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Using Prescription Drug Monitoring Program Data to Assess Likelihood of Incident Long-Term Opioid Use: a Statewide Cohort Study

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BACKGROUND: Limiting the incidence of opioid-naïve patients who transition to long-term opioid use (i.e., continual use for > 90 days) is a key strategy for reducing opioid-related harms.

OBJECTIVE: To identify variables constructed from data routinely collected by prescription drug monitoring programs that are associated with opioid-naïve patients' likelihood of transitioning to long-term use after an initial opioid prescription.

DESIGN: Statewide cohort study using prescription drug monitoring program data

PARTICIPANTS: All opioid-naïve patients in California (no opioid prescriptions within the prior 2 years) age ≥ 12 years prescribed an initial oral opioid analgesic from 2010 to 2017.

METHODS AND MAIN MEASURES: Multiple logistic regression models using variables constructed from prescription drug monitoring program data through the day of each patient's initial opioid prescription, and, alternatively, data available up to 30 and 60 days after the initial prescription were constructed to identify probability of transition to long-term use. Model fit was determined by the area under the receiver operating characteristic curve (C-statistic).

KEY RESULTS: Among 30,569,125 episodes of patients receiving new opioid prescriptions, 1,809,750 (5.9%) resulted in long-term use. Variables with the highest adjusted odds ratios included concurrent benzodiazepine use, ≥ 2 unique prescribers, and receipt of non-pill, non-liquid formulations. C-statistics for the day 0, day 30, and day 60 models were 0.81, 0.88, and 0.94, respectively. Models assessing opioid dose using the number of pills prescribed had greater discriminative capacity than those using milligram morphine equivalents.

CONCLUSIONS: Data routinely collected by prescription drug monitoring programs can be used to identify patients who are likely to develop long-term use. Guidelines for new opioid prescriptions based on pill counts may be simpler and more clinically useful than guidelines based on days' supply or milligram morphine equivalents.

KEY WORDS: opioid analgesics; pain; prescription drug monitoring programs; long-term opioid use; health policy.

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INTRODUCTION

States, insurers, and health systems have implemented many initiatives to decrease opioid prescribing in order to stem opioid use disorder and overdose.[1] These efforts have focused on reducing opioid use among patients taking opioids for chronic pain and minimizing new opioid use among opioid-naïve patients. A key goal of the latter strategy is to decrease the number of opioid-naïve patients who transition to long-term opioid use. One of the most prominent policy initiatives aimed at reducing long-term use has been the Centers for Disease Control and Prevention (CDC)'s opioid prescribing guidelines.[2] These guidelines recommend that clinicians limit new prescriptions to ≤ 7 days' supply, avoid doses > 50 mg morphine equivalents (MME) per day, review patients' records in the state's prescription drug monitoring program (PDMP) before prescribing opioids, and reassess the need for opioids 4 weeks after the initial prescription and regularly thereafter.

Payers, pharmacies, and health systems have responded to these guidelines by limiting the days' supply or daily dose clinicians can prescribe to opioid-naïve patients.[3,4] Patients prescribed longer days' supply or higher doses are more likely to develop long-term use;[5,6] however, these individual factors are only modest predictors of long-term opioid use and

overdose risk.[7] Thus, experts and guideline authors have cautioned against rigid dose thresholds and called for more nuanced approaches to assessing patient risk when starting prescription opioids.[8,9]

PDMPs record detailed, timely information on all controlled substance prescriptions dispensed from outpatient pharmacies in a state regardless of payment type; they also include a web interface clinicians can use to check a patient's prescription history in real time. A prior study using Oregon PDMP data conducted bivariate analyses of prescription characteristics associated with incident long-term opioid use.[10] To our knowledge, no study has conducted multivariable analysis using PDMP data to assess patients' overall risk of long-term use.

We used PDMP data to construct a cohort of all opioid-naïve patients in California who received an initial opioid prescription between 2010 and 2017 and then examined the prescription, patient, prescriber, and area-level factors potentially associated with patients' likelihood of transitioning to long-term opioid use (i.e., continued opioid use ≥ 90 days after their initial prescription). We constructed models using PDMP data through the day of the initial prescription and, alternatively, data up to 30 and up to 60 days after the initial prescription. These models incorporate data that would be available to clinicians writing a patient's initial opioid prescription and when checking the PDMP during follow-up visits 30 or 60 days later.

METHODS

This study was approved by the University of California, Davis Institutional Review Board, and the California Committee for the Protection of Human Subjects.

Prescription data were obtained from California's PDMP. Data included all Schedule II–IV prescriptions dispensed by outpatient pharmacies in California in 2008–2017. Prescription records included date dispensed, National Drug Code, quantity, strength per unit, days' supply, patient age, sex, and 5-digit ZIP code of patient residence. Records contained encrypted patient, prescriber, and pharmacy identifiers allowing us to track patients, prescribers, and pharmacies over time. We identified medications by cross-referencing National Drug Codes against prescription drug compendia. A clinical pharmacist manually reviewed and classified ambiguous medications.

Our cohort comprised all opioid-naïve patients in California age ≥ 12 years who received a new oral opioid analgesic prescription between 2010 and 2017 (Fig. 1). Patients were considered opioid naïve if they had no opioid prescriptions in the 2 years preceding their new prescription. Patients receiving a new opioid prescription > 2 years after their previous prescription were considered opioid naïve for each such instance during the study period. Opioid-containing antitussives (0.66% of all prescriptions), injectable (0.25%), and compounded opioid

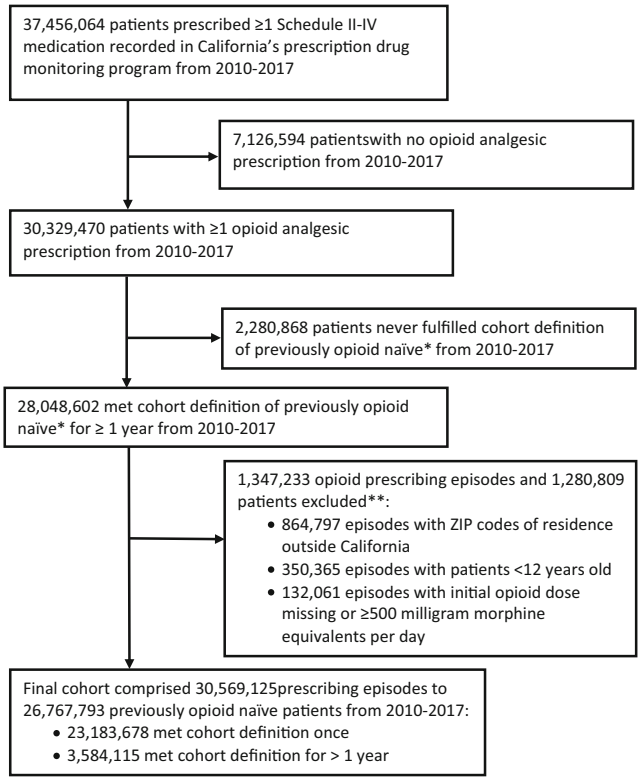

Figure 1 Identification of previously opioid-naïve patients from California's prescription drug monitoring program, 2010–2017. *Patients receiving a new opioid analgesic prescription and no active opioid prescription during the prior 2 years (730 days) were included in our cohort. Thus, patients who received an additional opioid prescription < 730 days after the run-out date of their prior opioid prescription were eligible to be in the cohort in more than 1 year. **Exclusion criteria were applied separately to each prescribing episode. For example, if a patient had one new prescribing episode in 2011 at age 10 and a second new prescribing episode in 2016 at age 15, then the prescribing episode in 2010 was excluded due to patient age and episode in 2016 was retained in the final cohort.

formulations (0.36%) were excluded. Buprenorphine formulations typically prescribed to treat opioid use disorder (1.64%) were also excluded; however, patients receiving these formulations were not considered opioid naïve. Patients with an initial opioid dose of ≥ 500 MME per day were excluded because in our clinical experience such patients are unlikely to be truly opioid naïve. Patients residing in ZIP codes outside California and prescription records with missing quantity (< 0.001% of all records) or patient identifier (0.5%) were also excluded.

Incident long-term opioid use was defined as an episode of opioid use lasting > 90 days with ≥ 3 opioid prescriptions and ≤ 60 days between the run-out date of one prescription and the dispensing date of the next. The 90-day threshold is based on prior observations that patients taking opioids for > 90 days tend to stay on opioids for years.[11] Our definition, adapted from prior studies,[12,13] assumes that patients consume opioids over the time period specified by the days' supply variable and consume the same dose each day. The definition allows for

gaps between prescriptions because days' supply is usually calculated based on the maximum allowed daily consumption and substantially underestimates anticipated duration for many opioid prescriptions, particularly new prescriptions, which usually instruct patients to take opioids "as needed," not on a fixed schedule.

We identified potential independent variables based on clinical experience and prior research[5,10,13–16] and operationalized them with the goal of constructing straightforward, clinically meaningful measures that took maximum advantage of available data. We favored the number of pills prescribed when constructing variables related to opioid dose, because pill counts do not depend on the days' supply variable or MME conversion factors.[13] We also examined dose based on total prescribed MME because MMEs are commonly used in research and define dose thresholds in the CDC guidelines.[2]

The numbers of pills prescribed, of prescriptions, and of unique opioid prescribers were highly correlated. To avoid multicollinearity, we created 3 variables based on cumulative totals from PDMP data: ratio of total pills prescribed to total prescriptions, ratio of total prescriptions to total unique opioid prescribers, and number of unique opioid prescribers.

Liquid opioid formulations (e.g., syrup) and other non-pill, non-liquid formulations (e.g., transdermal patch) comprised < 2% of all prescriptions and were not included in dose-related variables; quantities and strengths of these formulations are not directly comparable to pills. These formulations are also prescribed to opioid-naïve patients in unusual clinical circumstances, such as the inability to swallow.

Additional opioid-related independent variables were whether the patient was prescribed long-acting opioids, initial prescription opioid type (e.g., hydrocodone), and number of unique pharmacies filling opioid prescriptions. The day 30 and day 60 models included a variable indicating the change in each patient's total opioid pill count across all active prescriptions at day 30 and day 60 versus day 0.

We also included 2 variables indicating whether patients had an active prescription for a benzodiazepine or for any non-opioid, non-benzodiazepine controlled substance. To account for prescriber-level effects, we included a variable indicating whether the patient had received an opioid prescription from a prescriber in the top 5 percent of high-dose opioid prescribers using a formula adapted from Ringwalt et al.[17]

Finally, we included 2 area-level variables associated with opioid-prescribing rates.[18] We converted patient ZIP codes to ZIP code tabulation areas (ZCTAs) using a census relationship file[19] and obtained ZCTA-level measures of socioeconomic status and rurality from the 2013–2017 American Community Survey.[20] We constructed a socioeconomic status index based on the Yost criteria[21] using the first component from a principal component analysis of these rank-transformed variables: median household income; proportion of residents unemployed; proportion of households below 150% of the poverty threshold; and proportion of residents employed in the service, natural resource, construction, maintenance, production, transportation, or material moving industries. This index was categorized into quintiles. Rural status was determined from the 2010 Rural Urban Commuting Area Codes,[22] which were condensed into a binary "metropolitan" or "non-metropolitan" classification.

Our 2-year "lookback" period to identify opioid-naïve patients was more stringent than the 1-year or 6-month periods used elsewhere.[10,23,24] Nevertheless, patients could be classified as opioid naïve more than once, so we included a binary variable indicating whether the episode was the patient's first (i.e., earliest) in the dataset or one or more prior episodes had been included. Models also included patient sex, age, calendar year, and socioeconomic quintile, and rural status based on patients' ZIP code. Patients with missing or inconsistent values for sex, rural status, or socioeconomic quintile (all < 0.5%) were retained in analyses by including an "unknown" category for each of these variables.

We constructed 3 multiple logistic regression models with incident long-term opioid use as the dependent variable. The day 0 model used PDMP data through the day of each patient's initial prescription. The day 30 and day 60 models used PDMP data up to the first 30 or 60 days after the initial prescription. Mixed effects analyses accounting for within-patient correlation between episodes did not substantively change parameter estimates or inflate standard errors, so for simplicity, we report standard logistic regression models. Model fit was assessed by area under the receiver operating characteristic curve (C-statistic). Analyses were conducted using SAS 9.4.

We constructed separate models for each calendar year and examined differences in model parameters to determine whether testing interactions between year and other independent variables was warranted. We examined separate models for men and women to identify potential interactions involving

Table 1 Prevalence of Incident and Long-Term Opioid Use among Opioid-Naïve Patients in California, 2010–2017

Year	Patients with a new opioid prescription	Patients who transitioned to long-term use	Patients in cohort during prior years*
2010	3,879,007	221,197 (5.7%)	0
2011	3,901,591	235,118 (6.0%)	0
2012	3,759,169	224,897 (6.0%)	125,812 (3.3%)
2013	3,628,933	214,053 (5.9%)	359,691 (9.9%)
2014	3,938,476	286,980 (7.3%)	626,303 (15.9%)
2015	4,076,313	250,524 (6.1%)	819,662 (20.1%)
2016	3,824,390	204,187 (5.3%)	898,135 (23.5%)
2017	3,561,246	172,794 (4.9%)	971,729 (27.3%)
Total	30,569,125	1,809,750 (5.9%)	3,801,332 (12.4%)

**Study cohort comprised patients receiving a new opioid analgesic prescription with no active opioid prescriptions during the prior 2 years (730 days). Thus, patients who received an additional opioid prescription > 730 days after the run-out date of their prior opioid prescription were eligible to be in the cohort in more than 1 year. Our cohort starts in 2010 and our definition of opioid naïve requires 2 years without an opioid prescription, so by definition all patients with a new prescription in 2010 or 2011 appeared in the cohort for the first time*

sex. We also constructed models using MME-based measures of opioid quantity, because most prior studies on this topic have used MME-based definitions.[10,25,26] Finally, we conducted sensitivity analyses excluding patients whose initial prescription included a long-acting opioid (because patients are often started on long-acting formulations when long-term use is expected) and including only the first episode for each patient.

RESULTS

Our cohort comprised 26,767,793 previously opioid-naïve patients with 30,569,125 new prescription episodes, of which 5.9% led to long-term use (Table 1). The proportion of patients transitioning to long-term use peaked in 2014 (7.3%). Patients were 56.7% female with a mean age of 46.8 (SD 19.8); 93.5% lived in metropolitan areas. Most initial prescriptions contained hydrocodone (66.9%), followed by codeine (13.8%), oxycodone (8.3%), and tramadol (6.5%). PDMPs only recorded tramadol prescriptions after tramadol was moved to Schedule IV in 2014; 14.5% of initial prescriptions in 2015-2017 contained tramadol.

Table 2 shows distributions of prescription-related independent variables for day 0, day 30, and day 60 models. The median initial quantity for patients who did not develop long-term use was 24 pills versus 60 pills for patients who did. Compared to day 0, the number of pills prescribed at 30 and 60 days decreased for patients who did not develop long-term use; it was stable for patients who did.

Table 3 shows results for our final day 0, day 30, and day 60 logistic regression models. Parameter estimates were nearly all statistically significant ($P < 0.05$). C-statistics for the day 0, day 30, and day 60 models were 0.81, 0.88, and 0.94, respectively. Variables with the highest adjusted odds ratios (aOR) in the day 0 model were active benzodiazepine (aOR 1.72), other controlled substance (aOR 2.43), long-acting opioid (aOR 3.06), and non-pill, non-liquid formulation (aOR 6.67). The latter variable comprised nearly all transdermal patches (91% fentanyl, 9% buprenorphine).

In the day 30 model, benzodiazepine (aOR 2.42), other controlled substance (aOR 2.42), and non-pill, non-liquid opioid formulation (aOR 5.90) again had the highest aORs. Receiving prescriptions from ≥2 prescribers was also associated with long-term opioid use (aOR 2.56).

In the day 60 model, having an active non-pill, non-liquid opioid prescription effectively guaranteed transition to long-term use (aOR 25.50). Prescriptions from ≥ 2 different prescribers (aOR 5.09), liquid formulations (aOR 2.97), benzodiazepines (aOR 2.76), and other controlled substances (aOR 2.21) also had high aORs.

The number of pills per prescription was modestly associated with long-term use (aOR 1.23–1.38, per 10 pill increase). For the day 0 model, this variable approximates the impact of a single prescription because 97.9% of episodes involved a single initial prescription. For a patient with a 5% baseline likelihood of becoming a long-term user, an increase in the initial prescription quantity by 10 pills corresponds to a 1.2% absolute increase in the likelihood of developing long-term use.

The number of prescriptions per prescriber became more strongly associated with long-term use as models incorporated more data. The aOR for prescriptions per prescriber was 1.04 in the day 0 model versus 2.30 in the day 60 model. Receiving prescriptions from ≥ 2 unique prescribers was strongly associated with long-term opioid use in day 30 and day 60 models but not in the day 0 model (aOR 0.93) because patients receiving initial prescriptions from ≥ 2 prescribers were at lower risk than patients receiving one initial prescription from a high-dose prescriber (i.e., the aOR for receiving prescriptions from ≥ 2 prescribers dropped when the high-dose prescriber variable was added).

Results by year and patient sex are shown in Appendix 1 and Appendix 2, respectively. Parameter estimates were largely stable across years and for men versus women, so we did not explore interactions involving year or sex.

The proportion of patients included more than once in our cohort increased with time (Table 1). Patients who had been in our study cohort previously were less likely to become long-term users (aOR 0.76) than patients appearing for the first time. In sensitivity analyses, models using MME-based measures of quantity (Appendix 3) had lower C-statistics than our primary models, particularly for day 0 (0.74 for the MME model versus 0.81 for the primary model). C-statistics were unchanged when we excluded patients with initial prescriptions for long-acting opioids (Appendix 4) or when we restricted analyses to patients' first appearance in our cohort (results not shown).

DISCUSSION

In this cohort study of all California residents, we used PDMP data to identify opioid-naïve patients and assess their risk of transitioning to long-term opioid use. The prevalence of incident long-term use in California (5.9%) aligns with estimates of 6.0% from a prior national study[5] and 5.0% from a study using Oregon PDMP data.[10] Strengths of our study include use of population-based data including all outpatient controlled substance prescriptions in California regardless of the health system or insurance status, use of a 2-year "lookback" period to define opioid-naïve patients, and accounting for patients who appeared in our cohort multiple times.

Several patient and prescription factors associated with higher likelihood of long-term opioid use in our analyses have been identified in prior population-based studies of incident long-term opioid use, including increased dose, more prescriptions, multiple prescribers or pharmacies, concurrent benzodiazepine use, long-acting opioid formulations, and tramadol.[5,6,10,25,27] Several of these studies examined only initial prescription characteristics; our multivariable study examined

Table 2 Description of Prescription Characteristics among Previously Opioid-Naïve Patients in California Based on the PDMP data Available 0, 30, and 60 Days after the Initial Opioid Prescription, 2010–2017

Variable	Day of initial prescription			30 days after initial prescription			60 days after initial prescription		
	No long-term use	Long-term use*	All patients	No long-term use	Long-term use*	All patients	No long-term use	Long-term use*	All patients
Ratio of opioid pills to opioid prescriptions, median (10^{th}, 90^{th} percentile)†	24 (12, 60)	60 (20, 120)	25 (12, 60)	25 (12, 60)	60 (24, 120)	28 (12, 60)	25 (12, 60)	60 (27, 120)	28 (12, 60)
Ratio of opioid prescriptions to unique opioid prescribers, median (10^{th}, 90^{th} percentile) †	1 (1, 1)	1 (1, 1)	1 (1, 1)	1 (1, 1)	1 (1, 2)	1 (1, 1.5)	1 (1, 1.5)	2 (1, 4)	1 (1, 2)
≥2 unique opioid prescribers, %†	0.2%	0.4%	0.2%	7.8%	23.0%	8.7%	10.1%	39.9%	11.8%
≥2 unique pharmacies, %†	0.3%	0.4%	0.3%	4.1%	13.3%	4.6%	5.3%	24.6%	6.4%
Change in total number of pills for all active prescriptions since day 0, median (10^{th}, 90^{th} percentile)†	–	–	–	- 20 (- 45, - 6)	0 (- 60, 90)	- 20 (- 45, 0)	- 24 (- 60, 10)	0 (- 90, 60)	- 24 (- 60, - 10)
Prescription from a high-dose prescriber, %†‡	5.3%	20.2%	6.2%	6.0%	24.6%	7.1%	6.2%	29.2%	7.6%
Liquid opioid prescription, %	1.9%	1.2%	1.8%	0.2%	0.5%	0.2%	0.1%	0.5%	0.1%
Non-pill, non-liquid opioid prescription, %	0.2%	1.7%	0.3%	0.2%	2.3%	0.3%	0.1%	2.3%	0.2%
Long-acting opioid prescription, %	0.8%	6.4%	1.2%	0.5%	7.9%	1.0%	0.1%	7.3%	0.6%
Benzodiazepine prescription, %	4.9%	8.3%	5.1%	3.1%	15.4%	3.8%	2.3%	15.1%	3.1%
Non-opioid, non-benzodiazepine controlled substance prescription, %	1.7%	4.9%	1.9%	0.1%	0.6%	0.1%	0.1%	0.6%	0.1%

**An episode of opioid use lasting >90 days after the initial prescription, including at least 3 opioid prescriptions with no more than a 60-day gap between the run-out date of one prescription and the start date of the subsequent prescription*

†Only opioid prescriptions for opioid pill formulations (e.g., capsules, tablets, pills) were used to calculate these variables

‡Prescribers were ranked according to the following metric for high-dose prescribing adapted from the formula used by Ringwalt et al.[17]: Total number of instances during the prior calendar month that the prescriber wrote opioid pill prescriptions to a patient on the same day with a total daily dose of ≥ 100 mg morphine equivalents, divided by the number of days during the prior calendar month that the prescriber wrote ≥1 opioid pill prescription. Patients with ≥1 active prescription from a prescriber who was in the top 5 percent of this metric were classified as receiving opioids from a high-dose prescriber

variables at 0, 30, and 60 days after an initial prescription and was much larger than prior studies. We also identified several factors associated with long-term opioid use that, to our knowledge, have not been previously reported: concurrent receipt of other controlled substances, change in dose over 30 or 60 days, and receipt of transdermal or liquid (versus pill) formulations. These findings may help clinicians identify patients likely to continue receiving opioids long term, both when clinicians are considering prescribing opioids and when they are re-assessing patients after an initial prescription.

Our finding that patients are more likely to take opioids long-term if they see a high-dose prescriber is also novel, though prior research has found prescriber-level effects in emergency department settings.[15,28] It is also notable that aORs were generally stable over 8 years, despite substantial nationwide declines in overall opioid prescribing rates in 2016 and 2017.[29]

Finally, we found that models based on the number of pills prescribed had better discriminative capacity than models based on total MME prescribed, particularly for models based on initial prescription characteristics. This may be partially due to the fact that MME conversion factors are imprecise and differ among patients.[13,30] Alternatively, risks of overconsumption and of developing tolerance and physical

Table 3 Multivariable Logistic Regression Models for Incident Long-Term Opioid Use among Opioid-Naïve Patients in California Using PDMP Data Available 0, 30, and 60 Days after the Initial Opioid Prescription, 2010–2017

Variable	Day of initial prescription		30 days after initial prescription		60 days after initial prescription	
	C-statistic = 0.81		C-statistic = 0.88		C-statistic = 0.94	
	aOR	95% CI	aOR	95% CI	aOR	95% CI
Patient characteristics						
Age (per year older)	1.02	1.02–1.02	1.01	1.01–1.01	1.01	1.01–1.01
Male sex*	1.02	1.02–1.03	1.01	1.01–1.02	1.00	0.99–1.00
Present in cohort during prior years†	0.76	0.76–0.77	0.81	0.80–0.81	0.84	0.84–0.85
Prescription characteristics						
Ratio of opioid pills to opioid prescriptions‡§	1.23	1.23–1.23	1.25	1.25–1.25	1.38	1.38–1.38
Ratio of opioid prescriptions to unique opioid prescribers‡	1.04	1.03–1.05	1.59	1.59–1.59	2.30	2.30–2.31
≥2 unique opioid prescribers‡	0.93	0.90–0.96	2.56	2.55–2.57	5.09	5.06–5.11
≥2 unique pharmacies‡	1.06	1.03–1.10	1.33	1.32–1.34	1.43	1.42–1.43
Change in number of opioid pills for all active prescriptions since day 0‡§	–	–	1.11	1.11–1.11	1.16	1.16–1.16
Prescription from a high-dose prescriber‡	1.65	1.64–1.65	1.41	1.40–1.42	1.32	1.32–1.33
Liquid opioid prescription	0.55	0.54–0.56	1.02	0.99–1.05	2.97	2.85–3.09
Non-pill, non-liquid opioid prescription	6.67	6.56–6.79	5.90	5.79–6.00	25.50	24.80–26.21
Long-acting opioid prescription	3.06	3.03–3.09	1.59	1.57–1.60	1.80	1.77–1.82
Opioid in patient's initial opioid prescription						
Hydrocodone	Ref	–	–	–	–	–
Codeine	0.61	0.61 – 0.62	0.69	0.69 – 0.70	0.80	0.80 – 0.81
Tramadol	1.57	1.56–1.58	1.69	1.68–1.70	1.94	1.92–1.95
Oxycodone	0.92	0.91–0.92	0.82	0.81–0.82	0.72	0.71–0.72
Other¶	1.16	1.15–1.17	0.95	0.95–0.96	0.86	0.85–0.87
Benzodiazepine prescription	1.72	1.71–1.73	2.42	2.41–2.44	2.76	2.74–2.78
Non-opioid, non-benzodiazepine controlled substance prescription	2.43	2.37–2.49	2.42	2.36–2.49	2.21	2.14–2.28
Area-level characteristics						
Socioeconomic status#						
Very high	Ref	–	–	–	–	–
High	1.30	1.30–1.31	1.27	1.26–1.28	1.25	1.24–1.26
Medium	1.48	1.47–1.49	1.45	1.44–1.46	1.45	1.44–1.46
Low	1.62	1.62–1.63	1.56	1.55–1.57	1.56	1.55–1.57
Very low	1.79	1.78–1.80	1.75	1.74–1.76	1.82	1.81–1.83
Rural area**	1.19	1.19–1.20	1.15	1.14–1.16	1.12	1.11–1.13

aOR, adjusted odds ratio; 95% CI, 95% confidence interval; models are adjusted for all listed covariates and for calendar year

**Category of missing / unknown sex (n = 10,741, 0.04%) not shown; reference category is female sex*

†This variable was set to 0 for all patients in 2010 and 2011, because our cohort started in 2010 and our definition of opioid naïve required at least 2 years without an opioid prescription before patients were eligible for inclusion more than once

‡Only opioid prescriptions for opioid pill formulations (e.g., capsules, tablets, pills) were used to calculate these variables

§Odds ratio corresponds to a 10-unit increase in the predictor

Prescribers were ranked according to the following metric for high-dose prescribing adapted from the formula used by Ringwalt et al.[17]: Total number of instances during the prior calendar month that the prescriber wrote opioid pill prescriptions to a patient on the same day with a total daily dose of ≥100 milligram morphine equivalents, divided by the number of days during the prior calendar month that the prescriber wrote ≥1 opioid pill prescription. Patients with ≥1 active prescription from a prescriber who was in the top 5 percent of this metric were classified as receiving opioids from a high-dose prescriber

¶Includes all opioids except for tramadol, hydrocodone, codeine, and oxycodone, as well as all patients prescribed >1 opioid type on the day of their incident prescription

#Category of missing / unknown SES (n = 90,208, 0.30%) not shown; reference category is very high

***Category of missing / unknown area status (n = 58,601, 0.19%) not shown; reference category is metropolitan area*

dependence may be greater when patients have more pills, regardless of potency. Policymakers and insurers should consider developing guidelines for new opioid prescriptions based on pill counts rather than MME or days' supply. Such guidelines (already used by some states[31]) would have several advantages. Using pill counts avoids the need to calculate MMEs and consider days' supply and is simpler for patients taking >1 opioid.

All 3 of our models had good discriminatory capacity. Even models using only data through the day of the incident opioid prescription and up to 30 days afterwards effectively discriminated between patients who would and would not transition to long-term use (C-statistics 0.81 and 0.88, respectively). For reference, Framingham-type models widely used in clinical practice to assess cardiovascular risk typically have C-statistics <0.75.[32]

These results demonstrate that PDMP prescription data can help characterize opioid-naïve patients' overall likelihood of transitioning to long-term opioid use. Clinicians in many states are required to check PDMPs before writing new opioid prescriptions, and most PDMP web interfaces report simple PDMP-based metrics related to overdose risk (e.g., prescriptions from multiple prescribers and pharmacies[33]). Experts have called for PDMPs to

incorporate more sophisticated clinical warnings that translate information collected by PDMPs into more clinically useful indicators.[34] To our knowledge, no PDMPs have yet done so. Future research could build on our results to construct risk assessment models. Such models could eventually be incorporated into PDMP web interfaces, giving clinicians additional information to inform prescribing decisions. Design and implementation of risk assessment tools would need to include stakeholder input to avoid unintended consequence (e.g., promoting one-size-fits-all prescribing).

We used data from a single state with lower opioid-prescribing rates than the national average,[35] so our results may not generalize to other states. However, California is also the largest state—our model incorporates 12% of the US population—and has large within-state variation in sociodemographics. Some patients identified as opioid naïve were likely patients taking opioids who moved to California from elsewhere; similarly, we could not identify patients who left California and continued to use opioids. PDMP data only includes prescriptions from outpatient pharmacies and does not collect data on patient race or ethnicity. Finally, PDMPs do not collect clinical data that would enable the identification of patients for whom long-term opioid use is likely clinically appropriate. Despite these limitations, it is clearly valuable to characterize the extent to which statewide PDMP data can identify opioid-naïve patients' likelihood of transitioning to long-term use.

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