past work has found strong correlations between the total and lower-order facets (Taylor et al., 2007; Zvolensky et al., 2018), these correlations are somewhat higher than has been found in other work. It is possible that the global and lower order anxiety sensitivity factors are more strongly related to one another in chronic pain samples. Finally, while everyone in the current sample had chronic pain, the sample was heterogeneous in terms of location of chronic pain. It is possible that

the observed relationships may differ by primary pain location, as some research has found differences in opioid-mood associations by pain type (Banta-Green et al., 2009; Severino et al., 2018).

The present study highlights the concurrent explanatory roles of individual differences in both anxiety sensitivity and pain intensity in terms of opioid misuse and dependence among adults with chronic pain. These findings suggest that anxiety sensitivity may be relatively more important in these relations than pain intensity. Future research is needed to better understand anxiety sensitivity in the context of other pain (e.g., disability) and affect (e.g., negative mood propensity) in terms of opioid misuse and dependence among adults with chronic pain.

Table 1. Descriptive statistics and bivariate correlations among study variables.

		Mean/n	SD/%	1.	2.	3.	4.	5.	6.	7.	8	9.	10.	11.	12.	13.
1.	Age [a]	38.31	11.07	1	-.02	-.02	.02	-.28**	-.19**	-.19**	-.13**	.16**	-.24**	-.16**	-.30**	-.24**
2.	Gender (% Female) [a]	317	73.9%	-	1	.07	-.02	.25**	.20**	.14**	.05	-.08	.10*	.09	.14**	.05
3.	Income (% below $35,000) [a]	188	43.8%	-	-	1	.30**	.11*	.06	.01	.10	-.02	.07	.06	.06	.09
4.	Education (% with high school education or less) [a]	155	36.1%	-	-	-	1	.04	-.003	.04	.03	-.10*	.03	-.01	.04	.05
5.	Opioid Misuse [c]	17.95	17.18	-	-	-	-	1	.71**	.64**	.34**	.16**	.66**	.61**	.67**	.60**
6.	Severity of Opioid Dependence [c]	4.34	3.80	-	-	-	-	-	1	.50*	.29**	.20**	.54**	.50**	.54**	.49**
7.	Anxious/depressive symptoms [b]	3.93	3.87	-	-	-	-	-	-	1	.25**	.14**	.67*	.60**	.68**	.63**
8.	Drug Use										1	.06	.23**	.22**	.24**	.20**
9.	Pain Intensity [a]	21.88	5.45	-	-	-	-	-	-	-		1	.18**	.18**	.15**	.18**
10.	Anxiety Sensitivity	27.42	21.39	-	-	-	-	-	-	-	-	-	1	.95**	.95**	.95**
11.	Physical Concerns	9.44	7.41	-	-	-	-	-	-	-	-	-		1	.85**	.84**
12.	Mental Incapacitation Concerns	8.11	7.59	-	-	-	-	-	-	-	-	-	-	-	1	.85**
13.	Social Concerns	7.59	7.56	-	-	-	-	-	-	-	-	-	-	-	-	1

Note. N= 429; * p <.05, ** p<.01. [a] Covariate. [b] Predictor. [c] Outcome. Age = age in years; Gender = % listed as female (Coded: 0 = female, 1 = male); Income (Coded: 0 = less than $35,000, 1 = greater than $35,000); Education (Coded: 0 = high school education or less, 1 = some college or more); Opioid Misuse = Current Opioid Misuse Measure (range 0-68, >9 opioid problem; Butler et al., 2007); Dependence Severity = Severity of Dependence Scale (range 0-15) (Gossop et al., 1995; Castillo et al., 2010); Anxious/depressive symptoms = Patient Health Questionnaire (Löwe et al., 2010); Pain Intensity = Graded Chronic Pain Scale-Pain Intensity Subscale (range 0-10;Von Korff et al., 1992); Anxiety Sensitivity (including Physical Concerns, Mental Incapacitation Concerns, Social Concerns) = Anxiety Sensitivity Index-3 (Taylor et al., 2007)

Table 2. Regression models.

Model 1: Opioid Misuse

	b	*SE*	*t*	*p*	sr^2	ΔR^2
Step 1						.23
Age	-.38	.07	-5.63	< .001	.06	
Gender	8.69	1.61	5.42	< .001	.05	
Income	1.94	1.26	1.25	.08	.003	
Education	.75	1.60	.47	.64	<.001	
Drug Use	10.01	1.48	6.76	< .001	.08	
Step 2						.26
Anxious/depressive symptoms	2.41	.16	14.89	< .001	.26	
Step 3						.08
Pain intensity	.26	.11	2.45	.02	.01	
Anxiety sensitivity	.29	.04	8.06	< .001	.07	
Step 4						.004
Pain intensity*Anxiety sensitivity	.01	.004	1.93	.054	.004	

Model 2: Severity of Opioid Dependence

	b	*SE*	*t*	*p*	sr^2	ΔR^2
Step 1						.14
Age	-.05	.02	-3.39	.001	.02	
Gender	1.53	.38	4.09	< .001	.03	
Income	.16	.36	.43	.67	<.001	
Education	-.08	.37	-.20	.84	< .001	
Drug Use	1.97	.35	.26	5.68	.07	
Step 2						.17
Anxious/depressive symptoms	.42	.04	10.06	< .001	.17	
Step 3						.07
Pain Intensity	.09	.03	3.11	.002	.01	
Anxiety Sensitivity	.06	.01	5.75	< .001	.05	
Step 4						.01
Pain Intensity*Anxiety Sensitivity	.002	.001	2.00	.046	.01	

Note. N= 429; * p <.05, ** p<.01. Age = age in years; Gender = % listed as female (Coded: 0 = female, 1 = male); Income (Coded: 0 = less than $35,000, 1 = greater than $35,000); Education (Coded: 0 = high school education or less, 1 = some college or more); Opioid Misuse = Current Opioid Misuse Measure (range 0-68, >9 opioid problem; Butler et al., 2007); Dependence Severity = Severity of Dependence Scale (range 0-15) (Gossop et al., 1995; Castillo et al., 2010); Anxious/depressive symptoms = Patient Health Questionnaire (Löwe et al., 2010); Pain Intensity = Graded Chronic Pain Scale-Pain Intensity Subscale (range 0-10;Von Korff et al., 1992)

Table 3. Substance use characteristics of the sample.

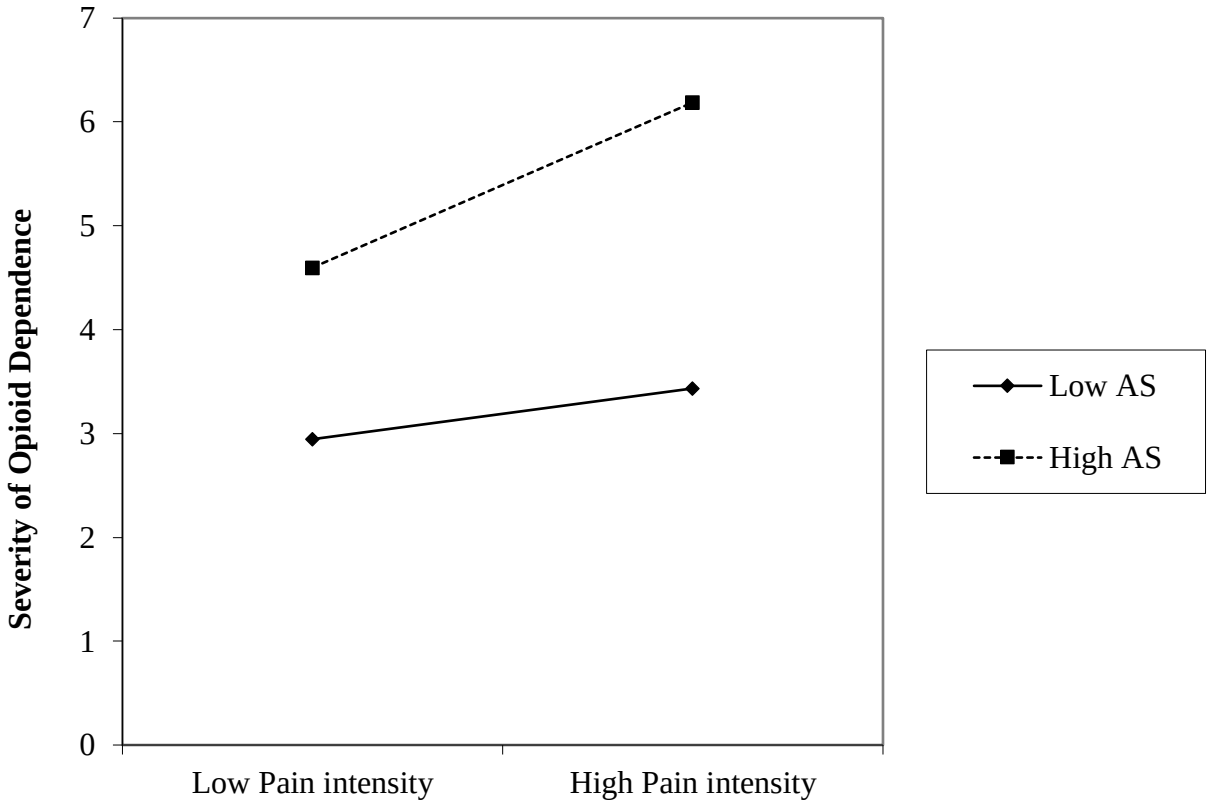
	Use *n* (%)	Frequency *n* (%)				Substance risk score *M* (SD)
		Once or twice	Monthly	Weekly	Daily/almost daily	
Tobacco	257 (59.9%)	36 (8.4%)	22 (5.1%)	23 (5.4%)	176 (41.0%)	19.03 (7.27)
Alcohol	242 (56.4%)	80 (18.6%)	60 (14.0%)	62 (14.5%)	40 (9.3%)	14.96 (10.77)
Cannabis	167 (38.9%)	41 (9.6%)	36 (8.4%)	32 (7.9%)	58 (13.5%)	16.28 (10.13)
Cocaine	62 (14.4%)	11 (2.6%)	16 (3.7%)	10 (2.3%)	25 (5.8%)	20.89 (10.73)
Amphetamine	89 (20.7%)	23 (5.4%)	18 (4.2%)	14 (3.3%)	34 (7.9%)	18.27 (11.05)
Inhalants	56 (13.1%)	12 (2.8%)	15 (3.5%)	11 (2.6%)	18 (4.2%)	22.20 (10.15)
Sedatives	196 (45.7%)	54 (12.6%)	36 (8.4%)	49 (11.4%)	57 (13.3%)	15.98 (9.78)
Hallucinogens	54 (12.6%)	14 (3.3%)	11 (2.6%)	9 (2.1%)	20 (4.7%)	21.07 (10.05)

Note. *N* = 429. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST; Ali et al., 2002); Use and Frequency = based on past 3 month use; Substance risk score = computed only among participants who endorsed using that substance in the past 3 months (lower risk = 0-10 for alcohol, 0-3 for all other substances; moderate risk = 11-26 for alcohol. 4-26 for all other substances; high risk = 27+ for all substances).

Table 4: Descriptive statistics of variables across Caucasian/white and non-Caucasian/white individuals.

	Caucasian/white (n = 334)	Non-Caucasian/white (n = 95)		
	M (SD)	M (SD)	*t*	*p*
Pain intensity	22.02 (5.32)	21.38 (5.90)	1.01	0.31
Opioid Misuse	17.48 (17.19)	19.60 (17.13)	-1.06	0.29
Opioid Dependence	4.29 (3.82)	4.52 (3.70)	-0.51	0.61
Anxiety sensitivity	26.88 (21.37)	29.32 (21.50)	-0.98	0.33
Anxious/depressive symptoms	3.86 (3.90)	4.12 (3.78)	-0.57	0.57

Figure 1. Interaction of pain intensity and anxiety sensitivity on severity of opioid dependence.



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