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High-Risk Prescribing to Medicaid Enrollees Receiving Opioid Analgesics: Individual- and County-Level Factors

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Abstract

Background—Prescription opioid overdoses have increased dramatically in recent years, with the highest rates among Medicaid enrollees. High-risk prescribing includes practices associated with overdoses and a range of additional opioid-related problems.

Objectives—To identify individual- and county-level factors associated with high-risk prescribing among Medicaid enrollees receiving opioids.

Methods—In a four-states, cross-sectional claims data study, Medicaid enrollees 18–64 years old with a new opioid analgesic treatment episode 2007–2009 were identified. Multivariate regression analyses were conducted to identify factors associated with high-risk prescribing, defined as high-dose opioid prescribing (morphine equivalent daily dose ≥ 100 mg for >6 days), opioid overlap, opioid-benzodiazepine overlap.

Results—High-risk prescribing occurred in 39.4% of episodes. Older age, rural county of residence, white race, and major depression diagnosis were associated with higher rates of all types of high-risk prescribing. Individuals with prior opioid, alcohol, and hypnotic/sedative use disorder diagnoses had lower odds of high-dose opioid prescribing but higher odds of opioid overlap and opioid-benzodiazepine overlap than individuals without such disorders. High-dose opioid prescribing in Massachusetts was less common than in California, Illinois, and New York, whereas the rate of benzodiazepine overlap in Massachusetts was more common than in other states.

Conclusions/Importance—High-risk prescribing was common and associated with several important demographic, clinical, and community factors. Findings can be used to inform targeted

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Declaration of interest

The authors declare that they have no conflict of interest. The authors alone are responsible for the content and writing of the article.

interventions designed to reduce such prescribing, and given state variation observed, further research is needed to better understand the effects of state policies on high-risk prescribing.

Keywords

Opioid analgesics; Medicaid; county characteristics; individual characteristics; depression; benzodiazepines

Introduction

Opioid addiction and overdoses are significant public health issues, with prescription opioid use and associated deaths increasing dramatically in recent decades (Rudd, Aleshire, Zibbell, & Gladden, 2016). At the federal level, multiple efforts to improve opioid prescribing practices include establishing prescribing guidelines for chronic noncancer pain (Dowell, Haegerich, & Chou, 2016), eliminating payments tied to patient survey questions about pain control that might unintentionally incentivize over-prescription of opioids (Centers for Medicaid and Medicare Services, n.d.), and supporting Prescription Drug Monitoring Programs (PDMPs), which by 2017 operate in every state but Missouri, and can assist in identifying patterns associated with higher risk for health harms, such as receiving opioids from multiple prescribers or pharmacies (Dowell, Zhang, Noonan, & Hockenberry, 2016; Katz et al., 2010; Logan, Liu, Paulozzi, Zhang, & Jones, 2013; Meara et al., 2016; Patrick, Fry, Jones, & Buntin, 2016; Paulozzi, Kilbourne, & Desai, 2011; Reifler et al., 2012; Reisman, Shenoy, Atherly, & Flowers, 2009; Wen, Schackman, Aden, & Bao, 2017).

Increased opioid analgesic use is associated with increased opioid-related morbidity and mortality, but specific high-risk prescribing practices such as high morphine equivalent daily doses (MEDD), overlapping opioid prescriptions (Liu, Logan, Paulozzi, Zhang, & Jones, 2013; Mack, Zhang, Paulozzi, & Jones, 2015; Paulozzi, Strickler, Kreiner, & Koris, 2015), and overlapping opioid and benzodiazepine prescriptions are associated with higher rates of negative outcomes, including opioid abuse and misuse (Hall et al., 2008), increased emergency department use and hospitalizations (Braden et al., 2010), and overdoses (Baumblatt et al., 2014; Dilokthornsakul et al., 2016; Ekstrom, Bornefalk-Hermansson, Abernethy, & Currow, 2014; Hall et al., 2008; Park, Saitz, Ganoczy, Ilgen, & Bohnert, 2015). Recent studies have examined the extent of high-risk opioid prescribing (Liu et al., 2013; Logan et al., 2013; Mack et al., 2015; Meara et al., 2016; Paulozzi et al., 2015), finding that almost a quarter of some populations receive overlapping opioid (Liu et al., 2013; Mack et al., 2015) and opioid/benzodiazepine prescriptions (Hackman et al., 2014; Hwang et al., 2016; Larochelle, Zhang, Ross-Degnan, & Wharam, 2015; Liu et al., 2013; Mack et al., 2015; Yang et al., 2015), and up to 16% receive high dose MEDD prescriptions (Logan et al., 2013; Mack et al., 2015; Meara et al., 2016; Paulozzi et al., 2015).

Compared to nonenrollees, Medicaid enrollees are at higher risk of prescription opioid-related mortality (Centers for Disease Control, 2009; Fernandes, Campana, Harwell, & Helgersson, 2015; Sharp & Melnik, 2015) and have higher rates of mental health and substance use disorders (Adelmann, 2003), yet, relatively few studies examine high-risk prescribing in this population (Yang et al., 2015). Medicaid enrollees with comorbid mental

health, nonopioid substance use, and pain disorders appear to have higher rates of some types of high-risk prescribing than do enrollees without such characteristics (Stein et al., 2017).

Rates of high-risk opioid prescribing in non-Medicaid populations vary, with several studies finding higher rates among females, older patients (Hwang et al., 2016; Liu et al., 2013; Paulozzi et al., 2015; Yang et al., 2015), and individuals residing in rural and poorer counties (Stein et al., 2017). Community characteristics can affect the care residents receive (Dick et al., 2015; Stein et al., 2015; Stein, Gordon, et al., 2015), yet, the relative influence of individual- and county-level factors on high-risk opioid prescribing is relatively unexamined. To address this gap, our study examines individual- and county-level factors associated with multiple types of high-risk prescribing among Medicaid enrollees receiving opioid analgesics, hypothesizing that females, Caucasians, older patients, patients with depression or substance use disorders, and individuals residing in rural, low income counties will have higher rates of high-risk prescribing than Medicaid enrollees without these characteristics (Gu, Dillon, & Burt, 2010; Paulozzi & Xi, 2008; Tamayo-Sarver, Hinze, Cydulka, & Baker, 2003).

Methods

Data and study population

Using 2007–2009 Medicaid claims from California, Illinois, Massachusetts, and New York, we identified enrollees ages 18–64 years who had filled two or more valid opioid analgesic prescriptions in a calendar year, allowing us to examine overlapping opioid analgesic prescribing rates. The data were obtained prior to federal redaction of substance use disorder treatment related claims and were a subset of the most populous states available from a larger project examining opioid use disorders among Medicaid enrollees. We excluded dually eligible individuals and individuals not consistently Medicaid-enrolled, defined as at least nine months enrollment in a calendar year. Consistent with other studies of high-risk prescribing, we excluded individuals with a cancer diagnosis (ICD-9 codes 140–172.9; 174–215.9, 217–229.10; 235–239.9, 338.3) (Liu et al., 2013; Mack et al., 2015; Paulozzi, Zhou, Jones, Xu, & Florence, 2016; Yang et al., 2015). We identified new opioid treatment episodes from February 1, 2007 through June 30, 2009 using National Drug Codes (NDC), quantity dispensed, and days' supply in pharmacy claims. A new episode was defined as the period from the first observed fill date of any opioid prescription after a 30-day period with no filled opioid prescriptions, through the last day of medication in the last filled opioid prescription, with no more than a 29-day gap between opioid prescriptions. Multiple prescriptions from a single provider for different doses of the same drug filled on the same day were considered a single prescription. The Institution's IRB approved the study.

Measures of high-risk opioid prescribing

Consistent with prior studies, we created three measures of high-risk prescribing. The first, *high MEDD*, converts opioid prescriptions to an equivalent morphine daily dose (Ripamonti et al., 1998), facilitating comparisons among different formulations and strengths. Various cutoffs to define high-dose prescribing have been proposed, notably Washington State and

the Centers for Disease Control have advocated for cutoffs of 120 and 90 mg MEDD, respectively. To facilitate comparisons with other populations, for the present study, we used a commonly cited cutoff in the literature (Liu et al., 2013; Logan et al., 2013; Paulozzi et al., 2015) and defined high MEDD as MEDD of 100 mg or more for an episode of at least 7 days. Our second measure, *overlapping opioid prescriptions*, was defined as an episode of at least 14 days with a minimum of 7 days of opioid possession in which >25% of episode days had overlapping opioid prescriptions. This modification of definitions used in prior studies (Liu et al., 2013; Mack et al., 2015; Paulozzi et al., 2015) allowed us to identify extended periods when the daily opioid dose might possibly be greater than the prescriber intended due to early refills, doctor shopping, or poorly coordinated care. The final measure, *overlapping opioid and benzodiazepine prescriptions*, was defined as a benzodiazepine prescription of at least 5 days' supply filled during an episode. This is a commonly used measure of high-risk prescribing (Hwang et al., 2016; Liu et al., 2013; Mack et al., 2015; Yang et al., 2015) given that concomitant use of benzodiazepines and opioids increases risk of respiratory distress and overdose (Ekstrom et al., 2014).

Individual-level factors

Individuals were categorized as having pre-existing alcohol use disorder, opioid use disorder, hypnotic or sedative use disorder, or major depressive disorder if they had a claim containing the respective International Classification of Disease version 9 (ICD-9) diagnosis code in the year prior to the opioid treatment episode. Consistent with prior research on high-risk opioid use (Mack et al., 2015), we used ICD-9 codes for pain and service utilization within 14 days of the start of the opioid treatment episode to categorize individuals with acute pain, chronic pain, both acute and chronic pain, or no pain. Information on patient age, gender, and race/ethnicity were obtained from Medicaid files.

County-level factors

We examined county-level factors for the patient's county of residence that had previously been associated with potentially inappropriate prescribing or opioid misuse. County urbanicity was categorized based on Rural–Urban Continuum Codes (RUCC) from the Area Resource File (ARF) as (1) metropolitan (urban population of at least 50,000), (2) large nonmetropolitan (population of at least 20,000), (3) medium nonmetropolitan (population 2,500–20,000), and (4) small nonmetropolitan (population less than 2,500) (Service, 2013). Primary care provider (PCP) supply was defined as the number of nonfederal PCPs per 100,000 population, derived from the 2007–2010 Area Resource File. Median household income was calculated from the American Community Survey (ACS), and educational attainment was defined as the percentage of adults greater than 25 years of age with no high school degree. PCP supply, educational attainment, and median household income were categorized by quartile for the purpose of the analysis.

Analyses

We calculated descriptive statistics for the three indicators of high-risk prescribing separately. We also examined *any* high-risk prescribing practice, defined as the presence of any of the three indicators. We used multivariate logistic regression to identify the association of individual- and county-level factors with measures of high-risk prescribing,

conducting separate analyses for any high-risk prescribing, high MEDD, overlapping opioids, and overlapping opioids and benzodiazepines. We used state level fixed effects as well as clustered standard errors at the level of the individual to adjust for individuals with multiple episodes. Episodes with missing covariate data (<5% of episodes) were excluded from regressions.

Results

We identified 801,413 Medicaid enrollees with 1,863,684 opioid treatment episodes, 2.33 episodes (SD = 1.59) per enrollee (Figure 1).

High-risk prescribing was common, with 39.4% of episodes involving at least one measure of such prescribing (Table 1). High-dose opioid prescribing was most common (29.0% of episodes), followed by overlapping opioid and benzodiazepine (9.6%), and overlapping opioid (7.3%) prescriptions. Approximately one-third of episodes (33.2%) involved one type of high-risk prescribing, with multiple types of potentially inappropriate prescribing occurring in 6.3% of episodes. As compared to episodes with no high-risk prescribing indicators, episodes with at least one high-risk prescribing indicator on average had higher MEDD (181.0 mg (SD = 144.8 mg) vs. 131.6 mg (SD = 197.8)), longer episode lengths (65.4 days (SD=103.4 days) vs. 25.7 days (SD = 59.5 days)), and a higher number of prescription fills (8.5 (SD = 10.2) vs. 4.9 (SD = 6.0)) (Table 2).

Enrollees in the sample were aged 18–64 years with a relatively even distribution of episodes among age groups and the majority of episodes were attributed to females (73.5%) (Table 3). Several factors were consistently associated with both any high-risk prescribing (Table 3) and the various types of high-risk prescribing (Table 4). For example, the relationship between older age cohorts and all types of high-risk prescribing were relatively consistent and robust, with individuals aged 55 to 64 significantly more likely to experience any high-risk prescribing than individuals age 18 to 25 (52% vs. 24%, OR 3.35, 95% CI 3.30 to 3.40). Similarly, individuals living in nonmetropolitan counties were more likely to have any high-risk prescribing overall and across all indicators of high-risk prescribing, and blacks were significantly less likely to have high-risk prescribing than whites (37% vs. 41%; OR 0.73, 95% CI 0.73 to 0.74). Individuals with a recent prior diagnosis of major depression were also consistently more likely to have all types of high-risk prescribing, and significantly higher rates of any high-risk prescribing than individuals without major depression (51% vs. 38%; OR 1.42, 95% CI 1.40 to 1.44).

However, a number of other factors varied by prescribing indicator. For example, compared to individuals without such disorders, individuals with prior opioid, alcohol, or hypnotic/sedative use disorder diagnoses had lower odds of high MEDD but higher odds of overlapping opioid prescriptions and overlapping opioid and benzodiazepine prescriptions (Table 4). Individuals with only acute pain or only chronic pain were both more likely to have potentially inappropriate prescribing across all indicators than were individuals with no pain. However, this pattern did not hold for individuals with both acute and chronic pain. Such individuals were more likely than individuals with no pain to have high MEDD and overlapping opioids and benzodiazepines but were less likely to have overlapping opioids.

Overlapping opioid use rates were also significantly lower in females compared to males (6.6% vs. 9.2%, OR 0.76, 95% CI 0.75 to 0.77), but overlapping opioids and benzodiazepines and high MEDD were significantly higher for females as compared to males.

With respect to county characteristics such as PCP supply, household income, and county population without a high school diploma, there were some significant differences across quartiles from the referent quartile, but there did not appear to be a clinically meaningful pattern either within an indicator of high-risk prescribing or across indicators. However, we found very different patterns across states in measures of high-risk prescribing. For example, the rate of high MEDD in Massachusetts (16.7%) was slightly more than half that seen in California, Illinois, and New York, whereas the rate of opioid and benzodiazepine overlap in Massachusetts was substantially higher than the other states and more than double than that seen in New York (Table 4).

Discussion

In examining potentially inappropriate opioid prescribing among Medicaid enrollees with at least two opioid prescriptions in four populous states, we found relatively high rates of high-risk prescribing, with approximately 4 in 10 opioid treatment episodes involving at least one type. Our findings from a sample of over 800,000 Medicaid enrollees from four states with over 2 million opioid treatment episodes over a 3-year period complement recent examinations of opioid prescribing among a national sample of disabled Medicare beneficiaries (Meara et al., 2016; Paulozzi et al., 2015), with both finding high rates of high-risk prescribing. The higher rate of high dose opioid episodes we observe in Medicaid enrollees filling two or more opioid analgesic prescriptions in a year compared to rates seen in studies of populations receiving at least one prescription (Meara et al., 2016; Paulozzi et al., 2015) suggest that initiatives targeting such populations may increase efficiency while decreasing unintended consequences. The frequency with which opioid treatment episodes involve high-risk prescribing also reinforces the need for further research examining the relationship of such prescribing with negative clinical outcomes, the motivations among prescribers and patients involved in these behavior patterns, as well as efforts to identify interventions that are effective in aligning prescribing behavior more consistently with practice guidelines and safe prescribing practices.

In 2012, the 259 million opioid prescriptions written were enough for every adult in the United States to receive a prescription (CDC, 2014), and the United States is now the top consumer of opioids per capita in the world (Board, 1968). The growth in opioid analgesic prescriptions has been associated with an increase in opioid-related overdoses (CDC, 2014). Given the consistently documented increased risk for opioid-related overdoses among Medicaid enrollees, it is concerning that we found that approximately one-third of new opioid treatment episodes in our study population involved high dosages of opioids and that rates of overlapping opioids and overlapping opioids and benzodiazepines, while less frequent, were also high. Given the high rates of high-risk prescribing observed, we are encouraged by recent efforts such as the dissemination of recent guidelines from the Centers for Disease Control which explicitly mentions the importance of not prescribing

benzodiazepines concurrently with opioids and avoiding high dose opioids (Dowell et al., 2016).

Prescribing potentially addictive medications such as opioids and benzodiazepines to individuals previously treated for substance use disorders must be done thoughtfully, with clinicians weighing the benefits of treatment with the increased risk of relapse or precipitating a new substance use disorder. We found individuals with previously diagnosed opioid use, alcohol use, and hypnotic/sedative use disorders were all significantly less likely to receive high-dose opioids but were all more likely to receive overlapping opioid and overlapping opioid and benzodiazepine prescriptions, consistent with previous research (Paulozzi et al., 2016). We are uncertain why such differences between indicators of high-risk prescribing may exist. Overlapping prescriptions may involve multiple prescribers, some of whom may be unaware of prior diagnoses or concurrent prescribers. It may also be that when prescribing to individuals with previously identified substance use disorders, prescribers are more sensitive to prescribing a higher dose on a single prescription than they are to potential issues associated with writing multiple prescriptions. Electronic health records and PDMPs have the potential to decrease such overlapping prescribing by providing timely information to prescribers and pharmacists (Brandeis Prescription Drug Monitoring Program Center of Excellence, 2016), and additional research can help provide a better understanding of the magnitude of risk such prescribing practices present to individuals previously identified with substance use disorders. Medicaid Patient Review and Restriction (PRR) programs are another potential tool to prevent opioid abuse. In these programs, Medicaid enrollees who meet certain criteria, such as having visited multiple prescribers, received a high volume of opioid prescriptions, or a previous substance dependency diagnosis, are “locked-in” to a restricted network of prescribers and pharmacists to better coordinate care and prevent doctor shopping (The Pew Charitable Trusts, 2016). None of the states in our analysis used prior substance dependence diagnosis as a criteria for enrollment in a PRR program (The Pew Charitable Trusts, 2016), but given the significant associations between prior substance dependence diagnosis and overlapping opioid and overlapping opioid and benzodiazepine prescriptions in our data, states may wish to consider adopting PRR programs which use these criteria.

Rural counties have higher rates of opioid-related overdoses (Centers for Disease Control, 2009; Hall et al., 2008) and nonmedical opioid use (Fiscella, Franks, Gold, & Clancy, 2000), yet, have far fewer resources to provide effective treatment for opioid use disorders (Bohnert et al., 2011; Fiscella et al., 2000). Even after controlling for county income, education, and physicians per capita—factors that have been associated with poor quality care in other areas of healthcare (Fiscella et al., 2000)—we found that rural counties had higher rates of high-risk prescribing, potentially contributing to their higher rates of opioid-related morbidity and mortality. Research has also found that whites and individuals with major depression have higher rates of clinically unsupported and nonmedical opioid use as well as higher opioid overdose rates than other individuals (Bohnert et al., 2011; Dunn et al., 2010; Sullivan, Edlund, Zhang, Unützer, & Wells, 2006). In our study, both groups had higher rates of high-risk prescribing than individuals without those characteristics. Understanding the characteristics of patients and communities at increased risk for high-risk prescribing may

be a first step toward targeted patient or community focused educational efforts designed to complement many current prescriber focused initiatives (Dowell et al., 2016).

Consistent with prior studies (Paulozzi et al., 2015), we found indicators of high-risk prescribing varied substantially across states. State policies and regulations that may influence high-risk prescribing practices, such as regulations related to the use of PDMPs, medication quantity limits, requirements associated with physician exams or verification by a pharmacist, and use of tamper-resistant prescription forms, vary greatly (Adelmann, 2003; Clark, Eadie, Kreiner, & Strickler, 2012; Meara et al., 2016). However, relatively few studies have examined in what way such policies may influence high-risk prescribing practices (Haegerich, Paulozzi, Manns, & Jones, 2014), and to date, studies examining the effects of state policies are inconsistent (Haegerich et al., 2014; Meara et al., 2016). Notably, all four states in our dataset had well-established PDMPs as of 2007, the start of the study period. However, our examination of information from four states over a three-year period is not well suited to examine the effectiveness of these types of policies. As states seek to identify and implement policies designed to address high-risk opioid prescribing and associated negative sequelae, a better understanding of the effects of policies is needed to inform policymaking.

Our findings must be interpreted within the context of the study's limitations. We used claims data from Medicaid enrollees from four states with fee-for-service or high quality managed care encounter data appropriate for research, and do not know to what extent our findings would generalize to non-Medicaid populations, dually eligible enrollees, or Medicaid-enrollees from other states. We also do not know to what extent Medicaid eligibility criteria or opioid prescribing policies in the states may explain between-state variation or affect generalizability with other states, and further research with more states and more years of data is needed to examine those issues. Furthermore, we do not observe opioid analgesics not paid for by Medicaid, prescriptions which are written and not filled, or nonprescription opioids, such as heroin. Our data are dated, having been obtained prior to federal redaction of information related to substance use disorders under 42 CFR. We are unable to examine how high-risk prescribing may have increased or decreased in more recent years, but in the absence of more recent data, our findings contribute to our understanding of patterns of high-risk prescribing, and help to establish a baseline through which the impact of policy changes using more recent data can be interpreted. By requiring a 30-day period with no prescribed opioids prior to the beginning of an opioid treatment episode and two filled opioid prescriptions, we systematically excluded individuals who were already receiving opioids and individuals who filled a single prescription. We are unable to consistently and confidently identify prescribers, dispensing pharmacies, and treatment setting of the initial opioid prescription in our data, and we are therefore unable to examine the characteristics of prescribers of high-risk opioids nor the treatment settings in which they were first prescribed. Because of this limitation, we are unable to determine the relative contribution of patient (demand) and provider (supply) characteristics to county-level variation in prescribing practices. We are also unable to determine to what extent multiple prescribers may have been involved in an episode with high-risk prescribing.

Most importantly, we have no clinical information on patient history, clinical severity, patient pain ratings, planned titration of medications, reactions to medications, and other circumstances of care that inform a prescriber's use of opioid analgesics. As a result, we are unable to judge the clinical appropriateness of the prescriptions filled by any given patient and instead rely on patterns of prescribing at a population level that appear to be inconsistent with prescribing guidelines.

Despite these limitations, the present study contributes valuable information for patients, providers, policymakers, and researchers on the frequency of high-risk prescribing in an at-risk population of individuals. The study population included a large number of individuals from four populous, diverse states representing different geographic regions, policy environments, and cultural norms, and the analysis examined a number of individual- and county-level factors exceeding those examined in prior studies. At a time of wide ranging efforts to address the public health crisis related to opioids, our findings suggest targets for patient and prescriber focused efforts designed to address some of the most questionable prescribing behaviors as well as the need for continued efforts to better understand some of the substantial state level variation that occurs with such prescribing.

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^aPrescriptions with 0, missing, or >180 days supply and prescriptions with 0, missing, or >1000 quantity dispensed excluded. Prescriptions were combined into a single prescription when they were prescribed and filled on the same date, by the same provider, and were the same generic drug. Duplicate prescriptions were excluded. Patients with ≥2 prescriptions in at least one calendar year were included in the initial population.

^bEpisodes are defined as a period of time over which a patient continuously (<30 days between the end of days supply of a previous prescription and the start of a new prescription) receives opioids.

^cPotentially censored episodes are defined as either beginning within the first 30 days of 2007 or within the last 6 months of 2009. Exclusion made at episode level.

^dEpisodes were excluded if criteria were not met for any portion of the episode.

Figure 1.
Study exclusion criteria.

Table 1

Frequency of episodes involving high-risk prescribing.

Outcome	Number of episodes	Percentage of episodes
Any high-risk prescribing	733,094	39.3%
>100 MEDD	540,036	29.0%
Overlapping opioids	135,784	7.3%
Overlapping benzodiazepines	178,974	9.6%
Number of high-risk indicators per episode		
0	1,130,590	60.7%
1	618,298	33.2%
2	107,892	5.8%
3	6,904	0.4%

Abbreviation: MEDD, morphine equivalent daily dose.

Table 2

Episode characteristics by presence of high-risk prescribing indicators.

Characteristic	No high-risk indicators	At least one high-risk indicator
MEDD, mean (SD)	131.6 (197.8)	181.0 (144.8)
Episode duration in days, mean (SD)	25.7 (59.5)	65.4 (103.4)
Number of prescription fills, mean (SD)	4.9 (6.0)	8.5 (10.2)

Abbreviations: MEDD, morphine equivalent daily dose; SD, standard deviation.

Table 3

Individual- and county-level characteristics of Medicaid enrollees receiving opioids overall and by high-risk prescribing and county-level characteristics by state.^a

Variable	N (%) of opioid analgesic episodes	% of opioid analgesic episodes with any high-risk prescribing	Multivariate regression OR (95% CI)
Total	1,863,684	39.4%	
Individual-level characteristics			
Age			
18–25	304,910 (16.4%)	24.1%	Reference
26–35	425,823 (22.8%)	31.6%	1.43 (1.41, 1.45) *
36–45	434,142 (23.3%)	41.0%	2.14 (2.12, 2.17) *
46–55	436,054 (23.4%)	48.1%	2.86 (2.82, 2.90) *
56–64	262,755 (14.1%)	52.2%	3.35 (3.30, 3.40) *
Gender			
Male	493,511 (26.5%)	40.4%	Reference
Female	1,370,173 (73.5%)	39.0%	1.04 (1.03, 1.05) *
Race			
White	804,532 (43.2%)	40.8%	Reference
Black	423,609 (22.7%)	36.6%	0.73 (0.73, 0.74) *
Hispanic	440,294 (23.6%)	38.5%	0.84 (0.83, 0.84) *
Other	195,249 (10.5%)	41.1%	0.85 (0.84, 0.87) *
Opioid dependency ^b			
No	1,781,300 (95.6%)	39.2%	Reference
Yes	82,384 (4.4%)	43.2%	1.04 (1.02, 1.06) *
Alcohol dependency ^b			
No	1,775,975 (95.3%)	39.1%	Reference
Yes	87,709 (4.7%)	43.7%	1.04 (1.02, 1.06) *
Hypnotic or sedative dependency ^b			
No	1,856,888 (99.6%)	39.3%	Reference
Yes	6,796 (0.4%)	51.7%	1.44 (1.35, 1.53) *
Major depression ^b			
No	1,716,878 (92.1%)	38.3%	Reference
Yes	146,806 (7.9%)	51.4%	1.42 (1.40, 1.44) *
Pain diagnoses			
No pain diagnoses ^c	167,673 (9.0%)	31.2%	Reference
Acute pain diagnoses only ^c	451,203 (24.2%)	49.1%	1.72 (1.70, 1.74) *
Non-acute pain diagnoses only ^c	156,966 (8.4%)	39.1%	1.29 (1.27, 1.31) *
Both acute and non-acute pain diagnoses ^c	1,087,842 (58.4%)	36.6%	1.16 (1.15, 1.18) *

Variable	N (%) of opioid analgesic episodes	% of opioid analgesic episodes with any high-risk prescribing	Multivariate regression OR (95% CI)
County-level characteristics RUCC ^d			
Metropolitan	1,679,205 (90.1%)	39.1%	Reference
Large nonmetropolitan	107,362 (5.8%)	40.8%	1.05 (1.03, 1.07) *
Medium nonmetropolitan	72,631 (3.9%)	43.0%	1.18 (1.15, 1.20) *
Small nonmetropolitan	4,486 (0.2%)	45.3%	1.23 (1.14, 1.33) *
PCPs per 100,000 population, ^d mean (SD)			
Q1 (lowest concentration)	458,464 (24.6%)	40.2%	Reference
Q2	483,775 (26.0%)	38.6%	0.98 (0.97, 1.00) *
Q3	445,644 (23.9%)	39.8%	1.04 (1.02, 1.05) *
Q4 (highest concentration)	475,801 (25.5%)	38.9%	0.99 (0.97, 1.01)
% No high school degree ^d			
Q1 (lowest %)	464,838 (24.9%)	36.7%	Reference
Q2	609,008 (32.7%)	39.4%	0.99 (0.98, 1.00)
Q3	342,205 (18.4%)	39.7%	1.02 (1.01, 1.04) *
Q4 (highest %)	447,633 (24.0%)	41.8%	1.21 (1.19, 1.23) *
Median household income, ^d mean (SD)			
Q1 (lowest median)	458,841 (24.6%)	40.2%	Reference
Q2	537,372 (28.8%)	40.7%	1.00 (0.98, 1.01)
Q3	285,365 (15.3%)	38.5%	1.04 (1.02, 1.05) *
Q4 (highest median)	582,106 (31.2%)	37.8%	0.87 (0.86, 0.88) *
State			
CA	751,592 (40.3%)	39.9%	Reference
IL	352,773 (18.9%)	39.0%	1.19 (1.17, 1.21) *
MA	178,689 (9.6%)	32.5%	0.80 (0.79, 0.82) *
NY	580,630 (31.2%)	40.9%	1.25 (1.23, 1.27) *

Abbreviations: PCP, primary care physician; RUCC, Rural–Urban Continuum Code.

^aNumbers are % and calculations are made at the episode level.

^bAt least one diagnosis present in calendar year prior to the episode start date.

^cWithin 14 days of start of episode, pain definitions used as described by Mack et al., 2015.

^dCounty attribute of patient's place of residence at the start of the episode.

* $p < 0.05$.

Table 4Logistic regression of high-risk prescribing outcomes on individual- and county-level variables.^a

Variable	>100 MEDD		Opioid overlap		Opioid-benzodiazepine overlap	
	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)
Individual level characteristics						
<i>Age</i>						
18–25	18.5	Reference	4.7	Reference	3.9	Reference
26–35	22.8	1.29 (1.28, 1.31) *	6.4	1.33 (1.30, 1.36) *	7.4	1.95 (1.89, 20.1) *
36–45	29.1	1.83 (1.80, 1.85) *	8.2	1.59 (1.55, 1.62) *	10.8	3.08 (2.99, 3.18) *
46–55	35.2	2.43 (2.40, 2.47) *	8.7	1.63 (1.59, 1.67) *	12.9	3.98 (3.86, 4.10) *
56–65	40.7	3.01 (2.96, 3.06) *	7.9	1.46 (1.42, 1.50) *	12.4	3.95 (3.81, 4.08) *
<i>Gender</i>						
Male	29.0	Reference	9.2	Reference	8.8	Reference
Female	29.0	1.04 (1.03, 1.05) *	6.6	0.76 (0.75, 0.77) *	9.9	1.37 (1.34, 1.39) *
<i>Race</i>						
White	27.6	Reference	8.3	Reference	13.0	Reference
Black	28.6	0.95 (0.93, 0.96) *	6.8	0.79 (0.78, 0.81) *	6.4	0.39 (0.38, 0.40) *
Hispanic	30.4	1.08 (1.07, 1.10) *	6.3	0.67 (0.66, 0.69) *	7.3	0.52 (0.51, 0.54) *
Other	32.4	1.13 (1.11, 1.15) *	6.6	0.69 (0.67, 0.70) *	8.1	0.49 (0.48, 0.51) *
<i>Opioid dependency^b</i>						
No	29.4	Reference	7.2	Reference	9.0	Reference
Yes	20.5	0.59 (0.57, 0.60) *	10.0	1.21 (1.18, 1.24) *	21.8	2.52 (2.45, 2.60) *
<i>Alcohol dependency^b</i>						
No	29.1	Reference	7.1	Reference	9.4	Reference
Yes	27.6	0.96 (0.94, 0.97) *	10.4	1.20 (1.17, 1.23) *	14.5	1.10 (1.07, 1.13) *
<i>Hypnotic or sedative dependency^b</i>						
No	29.0	Reference	7.3	Reference	9.5	Reference
Yes	21.1	0.91 (0.84, 0.97) *	13.8	1.38 (1.28, 1.49) *	30.7	2.00 (1.85, 2.17) *
<i>Major depression^b</i>						

Variable	>100 MEDD		Opioid overlap		Opioid-benzodiazepine overlap	
	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)
Individual level characteristics						
No	28.7	Reference	7.2	Reference	8.5	Reference
Yes	32.8	1.05 (1.03, 1.06)*	8.8	1.12 (1.10, 1.14)*	22.1	2.57 (2.52, 2.63)*
Pain diagnoses						
No pain diagnoses ^c	21.2	Reference	6.5	Reference	8.3	Reference
Acute pain diagnoses only ^c	36.2	1.73 (1.71, 1.76)*	10.5	1.56 (1.53, 1.60)*	11.4	1.21 (1.18, 1.23)*
Non-acute pain diagnoses only ^c	25.2	1.18 (1.16, 1.20)*	10.5	1.63 (1.58, 1.67)*	11.2	1.19 (1.16, 1.22)*
Both acute and non-acute pain diagnoses ^c	27.7	1.29 (1.27, 1.31)*	5.6	0.83 (0.81, 0.85)*	8.8	1.04 (1.02, 1.07)*
County characteristics RUCC ^d						
Metropolitan	28.6	Reference	7.3	Reference	9.6	Reference
Large nonmetropolitan	31.5	1.07 (1.04, 1.09)*	7.8	1.05 (1.02, 1.08)*	8.6	1.01 (0.97, 1.05)
Medium nonmetropolitan	33.0	1.15 (1.12, 1.17)*	7.0	1.13 (1.08, 1.17)*	11.5	1.27 (1.22, 1.32)*
Small nonmetropolitan	33.3	1.12 (1.03, 1.22)*	7.0	1.15 (1.01, 1.31)*	14.0	1.40 (1.22, 1.61)*
PCPs per 100,000 population, ^d mean (SD)						
Q1	30.8	Reference	7.4	Reference	9.1	Reference
Q2	27.9	0.96 (0.94, 0.97)*	7.3	0.99 (0.97, 1.01)	9.9	1.07 (1.05, 1.10)*
Q3	28.5	0.97 (0.95, 0.98)*	7.3	1.00 (0.98, 1.02)	10.9	1.15 (1.13, 1.18)*
Q4	28.8	1.01 (0.99, 1.03)	7.2	0.95 (0.92, 0.97)*	8.6	0.95 (0.92, 0.98)*
% No high school degree ^d						
Q1	25.1	Reference	7.2	Reference	10.9	Reference
Q2	29.7	1.03 (1.02, 1.04)*	7.7	0.91 (0.90, 0.93)*	7.9	0.94 (0.92, 0.97)*
Q3	28.4	1.11 (1.09, 1.13)*	6.4	1.01 (0.99, 1.03)	12.0	1.06 (1.04, 1.09)*
Q4	32.5	1.31 (1.28, 1.33)*	7.5	0.88 (0.85, 0.90)*	8.8	1.08 (1.04, 1.11)*
Median household income, ^d mean (SD)						
Q1	31.4	Reference	7.2	Reference	8.3	Reference
Q2	30.4	0.93 (0.91, 0.94)*	6.4	1.00 (0.98, 1.02)	11.0	1.30 (1.27, 1.34)*
Q3	26.2	0.93 (0.92, 0.95)*	8.6	1.16 (1.13, 1.19)*	10.6	1.27 (1.23, 1.31)*

Variable	>100 MEDD		Opioid overlap		Opioid-benzodiazepine overlap	
Individual level characteristics	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)
Q4	27.1	0.73 (0.72, 0.74)*	7.5	1.04 (1.01, 1.06)*	8.9	1.34 (1.30, 1.39)*
State						
CA	29.4	Reference	8.3	Reference	9.1	Reference
IL	30.1	1.37 (1.34, 1.39)*	4.5	0.47 (0.46, 0.49)*	11.5	1.46 (1.41, 1.50)*
MA	16.7	0.61 (0.59, 0.62)*	5.7	0.51 (0.50, 0.53)*	15.9	1.82 (1.76, 1.88)*
NY	31.6	1.46 (1.43, 1.48)*	8.2	0.92 (0.90, 0.94)*	7.2	0.82 (0.80, 0.84)*

Abbreviations: PCP, primary care physician; RUCC, Rural–Urban Continuum Code.

^aRegressions are conducted at the episode level with clustered robust standard errors at the individual level.

^bAt least one diagnosis present in calendar year prior to the episode start date.

^cWithin 14 days of start of episode, pain definitions used as described by Mack et al., 2015.

^dCounty attribute of patient's place of residence at the start of the episode.

* $p < 0.05$.