

Pain Catastrophizing Moderates Relationships between Pain Intensity and Opioid Prescription

Nonlinear Sex Differences Revealed Using a Learning Health System

Yasamin Sharifzadeh, B.S., Ming-Chih Kao, Ph.D., M.D., John A. Sturgeon, Ph.D., Thomas J. Rico, B.S., Sean Mackey, M.D., Ph.D., Beth D. Darnall, Ph.D.

ABSTRACT

Background: Pain catastrophizing is a maladaptive response to pain that amplifies chronic pain intensity and distress. Few studies have examined how pain catastrophizing relates to opioid prescription in outpatients with chronic pain.

Methods: The authors conducted a retrospective observational study of the relationships between opioid prescription, pain intensity, and pain catastrophizing in 1,794 adults (1,129 women; 63%) presenting for new evaluation at a large tertiary care pain treatment center. Data were sourced primarily from an open-source, learning health system and pain registry and secondarily from manual review of electronic medical records. A binary opioid prescription variable (yes/no) constituted the dependent variable; independent variables were age, sex, pain intensity, pain catastrophizing, depression, and anxiety.

Results: Most patients were prescribed at least one opioid medication (57%; $n = 1,020$). A significant interaction and main effects of pain intensity and pain catastrophizing on opioid prescription were noted ($P < 0.04$). Additive modeling revealed sex differences in the relationship between pain catastrophizing, pain intensity, and opioid prescription, such that opioid prescription became more common at lower levels of pain catastrophizing for women than for men.

Conclusions: Results supported the conclusion that pain catastrophizing and sex moderate the relationship between pain intensity and opioid prescription. Although men and women patients had similar Pain Catastrophizing Scale scores, historically “subthreshold” levels of pain catastrophizing were significantly associated with opioid prescription only for women patients. These findings suggest that pain intensity and catastrophizing contribute to different patterns of opioid prescription for men and women patients, highlighting a potential need for examination and intervention in future studies.

(ANESTHESIOLOGY 2017; 127:136-46)

WITH up to 40% of the global population experiencing ongoing pain,^{1,2} there is a need to better understand the experience of pain and associated treatment patterns. Pain catastrophizing^{3,4}—a cascade of negative thoughts and emotions in response to actual or anticipated pain—is a key factor in pain-related outcomes. In experimental and clinical settings, pain catastrophizing is associated with amplified pain processing,^{5,6} greater pain intensity,⁷ and greater disability.^{7,8} Pain catastrophizing may explain up to 20% of the variance in chronic pain intensity⁹ and thus may influence other pain treatments, including opioid medications.

Pain catastrophizing has been identified as a risk factor for prescription opioid misuse in patients with chronic pain generally¹⁰ and among those with a history of substance

What We Already Know about This Topic

- Pain catastrophizing is a cascade of negative thoughts and emotions in response to actual or anticipated pain
- It may explain up to 20% of the variance in chronic pain intensity and may, as a result, influence pain treatment

What This Article Tells Us That Is New

- A retrospective study of 1,794 patients with chronic pain seeking initial medical evaluation found a significant relationship between pain intensity and opioid prescription that was much stronger in women, especially those with high levels of pain catastrophizing
- Although men and women had similar levels of catastrophizing and opioid prescription, opioid prescriptions were more common at lower levels of catastrophizing for women

This article is featured in “This Month in Anesthesiology,” page 1A. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal’s Web site (www.anesthesiology.org).

Submitted for publication April 7, 2016. Accepted for publication March 16, 2017. From Stanford University School of Medicine, Department of Anesthesiology, Perioperative and Pain Medicine, Division of Pain Medicine, Stanford Systems Neuroscience and Pain Laboratory, Palo Alto, California.

Copyright © 2017, the American Society of Anesthesiologists, Inc. Wolters Kluwer Health, Inc. All Rights Reserved. Anesthesiology 2017; 127:136-46

use disorder.¹¹ Postsurgically, opioid use is quantified commonly either by dose or by time-to-opioid cessation.^{12,13} Perioperative studies have yielded mixed findings for pain catastrophizing, with some reporting a direct relationship with morphine dose delivered either by patient-controlled analgesia devices¹⁴ or by hospital staff,¹⁵ whereas other studies reported no association¹⁶ or an inverse association.¹⁷ Findings from a recent longitudinal study of 145 patients undergoing musculoskeletal trauma surgery suggested that pain catastrophizing predicted delayed opioid cessation after surgery.¹⁸ Using multivariate analyses, the authors found that pain catastrophizing was the strongest predictor of postsurgical opioid use 1 to 2 months after surgery. After the authors controlled for anxiety, depression, posttraumatic stress disorder symptoms, and disability, pain catastrophizing accounted for 23% of the unique variance in persistent postsurgical opioid use.

In the outpatient setting, catastrophizing has been associated with opioid craving,¹⁹ long-term opioid use in veterans,²⁰ and opioid misuse.²¹ Given the positive associations found between catastrophizing and the aforementioned opioid responses and behaviors, it would follow that a similar association might exist for catastrophizing and receipt of an opioid prescription in a larger civilian chronic pain population. However, to our knowledge, this latter relationship is unexplored. Characterization of the relationship between catastrophizing and opioid prescription in a larger chronic pain sample could enhance understanding and potentially reveal a therapeutic target for reducing need and use of opioids in chronic pain outpatients.

Accordingly, the purpose of this study was to characterize the relationship between existing opioid prescription and pain catastrophizing in a large sample of patients presenting for new evaluation at a chronic pain clinic. It has been found that in individuals with chronic noncancer pain, the presence of comorbid mental health diagnoses, particularly mood disorders, predicts the likelihood of opioid prescription,²¹ the degree of opioid use,¹¹ and the likelihood of aberrant opioid use (*e.g.*, opioid abuse or dependence).²² Consequently, we sought to characterize the relationship between pain catastrophizing and opioid prescription independent of the influences of these and other factors, including age,¹¹ sex,²³ and pain intensity,^{16,24} known to be relevant to opioid use, and pain catastrophizing, such as symptoms of anxiety and depression.²² We aimed solely to identify any relationships between our variables of interest, in turn allowing for future investigations to further explore any clinically significant findings.

Materials and Methods

Design and Setting

The current study used a retrospective, observational method to examine a large sample of adult patients with chronic pain. Patients were seeking treatment at a large, urban, tertiary

academic pain treatment center located in the San Francisco Bay Area in the United States. Data were extracted for patients with initial pain clinic visits between January 2014 and April 2015. Study procedures, which involved exclusively retrospective review of clinical data and therefore did not require informed consent from patients, were approved by the Institutional Review Board at Stanford University in Stanford, California.

Participants

All new patients who sought treatment at a tertiary academic outpatient pain management center in the San Francisco Bay Area between the aforementioned dates were eligible to be in the study. However, only those who had completed the Pain Collaborative Health Outcomes Information Registry (Pain-CHOIR) in its entirety, 1,794 patients, were included in the study.

Data Collection

Data were collected with the Pain-CHOIR^{25,26} (<http://snapl.stanford.edu/choir>). Pain-CHOIR is a learning health system that allows for deep phenotyping of patients while also identifying their treatment needs and facilitating rapid delivery of specialized pain services. The patient-reported outcomes component of Pain-CHOIR is an electronic patient survey. For simplicity, the survey alone will be referred to as Pain-CHOIR. Pain-CHOIR, administered to all patients in the Stanford Pain Management Center, serves as a key component of the new patient evaluation procedure. Five days before their scheduled new patient medical evaluation, all patients receive an email with instructions to follow a link to register with the Pain-CHOIR system and complete their new patient survey. Patients who do not complete their Pain-CHOIR before their visit or lack the technologies (computer/smartphone, Internet, email address) needed to access the survey are asked to complete the surveys at clinic check-in using a tablet computer provided by the clinic.

Data for the following measures were extracted from the initial Pain-CHOIR: demographic variables (education, marital status, and race), the Pain Catastrophizing Scale (PCS),²⁷ average pain intensity, and the Depression and Anxiety item banks of the National Institutes of Health Patient-Reported Outcomes Measurement Information System (PROMIS).²⁸ Other demographic variables, such as date of birth (used to calculate age) and sex, were extracted from Stanford Hospitals and Clinics electronic medical record system. In addition, all patients had accessible electronic medical records with physician notes that allowed for manual retrospective chart review. Finally, all pain diagnostic information was attained by collecting the International Classification of Diseases, Ninth Revision billing codes assigned to each patient at initial clinic visit. The codes were reviewed and categorized according to diagnoses relevant to the field.

Opioid Prescription. Patients self-reported all current opioid prescription data, either electronically *via* Pain-CHOIR

or verbally to clinic staff during their medical visit. For patients who verbally provided opioid medication information ($n = 711$, 40%), opioid data were extracted *via* retrospective chart review in a step-wise manner. Step 1 involved recording current opioid medications for the initial clinic visit from physician documentation (the clinical note) in the electronic medical record. If data were absent in step 1, step 2 was used, in which opioid data were extracted from the electronic medical record medication list. Step 2 was used for less than 10% of the manually extracted opioid prescription data. Data collection screened for codeine, duragesic, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, oxycodone, oxymorphone, tramadol, and suboxone. Active opioid prescription was recorded as a binary variable with 0 = no opioid prescriptions and 1 = any opioid prescription.

Midway through the study period, an opioid survey was included into Pain-CHOIR containing the following item: "Are you currently taking any opioid medications (such as Vicodin, Oxycontin, Oxycodone, Morphine, MS-Contin, Codeine, Actiq, Duragesic, Dilaudid, Demoral, Methadone, Percocet, Opana, Nucynta, Stadol, Ultram)?" The addition of the opioid question rapidly identified patients with current opioid prescriptions, thereby greatly facilitating data catchment. Thus, for 1,083 patients, opioid prescription data were extracted electronically directly from Pain-CHOIR.

Patient-reported Outcome Measures

Pain Catastrophizing Scale. Pain catastrophizing was measured with the PCS.²⁷ The PCS asks respondents to rate how frequently they respond to pain in a manner consistent with each of the 13 statements presented (*e.g.*, "It's awful and I feel that it overwhelms me."). Each item is rated on a 5-point scale ranging from 0 (not at all) to 4 (always). A total PCS score is computed by summing the 13 items (range = 0 to 52), with higher scores reflecting higher levels of catastrophizing. The PCS contains three subscales: rumination, magnification, and feelings of helplessness. The PCS has been shown to have good internal and cross-population psychometric consistency.^{27,29–31} The coefficient alpha for the total PCS is 0.87.²⁷

PROMIS Depression and Anxiety. Within Pain-CHOIR, PROMIS is delivered as a computer-based survey that uses a computerized adaptive testing approach based on item response theory to allow for item-level responses, greater precision achieved through lowered SE, and a smaller set of questions³² that gauge a psychometric domain on a continuum³³ with reduced sensitivity to population variability.³⁴ The PROMIS Depression and Anxiety item banks have demonstrated validity and consistency.³⁵ PROMIS instruments quantify level of symptoms, are normed on the U.S. population, and are reported with t scores with a mean of 50 and a SD of 10.²⁸

Average Pain Intensity. Average pain intensity was measured with the numeric rating scale, which operates on a 0 to 10 scale with "0" being no pain and "10" being the worst

pain imaginable.³⁶ Respondents were asked to consider the previous 7 days for rating their average pain intensity. The numeric rating scale has been validated for specificity and use in chronic pain research.

Statistical Analysis

In the statistical analysis of clinical trials and observational studies, valid characterizations of effects are contingent on the accurate selection of the statistical model. In the field of pain research, linear models predominantly are used. Linear models, including linear regression, logistic regression, and semiparametric methods such as Cox proportional hazard modeling, assume that the effects of the covariates on the outcome variable are linear and equal across the entire range of observed values. In situations in which the phenomenon under question is in fact nonlinear, model misspecification can lead to inaccurate estimates that can result in erroneous statistical inferences *via* outliers or dilution of true effects. Consequently, individual investigators may be misled into costly pursuits of inaccurate conclusions. Scientifically, neglecting nonlinearity may lead to inconsistent statistical estimates and paradoxical bodies of literature. In some cases, nonlinearity may be apparent visually during data analysis and accounted for by the incorporation of polynomial covariate terms. However, this is not always true, suggesting that this approach may not be sufficient for detecting and addressing potentially nonlinear relationships. Models involving binary outcome variables may present particular difficulties in this regard.

To bypass normal distribution assumptions and account for nonlinear relationships, we used both a generalized linear model and generalized additive model. General linear modeling is a flexible, linear statistical model that allows for the analysis of variables with non-normal distributions using a link function. General linear model building was performed with a logit link function for the binary outcome of "any opioids prescribed" with covariates (x) of pain intensity, anxiety, depression, pain catastrophizing, pain intensity \times pain catastrophizing (interaction), age, and sex.

$$\text{logit}[P(\text{Opioid})] = \beta_0 + \beta_1(x_1) + \beta_2(x_2) + \beta_3(x_3)$$

General additive modeling, a flexible nonlinear model, was used to identify and characterize the effect of potential nonlinear prognostic factors on the binary outcome of opioid prescription with smoothing spline curves to fully estimate nonlinear effects. Opioid prescription was analyzed as a possible prognostic factor in the association between pain intensity and pain catastrophizing, separately characterized by sex. Interaction terms (such as pain intensity \times pain catastrophizing) were used in moderation analyses, intended to determine whether the prognostic value of predictors such as pain intensity and pain catastrophizing in predicting opioid prescription were mutually dependent. In simpler terms, this interaction term was intended to reflect whether the independent prognostic value of pain intensity for opioid

prescription was dependent on co-occurring pain catastrophizing scores and *vice versa*.

We also used mediation analyses, an analytic approach designed to estimate the extent to which a third variable (the mediator) explains or accounts for the relationship between an independent and dependent variable. Given the known positive relationships between pain intensity and pain catastrophizing and the inconsistent relationship between pain catastrophizing and opioid use, one natural question that arose was whether the relationship between pain intensity and opioid use was mediated by pain catastrophizing. To test this, we used the causal mediation analysis framework from Imai *et al.*³⁷ for the whole sample and separately for men and women. Analogous to mediation analysis using structural equation modeling, this framework also relies on a series of regression models. It is able to estimate the average causal mediated effect and average direct effect nonparametrically.

All statistical analyses were completed in SPSS 22.0 (IBM Corporation, USA) and R (R 3.1.0, Austria) for Windows. General additive models were estimated with the R package. mgcv. Significance was set at $P < 0.05$ unless otherwise noted.

Results

Sample Demographic and Diagnostic Characteristics

Demographic characteristics for the 1,794 patients included in this study are described in table 1. The study sample was predominantly white ($n = 1,144$; 67%), married ($n = 794$; 54%), and women ($n = 1,129$; 63%), with at least some college education ($n = 1,199$; 83%). Mean age of the sample was about 50 yr (table 2) with an age range of 18 to 94 yr (table 1). In the current study, pain diagnoses were separated into a series of categories, representing the broad location and presumed etiology of pain complaints. Given that complete diagnostic information was not available for the sample used in this study, pain diagnosis information for all pain clinic patients presenting for an initial visit between January 2014 and May 2016 were analyzed to characterize the clinic overall. Although 10,707 (28%) of the total number of diagnoses were not pain related or listed, the most common diagnoses included headache (9.2%), thoracolumbar pain (8.7%), musculoskeletal pain (7.6%), cardiac pain (5.3%), and nerve pain (5.0%) (see Supplemental Digital Content 1, <http://links.lww.com/ALN/B433>, which lists the distribution of pain diagnoses for the clinic). The total number of diagnoses exceeded the number of patients visiting the clinic due to multiple diagnoses per patient per visit. Most patients had one major pain diagnosis (46%), whereas close to 20% had two or more diagnoses.

Clinical Measures by Sex

Clinical measures are reported by sex in table 2. Unpaired *t* test results revealed a slight age difference between men and

Table 1. Sample Demographic Characteristics

Variable	n (%)
Sex	
Woman	1,129 (63)
Man	665 (37)
Age, yr	
18–30	216 (12)
31–40	301 (17)
41–50	373 (21)
51–60	475 (26)
61–70	256 (14)
71–80+	173 (10)
Marital status* (19% of patients not included)	
Separated/divorced	225 (16)
Cohabiting	104 (7)
Widowed	49 (3)
Married	794 (54)
Never married	288 (20)
Education* (19% of patients not included)	
No high school diploma	111 (8)
High school diploma or GED	143 (10)
Some university/associate's degree	534 (37)
Bachelor's degree	343 (24)
Graduate degree	322 (22)
Unknown	4 (<1)
Race*† (5% of patients not included)	
American Indian or Alaska Native	7 (<1)
Asian	117 (7)
Black or African American	51 (3)
Native Hawaiian/Pacific Islander	16 (1)
White	1,144 (67)
Other	311 (18)
Patient declined to answer	34 (2)
Unknown	31 (2)

*Not all patients included due to incomplete surveys. †Due to limitations of the electronic medical records used, ethnicity data were unreliable and not reported. Hispanic is subsumed either in "white" or "other."

GED = General Educational Diploma.

Table 2. Clinical Measures by Sex

	Men	Women
Age	51 (15)	49 (15)*
Average pain intensity (NRS)	6 (2)	6 (2)*
PCS	21 (13)	20 (13)
Depression	57 (10)	58 (9)
Anxiety	58 (10)	59 (9)*

Scores are presented as mean (SD).

*Significant sex differences on a variable: $P < 0.05$.

NRS = numeric rating scale; PCS = Pain Catastrophizing Scale.

women, with men having greater average age. As expected, women had higher average pain intensity than men ($P = 0.02$). Despite higher pain intensity in women, we found no difference in PCS scores by sex ($P = 0.12$). Although there were no significant differences in depression between men and women, there was a difference in anxiety between the sexes, with women reporting greater anxiety.

Table 3. Clinical Measures by Opioid Status

	Full Sample	No Opioids	Opioids
Age	50 (15)	49 (16)	50 (15)
Average pain intensity	6 (2)	5 (2)	6 (2)*
PCS	20 (13)	19 (13)	21 (13)*
Depression	58 (9)	57 (9)	58 (10)†
Anxiety	58 (10)	58 (10)	59 (9)

Scores are presented as mean (SD).

Significant differences between opioid and nonopioid groups: * $P < 0.001$,

† $P < 0.05$.

PCS = Pain Catastrophizing Scale.

Clinical Measures by Opioid Status

Means for age and psychometric variables are reported in table 3. In the full sample, 57% ($n = 1,020$) had one or more opioid prescriptions. Age was unrelated to opioid prescription. A similar proportion of men (58%; $n = 387$) and women (56%; $n = 633$) had opioid prescription ($P = 0.38$). Overall, opioid prescription was associated with higher average pain intensity ($P < 0.001$), PCS scores ($P < 0.001$), and depression ($P = 0.04$).

Opioid Prescription as a Function of Pain Intensity and Pain Catastrophizing

Given the significant differences in pain intensity and pain catastrophizing observed between opioid prescription groups, we sought to attain a preliminary understanding of any underlying relationships through a visual display—a density plot of patients by opioid prescription status. Figure 1 displays a heat map of the density of patients according to opioid status as a function of pain intensity and pain catastrophizing, with red representing the greatest patient density. As

seen by the concentration of yellow at the bottom left-hand corner of the left graph, the density of patients with low levels of pain and catastrophizing without opioid prescription is much higher than that of those with opioid prescription. The data display for opioid prescription reveals a more horizontal distribution of patients with a wider range of pain catastrophizing. Also, there are a greater number of high patient-density patches spread over a larger range of catastrophizing. The data display in figure 1 allowed us to visually detect emerging relationships between pain intensity and pain catastrophizing in those without opioid prescription. However, the difference between the heat maps of the two groups called for the further modeling of these variables.

Generalized Linear Modeling of the Association between Opioid Prescription, Average Pain Intensity, and Additional Variables

We further investigated the differences in pain intensity and pain catastrophizing seen between opioid users and nonusers with a more sophisticated analysis, generalized linear modeling. Table 4 shows the result of using generalized linear modeling, a more flexible linear model, to show the association between opioid prescription, average pain intensity, and additional study variables. As a base model, pain intensity showed a significant positive association with opioid prescription. For every increase of one SD away from average pain intensity, the odds of having prescription opioids increased by 41%. The use of pain intensity with other variables showed no significant effects on opioid prescription. However, on modeling opioid prescription with pain intensity, pain catastrophizing, and their interaction term, significant associations were found. Pain intensity and pain

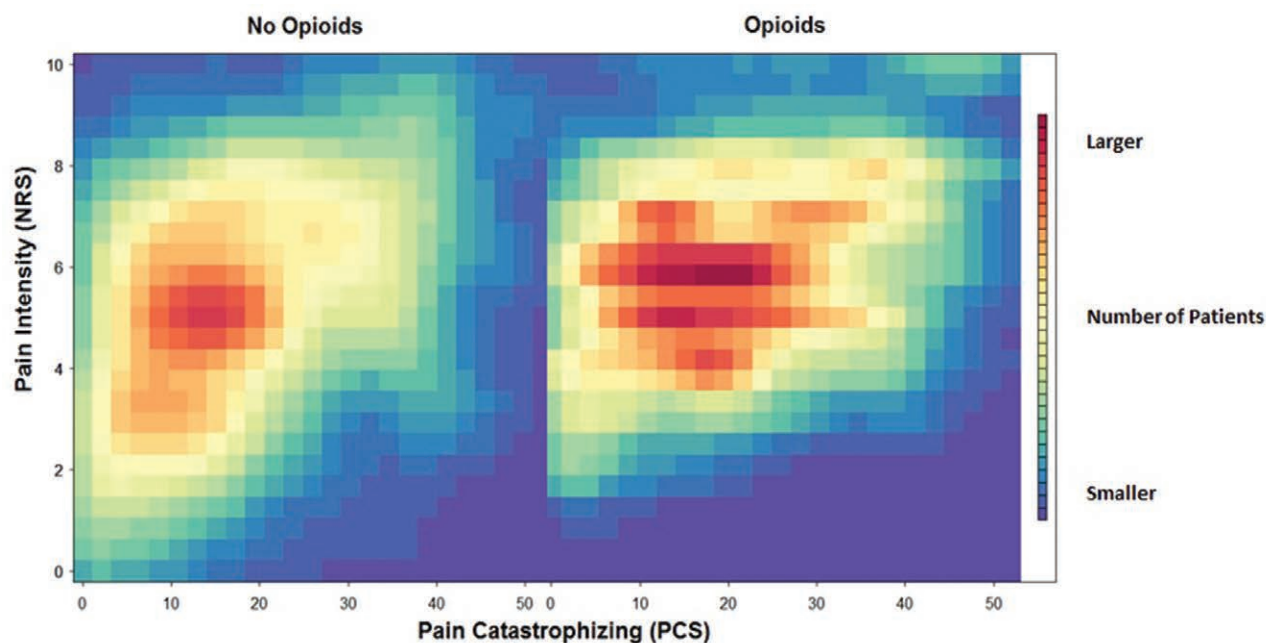


Fig. 1. Heat map of distribution of patients in terms of pain catastrophizing and pain intensity, by opioid prescription status. The color red represents the greatest patient density. NRS = numeric rating scale; PCS = Pain Catastrophizing Scale.

Table 4. General Linear Models for the Prediction of Opioid Prescription

	Variable	Estimate	OR (per SD)	SE	P Value
Base model					
1	Pain intensity	0.159	1.41	0.023	<0.001
Models with one additional predictor					
2	Anxiety	-0.001	0.99	0.006	0.834
3	Depression	0.003	1.03	0.006	0.643
4	Age	0.004	1.06	0.003	0.195
5	Woman	-0.131	0.88	0.101	0.192
6	PCS score	0.006	1.08	0.004	0.109
Model with PCS and interaction					
7	Pain intensity	0.236	1.66	0.041	<0.001
	PCS score	0.034	1.56	0.01	0.001
	PCS:pain intensity	-0.007	0.91 (PCS) 0.98 (pain intensity)	0.002	0.005
Model with PCS and interaction by sex					
8 Men	Pain intensity	0.32	2.03	0.07	<0.001
	PCS score	0.032	1.53	0.017	0.057
	PCS:pain intensity	-0.006	0.92 (PCS) 0.99 (pain intensity)	0.003	0.039
9 Women	Pain intensity	0.202	1.53	0.051	<0.001
	PCS score	0.035	1.57	0.013	0.008
	PCS:pain intensity	-0.005	0.94 (PCS) 0.99 (pain intensity)	0.002	0.032

Models were computed by using blocks of predictors in predicting opioid prescription. First, pain intensity was tested as an independent predictor. Next, psychologic and demographic factors were added. Third, pain intensity and PCS scores and an interaction between these variables were estimated for the entire sample, as well as separately in men and women.

OR = odds ratio; PCS = Pain Catastrophizing Scale.

catastrophizing independently yielded high odds ratios (1.66 and 1.56, respectively), but their interaction term, which introduced a greater degree of symmetric flexibility to the model, yielded odds ratios of about one (0.91 for PCS term, 0.98 for pain intensity term). Although the odds ratios were close to one, the *P* value of the interaction term was low (*P* = 0.005), indicating the presence of some significant variable overlap that merited more nuanced analysis.

Although we had found no sex differences in catastrophizing or opioid prescription status in our initial stages of analysis, differences in pain intensity between sexes prompted further analyses. The generalized linear models revealed pain intensity to be the best predictor for opioid prescription in both men and women. Although the overall model showed sex differences in the effect of pain catastrophizing on the prediction of opioid prescription, it also revealed the interaction between pain catastrophizing and pain intensity to have

significant predictive effects in both sexes (*P* = 0.039 in men, *P* = 0.032 in women). Given that these relationships existed when we analyzed the entire sample as well as when we analyzed the sample by sex, we next aimed to characterize the potential mediators underlying these interactions.

Test of the Moderating Effect of Opioid Prescription on the Relationship between Pain Intensity and Pain Catastrophizing

Given the existence of a relationship between opioid prescription, pain intensity, and pain catastrophizing, we examined potential mediators of these linear associations. As seen in table 5, the direct effect of pain intensity on opioid prescription was greater than the mediated effect of PCS on the relationship between pain intensity and opioid prescription in both sexes. The nonsignificant *P* values indicated that PCS did not mediate, or explain, the relationship between

Table 5. Pain Intensity and Opioid Prescription by Sex and the Mediation Effect of PCS

	Total Effect	Direct Effect of Pain Intensity on Opioid Prescription	PCS Mediation of the Effect of Pain Intensity on Opioid Prescription	Proportion	P Value for Mediated Effect
Full sample	0.164	0.151	0.014	0.08	0.11
Men	0.218	0.217	0.001	0.005	0.95
Women	0.136	0.119	0.017	0.120	0.09

This analysis involved using pain intensity and PCS scores as predictors of opioid prescription. PCS scores were tested as a statistical mediator of the relationship between pain intensity and opioid prescription. Proportion column refers to proportion of direct effect of pain intensity on opioid prescription accounted for by PCS scores.

PCS = Pain Catastrophizing Scale.

opioid prescription and pain intensity evidenced in the linear modeling analysis. This lack of mediation suggested that pain catastrophizing had a moderating effect on the relationship between pain intensity and opioid prescription. In other words, pain catastrophizing strengthened, rather than explained, their linear relationship. Furthermore, mediation analysis also revealed that sex serves as a moderating variable.

To further elucidate potential moderators of the relationship between sex, opioid prescription, pain intensity, and pain catastrophizing, we used general additive modeling to visualize any complex nonlinear relationships. Additive modeling P values revealed significant effects of opioid prescription on the relationship between pain intensity and catastrophizing in the entire sample ($P < 0.001$). However, a nonlinear model as provided by general additive modeling did not fit the interactions between pain intensity, pain catastrophizing, and opioid prescription in women ($P = 0.005$) as well as it did in men ($P < 0.001$). This reveals that the relationship between these variables may be different for men and women patients, leading to the conclusion that sex moderates the relationship between pain intensity, catastrophizing, and opioid prescription.

Figure 2 (green represents lower density of patients with opioid prescription, and red represents high density of patients with opioid prescription) shows that, as expected, in both men and women, low pain intensity and pain catastrophizing were associated with patients without opioid prescription. However, moving past the lower left-hand corner of both graphs in figure 2, the graphs shows that in men, the greatest density of patients with opioid prescription is found in those with high pain intensity and low pain catastrophizing. Paradoxically, men with high pain intensities and high

catastrophizing scores did *not* seem to have higher frequencies of opioid prescription. However, for women, opioid prescription was associated with both high pain intensity as well as high pain catastrophizing. Overall, there was a strong nonlinear relationship between pain intensity, pain catastrophizing, and opioid prescription in men, as seen by the horizontal gradations of increasing opioid prescription on increases in pain intensity. Given the increased density of women with opioid prescription who have high pain intensities and high levels of catastrophizing, there seems to be a more nuanced relationship between pain, pain catastrophizing, and opioid prescription in this group. Figures 3 and 4 represent these sex-dependent relationships.

Figure 3 reveals that men have a relatively flat association between opioid prescription and pain intensity, and the data for women suggest an inflection point on the numeric rating scale that emerges above pain intensity of 4 and persists until roughly pain intensity ratings of 7.

Figure 4 reveals that opioid prescription by sex diverges above scores of 10 on the PCS and similarly persists until the severe range of catastrophizing is reached, at which point the associations align for both sexes. Combined, figures 3 and 4 suggest that sensory and psychologic experience appear to associate more strongly with opioid prescription at lower levels (intensities) for women than for men.

Finally, to address concerns about model flexibility and cross-validation of our findings, we performed a bootstrapping on the general additive model fitting and the statistical inference using 500 replicates. All of the smoothed term P values in the bootstrap replicates were less than 0.05. In fact, the largest (least significant) P value was 0.0001. This suggests that the nonlinearity effect we described is highly robust.

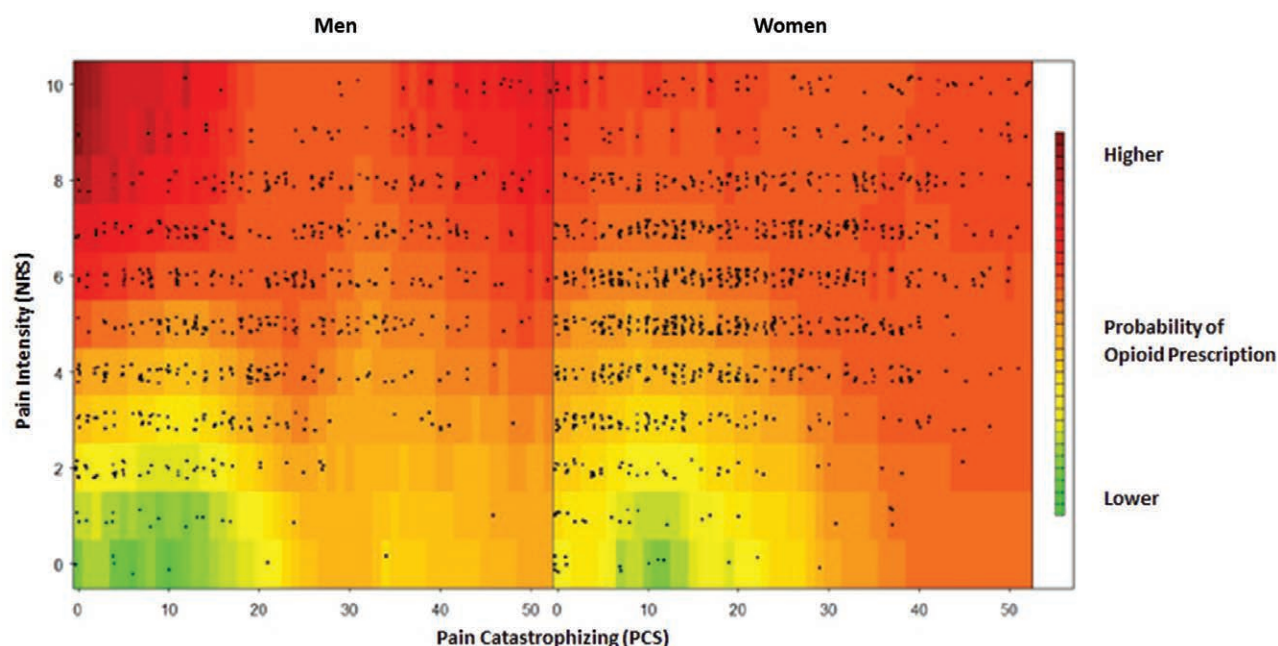


Fig. 2. Nonlinear relationship between pain intensity and pain catastrophizing, by sex. Points represent individual patients. NRS = numeric rating scale; PCS = Pain Catastrophizing Scale.

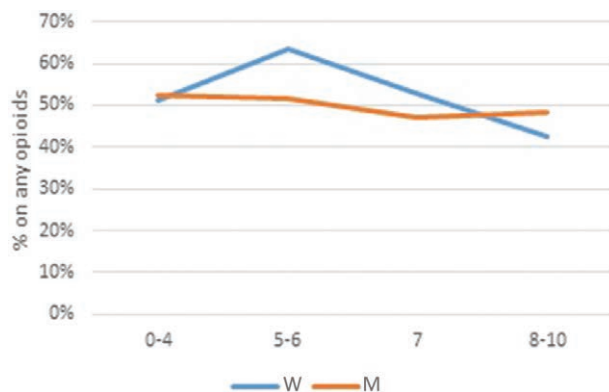


Fig. 3. Relationship between opioid prescription (Y-axis; % of sample prescribed any opioids) and pain intensity quartile (X-axis; 0 to 10 pain intensity ratings) by sex. M = men; W = women.

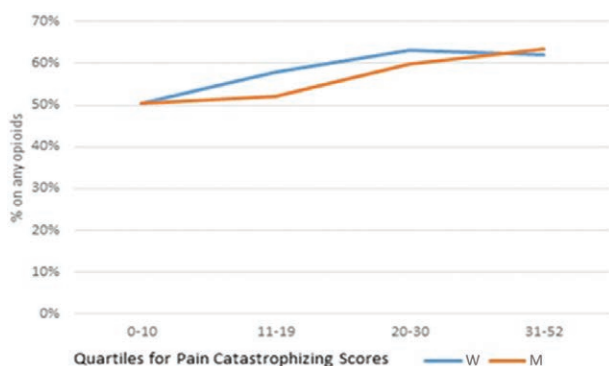


Fig. 4. Relationship between opioid prescription (Y-axis; % of sample prescribed any opioids) and quartiles of Pain Catastrophizing Scale scores (X-axis) by sex. M = men; W = women.

Discussion

In this study, we characterized the relationship between opioid prescription, pain intensity, and pain catastrophizing in 1,794 patients with chronic pain seeking initial medical evaluation at a multidisciplinary pain treatment center. Univariate analysis revealed that active opioid prescription was significantly associated with greater pain catastrophizing and higher pain intensity. Linear modeling revealed that (1) pain intensity was directly and significantly related to opioid prescription; (2) a significant interaction effect was found for pain catastrophizing and pain intensity on opioid prescription; and (3) this interaction effect remained significant yet differed by sex. Mediation analysis showed no mediating effects of pain catastrophizing or sex. In turn, catastrophizing and sex demonstrated moderating roles in the relationship between pain intensity and opioid prescription. Furthermore, additive modeling showed nuanced nonlinear relationships between the aforementioned variables in both men and women. Pain catastrophizing had greater association with opioid prescription in women. Although we could not make causal inferences due to the cross-sectional study design and opioid prescription being an outcome of previous

clinic visit, nor would we be able to make these inferences had we identified any significant mediated effects in our analyses, our data reveal sex-based differences in the relationship between pain intensity, pain catastrophizing, and opioid prescription, highlighting the impact that catastrophizing may have in women with chronic pain.

Pain catastrophizing relates directly to pain intensity and serves to undermine pain treatment efficacy.³⁸ Similarly, pain intensity directly relates to opioid use.^{39–41} Here, we show that opioid prescription is associated with greater pain catastrophizing. Notably, our univariate analysis of this large sample showed no significant sex differences in pain catastrophizing or opioid prescription. Previous studies have shown inconsistent relationships between sex and pain catastrophizing,^{42–44} making it unclear whether these discrepancies are a result of smaller sample sizes.³⁰ Consistent with previous work, we found greater average pain intensity for women.⁴⁵

The sex- and opioid status–based differences in pain and catastrophizing called for linear modeling to elucidate any underlying relationships between these variables. Our results showed that pain intensity was highly associated with the likelihood of having prescription opioids. However, adding pain catastrophizing and an interaction between catastrophizing and pain intensity demonstrated the strongest linear association with opioid prescription. Mediation analysis suggested that pain catastrophizing and sex served as moderating variables, strengthening the existing relationship between pain intensity and opioid prescription.

In addition to showing the moderating characteristics of pain catastrophizing and sex, we used additive modeling to show the impact of pain catastrophizing on opioid prescription by sex. For men, the greatest density of individuals with opioid prescription was colocated with lower pain catastrophizing and higher pain intensity. In women, however, the greatest density of those with opioid prescription was colocated with moderate-to-high pain intensities and pain catastrophizing levels, suggesting that pain catastrophizing has a stronger association with opioid prescription status. Given that opioids were prescribed before the study, causal inferences are impossible, but future studies may use prospective designs to confirm that these associations hold at the point of opioid prescription.

Our findings suggest that even relatively low levels of negative cognitive and emotional responses to pain may have a greater impact on opioid prescribing in women. Women may be more likely to influence provider prescribing patterns through behavioral cues during the medical visit; previous research has suggested women may engage in pain behavior for extended periods of time⁴⁶ and may appraise their pain as more threatening than men.⁴⁷ Although treatment for catastrophizing is important for both sexes, the higher additive modeling *P* values found for women suggests that risks are occurring at lower levels of catastrophizing for women than for men.

Additional studies are needed to replicate the associations we discovered. However, if confirmed, these findings would hold specific clinical relevance. Often, a pain catastrophizing scale score is considered clinically meaningful if it is near or more than 30.²⁷ However, given the moderating effect of pain catastrophizing and its possible predictive value for opioid prescription, treatments for pain catastrophizing may hold specific therapeutic value for women at levels considered clinically subthreshold for outpatients with chronic pain (e.g., PCS less than 20). Others recently have demonstrated catastrophizing risk inflection points occurring at similarly low levels of catastrophizing for outpatient pain rehabilitation outcomes (PCS greater than 14)⁴⁸ and post-surgical pain (PCS greater than 13),¹⁶ thereby suggesting the need for continued examination of how the field defines threshold for risk and treatment needs. We found no other studies to specifically report subthreshold associations with opioid prescription and sex differences therein.

Strengths and Limitations

Our study design involved single time-point data collection, which allowed for descriptive associations only, with no possibility for causal interpretations. Many of our variables, including about 40% of our opioid use data, were collected directly from medical records. For the 700 patients whose opioid use was collected manually from the electronic medical record, opioid dose was collected. After meticulous data cleaning and the calculation of opioid dose in morphine equivalents, opioid dosing information from the electronic medical records proved to be unreliable. Given that chart review was completed only for initial pain clinic visits, and given that not all physicians asked for nonpain-related medications, the accuracy of prescription and dosing of other medications, such as benzodiazepines, also was unreliable. We therefore structured our study to describe associations with opioid prescription and did not characterize relationships based on opioid dose or other medications.

Due to the deidentified nature of the data extracted from Pain-CHOIR, we were unable to attain the medical record numbers of all patients included in this study. For a third of the sample, we were able to locate medical record numbers by identifying exact data matches between our data set and that of Pain-CHOIR. Despite having only a small proportion of this sample's diagnostic codes, we believe that a comparison of these patients with the distribution of the entire pain clinic population is sufficient in characterizing the population, especially given that we did not use the diagnostic information for any significant analyses.

Despite the use of single time-point data, the electronic and easily accessible nature of the data allowed for the application of novel analytics on a large database, yielding more nuanced characterizations of the population. In addition to mediation analysis, we used highly flexible linear and nonlinear models, which together presented a novel battery of rigorous statistical tests that allowed for optimal characterization of the data.

Future Directions

Although our results are informative, the nature of some variables merits closer investigation. Given the limitation of using opioid prescription as a binary variable for measuring opioid use, future investigations should include opioid dose and possibly more reliable methods of opioid consumption quantification, such as a urine screen. Further investigation by pain condition or of other drugs that have shown relevance to opioid use, such as benzodiazepines, also is warranted.

Prospective, longitudinal studies also are needed to characterize patients at the point of opioid prescription. Moreover, despite our use of several important covariates, our analysis was not exhaustive. Consequently, there may be other variables (e.g., pain sensitivity, pain-related disability, and pain interference) that are relevant to pain intensity, pain catastrophizing, and opioid use.

As a learning health care system,^{25,26} Pain-CHOIR allowed for an inclusive range of pathology and patient characteristics that are not typical of most research studies or even registries that tend to be disease-specific. As such, it necessarily included wide ranges of patient characteristics and, more importantly, complex correlative relationships across the entire spectra of pathology. Although traditional linear model-based methods are valid and appropriate in studies with traditional data ascertainment, in all-comer learning health systems such as Pain-CHOIR, models with reduced restrictions about intervariable relationships should be more methodologically appropriate. In this work, we demonstrated that flexible models, such as additive models, can elucidate nonlinear relationships between several variables that are core to our field. In fact, these models suggest additional behavior-changing threshold effects that would be obscured in traditional methods. Although these methods are technically not new and have been in use in other fields of science, they have not seen wide use in the field of pain. Again, it is the all-encompassing nature of Pain-CHOIR that enables methods like this. Reciprocally, Pain-CHOIR and its clinical and research values are enabled by such methods.

Conclusions

This study used a large dataset of patients visiting a tertiary outpatient pain clinic. We elucidated relationships between sex, pain catastrophizing, pain intensity, and opioid prescription. Using an advanced analytic approach, we found a significant relationship between pain intensity and opioid prescription and found that this relationship was significantly stronger in women, especially those with high levels of pain catastrophizing. Despite similar levels of catastrophizing and opioid prescription among men and women, pain catastrophizing appears to have a stronger relationship with opioid status for women, calling for future studies to investigate lower pain catastrophizing thresholds for women and the potential impacts for reducing opioid prescription. These

results emphasize the importance of considering both obvious medical factors such as pain intensity and psychologic and demographic differences that may be salient predictors of the use of prescription opioids.

Research Support

The authors acknowledge funding support from the National Institutes of Health (NIH, Bethesda, Maryland), the National Center for Complementary and Integrative Health (NCCIH, Bethesda, Maryland) grant Nos. P01AT006651 (to Dr. Mackey) and P01AT006651S1 (to Drs. Mackey and Darnall); NCCIH grant No. R01 AT008561-01A1 (to Drs. Darnall and Mackey); NIH National Institute on Drug Abuse (NIDA, Bethesda, Maryland) grant Nos. K24DA029262 (to Dr. Mackey) and 3T32DA035165-02S1 (to Dr. Sturgeon); the NIH Pain Consortium grant No. HH-SN271201200728P (to Dr. Mackey); and from the Chris Redlich Pain Research Endowment (to Dr. Mackey).

Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Darnall: 1070 Arastradero, Suite 200, MC 5596, Palo Alto, California 94304-1336. bdarnall@stanford.edu. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

References

1. Tsang A, Von Korff M, Lee S, Alonso J, Karam E, Angermeyer MC, Borges GL, Bromet EJ, Demyttenaere K, de Girolamo G, de Graaf R, Gureje O, Lepine JP, Haro JM, Levinson D, Oakley Browne MA, Posada-Villa J, Seedat S, Watanabe M: Common chronic pain conditions in developed and developing countries: Gender and age differences and comorbidity with depression-anxiety disorders. *J Pain* 2008; 9:883-91
2. IOM (Institute of Medicine) Committee on Advancing Pain Research, Care, and Education: *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. Washington, DC, National Academies Press, 2011
3. Keefe FJ, Brown GK, Wallston KA, Caldwell DS: Coping with rheumatoid arthritis pain: Catastrophizing as a maladaptive strategy. *Pain* 1989; 37:51-6
4. Rosenstiel AK, Keefe FJ: The use of coping strategies in chronic low back pain patients: Relationship to patient characteristics and current adjustment. *Pain* 1983; 17:33-44
5. Seminowicz DA, Davis KD: Cortical responses to pain in healthy individuals depends on pain catastrophizing. *Pain* 2006; 120:297-306
6. Gracely RH, Geisser ME, Giesecke T, Grant MA, Petzke F, Williams DA, Clauw DJ: Pain catastrophizing and neural responses to pain among persons with fibromyalgia. *Brain* 2004; 127(Pt 4):835-43
7. Severeijns R, Vlaeyen JW, van den Hout MA, Weber WE: Pain catastrophizing predicts pain intensity, disability, and psychological distress independent of the level of physical impairment. *Clin J Pain* 2001; 17:165-72
8. Sullivan MJ, Lynch ME, Clark AJ: Dimensions of catastrophic thinking associated with pain experience and disability in patients with neuropathic pain conditions. *Pain* 2005; 113:310-5
9. Sullivan MJ, Rodgers WM, Kirsch I: Catastrophizing, depression and expectancies for pain and emotional distress. *Pain* 2001; 91:147-54
10. Martel MO, Wasan AD, Jamison RN, Edwards RR: Catastrophic thinking and increased risk for prescription opioid misuse in patients with chronic pain. *Drug Alcohol Depend* 2013; 132:335-41
11. Morasco BJ, Turk DC, Donovan DM, Dobscha SK: Risk for prescription opioid misuse among patients with a history of substance use disorder. *Drug Alcohol Depend* 2013; 127:193-9
12. Carroll I, Barelka P, Wang CK, Wang BM, Gillespie MJ, McCue R, Younger JW, Trafton J, Humphreys K, Goodman SB, Dirbas F, Whyte RI, Donington JS, Cannon WB, Mackey SC: A pilot cohort study of the determinants of longitudinal opioid use after surgery. *Anesth Analg* 2012; 115:694-702
13. Hah JM, Mackey S, Barelka PL, Wang CK, Wang BM, Gillespie MJ, McCue R, Younger JW, Trafton J, Humphreys K, Goodman SB, Dirbas FM, Schmidt PC, Carroll IR: Self-loathing aspects of depression reduce postoperative opioid cessation rate. *Pain Med* 2014; 15:954-64
14. Papaioannou M, Skapinakis P, Damigos D, Mavreas V, Broumas G, Palgimesi A: The role of catastrophizing in the prediction of postoperative pain. *Pain Med* 2009; 10:1452-9
15. Janda AM, As-Sanie S, Rajala B, Tsodikov A, Moser SE, Clauw DJ, Brummett CM: Fibromyalgia survey criteria are associated with increased postoperative opioid consumption in women undergoing hysterectomy. *ANESTHESIOLOGY* 2015; 122:1103-11
16. Pavlin DJ, Sullivan MJ, Freund PR, Roesen K: Catastrophizing: A risk factor for postsurgical pain. *Clin J Pain* 2005; 21:83-90
17. Banka TR, Ruel A, Fields K, YaDeau J, Westrich G: Preoperative predictors of postoperative opioid usage, pain scores, and referral to a pain management service in total knee arthroplasty. *HSS J* 2015; 11:71-5
18. Helmerhorst GT, Vranceanu AM, Vrahas M, Smith M, Ring D: Risk factors for continued opioid use one to two months after surgery for musculoskeletal trauma. *J Bone Joint Surg Am* 2014; 96:495-9
19. Martel MO, Jamison RN, Wasan AD, Edwards RR: The association between catastrophizing and craving in patients with chronic pain prescribed opioid therapy: A preliminary analysis. *Pain Med* 2014; 15:1757-64
20. Lovejoy TI, Dobscha SK, Turk DC, Weimer MB, Morasco BJ: Correlates of prescription opioid therapy in Veterans with chronic pain and history of substance use disorder. *J Rehabil Res Dev* 2016; 53:25-36
21. Arteta J, Cobos B, Hu Y, Jordan K, Howard K: Evaluation of how depression and anxiety mediate the relationship between pain catastrophizing and prescription opioid misuse in a chronic pain population. *Pain Med* 2016; 17:295-303
22. Sullivan MD, Edlund MJ, Steffek D, Unützer J: Regular use of prescribed opioids: Association with common psychiatric disorders. *Pain* 2005; 119:95-103
23. Campbell CM, McCauley L, Bounds SC, Mathur VA, Conn L, Simango M, Edwards RR, Fontaine KR: Changes in pain catastrophizing predict later changes in fibromyalgia clinical and experimental pain report: Cross-lagged panel analyses of dispositional and situational catastrophizing. *Arthritis Res Ther* 2012; 14:R231
24. Granot M, Ferber SG: The roles of pain catastrophizing and anxiety in the prediction of postoperative pain intensity: A prospective study. *Clin J Pain* 2005; 21:439-45
25. Kao M, Weber S, Cook K, Olson G, Pacht T, Darnall B, Weber S, Mackey S: Stanford-NIH Pain Registry: Open source platform for large-scale longitudinal assessment and tracking of modern patient-reported outcomes. *J Pain* 2014; 15: S40
26. Mackey S, Kao MC, Cook K, Olson G, Pacht T, Darnall B, Weber SC: Collaborative Health Outcomes Information Registry (CHOIR): Open source platform for large-scale clinical outcomes measurement to support learning healthcare systems. Poster presented at PAINWeek 2014, September 2-6, 2014; Las Vegas, Nevada

27. Sullivan MJ, Bishop SR, Pivik J: The pain catastrophizing scale: Development and validation. *Psychol Assess* 1995; 7: 524–32
28. Cella D, Riley W, Stone A, Rothrock N, Reeve B, Yount S, Amtmann D, Bode R, Buysse D, Choi S, Cook K, Devellis R, DeWalt D, Fries JF, Gershon R, Hahn EA, Lai JS, Pilkonis P, Revicki D, Rose M, Weinfurt K, Hays R; PROMIS Cooperative Group: The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005–2008. *J Clin Epidemiol* 2010; 63:1179–94
29. Van Damme S, Crombez G, Bijttebier P, Goubert L, Van Houdenhove B: A confirmatory factor analysis of the Pain Catastrophizing Scale: Invariant factor structure across clinical and non-clinical populations. *Pain* 2002; 96:319–24
30. Osman A, Barrios FX, Gutierrez PM, Kopper BA, Merrifield T, Grittmann L: The Pain Catastrophizing Scale: Further psychometric evaluation with adult samples. *J Behav Med* 2000; 23:351–65
31. Osman A, Barrios FX, Kopper BA, Hauptmann W, Jones J, O'Neill E: Factor structure, reliability, and validity of the Pain Catastrophizing Scale. *J Behav Med* 1997; 20:589–605
32. Choi SW, Reise SP, Pilkonis PA, Hays RD, Cella D: Efficiency of static and computer adaptive short forms compared to full-length measures of depressive symptoms. *Qual Life Res* 2010; 19:125–36
33. Edelen MO, Reeve BB: Applying item response theory (IRT) modeling to questionnaire development, evaluation, and refinement. *Qual Life Res* 2007; 16 Suppl 1:5–18
34. Fries JF, Bruce B, Cella D: The promise of PROMIS: Using item response theory to improve assessment of patient-reported outcomes. *Clin Exp Rheumatol* 2005; 23(5 suppl 39):S53–7
35. Pilkonis PA, Choi SW, Reise SP, Stover AM, Riley WT, Cella D; PROMIS Cooperative Group: Item banks for measuring emotional distress from the Patient-Reported Outcomes Measurement Information System (PROMIS®): Depression, anxiety, and anger. *Assessment* 2011; 18:263–83
36. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM: Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001; 94:149–58
37. Imai K, Keele L, Tingley D: A general approach to causal mediation analysis. *Psychol Methods* 2010; 15:309–34
38. Forsythe ME, Dunbar MJ, Hennigar AW, Sullivan MJ, Gross M: Prospective relation between catastrophizing and residual pain following knee arthroplasty: Two-year follow-up. *Pain Res Manag* 2008; 13:335–41
39. Eriksen J, Sjøgren P, Bruera E, Ekholm O, Rasmussen NK: Critical issues on opioids in chronic non-cancer pain: An epidemiological study. *Pain* 2006; 125:172–9
40. Ciccone DS, Just N, Bandilla EB, Reimer E, Ilbeigi MS, Wu W: Psychological correlates of opioid use in patients with chronic nonmalignant pain: A preliminary test of the downhill spiral hypothesis. *J Pain Symptom Manage* 2000; 20:180–92
41. Hudson TJ, Edlund MJ, Steffick DE, Tripathi SP, Sullivan MD: Epidemiology of regular prescribed opioid use: Results from a national, population-based survey. *J Pain Symptom Manage* 2008; 36:280–8
42. Campbell CI, Weisner C, Leresche L, Ray GT, Saunders K, Sullivan MD, Banta-Green CJ, Merrill JO, Silverberg MJ, Boudreau D, Satre DD, Von Korff M: Age and gender trends in long-term opioid analgesic use for noncancer pain. *Am J Public Health* 2010; 100:2541–7
43. Parsells Kelly J, Cook SF, Kaufman DW, Anderson T, Rosenberg L, Mitchell AA: Prevalence and characteristics of opioid use in the US adult population. *Pain* 2008; 138:507–13
44. Leung L: Pain catastrophizing: An updated review. *Indian J Psychol Med* 2012; 34:204–17
45. Unruh AM: Gender variations in clinical pain experience. *Pain* 1996; 65:123–67
46. Sullivan M, Tripp DA, Santor D: Gender differences in pain and pain behavior: The role of catastrophizing. *Cog Ther Res* 2000; 24: 121–34
47. Unruh AM, Ritchie J, Merskey H: Does gender affect appraisal of pain and pain coping strategies? *Clin J Pain* 1999; 15:31–40
48. Scott W, Wideman TH, Sullivan MJ: Clinically meaningful scores on pain catastrophizing before and after multidisciplinary rehabilitation: A prospective study of individuals with subacute pain after whiplash injury. *Clin J Pain* 2014; 30:183–90