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Original Research Article

Negative Affect–Related Factors Have the Strongest Association with Prescription Opioid Misuse in a Cross-Sectional Cohort of Patients with Chronic Pain

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Abstract

Objective. Increased opioid prescription to relieve pain among patients with chronic pain is associated with increased risk for misuse, potentially leading to substance use disorders and overdose death. We aimed to characterize the relative importance and identify the most significant of several potential risk factors for the severity of self-reported prescribed opioid misuse behaviors. **Methods.** A sample of 1,193 patients (mean age ± SD = 50.72 ± 14.97 years, 64.04% female) with various chronic pain conditions completed a multidimensional registry assessing four pain severity measures and 14 physical, mental, and social health status factors using the National Institutes of Health's Patient-Reported Outcomes Measurement Information System (PROMIS). A validated PROMIS measure of medication misuse was completed by 692 patients who endorsed currently taking opioid medication. Patients taking opioid medications were compared across all measures with those who do not take opioid medications. Subsequently, a data-driven regression analysis was used to determine which measures best explained variability in severity of misuse. We hypothesized that negative affect–related factors, namely anxiety, anger, and/or depression, would be key predictors of misuse severity due to their crucial role in chronic pain and substance use disorders. **Results.** Patients taking opioid medications had significantly greater impairment across most measures. Above and beyond demographic variables, the only and most significant predictors of prescribed opioid misuse severity were as follows: anxiety ($\beta = 0.15$, $P = 0.01$), anger ($\beta = 0.13$, $P = 0.02$), Pain Intensity–worst ($\beta = 0.09$, $P = 0.02$), and depression ($\beta = 0.13$, $P = 0.04$). **Conclusions.** Findings suggest that anxiety, anger, and depression are key factors associated with prescribed opioid misuse tendencies in patients with chronic pain and that they are potential targets for therapeutic intervention.

Key Words: Anxiety; Anger; Depression; Prescribed Opioids Misuse; Chronic Pain; CHOIR

Introduction

For the past 15 years, prescription opioids have been a mainstay treatment for chronic pain, especially in the United States; 5.4% of the entire US population (>17 million Americans) is taking legacy long-term prescription opioids, reflecting a threefold increase between 1999 and 2014 [1]. Crucially, prescription opioid risks, including opioid misuse, substance use disorders, and unintentional overdose death, increase with dose and length of use [2,3]. Misuse is a broad term generally referring to various patterns of medication use, contrary to that which was indicated in the prescription, regardless of any actual harm resulting from such usage [4]. Misuse behaviors may include, for example, occasional medication overuse or getting the same prescription medication from more than one health care provider [5]. Identifying modifiable factors that might contribute to more prescribed opioid misuse in patients with chronic pain is crucial to guide treatments for the prevention and reduction of misuse, to improve medication adherence, and to diminish the associated detrimental impact on health and well-being.

Risk factors associated with prescribed opioid misuse include various demographic, pain severity, physical, medical and substance use history, and psychosocial/mental factors, such as negative affect [6–15]. Negative affect is a general term that describes aversive and subjectively distressing mood states or negative emotionality, but also a dispositional dimension that may potentially indicate the condition of mental health [16–18]. Indeed, negative affect–related factors, most prominently anxiety [20], anger [21], and depression [22], are key characteristics of managing life with chronic pain [19]. Negative affect is inherent to the challenges of experiencing and coping with chronic pain, potential loss of physical and social function, and the related medical and financial burdens. Opioid misuse has been previously associated with negative affect, most notably depression and anxiety [23–30]. One reason for this association might be that in addition to their analgesic properties, many opioids also induce euphoria [7,31], which may alleviate such negative states by inducing a positive state. Notably, however, opioid therapy in patients with chronic pain is associated with adverse effects such as hyperalgesia, constipation, and respiratory depression, as well as reinforcing continued usage [32]. These adverse effects may in fact lead to additional negative affect. Notably, negative affect is also a crucial component in the transition from drug use to substance use disorders and is especially salient when the drug is absent [33,34].

Here we aimed to complement and extend previous findings by characterizing and identifying across multiple physical, mental, and social health status factors, as well as pain severity measures, the relative importance and the most significant associations with the level of severity of self-reported prescribed opioid misuse. We aimed to do so in a large cross-sectional cohort of patients with chronic pain presenting for consultation at a tertiary academic pain clinic. As part of their clinical care, they completed a patient-reported outcomes registry using Stanford University's Collaborative Health Outcomes Information Registry (CHOIR). CHOIR is an open-source learning health care system to monitor patients' health status as part of clinical care, quality improvement, and research. During the period of data collection, CHOIR included 14 of the National Institute of Health's (NIH's) Patient-Reported Outcomes Measurement Information System (PROMIS) instruments, as well as four Pain Intensity measures assessing pain severity. The PROMIS instruments were designed and validated for precise and efficient measurement of patient-reported symptoms reflecting health-related quality of life in patients with a wide variety of chronic diseases and conditions, including chronic pain [18,35–40]. Here we used all 14 PROMIS instruments available, which included key domains such as Pain Interference, Fatigue, Anxiety, and Depression, as well as additional domains such as Pain Behavior, Anger, Emotional Support, and Social Isolation. We also included the Misuse of Prescription Pain Medication instrument (Rx-Misuse) [41], recently developed by NIH-PROMIS for the assessment of potential misuse during prescribed medicinal treatment. The Rx-Misuse was completed by those patients who endorsed currently taking opioid medications.

We first compared patients taking and not taking opioid medications on all PROMIS and pain severity measures. Accumulated research indicates the limited evidence of benefit, the increased adverse effects, and the worse health status outcomes associated with long-term opioid therapy [2,3,8,32,42–44]. We therefore hypothesized that patients currently taking opioid medications would show worse status in all health and pain severity factors compared with those not taking opioid medications. We then focused on our main goal by utilizing a data-driven assumption-free approach, by means of a stepwise regression analysis. We underscore that the importance of not a priori reducing the various factors into higher-order constructs lies in the goal of individuating discrete and potentially modifiable targets for treatment aimed at reducing prescribed opioid misuse behaviors. This is of particular interest as research to date has largely overlooked the relative contribution of multiple factors in explaining individual differences in severity of prescribed opioid misuse. Nevertheless, in view of its central role in chronic pain and substance use disorders, we hypothesized that the negative affect–related factors, namely Anxiety, Depression, and/or Anger, would be key factors associated with severity of misuse in chronic pain patients.

Methods

Procedure and Participants

Data were collected using Stanford University's Collaborative Health Outcomes Information Registry

(CHOIR; http://choir.stanford.edu). Patients presenting for consultation at the Stanford Outpatient Pain Management Center, a large tertiary academic pain clinic, are enrolled in CHOIR as part of routine clinical care. CHOIR administers an electronic survey characterizing multiple domains of physical, psychological, and social functioning. Most of the National Institute of Health's PROMIS instruments are regularly administered in CHOIR, whereas other measures are occasionally added or deleted to meet clinical or research goals. Use of computerized adaptive testing (CAT) reduces participant burden through the selection of a subset of items from each PROMIS item bank until resulting measurements meet preset criteria for standard errors [45]. Patients who do not complete the survey before their appointment are asked to complete it at clinic check-in using a tablet computer. Although completing the survey is encouraged, it is nevertheless optional and based on patients' willingness and ability to collaborate. Thus, patients may choose or end up not responding to certain items or assessments. These procedures were approved by the Stanford University School of Medicine Institutional Review Board (IRB). Informed consent was waived by the IRB, as CHOIR data were initially collected for clinical care and quality improvement purposes.

The current cross-sectional study involved retrospective review of surveyed clinical data that were collected with CHOIR between December 2014 and March 2015. During this period, 1,193 patients with a heterogeneous mix of pain disorders [9,46–48] were asked whether they are currently taking opioid medications. Those patients replying "yes" to this question also completed the full Rx-Misuse item bank. All patients also completed a battery of legacy PROMIS measures assessing physical, mental, and social health factors, as well as four Pain Intensity measures.

PROMIS Rx-Misuse

The PROMIS RX-Misuse item bank was developed as a measure of prescription pain medication misuse as part of the NIH's PROMIS initiative [41]. The initial calibration and psychometric evaluation of this 22-item bank were done in community-dwelling adults and patients in an addiction treatment program. Recent efforts support the validity of this measure for the assessment of prescribed opioid misuse in patients with chronic noncancer pain [49]. In the current sample, Cronbach's reliability was $\alpha = 0.85$. Using previously published item parameters from the graded response model [41] and the catR package [50], we calculated theta scores from expected a posteriori estimates and transformed these scores into standardized T scores, such that $M = 50$ represents the average of the US general population and $SD = 10$. Lower scores represent less misuse. The effective mean for this sample (range) was 42.35 ± 5.94 (30.93–63.07).

Other PROMIS Measures

Data included responses to 12 PROMIS item banks measuring components of self-reported physical, mental, and social health: Pain Interference, Pain Behavior, Physical Function, Fatigue, Depression, Anxiety, Anger, Sleep Disturbance, Sleep Impairment, Emotional Support, Satisfaction with Social Roles and Activities, and Social Isolation. In addition a 10-item Global Health Scale provided two additional scores of global physical and mental health. Substantial evidence has accumulated for the validity of these PROMIS measures [18,35–40]. Additional details about measure development and validation are available at http://www.healthmeasures.net. All these PROMIS measures were administered using CAT and resulted in standardized T scores, such that $M = 50$ represents the average of the US general population and $SD = 10$. Higher scores represent more of the measured construct.

Pain Intensity Measures

Data included response to four Pain Intensity–focused numeric rating scales (NRS) measured on an 11-point scale of 0–10 (0 = no pain, 10 = pain as bad as you can imagine). Pain Intensity in the past seven days was measured for worst, average, current (now), and least pain. Such NRS scales have been validated for use in pain, including over the past seven days [51].

Data Analysis

Following the examination of demographic information, we compared patients taking and not taking opioid medications on all PROMIS and Pain Intensity measures using standard *t* tests with a Bonferroni correction for multiple comparisons. Pairwise deletion was used to handle missing data. Next, to provide a description of the independent associations between each of the independent measures and the dependent measure, we computed the Pearson correlation coefficients between all PROMIS and Pain Intensity measures and the Rx-Misuse measure. Bonferroni correction for multiple comparisons and pairwise deletion to handle missing data were used again.

To individuate which of the PROMIS and Pain Intensity measures was the strongest predictor(s) of the Rx-Misuse measure, we submitted all of them as independent variables in a stepwise regression analysis [52]. This procedure does not a priori determine which measures nor in what order they enter the regression model. Rather, it aims to determine the order of importance of the independent variables as long as they have an additional significant and unique contribution to the explanation of variability in the dependent variable. This approach thus prevents us from restricting the analysis to any a priori measure. Listwise deletion was used to handle incomplete data within this analysis, resulting in 650 patients in this analysis. To account for the limitations associated with this approach and to solidify our results,

we conducted an additional and more structured linear regression analysis, the details of which are presented in the *Results* section.

Results

The sample's mean age ± SD (range) was 50.72 ± 14.97 (18–93) years; 64.04% (N = 764) were female, 35.88% (N = 428) were male, and one participant did not provide gender information. The question of whether the participant was currently taking opioid medications had a positive response in 60.27% (N = 719), and 58.01% (N = 692) fully completed the PROMIS Rx-Misuse item bank. Additional demographic information per the two groups is presented in Table 1. Group comparisons between patients currently taking and not taking opioid medications on all PROMIS and Pain Intensity measures are presented in Table 2. The results were in line with our general hypothesis and indicated worse physical, mental, and social health across most metrics, as well as more intense pain ratings, in patients who reported currently taking opioid medications. Notably, of the three negative affect–related measures, there was a significant difference between the groups only in Depression.

The correlations between all PROMIS and Pain Intensity measures and the Rx-Misuse measure are presented in Table 3. Apart from Physical Function and Pain Intensity–Least, which did not pass the Bonferroni correction threshold, all other measures were significantly correlated to self-reported levels of misuse. Notably, the strongest correlation coefficients, each explaining about 12% of the variance, were the three negative affect–related measures: Depression, Anxiety, and Anger.

Patients' sex, age, ethnicity, and race were included as a first step in the stepwise regression analysis to account for potential nonmodifiable effects of demographic information. Table 4 presents these results. The first model included only the demographic variables and indicated that patients' sex ($\beta = 0.18$, $P < 0.001$) was a significant predictor of Rx-Misuse. Males (43.61 ± 6.15) had higher Rx-Misuse levels compared with females (41.64 ± 5.71). The final model included four additional predictors, each significantly contributing above and beyond the demographic measures: Anxiety ($\beta = 0.15$, $P = 0.01$), Anger ($\beta = 0.13$, $P = 0.02$), Pain Intensity–Worst ($\beta = 0.09$, $P = 0.02$), and Depression ($\beta = 0.13$, $P = 0.04$). This model explained 19% of the variability in Rx-Misuse and confirmed our hypothesis, as it included all three negative affect–related factors. Importantly, although there appears to be an overlap between the negative affect–related factors, each on its own explaining 12% of the variability in Rx-Misuse, adding first Anger and then Depression beyond Anxiety had a small but significant incremental value (each adding 1% more to the 12% explained by anxiety). On the other hand, no other measures except for Pain Intensity–Worst (also adding 1%) resulted in such a significant additive contribution.

Table 1. Participants' demographic information as per the opioid- and non-opioid-taking groups

	Currently Taking Opioid Medications (Missing Data)	Not Currently Taking Opioid Medications (Missing Data)	P*
No.	719	474	
Age, M ± SD, y	50.87 ± 14.79 (0.14%)	50.49 ± 15.49 (0%)	0.67
Sex (females)	64.53% (0.14%)	63.29% (0%)	0.64
Ethnicity			0.67
Hispanic/Latino	9.60%	9.90%	
Non-Hispanic/ non-Latino	78.72%	79.3%	
Patient refused	1.25%	1.90%	
Unknown	0.70%	0.60%	
No response (missing data)	9.74%	8.20%	
Race			0.10
American Indian or Alaska Native	0.83%	0.00%	
Asian	4.59%	8.20%	
Black or African American	3.62%	2.30%	
Native Hawaiian or other Pacific Islander	0.83%	0.20%	
Other	15.72%	17.50%	
White	62.87%	61.4%	
Patient refused	1.11%	1.30%	
Unknown	0.56%	0.80%	
No response (missing data)	9.87%	8.20%	

*Reflects the results of a chi-square test for categorical variables (categories with less than a minimum of five patients were removed), or *t* test for continuous variables.

To solidify our results, we conducted an additional and more structured linear regression analysis. This time, after the first step in which we entered the demographic variables, we added a step in which a single Pain Intensity composite averaging the scores across the four Pain Intensity ratings was entered. These four Pain Intensity measures had an average correlation of $r = 0.70$ among themselves. In the third step, we entered a single negative affect composite, which averaged the scores across Anxiety, Anger, and Depression. These three negative affect–related measures had an average correlation of $r = 0.74$ among themselves. Using composite scores in both these steps is commonly implemented [27,53,54] and can serve as a cautionary procedure to reduce potential issues of multicollinearity (though tolerance values were well above 0.1) [55] and allow for potential additional factors to emerge as significant predictors in the next step. Indeed, in the final step, we entered all the remaining measures in an order reflecting the strongest correlation coefficients (as in Table 3) to examine if any or all of these additional measures resulted in a significant additive contribution in explaining variability in

Table 2. Opioid- and non-opioid-taking group comparisons across all PROMIS and Pain Intensity measures

	Currently Taking Opioid Medications			Not Currently Taking Opioid Medications				
	No. (Missing Data)	M	SD	No. (Missing Data)	M	SD	*P*	Cohen's *d*
PROMIS Global Health								
Mental Score	671 (6.68%)	41.49	9.24	452 (4.64%)	43.65	8.99	<0.001*	0.24
Physical Score	671 (6.68%)	36.14	6.89	452 (4.64%)	39.67	8.10	<0.001*	0.47
PROMIS								
Pain Interference	697 (3.06%)	65.09	6.63	473 (0.21%)	62.12	8.15	<0.001*	0.40
Pain Behavior	692 (3.76%)	59.25	3.59	472 (1.05%)	57.54	5.14	<0.001*	0.39
Physical Function	690 (4.03%)	34.69	7.64	469 (1.69%)	38.36	9.22	<0.001*	0.44
Fatigue	687 (4.45%)	60.18	8.99	466 (1.69%)	58.05	10.19	<0.001*	0.22
Depression	687 (4.45%)	54.63	9.80	464 (2.11%)	52.85	9.74	<0.005*	0.18
Anxiety	684 (4.87%)	54.81	9.59	462 (2.53%)	54.65	9.81	0.78	0.02
Anger	677 (5.84%)	49.23	10.21	458 (3.38%)	49.22	9.91	0.98	0.00
Sleep Disturbance	683 (5.10%)	57.50	8.85	462 (2.53%)	55.79	8.94	0.001*	0.19
Sleep Impairment	681 (5.29%)	56.92	8.93	462 (2.53%)	55.89	10.27	0.08	0.11
Emotional Support	670 (6.82%)	51.69	9.49	450 (5.06%)	51.48	9.05	0.71	0.02
Satisfaction with Social Roles and Activities	666 (7.37%)	40.36	8.86	450 (5.06%)	43.87	9.07	<0.001*	0.39
Social Isolation	663 (7.79%)	48.04	9.80	448 (5.49%)	47.29	9.78	0.21	0.08
Pain Intensity								
Worst	719 (0%)	8.05	1.71	474 (0%)	6.80	2.46	<0.001*	0.60
Average	719 (0%)	5.90	1.92	474 (0%)	5.01	2.38	<0.001*	0.41
Now	719 (0%)	5.69	2.27	474 (0%)	4.55	2.62	<0.001*	0.47
Least	719 (0%)	3.83	2.31	474 (0%)	3.09	2.47	<0.001*	0.31
Pain Intensity Composite	719 (0%)	5.87	1.73	474 (0%)	4.86	2.20	<0.001*	0.51
Negative Affect Composite	677 (5.84%)	52.87	8.96	458 (3.38%)	52.25	8.97	0.26	0.07

The composite Pain Intensity is an average of the four Pain Intensity measures. The composite negative affect is an average of PROMIS Anxiety, Anger, and Depression.

PROMIS = Patient-Reported Outcomes Measurement Information System.

*Bonferroni corrected.

Table 3. Correlations between Rx-misuse and all PROMIS and Pain Intensity measures

	No.	*r*	*P*
PROMIS Global Health			
Mental Score	659	–0.30	<0.001*
Physical Score	659	–0.18	<0.001*
PROMIS			
Pain Interference	685	0.23	<0.001*
Pain Behavior	680	0.25	<0.001*
Physical Function	678	–0.11	0.005
Fatigue	675	0.22	<0.001*
Depression	675	0.36	<0.001*
Anxiety	672	0.36	<0.001*
Anger	665	0.35	<0.001*
Sleep Disturbance	671	0.19	<0.001*
Sleep Impairment	669	0.23	<0.001*
Emotional Support	658	–0.16	<0.001*
Satisfaction with Social Roles and Activities	654	–0.24	<0.001*
Social Isolation	651	0.28	<0.001*
Pain Intensity			
Worst	692	0.15	<0.001*
Average	692	0.12	0.001*
Now	692	0.13	0.001*
Least	692	0.08	0.03
Pain Intensity Composite	692	0.14	<0.001*
Negative Affect Composite	665	0.39	<0.001*

PROMIS = Patient-Reported Outcomes Measurement Information System.

*Bonferroni corrected.

Rx-Misuse. Table 5 presents these results, which confirm our previous findings. The third model indicated that in addition to sex ($\beta = 0.19$, $P < 0.001$), only the negative affect composite was a significant predictor ($\beta = 0.38$, $P < 0.001$), above and beyond both demographic variables and the Pain Intensity composite. This model similarly explained 19% of the variability in Rx-Misuse. The final model indicated that neither other measures ($P > 0.18$) nor all of them together ($P = 0.51$) had an additional significant contribution.

Discussion

The current study's findings indicate that patients with chronic pain who endorsed currently taking opioid medications had greater impairment across most physical, mental, and social health status factors that were measured, as well as worse pain severity, compared with patients not taking opioid medications. This is potentially evident by their need for opioid medications to manage chronic pain and the limited evidence of benefit for long-term opioid therapy [2,3,8,31,41–43]. Within this group of opioid-medicated patients, and in line with previous research [6,7,9,13], all but two of the measures associated with self-reported severity of prescribed opioid misuse behaviors. Crucially, our data-driven assumption-

Table 4. Results of a stepwise regression analysis with Rx-Misuse as the dependent variable

	Beta	*P*	Tolerance	F(df)	*P*	Adjusted R^2	F(df) Change	*P* of F Change
Model 1				F(4,645) = 6.01	<0.001	0.04	F(4,645) = 6.01	<0.001
Sex	0.18	<0.001	0.99					
Age	–0.01	0.78	0.98					
Ethnicity	–0.03	0.49	0.86					
Race	–0.06	0.19	0.85					
Model 2				F(5,644) = 25.85	<0.001	0.16	F(1,644) = 101.45	<0.001
Sex	0.19	<0.001	0.99					
Age	0.02	0.53	0.98					
Ethnicity	–0.03	0.40	0.86					
Race	–0.03	0.41	0.85					
PROMIS Anxiety	0.37	<0.001	0.99					
Model 3				F(6,643) = 23.86	<0.001	0.17	F(1,643) = 11.75	<0.001
Sex	0.18	<0.001	0.99					
Age	0.04	0.29	0.96					
Ethnicity	–0.03	0.45	0.86					
Race	–0.04	0.37	0.85					
PROMIS Anxiety	0.24	<0.001	0.48					
PROMIS Anger	0.18	<0.001	0.48					
Model 4				F(7,642) = 21.54	<0.001	0.18	F(1,642) = 6.41	0.01
Sex	0.18	<0.001	0.99					
Age	0.04	0.29	0.96					
Ethnicity	–0.03	0.45	0.86					
Race	–0.03	0.37	0.85					
PROMIS Anxiety	0.23	<0.001	0.48					
PROMIS Anger	0.17	<0.001	0.47					
Pain Intensity–Worst	0.09	0.01	0.96					
Final Model				F(8,641) = 19.47	<0.001	0.19	F(1,641) = 4.23	0.04
Sex	0.18	<0.001	0.99					
Age	0.04	0.29	0.95					
Ethnicity	–0.03	0.45	0.86					
Race	–0.03	0.37	0.85					
PROMIS Anxiety	0.15	0.01	0.32					
PROMIS Anger	0.13	0.02	0.42					
Pain Intensity–Worst	0.09	0.02	0.95					
PROMIS Depression	0.13	0.04	0.33					

The first step included all demographic measures as independent variables, and all PROMIS and Pain Intensity measures were subsequently added in a stepwise process. The final model included all significant predictors above and beyond the demographic measures. No other measures resulted in a significant contribution.
PROMIS = Patient-Reported Outcomes Measurement Information System.

free approach applied in the regression analysis indicated that negative affect–related factors, namely Anxiety, Anger, and Depression (explaining 14% of variability), together with Pain Intensity at its worst (explaining 1% of variability), were the strongest factors associated with severity of misuse, above and beyond demographic information (explaining 4% of variability). This result was corroborated also when using a more structured and traditional regression analysis. Taken together, these findings suggest that negative affect–related factors might have a role as key risk factors for prescribed opioid misuse and further support negative affect's central role in managing chronic pain and in substance use disorders [20–22,33,34]. Although this was a cross-sectional study, it is noteworthy that unlike pain severity [56], various treatment strategies have been consistently applied for the reduction of anxiety, anger, and depression symptomatology [57–60].

Several previous studies have marked negative affect–related factors, particularly anxiety and depression, as increasing the risk for prescribed opioid misuse. Indeed, anxiety and depression are highly comorbid in the general population [61], as well as in chronic pain patients [62,63]. Each of these two factors was associated with increased risk for opioid misuse [6,23–26,29,30]. A recent cross-sectional study indicated that each might in fact independently contribute to such increased risk, above and beyond the other [64]. Although our findings are cross-sectional, they provide support for these findings, but also extend them in several important ways. First, findings reported here show that the negative affect–related factors superseded other physical, mental, and social health factors in explaining variability of misuse severity. Most previous findings did not include such a vast and varied number of factors as a comparison. Second, in most of these studies, anxiety and depression were measured as symptoms of psychiatric disorders. In the current study, these factors were measured using PROMIS, incorporating also the frequency of experiencing negative feelings in the last seven days and reflecting general

Table 5. Results of a regression analysis with Rx-Misuse as the dependent variable

	Beta	*P*	Tolerance	F(df)	*P*	Adjusted R^2	F(df) Change	*P* of F Change
Model 1				F(4,645) = 6.01	<0.001	0.03	F(4,645) = 6.01	<0.001
Sex	0.18	<0.001	0.99					
Age	–0.01	0.78	0.98					
Ethnicity	–0.03	0.49	0.86					
Race	–0.06	0.19	0.85					
Model 2				F(5,644) = 7.93	<0.001	0.05	F(1,644) = 15.07	<0.001
Sex	0.18	<0.001	0.99					
Age	0.00	0.86	0.98					
Ethnicity	–0.03	0.42	0.86					
Race	–0.03	0.42	0.84					
Pain Intensity Composite	0.15	<0.001	0.98					
Model 3				F(6,643) = 25.49	<0.001	0.19	F(1,643) = 106.79	<0.001
Sex	0.18	<0.001	0.99					
Age	0.04	0.27	0.97					
Ethnicity	–0.03	0.47	0.86					
Race	–0.03	0.42	0.84					
Pain Intensity Composite	0.06	0.08	0.93					
Negative Affect Composite	0.38	<0.001	0.93					
Final Model				F(17,632) = 9.59	<0.001	0.18	F(11, 632) = 0.936	0.51
Sex	0.18	<0.001	0.95					
Age	0.05	0.17	0.88					
Ethnicity	–0.03	0.41	0.85					
Race	–0.04	0.30	0.80					
Pain Intensity Composite	0.06	0.18	0.63					
Negative Affect Composite	0.36	<0.001	0.28					
Global Health Mental Score	–0.01	0.91	0.30					
Social Isolation	0.02	0.66	0.41					
Pain Behavior	0.04	0.44	0.46					
Satisfaction with Social Roles	–0.07	0.18	0.46					
Pain Interference	0.05	0.43	0.38					
Sleep Impairment	–0.07	0.25	0.35					
Fatigue	0.03	0.55	0.40					
Sleep Disturbance	0.06	0.22	0.50					
Global Health Physical Score	0.09	0.18	0.29					
Emotional Support	0.04	0.36	0.70					
Physical Function	0.05	0.29	0.48					

The first step included all demographic measures as independent variables. The second and third steps included Pain Intensity and negative affect composite measures as independent variables, respectively. All other PROMIS measures were subsequently added, but none of them resulted in a significant contribution. The analysis thus indicated that composite negative affect was the most important predictor, above and beyond both demographic and Pain Intensity measures.

PROMIS = Patient-Reported Outcomes Measurement Information System.

mood (e.g., "I felt fearful," "I felt sad," and "I felt angry" for Anxiety, Depression, and Anger, respectively) [18]. Future studies should aim to examine how these two ways of assessing negative affect may impact their relationship to misuse behaviors.

We further extend previous findings by revealing that anger has a significant additive contribution in explaining individual differences in misuse behaviors, beyond solely anxiety and depression. In addition to being a major precursor to aggression and violence, anger may have detrimental effects on one's health, well-being, and social environment [65]. Compared with anxiety and depression, anger seems to play a unique and differential role in chronic pain [19,21]. Patients with chronic pain often demonstrate an increased tendency to be angry, and the way they think about, cope with, and express their anger may have various deleterious effects on both acute and chronic pain severity [66–68]. Moreover, consistent findings indicate an important interaction between anger expression tendencies and endogenous opioid functioning in determining sensitivity to pain, as well as opioid pain analgesia, in both healthy and chronic pain patients [69–72]. Anger is also a symptom of abstinence and withdrawal from various substances [73–75], including opioids [76,77]. In fact, following the induction of a negative experience, individuals with prescribed opioid dependence, but not healthy controls, showed an increase in anger and craving [78]. Taken together, this emphasizes the important and largely overlooked link between chronic pain, anger, and opioid misuse and substance use disorders, urging further investigations.

Notably, although anxiety, anger, and depression were the factors most strongly associated with severity of misuse, only depression differed between patients taking opioid medications compared with those not taking opioid medications. This does not diminish the importance

of the fact that in most other factors, such as pain behavior, physical function, fatigue, and sleep disturbance, as well as in all four pain severity measures, the patients taking opioid medications were worse off. This might suggest, however, that the misuse of prescribed opioids in patients with chronic pain is not necessarily a strategy to decrease excessive negative affect per se [24,79,80]. Rather, negative affect might be linked to coping with craving [81,82] or to other symptoms [33,83] that may mediate the propensity to misuse the medication. Indeed, craving, but not pain severity, was found to mediate the positive relationship between negative affect and opioid misuse [27]. These relationships could not be addressed in the current study and require further research.

An additional issue we would like to address concerns a previously suggested argument that women are at greater risk than men for opioid misuse, allegedly because of their susceptibility to distress [11]. However, we have found no support for this claim. In line with previous findings [9,84], the sex differences that were found indicated that males had a higher self-reported severity of misuse than females. Moreover, the effect of negative affect prevailed above and beyond the effect of sex. In fact, there were no sex differences in any of the negative affect–related factors in the entire sample (all $P > 0.24$), nor strictly in the group of patients currently taking opioid medication (all $P > 0.26$).

Finally, it is important to note that while we had a host of 18 different measures to characterize our patients and identify their relation to severity of misuse, by no means are these measures exhaustive. Indeed, 80% of the variance in severity of misuse remains unexplained. Other factors that were not available to us such as prior trauma or opioid dosing could further contribute, though they might be more challenging to treat. Of particular interest in the realm psychosocial factors is pain catastrophizing—a cluster of persistent negative thought patterns in response to actual or anticipated pain [85]. Pain catastrophizing in patients with chronic pain has been associated with various negative outcomes [47,86], including risk for prescribed opioid misuse [87,88]. In fact, the relationship between pain catastrophizing and risk for opioid misuse was partially mediated by negative affect, whereas pain catastrophizing in itself remained a significant predictor for risk of misuse even beyond negative affect symptoms [87]. Replicating this effect by directly addressing the unique and incremental contributions of negative affect and pain catastrophizing in actual severity of opioid misuse and in larger cohorts would provide additional support for their unique contribution in understanding and reducing opioid misuse. Critically for this goal, like negative affect, pain catastrophizing was demonstrated to be modifiable by treatment [86,89,90].

Limitations

Several limitations warrant consideration. Primarily, this is a cross-sectional study, and its correlational nature precludes us from drawing any sequential or causal conclusions. For that matter, it might be that the misuse of medications in itself is a cause for distressful feelings such as anxiety, anger, and depression. Furthermore, stepwise regression's main limitations relate to sample size and potential selection bias, which may lead to overfitting of the data. Although our sample size provided an average of 29.55 participants per each variable entered in this regression analysis and it was thus large enough to address these limitations according to many [91–93], others recommend a higher number of about 40 per variable [52]. Notably, however, negative affect–related factors' centrality in explaining variability in opioid prescription misuse has also been demonstrated here using standard linear regression analysis.

An additional limitation may be found in the kind of measures we utilized; all measures were based on self-report, and we had no access to actual prescribed opioid type, duration, dose, or frequency. Longitudinal and empirical studies with additional measures and characterizations of chronic pain patients endorsing opioid usage are required to replicate and solidify our findings. The finding of a relationship between anger and opioid misuse necessitates particular attention, especially considering the complex and multifaceted nature of anger as an emotional experience [65], as well as a feature of acute and chronic pain [68,94]. Moreover, the measurement and potential direct relationship between negative affect–related factors and various abstinence and withdrawal symptoms will benefit a better understanding of opioid misuse. Another potential limitation refers to the usage of the PROMIS Rx-Misuse to assess the severity of prescribed opioid misuse [41]. Although recent findings support its validity [49], it has yet to obtain the psychometric properties and widespread usage that other previously established measures of misuse such as the Current Opioid Misuse Measure have [95]. Nevertheless, these measures are similarly based on self-reports and therefore similarly limited in their diagnostic properties. Finally, the study sample was comprised of patients seeking clinical care in a tertiary pain clinic. This limits generalizability, as individuals with lower levels of pain and potentially other socioeconomic backgrounds, who were not necessarily seeking or were not capable of specialized medical treatment, were not part of the sample.

Conclusions

The current study examined the clinical data of a large group of chronic pain patients on opioid medication to characterize the relative importance and identify the most significant of several potential risk factors for the severity of self-reported prescribed opioid misuse behaviors. This might be crucial for prevention of such behaviors. However, considering the importance of therapeutic intervention and improvement of medication adherence, we adopted a data-driven approach to individuate

potentially modifiable targets that may guide treatments to reduce such existing misuse. While taking note of the limitations, this study replicates and extends previous findings regarding the link between negative affect, specifically feelings associated with anxiety, anger, and depression, and prescribed opioid misuse. Moreover, results indicate that these factors explain most variability in misuse tendencies across multiple physical, mental, and social health status factors, and above and beyond both demographic variables and pain severity measures. Importantly, various treatment strategies were able to show that negative affect–related factors are modifiable and susceptible to treatment. Taken together, this study thus urges further empirical and intervention-based investigations triangulating chronic pain, negative affect, and opioid misuse.

Authors' Contributions

GG and SCM conceived the study. GG analyzed and interpreted the data and wrote the manuscript. JAS and DSY contributed to data analysis. All authors discussed the analyses, the results and their interpretation, and revised and approved the manuscript.

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