ORIGINAL ARTICLES

Prospective Investigation of Factors Associated with Prescription Opioid Dose Escalation among Patients in Integrated Health Systems

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BACKGROUND: Prior research has identified factors associated with prescription opioid initiation, but little is known about the prevalence or predictors of dose escalation among patients already prescribed long-term opioid therapy (LTOT).

OBJECTIVE: This was a 2-year prospective cohort study to examine patient and clinician factors associated with opioid dose escalation.

DESIGN: A prospective cohort study. Participants were seen at baseline and every 6 months for a total of 2 years.

PARTICIPANTS: Patients prescribed a stable dose of LTOT for musculoskeletal pain were recruited from two integrated health systems (Kaiser Permanente and the Department of Veterans Affairs, respectively).

MAIN MEASURES: The prescription opioid dose was based on pharmacy records and self-report. Administrative data were gathered on characteristics of the opioid-prescribing clinician and healthcare utilization. Participants completed measures of pain, functioning, and quality of life.

KEY RESULTS: Of enrolled participants ($n = 517$), 19.5% had an opioid dose increase. In multivariate analyses, patient variables associated with dose escalation were lower opioid dose (hazard ratio [HR] = 0.86, 95% confidence interval [CI] = 0.79–0.94, for every 10-mg increase in baseline dose) and greater pain catastrophizing (HR = 1.03, 95% CI = 1.01–1.05). Other variables associated with dose escalation were as follows: receiving medications from a nurse practitioner primary care provider (HR = 2.10, 95% CI =

1.12–3.96) or specialty physician (HR = 3.18, 95% CI = 1.22–8.34), relative to a physician primary care provider, and having undergone surgery within the past 6 months (HR = 1.80, 95% CI = 1.10–2.94). Other variables, including pain intensity, pain disability, or depression, were not associated with dose escalation.

CONCLUSIONS: In this 2-year prospective cohort study, variables associated with opioid dose escalation were lower opioid dose, higher pain catastrophizing, receiving opioids from a medical specialist (rather than primary care clinician) or nurse practitioner, and having recently undergone surgery. Study findings highlight intervention points that may be helpful for reducing the likelihood of future prescription opioid dose escalation.

KEY WORDS: prescription opioid dose escalation; long-term opioid therapy; chronic pain; cohort study.

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INTRODUCTION

Prescription opioids are commonly prescribed for chronic pain. However, there is controversy about their use, as opioids have not demonstrated long-term efficacy^{1, 2} and are associated with adverse effects.^{3–5} Additionally, some adverse effects associated with opioids are dose-dependent, such as overdose, emergency room visits, and death.^{6–8}

There is a recent shift away from long-term opioid therapy (LTOT) for chronic pain. This has resulted in modest decreases in the number of patients prescribed opioids generally,⁹ as well as reductions in high-dose use.¹⁰ However, adverse effects related to prescription opioids, including overdose deaths, remain a concern,^{11, 12} and higher opioid doses play a key role.^{13, 14} Comprehensive data are needed about factors associated with prescription opioid dose escalation. Developing a better understanding of the factors that place

These findings have been presented at the 2018 American Pain Society Annual Meeting.

Public Health Significance Among patients with chronic pain prescribed long-term opioid therapy, 19.5% experienced an increase in prescription opioid dose in the subsequent 2 years. Variables associated with prescription opioid dose escalation include a lower opioid dose, higher scores of pain catastrophizing, receiving opioids from a medical specialist or nurse practitioner rather than a physician primary care provider, and having recently undergone surgery. Study findings highlight intervention points that may be helpful in reducing the likelihood of prescription opioid dose escalation.

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patients at risk of opioid dose escalation could inform intervention targets, which could potentially reduce opioid-related adverse effects and improve pain-related outcomes.

Prior research has identified factors associated with prescription opioid initiation and development of LTOT, which include higher pain intensity and disability, as well as comorbid psychiatric disorders and substance use disorders.^{15, 16} These variables are also associated with high-dose opioid therapy.^{17–20} However, the extent to which these variables are predictive of opioid dose escalation is unclear.

Prescriber characteristics may also be associated with opioid dose escalation. Previous research has identified considerable variability in primary care provider (PCP) opioid-prescribing practices, and medical training as a nurse practitioner or physician assistant (compared with a physician) has been associated with an increased likelihood of opioid medication use.^{21–24}

The purpose of this study was to build on prior research by recruiting patients who were already prescribed LTOT to examine factors associated with subsequent dose escalation. Based on prior research, we hypothesized that higher pain scores, more symptoms of depression and anxiety, and comorbid alcohol and substance use problems would be associated with opioid dose increases. It was also hypothesized that having a physician as a PCP (as opposed to nursing practitioner) would be associated with a decreased likelihood with opioid dose escalation. We also examined psychological factors associated with pain, including pain catastrophizing, self-efficacy for managing pain, and fear-avoidance beliefs. These variables are strongly associated with pain-related outcomes and can be modified with psychological interventions for pain.²⁵

METHODS

Participants

Participants were recruited between December 2013 and October 2015 from Kaiser Permanente Northwest (KPNW) and the VA Portland Health Care System (VAPORHCS). KPNW is an integrated health plan in Oregon and southwest Washington. The VAPORHCS is a Department of Veterans Affairs hospital and treatment system located in Portland, OR.

A description of the recruitment methods and analyses of baseline data have been published.²⁰ Patients were eligible if prescribed a stable dose of LTOT, a current musculoskeletal pain diagnosis, were receiving outpatient care at one of the study institutions and could read and write in English. A stable dose of LTOT was defined as receiving prescription opioids daily for 90+ days²⁶ and having no more than a 10% fluctuation in dose during that time. A change of less than 10% in morphine equivalent dose (MED) was permitted as this allowed for mild changes in dose intended for a short duration (e.g., following a dental procedure) or instances of brief delays in refilling medication. To confirm the opioid dose for each participant, pharmacy data were extracted from the electronic

health record (EHR) to calculate an average daily dose. Each prescription was categorized by type and multiplied by a conversion factor.²⁰ Only outpatient prescriptions were considered. Musculoskeletal pain diagnoses were chosen as an inclusion criterion because they are the most common pain-related diagnoses^{27, 28}; a diagnosis was regarded as present if it was coded in the EHR in the past 12 months.

Participants were excluded if they endorsed pending litigation related to pain, younger than 18 years old, had cancer, enrolled in an opioid-substitution program in the last year, lacked telephone access, or had a current opioid dose greater than 120 mg MED. This was an exclusion criterion because an institutional policy at one site limited opioid doses above a certain threshold, which may have resulted in site-specific differences in the likelihood of escalation. Participants whose only prescriptions were for tramadol or buprenorphine were also excluded.

Procedures

Potential study participants were identified from a review of EHR data. A personalized study invitation was mailed to each patient, which described the study, provided contact information, and included a prepaid postcard to indicate or decline interest. Research staff followed up by phone to provide additional study details, answer questions, and conduct a brief screening.

Research visits were completed at baseline and every 6 months for 2 years. Baseline visits were conducted face-to-face, where procedures were reviewed, and participants signed written informed consent; follow-up visits were completed by phone or in-person (based on participant preference). Participants received a \$50 store gift card for completing the baseline assessment, \$25 for each 6-month follow-up visit, and \$50 for the final research visit. Fig. 1 displays retention data at each study time point. All procedures were reviewed, approved, and monitored by the institutional review boards at the respective institutions.

Measures

A baseline prescription opioid dose was calculated for each participant, which was the average daily MED over the 90 days prior to enrollment.²⁰ Opioid dose escalation was defined as an increase in average daily MED of 15% or more from baseline; this accounts for recommendations to take a personalized approach to prescribing and identifies purposeful efforts to increase total dose. To count as a dose increase, the escalation must have persisted for two or more 28-day prescription periods, which would exclude patients whose dose increase was never intended to be lasting, such as a short-term prescription following a procedure. Although the majority of opioid prescriptions were provided by the two health systems under study, participants were queried at each visit about opioids prescribed from outside these health systems. All self-report data about additional opioids prescribed from a

Figure 1 Participant retention.

non-KPNW or non-VAPORHCS prescriber were added to a participants' total MED.

Demographic characteristics that were assessed include age, gender, race, marital status, employment, socioeconomic status, disability status, and current nicotine use.

The Chronic Pain Grade (CPG), a 7-item self-report measure, was used to assess pain.²⁹ The CPG includes subscales for pain intensity and pain disability.

Symptoms of depression were assessed with the Patient Health Questionnaire (PHQ-8), an 8-item self-report measure.³⁰ The Generalized Anxiety Disorder-7 (GAD-7) scale was used to measure anxiety.³¹

The 3-item Alcohol Use Disorders Identification Test (AUDIT-C) was used to screen for hazardous alcohol use. Male participants with scores ≥ 4 , and females with scores ≥ 3 , were coded as having current hazardous alcohol use.³² The Drug Abuse Screening Test-10 (DAST-10) is a 10-item self-report measure used to assess misuse of illicit substances.³³ A potential substance use disorder was defined as a DAST-10 score ≥ 2 .³⁴

The Fear-Avoidance Beliefs Questionnaire (FABQ) is a 16-item self-report measure assessing how physical activity and work affect pain.³⁵ We administered the 5-item subscale about physical activity. The 13-item Pain Catastrophizing Scale (PCS) was used to assess pain catastrophizing.³⁶ The Pain Self-Efficacy Questionnaire (PSEQ) is a 10-item self-report measure used to assess self-efficacy for managing pain.³⁷

Overall medical comorbidity was measured with the Selim Comorbidity Index, a validated method for assessing medical

comorbidity with administrative data^{38, 39}; scores include an assessment of whether 31 chronic physical and 6 mental health diagnoses have been present in the past year.

Participants rated the frequency of their participation in non-pharmacological interventions for chronic pain. Each person was classified on a scale of 0 (no engagement) to 3 (high level of engagement) on their use of clinician-directed non-pharmacological pain treatments (physical therapy, transcutaneous electrical nerve stimulation, chiropractic treatment, acupuncture, group pain management classes, massage therapy) and self-directed non-pharmacological pain treatments (herbal medicines, weight/strength training, yoga, tai chi, pool exercises/swimming).⁴⁰

Characteristics of the opioid prescriber were gathered from the EHR. Each participant was classified as having one prescriber. For participants who received opioids from more than one prescriber during the study period, the clinician who prescribed the increase in opioid dose was prioritized, followed by the clinician who wrote the largest proportion of prescriptions. Characteristics of the opioid-prescribing clinician that were collected included classification of PCP as a physician, PCP as a nurse practitioner, or physician specialist. Specialists included physicians who did not have a primary care panel and often had specialization in orthopedics, surgery, infectious disease, or other medical specialty services.

Additional healthcare utilization data were extracted from the EHR and examined if each participant experienced any of the following within 6 months prior to each assessment. These include surgery, treatment in a specialty pain clinic, or

participation in physical therapy or with mental health. Data were extracted if a participant had a benzodiazepine prescription at the time of each study visit.⁴¹

Analytic Approach

Participants were categorized based on whether they had a prescription opioid dose increase of 15% or higher from their baseline dose. To compare demographic and clinical factors between groups, chi-square tests were used for categorical variables and *t* tests for continuous variables.

Multivariable cox regression models were used to evaluate risk factors of dose escalation. Covariates included baseline assessment of site (KPNW versus VA), age, gender, race, nicotine use, and primary opioid prescriber. Other clinical covariates were included as time-varying covariates to account for changes and assessed every 6 months; clinical covariates included MED, pain intensity, pain disability, depression, anxiety, fear-avoidance beliefs, pain catastrophizing, pain self-efficacy, medical comorbidity, alcohol use, substance use, healthcare utilization (recent surgery, mental health visit, physical therapy visit; participation in non-pharmacological interventions for chronic pain), and benzodiazepine prescription. Because patients were clustered within prescribers, standard errors were calculated using robust variance estimation to account for the intra-cluster correlation. Survival time was defined as months from enrollment to the date of dose escalation, the end of the 2-year study period, or the date of voluntary withdrawal or death (whichever came earlier). Data analyses were conducted using SAS®9.4.⁴²

RESULTS

Of the 517 participants who enrolled, 19.5% (*n* = 101) had an increase of 15% or more from their baseline dose during the 2-year study period. The average daily opioid dose at baseline for the entire sample was 36.2 mg MED (*SD* = 27.8). Of the participants with an increase in opioid dose, the range of increases was 2–112 mg MED (6–600% above baseline). The mean dose change, for those who had an increase, was 22.7 mg MED (*SD* = 23.4), which was 104% (*SD* = 105) higher than baseline. The 25th and 75th percentiles were 6 mg MED and 30 mg MED, respectively (33% and 150% higher than baseline).

A comparison of participant demographic characteristics and prescriber type between groups at baseline is presented in Table 1. The only difference in demographic characteristics between groups was age, as participants who had a dose increase were older at baseline (60.9 years versus 59.0 years). Forty-seven percent of the sample was female and 82.8% endorsed white race/ethnicity. There was a difference in rate of dose escalation based on clinician type. Of patients whose PCP was a physician, 17.7% had a dose increase, whereas patients who had a nurse practitioner as PCP, a specialist, or someone with an unknown background were more likely to

Table 1 Comparison of Participant Demographic Characteristics and Prescriber Type at Baseline

	No dose increase (<i>n</i> = 416)	Dose increase group (<i>n</i> = 101)	<i>p</i> value
Age, M (<i>SD</i>)	59.0 (11.5)	60.9 (10.5)	0.046
Female gender	47.1%	48.5%	0.801
White race/ethnicity	81.7%	87.1%	0.197
Education			0.620
High School or less	83.0%	17.0%	
Some college or technical school	80.6%	19.4%	
College graduate or more	78.0%	22.1%	
Marital status			0.105
Single	65.6%	34.4%	
Married/living with partner	80.3%	19.7%	
Divorced/separated	84.6%	15.4%	
Widowed	78.7%	21.3%	
Employment status			0.413
Working	80.5%	19.6%	
Unemployed	75.8%	24.2%	
Retired	78.1%	21.9%	
Disabled	85.2%	14.8%	
Household income			0.420
< \$30,000	77.7%	22.3%	
\$30,000–\$69,999	82.9%	17.1%	
\$70,000 or more	79.2%	20.8%	
Prescriber type			0.026
Physician primary care provider	82.3%	17.7%	
Nurse practitioner primary care provider	66.7%	33.3%	
Physician specialist	60.0%	40.0%	
Other/unknown	77.8%	22.2%	

Note. Scores reported here represent mean (standard deviation) or proportion of the sample

have a dose increase (33.3%, 40.0%, and 22.2%, respectively; *p* = 0.026).

Comparing clinical characteristics at baseline of participants who subsequently had a dose increase, versus those that did not, identified that participants who experienced an opioid dose increase had lower opioid doses at baseline, compared with those who did not have an opioid dose increase (27.1 mg versus 38.5 mg, *p* < 0.001). There were no significant differences between groups on baseline scores of pain intensity, disability, depression, anxiety, or symptoms of alcohol or substance use (all *p* values > 0.05). Participants who had a dose increase had higher baseline scores of pain catastrophizing (17.9 versus 14.5, *p* = 0.002) and higher medical comorbidity (4.9 versus 4.3, *p* = 0.028) than participants who did not have a dose increase (data not shown). Table 2 includes a summary of opioid dose data and clinical variables based on groups across each of the research visits.

In the multivariate cox proportional hazards model, the variables significantly associated with dose escalation were prescription opioid dose, pain catastrophizing, type of opioid-prescribing clinician, and having undergone surgery in the past 6 months (Table 3). With every 10 mg higher MED, the likelihood of dose escalation decreased by 14% (HR = 0.86, 95% CI = 0.79–0.94). With every 1-unit increase in pain catastrophizing score, the risk of dose escalation rose by 3%

Table 2 Summary of Clinical Scores at Each Time Point

	No dose increase (n = 517)	No dose increase (n = 446)	Dose increase group (n = 46)	No dose increase (n = 397)	Dose increase group (n = 77)	No dose increase (n = 366)	Dose increase group (n = 85)	No dose increase (n = 350)	Dose increase group (n = 91)
Prescription opioid dose in MED	36.3 (27.8)	35.9 (28.5)	53.2† (40.9)	33.6 (29.0)	41.4 (38.9)	32.9 (32.8)	35.9 (32.9)	30.4 (28.8)	33.5 (28.6)
Pain intensity	62.3 (14.2)	61.9 (15.3)	62.3 (14.5)	61.3 (15.9)	59.1 (15.9)	61.3 (16.3)	61.0 (16.0)	60.3 (16.4)	61.2 (16.0)
Pain disability	50.7 (24.8)	46.5 (27.0)	50.4 (27.0)	46.6 (26.7)	50.2 (27.5)	46.3 (27.2)	52.4 (27.8)	46.5 (26.8)	49.7 (29.4)
Depression severity	9.5 (5.5)	8.7 (5.6)	9.4 (5.7)	8.6 (5.6)	8.3 (5.3)	8.3 (5.6)	8.6 (5.5)	7.9 (5.4)	8.9 (5.4)
Anxiety severity	6.8 (5.5)	6.3 (5.6)	6.5 (5.8)	5.9 (5.4)	6.2 (5.5)	5.9 (5.6)	6.3 (5.5)	5.2 (5.0)	6.4 (5.3)*
Medical comorbidity	4.4 (2.7)	3.9 (2.6)	5.3 (3.4)†	3.8 (2.8)	4.5 (2.9)*	3.8 (2.9)	4.7 (3.2)†	3.9 (2.9)	4.3 (2.9)
Hazardous alcohol use	15.1%	12.8%	15.2%	11.6%	16.9%	12.4%	15.3%	11.5%	17.6%
Possible SUD	13.2%	10.7%	10.9%	7.8%	9.1%	4.9%	8.2%	4.6%	5.5%
Pain catastrophizing	15.2 (11.5)	12.5 (11.0)	16.0* (11.9)	12.0 (11.1)	14.4 (11.8)	12.0 (11.5)	13.4 (12.5)	10.6 (10.8)	14.0 (13.0)*
Fear avoidance	17.6 (6.7)	17.4 (6.7)	16.7 (7.3)	16.7 (7.4)	18.2 (7.4)	16.6 (7.6)	18.2 (7.0)	16.4 (7.4)	18.1 (7.8)
Pain self-efficacy	35.6 (13.0)	35.3 (13.1)	33.2 (15.4)	35.9 (13.3)	33.6 (14.3)	35.9 (13.7)	34.2 (14.1)	36.7 (13.6)	34.3 (14.1) *
Opioid-prescribing clinician									
PC—Physician	86.5%	87.9%	78.3%	87.8%	81.8%	87.9%	78.8%	88.5%	78.0%
PC—Nurse practitioner	8.1%	7.4%	17.4%	7.8%	11.7%	8.2%	11.8%	7.5%	13.2%
Physician specialist	1.9%	2.0%	2.2%	2.0%	2.6%	1.6%	4.7%	1.7%	4.4%
Unknown	3.5%	2.7%	2.2%	2.3%	3.9%	2.2%	4.7% *	2.3%	4.4% *
Clinician-directed non-pharmacological pain treatments									
No engagement	41.6%	42.3%	34.8%	46.8%	37.7%	45.1%	35.3%	47.1%	34.1%
Low engagement	34.2%	32.2%	28.3%	27.8%	33.8%	32.4%	27.1%	27.6%	42.9%
Moderate engagement	17.0%	18.8%	23.9%	19.2%	19.5%	15.4%	24.7%	17.5%	16.5%
High level of engagement	7.2%	6.7%	13.0%	6.1%	9.1%	7.1%	12.9%	7.8%	6.6%
Self-directed non-pharmacological pain treatments									
No engagement	55.1%	58.4%	43.5%	52.4%	51.9%	54.9%	57.6%	56.9%	53.8%
Low engagement	21.1%	22.6%	26.1%	25.3%	23.4%	23.4%	15.3%	20.7%	14.3%
Moderate engagement	14.1%	11.2%	21.7%	12.9%	15.6%	11.0%	17.6%	12.6%	25.3%
High level of engagement	9.7%	7.8%	8.7%	9.4%	9.1%	10.7%	9.4%	9.8%	6.6%
Surgery	18.2%	9.2%	28.3%‡	9.9%	18.2%*	9.3%	17.6%*	8.0%	13.2%
Specialty pain clinic visit	8.3%	5.6%	15.2%*	4.1%	9.1%	4.1%	8.2%	4.3%	11.0%*
Mental health visit	26.7%	19.7%	26.1%	17.7%	15.6%	17.3%	21.1%	15.2%	20.9%
Physical therapy visit	25.0%	15.7%	19.6%	12.7%	20.8%	11.0%	22.4%†	14.4%	15.4%
Concurrent benzodiazepine prescription	24.8%	19.5%	19.6%	19.5%	19.5%	17.3%	14.1%	15.2%	13.0%

Note. Scores reported here represent mean (standard deviation) or proportion of the sample. Dose increase status is time-dependent, meaning before a person had a dose increase, this person was considered as no dose increase; on and after the day of dose increase, this person was switched to the dose increase group. Analyses compared groups on each clinical variable at each time point; statistically significant results reflect group differences at the identified follow-up time

* $p < 0.05$

† $p < 0.01$

‡ $p < 0.001$

Although $n = 101$ experienced a dose increase, there are $n = 91$ reported at the 24-month follow-up; these differences in sample size are due to attrition PC, primary care

Pain intensity and pain disability were assessed with the chronic pain grade; scores range from 0 to 100. Depression severity was assessed with the PHQ-8; scores range from 8 to 32. Anxiety severity was assessed with the GAD-7; scores range from 7 to 28. Medical comorbidity data were measured with the Selim Comorbidity Index; scores range from 0 to 37, with higher scores indicating greater medical comorbidity. Hazardous alcohol use and possible SUD are dichotomous variables, and the numbers reported reflect the proportion who met the criteria for each; alcohol was assessed with the AUDIT-C and SUD was assessed with the DAST-10. Pain catastrophizing was assessed with the PCS; scores range from 0 to 52, with higher scores reflecting more severe catastrophizing. Fear avoidance was assessed with the FABQ; we administered the 5-item subscale about physical activity. Scores range from 5 to 35; higher scores indicate greater fear avoidance. Pain self-efficacy was assessed with the PSEQ. Scores range from 0 to 60; higher scores indicate greater self-efficacy for managing pain. Engagement in non-pharmacological interventions for chronic pain was based on self-report, which resulted in classifying each participant into one of four categories (no engagement, low engagement, moderate engagement, or high engagement); each participant was classified on their self-reported participation in both clinician-directed and self-directed activities. Healthcare utilization variables were collected from the EHR and identified if the participant had a visit any time in the 6 months prior to the completed research appointment

Table 3 Multivariate Cox Regression Analysis Examining Variables Associated with Prescription Opioid Dose Escalation (n = 511)

Variable	Estimate	Standard error	Hazard ratio	95% confidence interval
Site	− 0.47	0.35	0.62	0.31–1.24
Age	0.01	0.01	1.01	0.99–1.03
Female gender	− 0.24	0.23	0.80	0.50–1.04
White race/ethnicity	− 0.39	0.29	1.48	0.84–2.63
Prescription opioid dose (per 10-mg increments)	− 0.15	0.05	0.86*	0.79–0.94
Pain intensity	− 0.01	0.01	1.00	0.98–1.01
Pain disability	0.01	0.01	1.01	0.99–1.02
Medical comorbidity	0.04	0.04	1.04	0.96–1.12
Depression severity	− 0.02	0.04	0.98	0.91–1.04
Anxiety	− 0.01	0.03	0.98	0.93–1.06
Hazardous alcohol use	0.04	0.06	1.04	0.91–1.18
Substance use	− 0.09	0.12	0.92	0.73–1.15
Nicotine user	− 0.06	0.27	0.94	0.55–1.60
Fear avoidance	< − 0.01	0.02	0.99	0.97–1.03
Pain catastrophizing	0.03	0.01	1.03*	1.01–1.05
Pain self-efficacy	− 0.02	0.01	0.98	0.97–1.00
Nurse practitioner primary care provider	0.74	0.32	2.10*	1.12–3.96
Physician specialist	1.15	0.50	3.18*	1.22–8.34
Other/unknown opioid-prescribing clinician	0.45	0.64	1.54	0.43–5.46
Clinician-directed engagement in non-pharmacological pain interventions				
Low engagement	− 0.09	0.25	0.92	0.56–1.51
Moderate engagement	0.32	0.31	1.38	0.75–2.55
High level of engagement	0.12	0.42	1.13	0.49–2.57
Self-directed engagement in non-pharmacological pain interventions				
Low engagement	0.03	0.27	1.03	0.61–1.74
Moderate engagement	− 0.24	0.38	0.79	0.37–1.67
High level of engagement	0.12	0.42	1.24	0.63–2.43
Surgery	0.59	0.25	1.80*	1.10–2.94
Specialty pain clinic	− 0.13	0.38	0.88	0.42–1.85
Mental health	− 0.18	0.30	0.84	0.47–1.51
Physical therapy	0.33	0.26	1.39	0.83–2.33
Benzodiazepine prescription	− 0.04	0.27	0.96	0.57–1.62

*Result was statistically significant ($p < 0.05$). The reference group for opioid-prescribing clinicians was physician primary care provider. The reference group for engagement in non-pharmacological pain interventions was no engagement. In this analysis, the variables for clinical site, demographic characteristics of the study participant, and type of opioid-prescribing clinician were measured at baseline; all other variables were time-varying covariates

(HR = 1.03, 95% CI = 1.01–1.05). Relative to patients who received opioids from a physician PCP, those who received medications from a nurse practitioner (HR = 2.10, 95% CI = 1.12–3.96) or specialty physician (HR = 3.18, 95% CI = 1.22–8.34) were more likely to have an opioid dose increase. Additionally, having undergone surgery in the prior 6 months was associated with an increased likelihood of a sustained dose escalation (HR = 1.80, 95% CI = 1.10–2.94).

DISCUSSION

This was a longitudinal examination of factors predictive of prescription opioid dose escalation among patients already prescribed a stable dose of LTOT. Nearly 20% of the sample had a dose increase of 15% or more during the 2-year study period. A consistent predictor of dose escalation was having a lower dose. This finding is encouraging, as clinicians appeared more likely to increase the prescription opioid doses for those with lower doses, a strategy consistent with opioid treatment guidelines.¹

Higher pain catastrophizing and undergoing surgery sometime in the prior 6 months were associated with an increased likelihood of prescription opioid dose escalation. These findings are consistent with other research demonstrating that higher

pain catastrophizing scores are associated with greater likelihood of being maintained on prescription opioids following a surgical procedure.^{43, 44} Prior research demonstrates that pain catastrophizing is predictive of pain and disability and mediates treatment outcome.^{25, 45} Severity of pain catastrophizing is modifiable^{46, 47} and results from this study suggest that this may be an important focus for intervention with patients who are prescribed LTOT, to potentially decrease the likelihood of prescription opioid dose escalation and improve pain outcomes.

The finding that recent surgery was associated with an increased likelihood of sustained dose escalation suggests that long-term escalation may occur in situations where only temporary dose increases may have been intended. Other research suggests postoperative opioid-prescribing often exceeds what patients find necessary for analgesia.^{48–50} Together, our study and the postoperative pain literature suggest that primary care clinicians, along with surgeon prescribers, should be vigilant about keeping postoperative dose increases relatively brief.

Study findings point to characteristics of the opioid-prescribing clinician that are associated with the likelihood of dose escalation. Compared with patients who receive opioid medications from PCPs who are physicians, patients whose prescriber is a physician specialist or a nurse practitioner as PCP were more likely to have an increase in opioid dose.

These results are consistent with other research demonstrating that professional background of the clinician is associated with opioid-prescribing practices.²¹ The findings suggest a need for better understanding of why different groups of practitioners have different prescribing habits, and whether training innovations might mitigate these variations.

Contrary to study hypotheses, several other clinical factors were not associated with dose escalation. Prior research has identified that mental health factors, including substance use disorder status, are associated with prescription opioid initiation,^{15, 51, 52} high-dose opioid therapy,^{18, 19} and other risky opioid-prescribing practices.⁵³ In the current analyses, pain-related factors and psychiatric disorders were not associated with dose escalation. Because few patient-reported clinical factors are predictive of opioid dose escalation, clinicians may encourage treatment approaches with limited risk of adverse events for all patients with chronic pain.

While this study examined factors predictive of prescription opioid dose escalation, the dose change selected for examination may not have been clinically meaningful for all patients. Furthermore, decisions about dose escalation are made on an individual basis and ideally centered around clinician and patient assessment of risk versus benefit. More work is needed to understand clinician decision-making and rationale behind reasons to increase the prescription opioid dose for some patients, while alternative treatment options may instead be offered for others.

There are additional study limitations that should be considered when interpreting these results. We defined a dose escalation as an increase of 15% or more from baseline; study results may have differed if an alternative threshold was used. Additionally, due to the way data were collected, we are unable to evaluate if participants received multiple sustained escalations. Participants were recruited from a private health plan and a VA medical center, both located in the Pacific Northwest of the USA. There may be regional patterns that impacted the study in unanticipated ways. Prescription opioid dose escalation was based on administrative data from the health system in which the patient was recruited. The research team did not confirm prescription opioid status with state prescription drug monitoring programs and could not detect receipt of prescription opioids from multiple sources.⁵⁴ This study recruited patients already prescribed LTOT and results may not generalize to those with recent initiations. While this research did include some examination of characteristics of the opioid-prescribing clinician, these data were abstracted from administrative data. Clinician perceptions and beliefs about opioid prescribing may be more robust predictors of likelihood of prescription opioid dose escalation.

In summary, results from this 2-year prospective cohort study of patients already prescribed a stable dose of LTOT found that the factors associated with an increased likelihood of prescription opioid dose escalation were lower opioid dose, higher pain catastrophizing, opioid prescriptions coming from a PCP who is a nurse practitioner

(rather than physician PCP) or from a specialist physician, and recently undergoing surgery. Many commonly identified predictors of opioid initiation had little if any independent association with dose increases. Thus, other factors should be investigated to understand why some patients experience dose escalations. Furthermore, future such studies should focus on patients currently prescribed relative low opioid doses, for whom dose escalation appears more likely. These findings also have implications for clinicians seeking to adhere to opioid treatment guidelines. To decrease likelihood of future prescription opioid dose escalations, primary care clinicians should remain closely involved in care (including when patients receive consultation from specialists), regularly screen for pain catastrophizing, and offer clinical resources that address ways that these cognitions contribute to pain outcomes.

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Compliance with Ethical Standards:

All procedures were reviewed, approved, and monitored by the institutional review boards at the respective institutions.

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