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The Concentration of Opioid Prescriptions by Providers and Patients in the Oregon Medicaid Program

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Abstract

Objective—This study seeks to understand the distribution of opioid prescribing across providers and patients, and examines how this concentration predicts opioid misuse.

Methods—Using 2013 Oregon Medicaid claims and National Provider ID registry, this study identified patients who filled at least one opioid prescription and providers who prescribed opioids for those patients (N=61,477 Medicaid patients). This study examined the distribution of opioid prescriptions by provider and patient, the extent to which high-volume opioid use was associated with potential opioid misuse, and how this association changes when patients received opioids from providers in the top decile of morphine equivalents (MEQ) prescribed in 2013. This study used four indicators of opioid misuse: doctor and pharmacy shopping for opioid prescriptions, opioid prescription overlap, and opioid and benzodiazepine prescription overlap.

Results—Opioid use and prescriptions were heavily concentrated among the top 10% opioid users and prescribers. Those high-volume opioid users and prescribers accounted for 83.2% and 80.8% in MEQ of entire opioids prescribed. Patients' increasing use of MEQ was associated with most measures of opioid misuse. Patients receiving opioids from high-volume prescribers had a higher probability of opioid prescription overlap and opioid and benzodiazepine prescription

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overlap, but the increase was significant only among patients who received high doses of opioids and the size of the increase was modest.

Conclusions—Whereas current policies emphasize reducing opioid prescriptions across all patients and providers, study results suggest potential for policies that focus on high-volume opioid users and prescribers.

Death rates from prescription opioid overdoses in the United States more than tripled between 1999 and 2012, creating an urgent need for policies that can effectively reduce the mortality and morbidity associated with opioid misuse.¹ The effectiveness of policies may depend, in part, on how providers prescribe opioids. If, for example, providers are uniform in the ways in which they prescribe opioids, then policies that broadly apply to all providers may be warranted. On the other hand, if the majority of opioids are obtained through a relatively small number of providers or a certain provider specialty, it may be more effective to tailor policy interventions to affect a narrower group of providers.

Opioid misuse is generally concentrated among patients who are prescribed higher volumes of opioids.^{2–5} However, less is known about variations in provider prescribing patterns and their implications. Heavy prescribing could be a marker for inappropriate use. In a recent study, opioid-related deaths were concentrated among patients treated by physicians who prescribed high volumes of opioids for each patient, although this study did not control for patient characteristics that could potentially affect patient health outcomes.⁶ On the other hand, high-volume providers could be associated with lower rates of opioid misuse and better patient outcomes because they specialize in pain treatment.

This study begins with simple questions for which we have relatively little data: within a specified region and patient population, how concentrated is opioid prescribing and use and does this concentration predict opioid misuse? Specifically, we seek to understand whether the top decile of providers and patients account for a majority of opioid prescription and test the relationships of the opioid prescription concentration to indicators of opioid misuse.

We focused on Medicaid enrollees in Oregon. Compared to privately-insured individuals, Medicaid patients are more likely to receive opioid prescriptions, at higher doses of opioids, for longer periods of time,^{7–9} and have higher death rates from overdoses.^{10,11} Oregon has taken a progressive stance in providing access to opioids for treatment of pain. The Oregon Intractable Pain Act (1995) allows physicians to prescribe opioids for treatment of chronic pain at levels which could trigger sanctions from state medical boards elsewhere in the country.¹² This law has been celebrated by advocates concerned about inadequate pain treatment. Nonetheless, Oregon's death and hospitalization rates from prescription opioid overdose increased more than five-fold between 2000 and 2011,¹³ leading to calls for policies to limit opioid prescribing. Although there has been widespread speculation about the ways in which opioids are obtained and subsequently abused, relatively little is known about what heavy users look like, and even less is known about different provider prescribing patterns. The goal of this study is to assess these patterns to provide insight for policies aimed at reducing opioid misuse among a vulnerable population of Medicaid enrollees.

METHODS

Data

We used year 2013 data from Oregon Medicaid claims for opioid users' demographics, health characteristics, and opioid use patterns and National Provider Registry for prescribers' basic characteristics. We combined these two datasets using each provider's national provider ID, creating a patient-provider linked data set. We limited the sample to Medicaid beneficiaries who filled opioid prescriptions at least once in year 2013 and providers who prescribed opioid for those beneficiaries. We further excluded patients who were diagnosed with cancer at any time in 2013, were not continuously enrolled in Medicaid, and were eligible for Medicare. The final dataset includes 61,477 Medicaid beneficiaries.

Potential Opioid Misuse Measures

We used four measures of potential opioid misuse capturing inappropriate opioid prescribing practices and patient behaviors. Each measure indicates whether the respective practice or behavior occurred at least once in 2013. Two measures reflect illicit patient behaviors: doctor and pharmacy shopping for opioid prescriptions. We defined doctor shopping as having received opioid prescriptions from six or more providers during one year and pharmacy shopping as getting opioid prescriptions filled from eight or more pharmacies.¹⁴ Previous studies found that patients involved with doctor/pharmacy shopping were more likely to be associated with opioid overdose death.^{14,15}

We also used two indicators of inappropriate opioid prescribing practices: opioid prescription overlap (i.e., at least one-week overlap for two prescriptions of same opioid drugs from either single or multiple prescribers) and opioid and benzodiazepine prescription overlap (at least one-week overlap). All the measures of prescribing practices have been used in previous studies.¹⁶⁻¹⁹

Concentration of Opioid Prescriptions

We defined high-volume opioid users and prescribers as those in the top decile in morphine equivalents (MEQ) prescribed throughout the year.⁸ In this definition, we used MEQ to make opioid doses comparable across products. We preferred MEQ as a measure of concentration to the number of prescriptions because opioid doses differ across prescriptions. To calculate MEQ for each prescription, the quantity of pills/patches dispensed was multiplied by the strength of each pill/patch. We then multiplied this by a morphine equivalents conversion factor (Appendix Table 2). Lastly, we summed MEQ of all prescriptions written throughout 2013 for each patient and prescriber.

Prescribers' high annual MEQ could be attributable to multiple factors. For example, high-volume prescribers could just prescribe a moderate amount of opioids for many patients. Alternatively, they might prescribe high doses of opioids for a moderate number of patients. To distinguish these two groups, in our sensitivity analysis, we used an alternative definition of high-volume opioid prescribers: those in the top decile in annual MEQ prescribed per patient.

Other Variables

We controlled for patient age, gender, rurality²⁰, and pain-related diagnoses.^{21,22} We also controlled for health conditions which often co-occur among opioid users, including depression, bipolar, schizophrenia, alcohol problems, and drug problems (Appendix Table 1).^{23–26} For risk adjustment, we used the Chronic Illness and Disability Payment System indicators, which have been validated and used for risk adjustment in Medicaid populations.²⁷ We also accounted for each provider's gender, entity type (sole or group practice) and provider type/specialty. Lastly, we controlled for each patient's health plan.¹²

Data Analysis

We conducted two sets of regression analyses. First, to examine to what extent high-volume opioid users are involved with opioid misuse, we estimated a patient-level regression of four measures of opioid misuse controlling for a patient's MEQ decile group, demographics, comorbidities, and Medicaid health plan.

The second set of regressions controlled for prescriber characteristics including gender, entity type, and provider type/specialty. We also added an interaction term between a patient's MEQ decile group and a dummy variable indicating whether her provider was a high-volume prescriber in the top MEQ decile. We considered this interaction term because opioid users' experience of opioid misuse could be influenced by whether they were prescribed by a high-volume prescriber. In the second set of regressions, we did not examine doctor/pharmacy shopping as outcome variables because the number of doctors/pharmacies each patient visits for opioid prescription would be unlikely to be affected by her prescriber.

In the second set of regressions, we assigned one prescriber to each patient to take into account provider characteristics in the patient-level regression analyses. Many patients (44%) had, however, more than one prescriber. For patients with multiple prescribers, we selected the provider who prescribed opioids the most times and accounted for at least one third of the patient's total number of prescriptions. Based on this assignment rule, 11,712 out of 61,477 patients were dropped from the original sample because they did not have a provider who meets the listed condition. As a sensitivity analysis, we examined different assignment rules.

All regressions used a linear-probability model instead of logit regressions to avoid a sample size reduction caused by perfect prediction. Standard-errors were clustered at the provider-level.

RESULTS

A relatively small share of providers account for the majority of all opioids prescribed. The top 10% of providers accounted for 80.8% of all MEQ provided to Oregon Medicaid beneficiaries. The top 1% of providers accounted for 43.4% of MEQ prescribed. As seen in Figure 1(a), the majority of providers (those under the top 10% reference line on the y-axis) prescribed relatively low amounts of MEQ. The average annual MEQ prescribed by providers in deciles 1–9 was 7,267; providers in the top decile prescribed an average annual MEQ of 275,503. High-volume opioid prescribers in the top decile also had prescription

counts that were more than five times higher than the average counts of prescribers in deciles 1–9.

We found a similar concentration of opioid use among patients. The top 10% of patients accounted for 83.2% of all MEQ prescribed to Oregon Medicaid beneficiaries. The top 1% of patients accounted for 27.7% of MEQ prescribed. As seen in Figure 1(b), the majority of patients (those under the top 10% reference line on the y-axis) received relatively low volumes of MEQ. The average annual MEQ prescribed to patients in deciles 1–9 was 863; patients in the top decile averaged annual MEQ of 38,368 and received eight times more prescriptions than those in deciles 1–9.

Table 1 displays differences across Medicaid beneficiaries who received no opioid prescriptions, opioid users in lower MEQ decile 1–9, and those in the top MEQ decile. Almost one in five (18%) Medicaid beneficiaries received prescriptions for opioids. Compared to individuals who received no opioid prescriptions, individuals with an opioid prescription were older, more likely to be female, and had higher rates of joint and back pain diagnoses as well as diagnoses for depression. The mean daily dose for individuals in the top decile was 87.6mg MEQ, close to the 100mg level where overdose risks dramatically increase.^{2,19} High-volume users in the top decile were far more likely to experience doctor/pharmacy shopping, overlap in opioid prescriptions, and opioid and benzodiazepine overlap.

Table 2 displays differences across providers who never prescribed opioids, those in the lower nine deciles, and providers in the top decile of prescribers. Two of three prescribers (66%) who wrote prescriptions for Medicaid patients prescribed opioids. Provider type/specialty varied substantially across all three groups. Lower-volume prescribers in MEQ decile 1–9 were more likely to be a physician in family medicine, emergency medicine, obstetrics/gynecology, physician assistant, or dentist. Among high-volume prescribers in the top decile, however, the proportion of physicians in emergency medicine and obstetrics/gynecology and dentists was significantly lower (<1%). About 63% of high-volume prescribers were physicians in family or internal medicine. High-volume prescribers had substantially different opioid prescription patterns. They not only prescribed opioids for more patients but also prescribed higher doses per patient compared to lower-volume prescribers. About 96.8% and 68.1% of high-volume prescribers ever prescribed more than 100mg and 200mg MEQ per day for a patient.

Table 3 displays regression results for our four outcomes of interest (physician shopping, pharmacy shopping, opioid prescription overlap, and opioid/benzodiazepine overlap). Consistent with other studies^{2–5}, increasing use of MEQ was associated with most measures of opioid misuse after adjusting for patient demographics, comorbidities, and health plan. For opioid prescription overlap and opioid/benzodiazepine prescription overlap, the coefficients tend to increase as the amount of MEQ each patient obtained increases, and the increase becomes steeper among patients in MEQ decile 9 and 10. The probability of opioid prescription overlap in deciles 9 and 10 was 13.4 and 24.9 percentage point higher than individuals in the first decile; the probability of opioid/benzodiazepine prescription overlap in deciles 9 and 10 was 16.1 and 29.9 percentage point higher compared individuals in the first decile. Given the average probabilities of these measures (4.4% and 6.9%), these

discrepancies are relatively substantial. This suggests that high-volume opioid users were more likely to experience opioid prescription overlap and opioid/benzodiazepine prescription overlap. For doctor shopping, the coefficient increases steeply among patients in decile 7 through 9, but then declines in decile 10. Appendix Table 3 provides full regression estimates.

Figure 2 displays predicted probabilities of opioid misuse associated with obtaining prescriptions from lower-volume prescribers (decile 1–9) and high-volume prescriber (decile 10). Patients receiving opioids from high-volume prescribers had a higher probability of overlap in opioid prescriptions and opioid and benzodiazepine prescriptions, although the increase was significant only among patients who received high amounts of opioids (patients in MEQ deciles 8 and higher for overlap in opioid prescriptions, and deciles 6 and higher for opioid/benzodiazepine overlap). The size of the increase was relatively small: 2.3–4.5 percentage points for overlap in opioid prescriptions and 2.5–5.3 percentage points for opioid/benzodiazepine overlap. These numbers are smaller than the increases in the probability of opioid misuse we found across patient MEQ group, but are still significant. This suggests that being treated by a high-volume provider is associated with higher probabilities of experiencing opioid misuse. Appendix Table 4 provides coefficients used to calculate the predicted values in Figure 2.

We defined high-volume prescribers as those in the top decile in annual MEQ. As a sensitivity analysis, we used a separate definition wherein providers were categorized as high-volume if they were in the top decile of annual MEQ per patient. We found similar results with this alternative definition (Appendix Table 5).

The analyses in Figure 2 required us to assign patients to a single provider, based on our rule of assigning the provider who prescribed the majority of opioids and accounted for at least one third of each patient's total number of prescriptions. This rule, however, resulted in dropping approximately 20% of our sample, which might lead to biased estimates. To address this concern, we conducted another sensitivity analysis using three additional assignment rules, and found qualitatively similar results across different rules (Appendix Table 6).

DISCUSSION

Opioid prescriptions were common among Oregon Medicaid beneficiaries and their providers. Almost one in five beneficiaries filled at least one opioid prescription, and 66% of providers wrote at least one opioid prescription. Despite a high prevalence of opioid use among Medicaid beneficiaries, opioid use and prescriptions were heavily concentrated among the top 10% opioid users and prescribers. Those high-volume opioid users and prescribers accounted for 83.2% and 80.8% of MEQ of all opioids prescribed, respectively. This concentration of use in patients in Oregon is higher than what was observed in a similar study of Arkansas's Medicaid population, which found that the top decile of patients were prescribed 62.9% of opioids.⁸ The concentration in the prescription among Oregon providers, however, is slightly lower than the corresponding among the California workers' compensation system (86.8%).²⁸

High-volume prescribers were more likely to be physicians in family or internal medicine, nurse practitioners, or physician assistants. They prescribed higher daily doses of opioids for more Medicaid patients. 96.8% of high-volume prescribers had ever prescribed more than 100mg per day; 68.1% ever prescribed more than 200mg MEQ per day. Given that the risk for opioid overdose death increases at 100mg MEQ per day, the high percentage of providers prescribing daily doses of 100mg or more may be of concern,¹⁹ although these high dosage amounts may be attributable to providers who treat patients with health conditions which require higher doses of opioids.

Overall, opioid misuse was more likely to be found among high-volume opioid users. The probability of three types of misuse – opioid prescription overlap, opioid benzodiazepine overlap, and pharmacy shopping – tends to increase with the amount of MEQ obtained by patients. Opioid users' probability of experiencing opioid misuse increased when they were prescribed by a high-volume prescriber instead of a lower-volume one, although this finding was applied only to the group of patients receiving the highest amount of opioids. While our analyses measured association only, these findings suggest that provider prescribing patterns may be a risk factor for patients who obtain large amounts of opioids. These results suggest potential gains from interventions that target prescription patterns among high-volume opioid users and prescribers.

Opioid policies frequently focus on patient behavior. For example, prescription drug monitoring programs, currently used in 49 states including Oregon (begun on June 1, 2011), monitor patients' opioid use within a state to reduce opioid misuse.^{29,30} This effort is valid given the substantial discrepancy we found in probabilities of opioid misuse across patients with different MEQs. Many Medicaid agencies implemented patient lock-in programs, limiting patients at a high risk for opioid misuse to one prescriber and pharmacy to prevent opioid misuse.^{31,32} However, our results suggest the potential for policies specifically focusing on providers. In Oregon, several organizations have developed educational materials to improve opioid prescribing. For example, a group of providers created and disseminated opioid prescribing guidelines.³³ The state government also hosted education sessions on safe opioid prescription.¹² Other educational interventions, such as provider profiling or academic detailing, may also be effective at improving opioid prescribing.^{34,35} Regulatory interventions such as monitoring for adherence to guidelines might, however, further reduce opioid misuse. Ideally, these policies would not inhibit access to opioids that provide safe and reliable pain management.

One intervention to reduce opioid overdoses without inhibiting access could be to encourage high-volume providers to co-prescribe naloxone with opioid prescriptions. Naloxone is an effective overdose rescue medication,³⁶ but it is likely underprescribed partially due to physicians' reluctance or lack of knowledge. Physician training on the efficacy of naloxone and policies addressing provider's legal and social concerns about naloxone prescription can facilitate the distribution of naloxone.³⁷

Our study has limitations. Our study only includes data from Medicaid patients. Unlike studies that used data from prescription drug monitoring programs, it is uncertain whether the same patterns of prescribing exist in the commercially insured or Medicare population.

Thus, our results should be understood from Medicaid's perspective. Our data are also from Oregon, and generalizability to other states could be limited. The data do not reflect opioid use paid in cash.^{38,39} There could still remain factors which we could not control for but are correlated with indicators of opioid misuse, and this could potentially bias estimates.

CONCLUSIONS

Our study suggests that, at least in the Medicaid population, the majority of opioids are prescribed by a relatively small number of providers, to a relatively small number of patients. Those high-volume opioid prescribers and users are also more strongly associated with opioid misuse. Educational interventions, interventions that encourage overdose rescue medications, or reviews of utilization or appropriateness may be more feasible if focused on these high-volume but relatively small populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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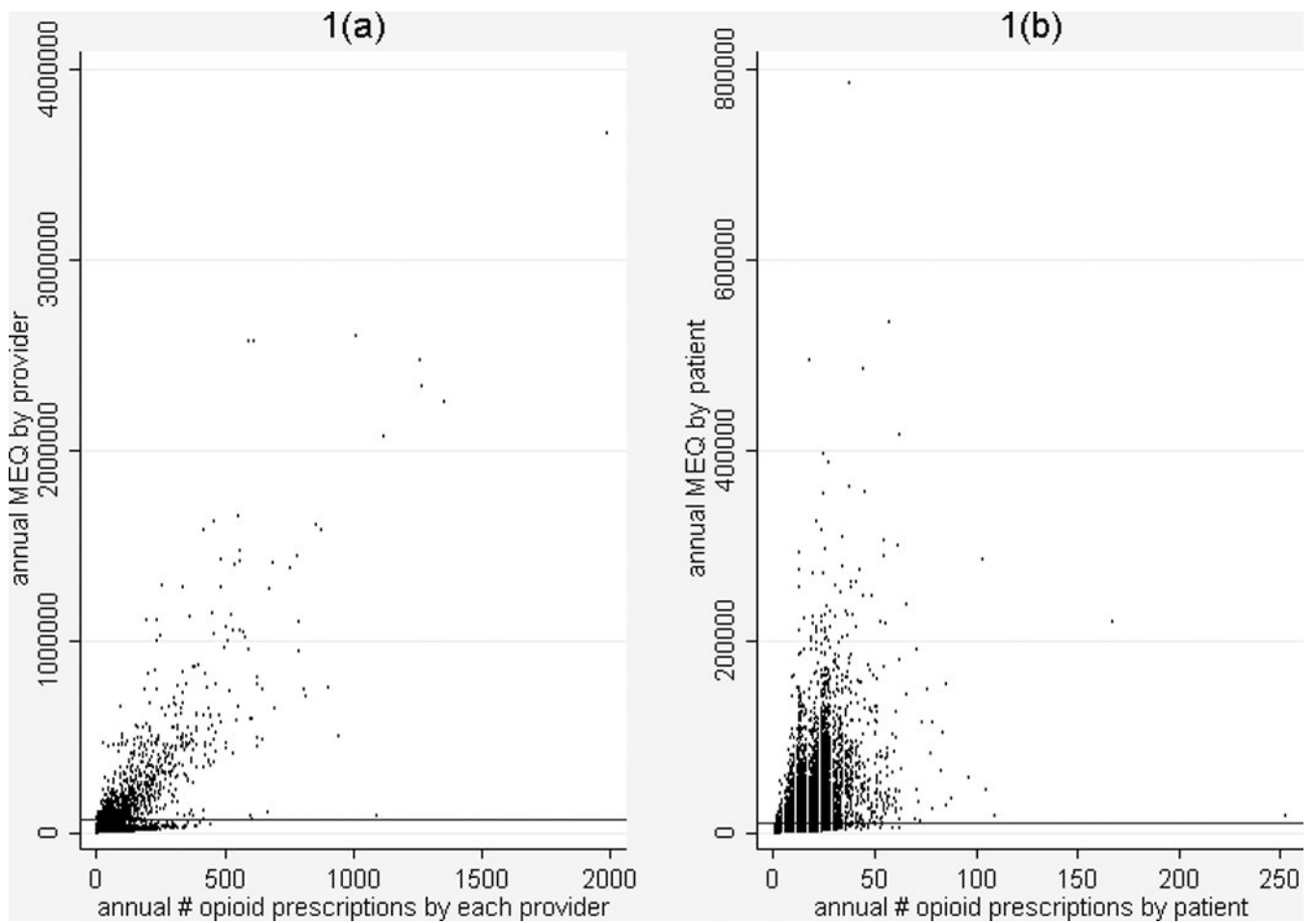


Figure 1. Concentration in opioid use and prescription

(a) Annual MEQ and number of opioid prescriptions by provider

(b) Annual MEQ and number of opioid prescriptions by patient

^a The reference lines (top 10% cutoff) for y-axis are at 68,383mg and 9,905mg MEQ in Figure 1(a) and Figure 1(b), respectively.

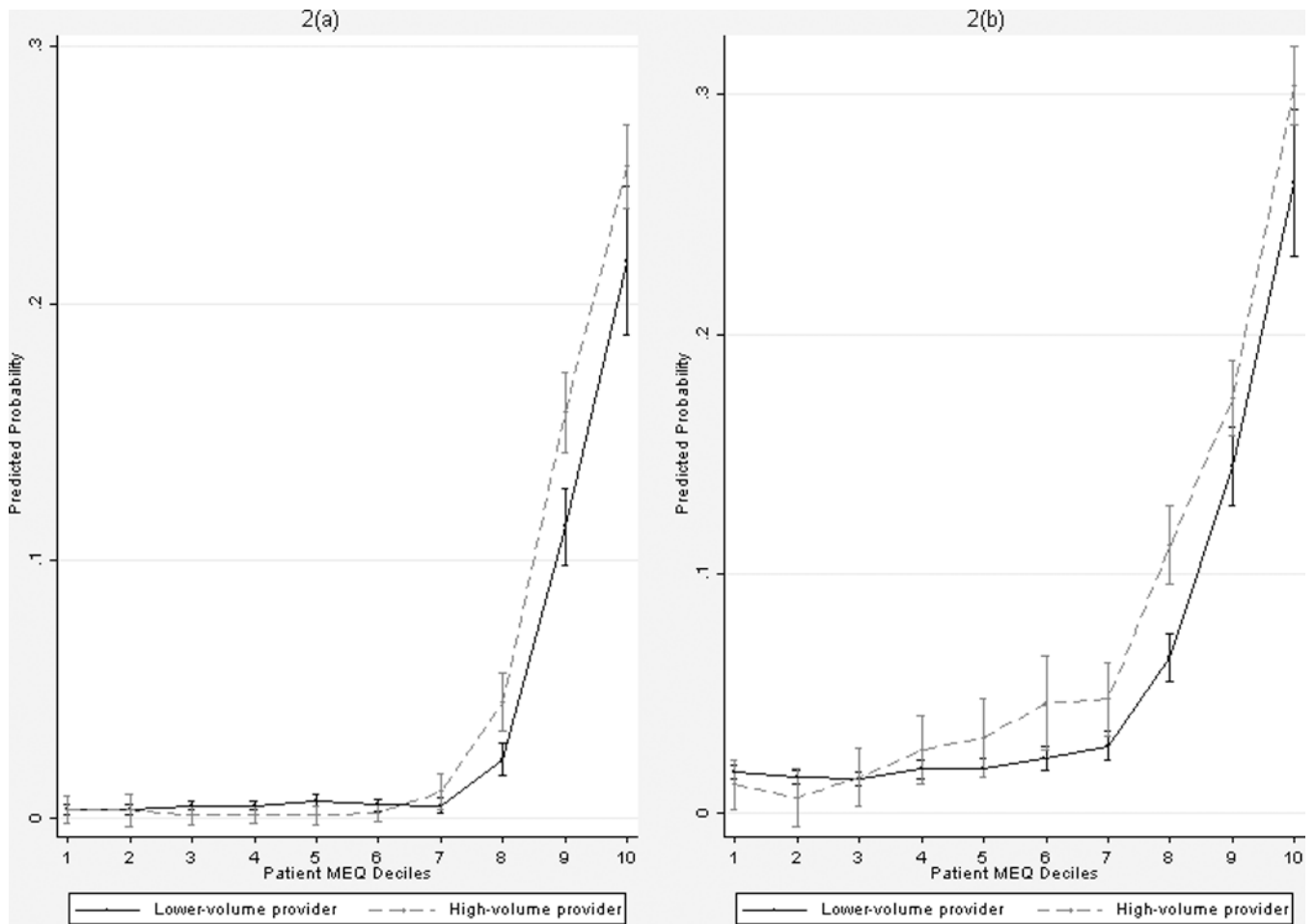


Figure 2. Predicted probability of opioid misuse (with 95% confidence interval) by lower- and high-volume opioid prescribers

(a) Opioid prescription overlap

(b) Opioid/benzodiazepine overlap

^a High-volume providers are the ones in the top MEQ decile with 68,383mg or higher MEQ.

^b Each equation was estimated using an ordinary least squares regression, with standard errors clustered on provider. Each outcome variable was then predicted and then how the predicted outcome varies across patient MEQ decile and lower-volume/high-volume provider was presented.

Table 1

Demographics, health characteristics, prescription opioid fill patterns, and opioid misuse across patient groups defined by opioid use

	Opioid users		
	Opioid non-users ^a (N=280,660)	Patients in lower MEQ deciles ^b (N=55,332)	Patients in top MEQ decile ^c (N=6,145)
Demographics			
Age Group %			
0–17	75.1	19.0	.08
18–39	15.7	48.9	24.4
40–59	7.6	27.6	62.1
60–79	1.6	4.5	13.3
80+	.02	.04	.00
Male %	47.6	34.0	37.8
Rurality of residence %			
Isolated small rural town	2.2	2.3	2.7
Small rural town	13.0	3.7	4.5
Large rural town	3.2	13.9	12.6
Urban	81.6	80.1	80.1
Pain-related diagnosis %			
Arthritis/joint pain	15.4	49.5	78.9
Back pain	5.0	31.1	62.0
Neck pain	2.0	12.2	26.2
Headache/migraine	1.8	9.0	12.3
Fractures	2.6	11.7	13.3
Visceral pain	1.0	9.2	12.5
Wound/injury	14.3	28.4	28.2
Neuropathy	0.9	6.5	18.4
Reproductive system pain	3.4	14.5	9.2
Other pain	0.2	1.1	4.6
Other diagnosis %			
Depression	5.6	21.7	35.9
Bipolar	.8	3.6	5.9
Schizophrenia	1.0	2.2	2.6
Alcohol problem	1.1	4.7	7.7
Drug problem	1.1	4.4	7.6
Opioid fill pattern			
# Opioid prescriptions ^d	--	3.3	18.8
Daily dose (MEQ mg) ^e	--	34.1	87.6
Opioid misuse %			
Doctor shopping	--	3.1	9.2

	Opioid non-users ^a (N=280,660)	Opioid users	
		Patients in lower MEQ deciles ^b (N=55,332)	Patients in top MEQ decile ^c (N=6,145)
Pharmacy shopping	--	.1	.7
Opioid prescription overlap	--	2.0	26.2
Opioid benzodiazepine overlap	--	3.7	32.7

^aOpioid non-users who were not continuously enrolled and/or eligible for Medicare were excluded.

^blower deciles indicate patients in deciles 1 through 9 in MEQ.

^cPatients in top decile got prescribed $\geq 9,905$ mg MEQ

^dThe standard deviation for # opioid prescription is 4.0 and 10.5 for patients in lower- and top MEQ decile, respectively.

^eThe standard deviation for daily dose is 22.2 and 72.6 for patients in lower- and top MEQ decile, respectively.

Table 2

Basic characteristics and opioid prescription pattern across provider groups defined by opioid prescription

	Opioid prescribers		
	Opioid non-prescribers (N=5,153)	Providers in lower MEQ deciles ^a (N=8,923)	Providers in top MEQ decile ^b (N=991)
Male %	52.7	56.7	56.6
Organization %			
Sole practice	19.7	16.5	14.4
Group practice	80.3	83.5	85.6
Type of providers %			
MD: Family medicine	7.1	13.0	39.5
MD: Internal medicine	20.6	13.7	23.4
MD: Emergency medicine	2.9	9.0	.9
MD: Ob/Gyn	2.0	5.5	.3
Nurse practitioner	11.6	8.2	14.4
Physician assistant	4.5	8.7	9.5
Dentist	4.6	10.6	.5
Others ^c	46.7	31.4	11.5
Opioid prescription pattern			
# Medicaid patients they prescribed opioid ^d	--	17.4	42.5
Daily dose (MEQ mg) in prescription ^e	--	46.3	77.7
Percent of providers ever prescribing >100mg MEQ per day %	--	34.4	96.8
Percent of providers ever prescribing >200mg MEQ per day %	--	8.2	68.1

^aLower deciles indicate providers in deciles 1 through 9 in MEQ.

^bProviders in top decile got prescribed $\geq 68,383$ mg MEQ

^cOther types of providers include 69 different types of providers including MDs in orthopedic surgery, neurology, pediatrics, and etc.

^dThe standard deviation for # Medicaid patients they prescribed opioid is 31.5 and 47.0 for opioid prescribers in lower and top decile, respectively.

^eThe standard deviation for daily dose in prescription is 31.1 and 49.9 for opioid prescribers in lower and top decile, respectively.

Table 3

Linear probability regression results of opioid misuse

MEQ deciles	(1) Doctor shopping (N=61,477)		(2) Pharmacy shopping (N=61,477)		(3) Opioid prescription overlap (N=61,477)		(4) Opioid/benzodiazepine overlap (N=61,477)	
	Coef	SE	Coef	SE	Coef	SE	Coef	SE
Decile 1:Ref group	--	--	--	--	--	--	--	--
Decile 2 (MEQ 61.2)	-.0017	.0010	.0000	.0001	-.0003	.0005	-.0027***	.0010
Decile 3 (MEQ 81)	-.0010	.0010	.0000	.0001	.0005	.0005	-.0018	.0010
Decile 4 (MEQ 112.5)	-.0040***	.0011	-.0002	.0001	-.0003	.0005	.0033**	.0014
Decile 5 (MEQ 151.2)	-.0094***	.0011	-.0005***	.0001	-.0002	.0006	.0014	.0013
Decile 6 (MEQ 240)	-.0128***	.0013	-.0007***	.0002	-.0007	.0008	.0088***	.0018
Decile 7 (MEQ 390)	.0051**	.0025	-.0011***	.0002	.0008	.0012	.0199***	.0024
Decile 8 (MEQ 750)	.1048***	.0055	.0021***	.0008	.0216***	.0026	.0673***	.0040
Decile 9 (MEQ 2,228)	.1099***	.0055	.0049***	.0010	.1338***	.0053	.1613***	.0054
Decile 10 (MEQ 9,905)	.0796***	.0048	.0065***	.0011	.2488***	.0069	.2988***	.0067

^aIn each regression, other control variables include patient demographics (age, gender, and rurality), pain-related diagnoses (joint pain, back pain, neck pain, headache, fractures, visceral pain, wound/injury, neuropathy, reproductive system pain, and other pain) other diagnoses (depression, bipolar, schizophrenia, alcohol program, and drug problem), risk-adjusters of CDPS, and coordinated care organization.

^bEach regression is estimated using an ordinary least squares regression.

^c*** p<0.01, ** p<0.05