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Prescribed Opioid Difficulties, Depression, and Opioid Dose Among Chronic Opioid Therapy Patients

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Abstract

Background—Chronic opioid therapy has increased dramatically, as have complications related to prescription opioids. Little is known about the problems and concerns attributed to opioids by patients receiving different opioid doses.

Methods—We surveyed 1883 patients who were receiving chronic opioid therapy for chronic non-cancer pain. Opioid regimen characteristics were ascertained from electronic pharmacy records. Patient-reported opioid-related problems and concerns were measured using the Prescription Opioid Difficulties Scale. Depression was assessed with the Patient Health Questionnaire.

Results—Patients prescribed higher opioid doses reported modestly higher pain intensity and pain impact. After adjustment, patients on higher doses attributed higher levels of psychosocial problems and control concerns to prescribed opioids ($p<.0001$). They also had higher levels of depression and were more likely to meet criteria for clinical depression. Over 60% of patients receiving 120+ mg daily (morphine equivalent) were clinically depressed, a 2.6-fold higher risk (95% CI of 1.5 to 4.4) than patients on low dose regimens (< 20 mg daily).

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Conclusions—Higher opioid doses were associated with somewhat higher pain severity and higher levels of patient-reported opioid-related psychosocial problems, control concerns, and depression. These findings may result from patient selection for high dose therapy or problems caused by higher dose opioids.

Keywords

Opioid; Dosage; Chronic Pain; Depression; Addiction

Introduction

Chronic opioid therapy for non-cancer pain has become increasingly prevalent over the last decades [7,37]. Accompanying this have been worrisome trends in prescription opioid abuse by youth, emergency department and addiction treatment admissions associated with prescription opioids, and opioid-related overdose deaths [23,26,30]. These trends highlight the importance of opioid prescribing decisions for chronic non-cancer pain.

A key clinical decision confronting physicians is the dose of opioids during chronic opioid therapy. No clinical trials comparing opioid dose levels for chronic non-cancer pain have been reported [29], and clinical guidelines suggest that opioid dose should be individualized, with caution recommended at higher doses [10,13,28]. While opioid dosing over 180 mg morphine equivalent has no clinical trial support [2], a recent guideline from Washington State generated controversy by recommending that physicians obtain specialty pain consultation for daily doses of 120 mg morphine equivalent with inadequate therapeutic response in terms of pain and function [43].

Recent reports have highlighted the association between higher prescribed opioid doses and complications of chronic opioid therapy, including: risk for overdose and overdose death [16, 6, 22]; fractures among the elderly [33]; risk of opioid misuse [38]; alcohol and drug-related emergency department visits [8]; and opioid use disorder diagnoses [19]. However, little information is available about the clinical status of patients prescribed different opioid dose levels.

The effects of higher opioid doses may have a larger impact on patients whose chronic pain is complicated by depression. A growing body of evidence supports the association between mental health or addiction problems and the prescription of higher opioid doses [27,17,18,9,44]. However, these studies have rarely included self-report measures of pain and psychological status of chronic opioid therapy patients in relation to prescribed dose.

Measurement of problems during opioid therapy has primarily focused on the risk of addiction or aberrant behaviors [11,12,14,21], although traditional constructs of abuse and dependence have been difficult to apply in this population [3]. A related approach has sought to understand patients' perspective on problems they attribute to opioids [4,14,34]. Two types of patient-reported problems, psychosocial problems and opioid control concerns, have been identified among patients receiving chronic opioid therapy [5, 39]. Measurement of these patient-reported problems with opioid therapy provides an opportunity to explore the clinical status of patients prescribed differing opioid dose regimens.

We used data from a large study of opioid risks and trends that combines comprehensive pharmacy records and patient interview data to describe the characteristics and clinical status of patients prescribed different opioid dose levels. We assessed whether opioid dose was associated with differences in patient-reported psychosocial problems and control concerns attributed to opioids and with symptoms of depression.

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Methods

Setting and participants

The CONSORT study (CONsortium to Study Opioid Risks and Trends) was designed to study chronic opioid therapy for non-cancer pain in Group Health Cooperative (GHC), in Washington State, and Kaiser Permanente of Northern California (KPNC) [42]. Together, these health plans include about four million patients. CONSORT research plans were approved by the Institutional Review Boards of both health plans. Patients in these analyses were receiving chronic opioid therapy and completed a telephone interview about pain, mental health and opioid use.

Automated pharmacy and medical encounter data

Both health plans maintain detailed automated pharmacy and medical encounter data for all covered services. Surveys at both health plans have consistently found that more than 90% of patients obtain almost all of their prescription medications through health plan pharmacies [32,35].

Eligibility

Those aged 21-80 years and continuously enrolled in the health plans for at least one year before sampling were eligible if they had filled an opioid prescription that extended beyond the sample selection date, and had filled at least 10 opioid prescriptions and/or received at least 120 days supply in a one-year period prior to the sample selection date, with at least 90 days between the first and last opioid dispensing in that year. These criteria for chronic opioid therapy have been shown to predict a high probability of sustained opioid use one year later [42]. We excluded patients with a cancer diagnosis (except for non-melanoma skin cancer) in local cancer registries or who had two or more cancer diagnoses in automated visit records in the year prior to sampling.

Sampling

We sampled chronic opioid therapy patients receiving higher dose with increased probability because most patients receiving chronic opioid therapy in these health plans receive low dose [7], while higher dose patients account for a large share of opioids prescribed [42, 18]. We selected patients within dosage strata and weighted observations by the inverse of the probability of selection. Estimates reported in this paper are representative of the population of long-term opioid users from which the sample was selected.

Telephone Survey

Interviews were conducted from June to November 2008 at GHC and from January to October 2009 at KPNC. Potentially eligible patients were mailed a letter explaining the study and a pre-incentive (a $2 bill at GHC and a $5 gift card at KPNC). Experienced non-clinician survey interviewers at each health plan research center conducted Computer-Assisted Telephone Interviews. Patients were asked to participate in a 25-30 minute telephone interview and to allow the study to access their electronic health care data from the time they enrolled in the health plan until three years after the date of the interview. Patients who completed the interview were mailed $20 cash at GHC and a $50 gift card at KPNC. The differential in incentive payments was based on prior experience in the two populations suggesting the level of incentive payments needed to achieve an acceptable response rate.

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Opioid Type and Dose Variables

Based on electronic pharmacy data, characteristics of opioid prescription were estimated using methods described elsewhere [42]. Our primary dose measure was the average daily dose, which was estimated by the total morphine equivalent dose (MED) during the 90 days before each subject's interview date, divided by 90. Morphine equivalent doses were based on opioid conversion factors described previously [42]. Days supply for each opioid in the past 90 days is calculated by pharmacists using the maximum dose and frequency permitted within the prescribed range. Opioids were classified into long-acting opioids (methadone, transdermal fentanyl, and sustained release formulation of oxycodone, morphine, hydromorphone, oxymorphone and levorphanol tartrate) and short-acting opioids. Subjects were classified as predominate users of short- or long-acting opioids depending on which type had the larger days supply in the 90 days prior to their interview. In case of ties, the opioid type with the larger MED was chosen.

Psychosocial Problems and Control Concerns

Patient problems and concerns attributed to opioids were measured using the Prescribed Opioid Difficulties Scale (PODS) [5, 39]. The PODS scale focuses on recent problems and concerns related to opioid use from the patient's perspective (in the past two weeks for common problems, in the past month or year for less common problems) and has two sub-scales. The PODS Psychosocial Problems sub-scale and the PODS Control Concerns sub-scale each include 7 difficulties attributed to opioid use. Higher scores indicate that patients attributed more problems to their use of opioid medications, with each question contributing up to 4 points for a positive response. Patients were also asked to rate how helpful opioids were for pain control [5].

Other Measures

Pain intensity was measured using a 0-10 average pain intensity rating scale from the Graded Chronic Pain Scale [40, 41]. The *Pain Impact Scale* [15] consisting of 11 yes-no items concerning effects of pain in the last two weeks (e.g., staying in bed more, avoiding jobs around the house, doing fewer social activities) was also included. The severity of depressive symptoms was measured with the 8-item version of the *Patient Health Questionnaire (PHQ)*, a validated and widely used self-report measure of depressive symptoms [24, 25]. This version of the PHQ has cut off score of 10 indicating likely major depression. *Body mass index* (BMI) was calculated from self-reported weight and height. Chronic disease comorbidity was assessed using the Romano version of the *Charlson comorbidity score* [31]. Patients were also asked "have you ever had an alcohol or drug problem?"

Analyses

Only patients who reported using opioid medications every day in the two weeks prior to the interview were included in these analyses. Analyses used SAS PROC SURVEYMEANS, PROC SURVEYREG, or PROC SURVEYLOGISTIC commands to account for the stratified random sampling approach, providing estimates for the population surveyed. We used basic statistics (proportions, means and standard errors) to describe patients in the population surveyed.

Between group differences in proportions were tested using chi-square statistics. We examined the association between opioid dose category and PODS subscales and total score using linear regression models, adjusting for factors that might confound the observed association between opioid dose and measures of psychosocial problems and concerns. Initially, we adjusted only for health plan, and then tested a full model which included health

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plan, demographics (age, sex, BMI, education), pain characteristics (pain intensity, pain days, Pain Impact Scale), comorbidity (Charlson Score), opioid type (predominantly long versus short acting opioids), and self-reported substance abuse problem. PROC SURVEYREG was used to estimate least square adjusted means and test statistics for the adjusted regression models taking the stratified random sampling approach into account. We also examined the association between dose category and individual PODS questions after adjustment for opioid type and health plan.

We used similar regression models to examine the association between opioid dose category and depressive symptoms (PHQ-8 score), adjusting first for health plan, then for the potential confounders listed above. Finally, we assessed the association between opioid dose category and the proportion of patients meeting criteria for major depression, adjusting for health plan and potential confounders using PROC SURVEYLOGISTIC.

Results

Survey Response

Overall, 3790 patients were approached (2185 at GHC and 1605 at KPNC), 185 were ineligible (76 at GHC and 109 at KPNC), and interviews were completed for 2163 (1191 at GHC and 972 at KPNC), for an overall response rate of 60% (57% at GHC and 65% at KPNC). Response rates were higher for patients over the age of 65 (65% at GHC and 68% at KPNC), but gender differences were small. Response rates increased with higher average daily dose at KPNC (58% for <50 mg. MED; 66% for 50 to <100 mg. MED; and 71% for 100+ mg. MED), but this was not seen at GHC (58% for <50 mg. MED; 57% for 50 to <100 mg. MED; and 55% for 100+ mg. MED), possibly due to lower incentive payments at GHC. Among 2163 survey respondents, 1883 (87%) reported using opioid medications every day for the past two weeks and were included in the analytic sample.

Characteristics of patients by dose categories

Of those patients meeting our definition of long term opioid use, 26% were prescribed 1-19 mg MED daily during the 90 days prior to the interview, 36% were prescribed 20-49 mg MED daily, 23% were prescribed 50-119mg MED daily, and 16% were prescribed 120 mg MED daily or more (weighted estimates). Patients in higher dose opioid categories were younger than those on lower doses ($p<.0001$) but were similar in gender, BMI, and education status. In the three months prior to the interview, 32% (N=969) of patients were dispensed predominantly long-acting opioids and 68% (N=914) used short-acting opioids predominantly (Table 1). Patients predominantly prescribed long-acting opioids took a substantially higher average daily opioid dose (159.9 mg MED versus 43.9 mg MED) (data not shown). Patients in all dose groups reported near daily pain in the two weeks prior to the interview, with patients on higher doses reporting higher levels of average pain intensity and Pain Impact Score ($p<.0001$ for both), though these differences were relatively small. For example, the difference in average pain intensity (on a 0-10 rating scale) was only 0.4 points between patients in the highest versus the lowest opioid dose groups. A somewhat higher percentage of patients in higher dose categories reported opioid pain medication to be very or extremely helpful for their pain, but this difference was not statistically significant ($P=0.26$). Differences in self-reported substance abuse problems and Charlson co-morbidity scores between dose groups were marginally significant (Table 1).

Prescription Opioid Difficulties Scale scores by dose categories

Before adjustment, patients in higher opioid dose categories attributed more psychosocial problems and opioid control concerns to their opioid medication than those in lower dose categories, as measured by the Prescription Opioid Difficulties Scale (PODS) ($P<.0001$,

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Table 2). These differences were significant for the total PODS score and for both the Psychosocial Problems and the Control Concerns subscales, and the differences by dose were only slightly attenuated with adjustment for potential confounders (Table 2).

The specific psychosocial problems that patients in higher dose categories more frequently attributed to their opioid use included loss of interest in activities, trouble concentrating, feeling slowed down and sluggish, feeling depressed or anxious, interference with activities, and decreased alertness. Specific opioid control concerns attributed to opioid medications by patients in higher dose categories included needing a higher dose to get the same effect, being worried about opioid dependence, wanting to stop or cut down use of opioids, and reporting that family or friends think the patient may be addicted to opioids (Table 3).

Symptoms of depression

Consistent with the higher levels of psychosocial problems attributed to opioids, after adjusting for potential confounding variables, patients on higher opioid doses reported higher levels of depression symptoms. They were also were more likely to meet criteria for clinical depression (Table 4). Over 60% of patients receiving 120+ mg morphine equivalent were clinically depressed, a 2.6-fold (95% CI 1.5, 4.4) higher risk than patients on low dose regimens (< 20 mg per day).

Discussion

This report provides new information about the characteristics, clinical status, and patient-perceived opioid-related difficulties of patients prescribed different opioid dose regimens in a population-based sample. We found that higher dose treatment was associated with increased rates of patient-reported opioid-related psychosocial problems and control concerns and with increased symptoms of depression. While differences in depression symptoms may result from the selection of patients for high dose therapy or from depression caused by higher dose opioids, psychosocial and control concerns attributed to opioids were more common among patients receiving higher opioid doses.

The use of higher dose opioid regimens has been questioned [2]. Higher opioid dose has been associated with a number of complications potentially related to opioids [16,33,8,19,38,4], although no previous study has associated higher dose levels with higher levels of patient-reported problems attributed directly to opioid medications after controlling for potential confounders. It should be noted that patients receiving higher opioid doses were somewhat more likely to rate opioids as “very helpful,” though these findings did not reach statistical significance. Further research is needed to better understand the relationship between perceived helpfulness, pain intensity and impact, and patient-reported problems with opioids.

These cross-sectional data do not provide a strong basis for causal inference, in this case regarding relationships between opioid dose and benefits or adverse effects of chronic opioid therapy. Observed associations may be due to pre-existing patient differences and/or differences in prescribing for patients with different risks. Patients may attribute depression symptoms to poorly controlled pain, prompting them to seek and physicians to prescribe higher doses of opioids. We have previously noted widespread “adverse selection” of patients with mental health and substance abuse problems in chronic opioid initiation, continuation, and dose escalation [36]. However, patients in this study attributed problems to opioids that are relevant to depressive illness. Whatever the causal chain, higher opioid dose appears to be a marker for patients whose clinical status and opioid difficulties warrant close attention. Also, physicians may find that patients who attribute psychosocial problems or

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control concerns to their use of prescribed opioids are willing to consider a trial of dose reduction.

Depression and chronic pain are often intertwined [1,20]. This study supports special attention to depression in patients on higher dose opioids, both due to the high prevalence of depressive symptoms in this group and due to safety concerns with the use of higher opioid doses. Whether the higher rates of overdose seen in patients on higher doses of opioids are related to underlying depression and whether diagnosis and treatment of depression can make opioid therapy safer are important future research questions. Until these questions are answered, special attention to the mental health status of patients on higher opioid doses seems prudent.

Limitations of this study include the cross-sectional survey design, use of a population with continuous health insurance access, and a survey response rate of 60%. We controlled for variables known to be associated with response rate, including age, health plan, and opioid dose, but unmeasured differences could not be controlled. Some potentially confounding variables, such as self-reported alcohol or drug problems, may underestimate actual problems. The complex clinical status of patients on chronic opioid therapy and concerns about future access to opioids may reduce their ability or willingness to participate in surveys. The measurement of psychosocial problems and control concerns using the PODS may not capture all relevant difficulties and the clinical significance of the differences in PODS scores between groups is not clear. Strengths include a large sample size, supplementation of pharmacy and administrative data with direct patient interviews, and a population-based sampling in two health plans enriched to include adequate numbers of higher dose patients. Longitudinal data on the relationship between opioid dosing and adverse psychosocial and control concerns would further inform clinical practice and interventions to improve the safety of opioid prescribing for chronic non-cancer pain.

In conclusion, patients receiving higher dose chronic opioid therapy reported higher levels of psychosocial problems and control concerns which they attributed to opioids. Higher dose patients were also more likely to be clinically depressed. This association of higher doses with a wide range of patient-reported problems should be taken into account when selecting patients for higher dose opioid prescribing and when discussing changes in opioid dosing with patients on opioids for chronic non-cancer pain.

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Table 1

Characteristics of chronic opioid therapy patients by average daily morphine equivalent dose.[a]

	Opioid Morphine Equivalent Daily Dose					
Variable	**1-19 mg**	**20-49 mg**	**50-119 mg**	**120+ mg**	**All persons**	**p-value[b]**
Number of patients (weighted %)	216 (25.7%)	332 (35.5%)	724 (23.1%)	611 (15.7%)	1883	
Female, %	65.4	59.7	64.4	59.6	62.3	0.30
Mean age (SE), y	58.5 (0.9)	55.7 (0.8)	54.8 (0.6)	52.6 (0.5)	55.7 (0.4)	<**.001**
BMI (SE)	32.2 (0.7)	30.3 (0.5)	30.8 (0.7)	30.3 (0.4)	30.9(0.3))	0.26
Some college education, %	60.4	58.3	59.2	65.9	60.3	0.43
Mean days with pain in prior 6 months (SE)	163.8 (3.2)	171.4 (2.1)	168.5 (1.7)	167.3 (1.6)	168.1 (1.2)	0.17
Using opioids for more than one pain condition, %	62.7	64.6	59.8	73.2	64.4	**0.002**
Predominate use of long-acting opioids in the prior 3 months, %	2.4	20.8	50.7	75.6	31.6	<**.001**
Self-reported drug or alcohol problem, %	15.7	22.9	21.9	30.9	22.0	0.053
Mean Charlson Score (SE)	1.3 (0.2)	1.0 (0.1)	1.2 (0.1)	1.4 (0.1)	1.2 (.06)	0.048
Number of Times per Day took opioids last 2 weeks (SE)	2.1 (0.07)	3.0 (0.09	3.3 (0.08)	3.7 (0.24)	2.9 (0.06)	<**.001**
Average pain intensity (0-10) (SE)	5.7 (0.14)	5.8 (0.14)	5.9 (0.1)	6.1 (0.09)	5.8 (0.07)	<**.001**
Mean Pain Impact Score (0-10) (SE)	6.0 (0.24)	6.9 (0.23)	7.3 (0.16)	7.9 (0.15)	6.9 (0.11)	<**.001**
Rate opioids as very or extremely helpful, %	57.2	53.2	61.2	66.0	58.1	0.26

[a]Opioid regimens defined in the 3 months prior to the interview. Patients reported taking opioids every day in the last 2 weeks.

[b]P-values adjusted for health plan, gender, age and opioid type (predominant use of long versus short acting opioids), except for gender (controlled for age and type), age (controlled for gender and type) and predominant use of long-acting opioids (controlled for gender and age).

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Table 2

Prescription Opioid Difficulties Scale (PODS) scores: Mean total and subscale scores by opioid dose. [a]

	Opioid Morphine Equivalent Daily Dose				
Variables included in adjusted model [b]	**1-19mg**	**20-49mg**	**50-119mg**	**120+mg**	**p-value [c]**
PODS Total Score (SE of the mean)					
Unadjusted except for health plan	6.6 (0.58)	9.8 (0.84)	11.8 (0.56)	15.2 (0.64)	<**.001**
Adjusted for age, sex, BMI, education, pain intensity, pain days, Charlson Score, Pain Impact Scale, opioid type, selfreported substance problem, health plan	8.3 (0.68)	10.3 (0.77)	11.5 (0.56)	13.9 (0.77)	<**.001**
PODS Psychosocial Problems Subscale (SE of the mean)					
Unadjusted except for health plan	3.1 (0.35)	4.6 (0.5)	5.4 (0.3)	7.6 (0.4)	<**.001**
Adjusted for age, sex, BMI, education, pain intensity, pain days, Charlson Score, Pain Impact Scale, opioid type, selfreported substance problem, health plan	4.2 (0.4)	4.9 (0.45)	5.1 (0.34)	6.7 (0.48)	**0.004**
PODS Control Concerns Subscale (SE of the mean)					
Unadjusted except for health plan	3.5 (0.34)	5.2 (0.42)	6.4 (0.31)	7.5 (0.34)	<**.001**
Adjusted for age, sex, BMI, education, pain intensity, pain days, Charlson Score, Pain Impact Scale, opioid type, selfreported substance problem, health plan	4.1 (0.40)	5.4 (0.40)	6.4 (0.31)	7.2 (0.40)	<**.001**

[a] Higher PODS score indicates that patients attributed more problems to their use of opioid pain medications. Least square means adjusted for indicated variables.

[b] Sex, dose, education, health plan, self-reported substance problem, and opioid type entered in the model as class variables; remaining variables are continuous

[c] P-values and standard errors corrected for stratified design

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Table 3

Problems and concerns patients attribute to opioid use by average daily dose (weighted estimates)

	Opioid Morphine Equivalent Daily Dose				
	1-19mg	**20-49mg**	**50-119mg**	**120+mg**	**p-value [a]**
Psychosocial Problems					
Loss of interest in activities, %	4.9	9.6	8.0	14.6	**0.01**
Trouble concentrating, %	6.5	15.6	17.2	24.0	**0.04**
Feeling slowed down, sluggish, %	14.8	15.7	18.0	25.1	**0.03**
Feeling depressed, anxious, %	4.0	7.8	8.2	15.1	**0.0004**
Interference with work, family social activities, %	10.8	16.9	22.9	32.2	<**.0001**
Hard to think clearly, %	8.6	14.6	17.1	24.2	0.15
Less alert when driving or other activity require vigilance, %	20.8	28.7	35.8	45.4	**0.007**
Control Concerns					
Preoccupied with opioids, %	5.0	10.1	7.2	9.2	0.24
Concern about control over use, %	2.8	4.7	5.4	8.0	0.63
Need higher dose for same effect, %	19.5	24.8	34.6	41.5	<**.0001**
Worry about opioid dependence, %	17.2	30.1	37.4	46.8	<**.0001**
Want to stop or cut-down on opioids, %	33.9	44.5	50.3	51.5	**0.01**
Opioids caused family problems, %	1.7	4.5	7.4	10.7	**0.046**
Family or friends thought might be addicted to opioids, %	5.8	11.0	18.2	24.9	<**.0001**

[a] p-value for opioid dose adjusted for health plan and opioid type.

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Table 4

PHQ-8 depression by opioid morphine equivalent daily dose.[a]

	Opioid Morphine Equivalent Daily Dose				
Variables included in adjusted model [b]	**1-19mg**	**20-49mg**	**50-119mg**	**120+mg**	**p-value**
PHQ-8 score - adjusted least square mean (SE of the mean)					
Adjusted for health plan	7.3 (0.43)	9.1 (0.43)	10.0 (0.32)	11.5 (0.30)	<**.001**
Adjusted for age, sex, BMI, education, pain intensity, pain days, Charlson Score, Pain Impact Scale, opioid type, selfreported substance problem, health plan	8.9 (0.41)	9.7 (0.33)	9.9 (0.26)	10.8 (0.32)	**0.008**
Percent with major depression (PHQ-8 ≥10)	26.8	38.5	51.7	61.4	<**.001**
Odds ratio adjusted for age, sex, BMI, education, pain intensity, pain days, Charlson Score, Pain Impact Scale, opioid type, self-reported substance problem, health plan (95% CI)	1.00	1.4 (0.8, 2.3)	2.1 (1.3, 3.3)	2.6 (1.5, 4.4)	**0.002**

[a] P-values and standard errors corrected for stratified design. Least square means adjusted for indicated variables.

[b] Sex, dose, education, health plan, self-reported substance problem and opioid type entered in the model as class variables; remaining variables are continuous