Trends in Opioid and Psychotropic Prescription in Pregnancy in the United States From 2001 to 2015 in a Privately Insured Population

A Cross-sectional Study

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Background: Opioid and psychotropic prescriptions are common during pregnancy. Little is known about coprescriptions of both medications in this setting.

Objective: To describe opioid prescription among women who are prescribed psychotropics compared with women who are not.

Design: Cross-sectional study.

Setting: U.S. commercial insurance beneficiaries from MarketScan (2001 to 2015).

Participants: Pregnant women at 22 weeks' gestation or greater who were insured continuously for 3 months or more before pregnancy through delivery.

Measurements: Opioid prescription, dosage thresholds (morphine milligram equivalents [MME] of ≥50/day and ≥90/day), number of opioid agents (≥2), and duration (≥30 days) among those with and without prescription of psychotropics, from 2011 to 2015.

Results: Among 958 980 pregnant women, 10% received opioids only, 6% psychotropics only, and 2% opioids with coprescription of psychotropics. Opioid prescription was higher among women prescribed psychotropics versus those who were not (26.5% vs. 10.7%). From 2001 to 2015, psychotropic prescription overall increased from 4.4% to 7.6%, opioid prescription without coprescription of psychotropics decreased from 11.9% to 8.4%, and opioids with coprescription decreased from 28.1% to 22.0%. Morphine milligram equivalents of 50 or greater per day decreased for women with and without coprescription (29.6% to 17.3% and 22.8% to 18.5%, respectively); MME of 90 or greater per day also decreased in both groups (15.0% to 4.7% and 11.5% to 4.2%, respectively). Women prescribed opioids only were more likely to have an antepartum hospitalization compared with those with neither prescription, as were women with coprescription versus those prescribed psychotropics only. Compared with those prescribed opioids only, women with coprescriptions were more likely to exceed MME of 90 or greater per day and to be prescribed 2 or more opioid agents and for 30 days or longer. Number and duration of opioids increased with benzodiazepine and gabapentin coprescription.

Limitation: Inability to determine appropriateness of prescribing or overdose events.

Conclusion: Opioids are frequently coprescribed with psychotropic medication during pregnancy and are associated with antepartum hospitalization. A substantial proportion of pregnant women are prescribed opioids at doses that increase overdose risk and exceed daily recommendations.

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The U.S. opioid epidemic affects all segments of the population; pregnant women are no exception (1). Opioid use at delivery has quadrupled from 1.5 per 1000 delivery hospitalizations to 6.5 in 2014 (1–3). Opioid use and overdose are closely linked to mental health conditions, including substance use and psychiatric illness (4). The risk for drug overdose and opioid-related death increases when opioids are taken with psychotropic medications, including benzodiazepines and gabapentin, in the nonpregnant population (5, 6). Among deaths of pregnant and postpartum women, the presence of opioids and psychotropic medications (including antidepressants, antipsychotics, neuropathic pain medications, benzodiazepines, anxiolytics, hypnotics, mood stabilizers, stimulants, and barbiturates) is common (7, 8).

There is growing public health concern about the use of opioid and psychotropic medications in pregnancy and the postpartum period (9–13). Emerging state-level data indicate that more than half of pregnant women who died of drug overdose were treated for a mental health condition in the year before death (7, 8, 14, 15). Nearly 1 in 5 women with Medicaid insurance are prescribed opioids during pregnancy (16), and 1 in 10 women with private insurance are prescribed psychotropics during pregnancy (17).

Previous population-level studies have independently investigated the use of prescription opioids and psychotropics in pregnancy, but not whether opioids were prescribed with psychotropics (coprescription), including their levels and overdose risk (13, 16, 18, 19).

See also:

Web-Only
Supplement

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Limited data suggest that preterm birth, fetal growth restriction, and cesarean delivery are magnified with coprescription (20–23). A recent analysis of Medicaid beneficiaries suggested that the risk for neonatal abstinence syndrome was higher among women with coprescription than with either medication class alone (24).

Opioid prescribing among women who are prescribed psychotropics compared with those who are not prescribed psychotropics during pregnancy remains to be defined (25). As use of psychotropics increases, the rate of coprescription with opioids may increase even if opioid prescribing stabilizes or declines over time. Understanding the epidemiology of opioid prescription among those with and without concurrent psychotropic prescriptions can guide strategies to address the rising burden of mental health and substance use conditions in pregnancy and minimize potential maternal and neonatal risks (26–28).

The objective of this descriptive study was to determine patterns and associated characteristics of opioid prescription among commercially insured U.S. pregnant women with and without psychotropics. We describe patterns of opioid prescription from 2001 to 2015, with a focus on the most recent 5-year time period (2011 to 2015). We hypothesized that the number of pregnant women coprescribed both opioids and psychotropics would increase over time and be associated with longer duration of opioid prescription, prescriptions of multiple opioid agents, and opioids prescribed at higher dosage thresholds (MME ≥50/day and ≥90/day) compared with those prescribed opioids only.

Methods

Population

Our study population of pregnant women at 22 weeks' gestation or greater (live birth or stillbirth; singleton or multiple gestation) was derived from IBM Watson Health's MarketScan Commercial Claims and Encounters database from 1 January 2001 to 30 September 2015. The MarketScan database captures patient-level data on inpatient, outpatient, and prescription drug claims from approximately 100 large employers and health plans that insure employees and their dependents in all 50 states (29, 30). Other investigators have used this database to describe opioid and psychotropic prescription independently in pregnancy and the postpartum period (11, 17, 30), but opioid prescription with and without psychotropics has not been investigated. The use of this deidentified database was approved by the Institutional Review Board at the University of North Carolina, Chapel Hill.

Measures

Pregnancies and an estimate of gestational age were defined based on inpatient and outpatient codes indicating infant delivery (and not gestational age at delivery, which was not available) using a hierarchical algorithm based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic and procedure codes, which have been described and validated for this data set by our group of investigators (**Supplement Table 1**, available at Annals.org) (30). This study was censored on 30 September 2015, after which ICD-10-CM was used. We defined the delivery date as the service date of an ICD-9-CM delivery code (V27.0 to V27.6). The date of pregnancy onset was estimated by subtracting the estimated gestational age from the delivery date. The prepregnancy period included the 90 days before the imputed last menstrual period (LMP), which was back calculated by subtracting from the gestational age at delivery, consistent with prior studies (18). The first trimester extended from the LMP through day 84 (week 12), the second trimester was the next 105 days, and the third trimester began 190 days after the LMP and lasted through delivery.

Prescriptions of oral opioids (tablet, capsule, or liquid formulation) and psychotropics were identified using outpatient pharmacy-dispensing claims. We included the following opioids: hydrocodone, codeine, oxycodone, propoxyphene, tramadol, meperidine, hydromorphone, morphine, fentanyl, pentazocine, tapentadol, oxymorphone, butorphanol, buprenorphine, methadone, naltrexone, and naloxone (**Supplement Table 2**, available at Annals.org). We classified psychotropics into categories based on drug class and clinical indication: antidepressant, antipsychotic, neuropathic pain medication (including gabapentin), benzodiazepine, anxiolytic, nonbenzodiazepine hypnotic, mood stabilizer, stimulant, and barbiturate (**Supplement Table 3**, available at Annals.org).

Demographic characteristics included maternal age at delivery, delivery year (2001 to 2015), number of other dependent children aged 18 years or younger covered by the same insurance policy on the delivery date, health insurance type, geographic region, and state (30). We assessed opioid misuse as well as reported substance use and psychiatric and medical conditions for which opioids and psychotropics were prescribed, based on associated ICD-9-CM codes from 90 days before imputed LMP until delivery. During the current study, the *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition (DSM-IV),* was the contemporary standard; therefore, we used opioid misuse. Substance use diagnoses included disorders related to opioid misuse as well as alcohol, tobacco, and drug use (including marijuana, cocaine, heroin, and amphetamines). Psychiatric diagnoses were classified as depression, anxiety, bipolar disorder, schizophrenia, sleep disorder, and personality disorder (**Supplement Table 4**, available at Annals.org). Medical diagnoses were classified as neuropathic pain, musculoskeletal, fibromyalgia, headache, postoperative pain, and other medical diagnoses (**Supplement Table 5**, available at Annals.org). Health care utilization, which served as a proxy measure for more complicated pregnancies, was measured as the number of antepartum hospital admissions (0, 1, and ≥2) and antepartum hospitalization length of stay (0, 1 to 3, or ≥4 days), both of which were assessed before the delivery admission.

Opioid and Psychotropic Prescriptions

We classified women into 4 prescription categories: opioid prescription with psychotropic (coprescription), psychotropics only, opioid prescription without psychotropic (opioids only), and neither prescription. We also characterized daily opioid doses based on calculating morphine milligram equivalents (MME), number of opioid agents prescribed (≥2 vs. <2), and opioid duration (≥30 days vs. <30 days). For opioid dosage, we defined 2 thresholds: 1) MME of 50 or greater per day per Centers for Disease Control and Prevention (CDC) national prescribing guidelines for individuals prescribed opioids at risk for overdose, and 2) MME of 90 or greater per day, which is the maximum recommended daily dosage (31). We classified patterns of opioid prescription based on number of different agents (≥2) and duration of prescription (≥30 days), consistent with prior studies (16, 18).

To arrive at these measures, we derived the cumulative days of opioid prescription based on the accumulated days' supply for each opioid and then calculated the opioid dose in MME per day and the median cumulative MME during pregnancy (31, 32). We allowed days' supply from prescriptions started before pregnancy to carry over into pregnancy, and days' supply to accumulate for opioids prescribed before the prior medication was to be completed. We assumed that opioids were consumed at the specified prescribed interval. Two important methodological limitations include our inability to adequately identify overdose events using ICD-9-CM overdose codes to reconcile clinical indications for treatment and opioid and psychotropic prescriptions using a large claims database.

Statistical Analysis

In this multiyear cross-sectional cohort, we compared women with opioid prescription with (coprescription) and without (opioids only) psychotropics. In descriptive analyses, we determined the opioid and psychotropic agents prescribed by time period (2001 to 2005, 2006 to 2010, and 2011 to 2015). To examine geographic variation within the United States, the frequency of coprescription was calculated by U.S. census region (Northwest, Midwest, South, West, or unknown) and by state. Because of variation in database enrollment by state across years, estimates presented by calendar year were standardized by age and geographic region (state) to the overall cohort.

Given effect measure modification by time period, all analyses were stratified by 5-year time periods (2001 to 2005, 2006 to 2010, and 2011 to 2015). The primary analysis was conducted for 2011 to 2015 because this recent time period is most relevant for public health decision making; in sensitivity analyses, we replicated the same analyses for the earlier 2 time periods (2001 to 2005 and 2006 to 2010). We assessed sociodemographic and clinical characteristics associated with opioid prescription without psychotropics (opioids only vs. neither medication class) and then opioids with psychotropics (coprescription vs. psychotropics only). We assessed opioid dosing at clinically significant CDC thresholds (MME ≥50/day [overdose risk doubles] and ≥90/day [maximum recommended daily dosage]), quantity (≥2 opioid agents), and duration (≥30 days' opioid prescription) among women prescribed opioids with versus without psychotropics (coprescription vs. opioids only). In secondary analyses, because emerging data showed that drug overdose and opioid-related death are associated with opioids taken with benzodiazepines and gabapentin (5, 6), we assessed the above measures of opioid prescription (dosing, prescription of multiple agents, and duration) among women with opioids with benzodiazepine and gabapentin, respectively. After standardization as previously described, log-binomial regression was used. We calculated unadjusted risk ratios (RRs) and adjusted risk ratios (ARRs). A linear trend was confirmed for covariates that were modeled as continuous variables. A directed acyclic graph was used to assess for confounding variables a priori, and all adjusted models included maternal age (continuous), region, insurance plan type, and number of dependent children (categorical: 0, 1, ≥2). All analyses were conducted using SAS, version 9.4 (SAS Institute).

Role of the Funding Source

This study received no funding.

Results

Among approximately 48 million women aged 15 to 55 years, we identified 1.9 million pregnancies at 22 weeks' gestation or greater. We restricted the cohort to 1 046 773 women with continuous insurance enrollment with prescription coverage from 90 days or more before the estimated LMP through 30 days or more after delivery to capture prescriptions immediately before and during pregnancy. For women with multiple pregnancies during the study period, we used the first pregnancy only and excluded consequent pregnancies (n = 87 993). This analysis consisted of 958 980 pregnant women from 2001 to 2015.

The mean age was 30.9 years (SD, 4.74). More than one third of women lived in the South (39.6%), and most women (57.2%) had dependent children (**Supplement Table 6**, available at Annals.org). Overall, 789 083 (82.3%) women had neither an opioid nor a psychotropic prescription, 94 673 (9.9%) had an opioid prescription without a psychotropic (opioids only), 55 317 (5.8%) had only a psychotropic prescription, and 19 907 (2.1%) had an opioid prescription with a psychotropic (coprescription) any time during pregnancy (**Table 1**). Opioid prescription was more than 2-fold higher among those who were prescribed psychotropics versus those without psychotropics (26.5% vs. 10.7%). Throughout the United States, women prescribed opioids and psychotropics (coprescription) exceeded 3% of all pregnancies in 9 states, primarily in the South and Rocky Mountain regions (**Figure 1**). Few women were prescribed 2 or more opioid agents and 2 or more classes of psychotropics. The most common opioid agents pre-

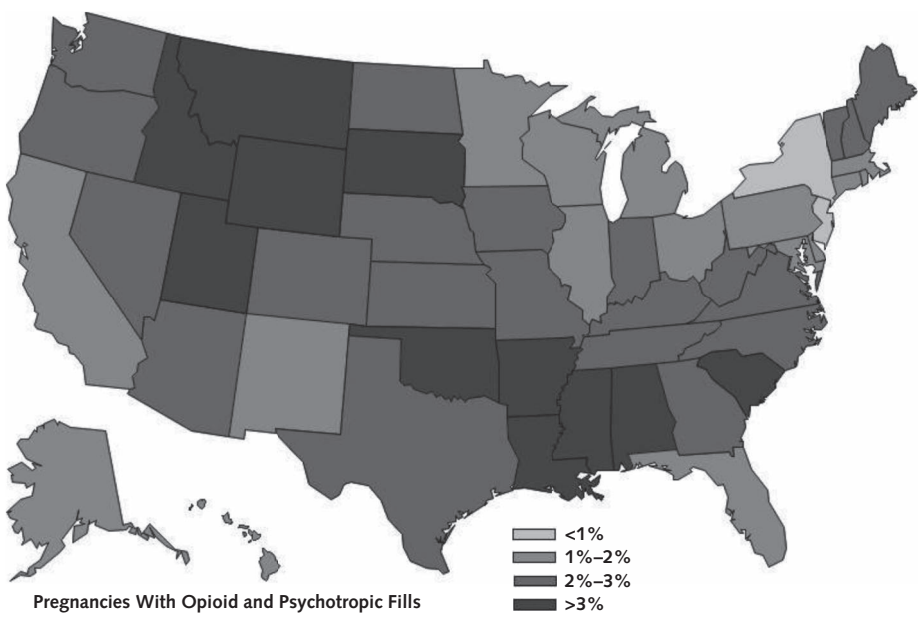
Table 1. Frequency of Opioid and Psychotropic Prescription Over Time*

Opioid or Psychotropic Drug	Overall (*n* = 958 980)	2001–2005 (*n* = 133 372)	2006–2010 (*n* = 323 315)	2011–2015 (*n* = 502 293)
Number of different opioid agents prescribed				
1	99 344 (10.36)	15 492 (11.62)	36 860 (11.40)	46 992 (9.36)
2	13 031 (1.36)	2023 (1.52)	5215 (1.61)	5793 (1.15)
≥3	2205 (0.23)	352 (0.26)	950 (0.29)	903 (0.18)
Number of different psychotropic classes prescribed				
1	63 663 (6.64)	8194 (6.14)	22 513 (6.96)	32 956 (6.56)
2	9299 (0.97)	877 (0.66)	3189 (0.99)	5233 (1.04)
≥3	2262 (0.24)	158 (0.12)	729 (0.23)	1375 (0.27)
Opioid agents prescribed†				
Hydrocodone	51 391 (5.36)	6399 (4.80)	18 385 (5.69)	26 607 (5.30)
Codeine	48 265 (5.03)	9385 (7.04)	18 506 (5.72)	20 374 (4.06)
Oxycodone	16 389 (1.71)	1334 (1.00)	5165 (1.60)	9890 (1.97)
Propoxyphene	8394 (0.88)	2330 (1.75)	5666 (1.75)	398 (0.08)
Tramadol	3590 (0.37)	225 (0.17)	993 (0.31)	2372 (0.47)
Psychotropic medication classes prescribed‡				
SSRI	44 705 (4.66)	6116 (4.59)	15 534 (4.80)	23 055 (4.59)
Benzodiazepine, short-acting	6724 (0.70)	621 (0.47)	2196 (0.68)	3907 (0.78)
Nonbenzodiazepine hypnotic	19 364 (2.02)	2342 (1.76)	8079 (2.50)	8943 (1.78)
Stimulant	5903 (0.62)	174 (0.13)	1294 (0.40)	4435 (0.88)
Mood stabilizer	2357 (0.25)	152 (0.11)	786 (0.24)	1419 (0.28)
Other antidepressant	1780 (0.19)	210 (0.16)	521 (0.16)	1049 (0.21)
SNRI	1849 (0.19)	21 (0.02)	818 (0.25)	1010 (0.20)
Tricyclic antidepressant	1500 (0.16)	249 (0.19)	479 (0.15)	772 (0.15)
Anxiolytic	2352 (0.25)	191 (0.14)	638 (0.20)	1523 (0.30)

SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.
* Values are numbers (percentages).
† Overall frequency <0.1% in pregnancy not reported for pethidine, buprenorphine, hydromorphone, morphine, fentanyl, tapentadol, methadone, pentazocine, and oxymorphone.
‡ Overall frequency <0.1% in pregnancy not reported for barbiturates; neuropathic pain; atypical antipsychotic; and benzodiazepine, long-acting.

scribed were hydrocodone and codeine. The most common psychotropic classes prescribed were selective serotonin reuptake inhibitors and hypnotics. Few women (0.1%) were prescribed pharmacotherapy frequently used for opioid use disorder (buprenorphine and methadone). A total of 14.4% (1403 of 9750) of women were coprescribed opioids with a benzodiazepine and 4.0% (385 of 9750) with gabapentin.

Figure 1. Percentage of pregnant women coprescribed opioids and psychotropics from 2001 to 2015.



Over time, women prescribed opioids but not psychotropics decreased by 30% from 2001 to 2015 (11.9% to 8.4%), and women coprescribed opioids and psychotropics decreased by 22% (28.1% to 22.0%); in comparison, women prescribed psychotropics increased by 74%, from 4.4% to 7.6% (Figure 2). The proportion with MME of 50 or greater per day (at which the risk for overdose doubles) decreased overall, but more so for women prescribed opioids and psychotropics, which decreased by 41% from 2002 to 2015 (29.6% to 17.3%), compared with women prescribed opioids but not psychotropics, which decreased by 19% (22.8% to 18.5%) (Figure 3). Similarly, the proportion with MME of 90 or greater per day (the maximum recommended daily dose) decreased for women coprescribed opioids and psychotropics (15.0% to 4.7%) and for those prescribed opioids but not psychotropics (11.5% to 4.2%). When MME was assessed across pregnancy, the cumulative quantity of opioids prescribed during pregnancy was 48% greater for those with versus without psychotropics (median cumulative MME, 200 mg [interquartile range, 90 to 600 mg] vs. 135 mg [interquartile range, 72 to 225 mg]). We also assessed ICD-9-CM overdose codes (Supplement Table 4), which were present for only 39 women (20 with opioid and/or psychotropic prescription [51%]) in the entire cohort, precluding further analysis.

By pregnancy period, the proportion of pregnant women receiving an opioid prescription decreased between the prepregnancy period (that is, 90 days before pregnancy) and the first trimester (8.4% vs. 4.4%, respectively), as did psychotropic prescriptions (7.7% to 5.4%). Among women with coprescription, a psychotropic preceded an opioid (was prescribed in an earlier trimester) for 35.2%, an opioid was prescribed first for 17.5%, and the remaining 47.3% received both in the same trimester.

Figure 2. Percentage of pregnant women prescribed opioids with and without psychotropics from 2001 to 2015.

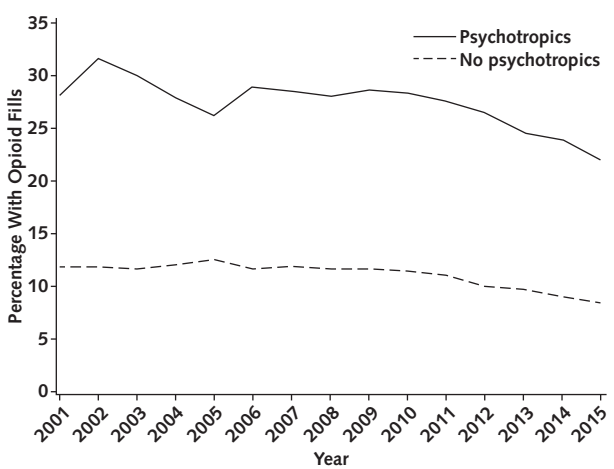
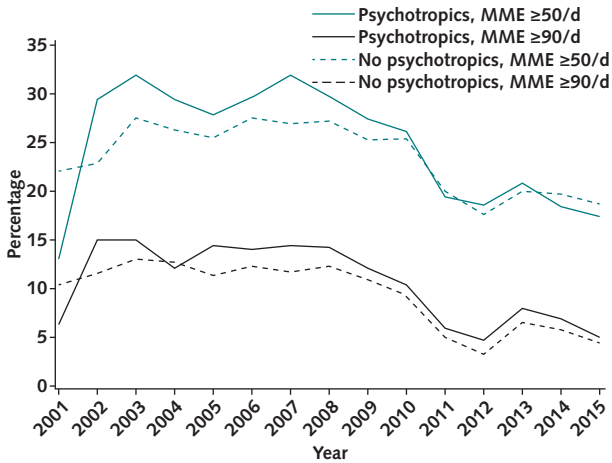


Figure 3. Percentage of pregnant women prescribed opioids with and without psychotropics at risk for overdose (MME ≥50/d) and exceeding the maximum recommended daily dosage (MME ≥90/d) from 2001 to 2015.



MME = morphine milligram equivalents.

Table 2 presents participant characteristics of those prescribed opioids according to whether they were also prescribed psychotropics during the most recent time period, 2011 to 2015. Younger women, those with an increasing number of dependent children, and those who lived in the South were more likely to be prescribed opioids, regardless of coprescription with psychotropics. Women with psychiatric and pain-related diagnoses were more likely to be prescribed opioids, and the likelihood was generally higher without, rather than with, psychotropics. These findings held during the 2 earlier time periods, 2001 to 2005 and 2006 to 2010 (Supplement Tables 7 and 8, available at Annals.org).

From 2011 to 2015, women with at least 1 diagnosis code for opioid misuse, tobacco, alcohol, or any drug were at an increased risk for opioid prescription, but this risk was higher for women without psychotropics than for women with psychotropics (Table 3). Similarly, women with antepartum hospitalization before delivery were at an increased risk for opioid prescription, but this risk was higher for women without psychotropics than for women with psychotropic coprescription. A similar pattern was observed for the duration of antepartum hospitalizations. These findings held during the 2 earlier time periods, 2000 to 2005 and 2006 to 2010 (Supplement Tables 7 and 8).

Women coprescribed opioids and psychotropics had a higher risk for MME of 90 or greater per day (the maximum recommended daily dose) compared with women prescribed opioids only from 2011 to 2015 (Table 3). Opioid duration for 30 days or longer was more frequent for opioid prescription with versus without psychotropics, as was opioid prescription of 2 or more opioid agents. Although nearly one fifth of women had

Table 2. Characteristics of Opioid Prescription According to Whether Pregnant Women Were Coprescribed Psychotropics (2011 to 2015)

Characteristic	Opioids Without Psychotropics			Opioids With Psychotropics		
	No Prescription, % (*n* = 418 791)	Opioids Only (Opioids Without Psychotropics), % (*n* = 43 938)	ARR (95% CI): Opioids Only vs. No Prescription*	Psychotropics Only, % (*n* = 29 814)	Coprescribed (Opioids With Psychotropics), % (*n* = 9750)	ARR (95% CI): Coprescription vs. Psychotropics Only*
Age						
<25 y	6.5	8.2	Reference	5.4	6.4	Reference
25–35 y	76.8	74.0	0.80 (0.78–0.83)	74.0	72.3	0.85 (0.79–0.91)
>35 y	16.6	17.8	0.86 (0.83–0.89)	20.6	21.2	0.86 (0.80–0.93)
U.S. region†						
North Central	25.6	22.5	Reference	27.1	24.2	Reference
Northeast	17.6	11.4	0.76 (0.74–0.79)	14.7	9.9	0.81 (0.76–0.87)
South	34.8	43.0	1.36 (1.33–1.39)	38.9	44.1	1.20 (1.15–1.26)
West	20.3	21.5	1.15 (1.12–1.19)	17.1	19.9	1.22 (1.16–1.29)
Insurance plan indicator†						
CDHP	6.6	6.0	Reference	6.6	6.2	Reference
PPO/EPO	64.8	64.3	1.11 (1.07–1.16)	65.6	66.7	1.07 (0.99–1.15)
HMO	12.6	14.7	1.28 (1.23–1.34)	12.0	12.1	1.06 (0.97–1.16)
POS/POS with cap	6.7	6.7	1.15 (1.09–1.21)	7.1	6.9	1.08 (0.98–1.19)
Number of dependent children						
0	45.0	40.3	Reference	42.5	36.6	Reference
1	35.2	36.1	1.14 (1.12–1.16)	34.6	35.3	1.15 (1.10–1.20)
≥2	19.8	23.6	1.30 (1.27–1.33)	22.9	28.0	1.31 (1.25–1.37)
Psychiatric diagnoses (not mutually exclusive)						
Anxiety	3.1	4.8	1.54 (1.48–1.60)	27.9	27.2	1.01 (0.97–1.05)
Depression	2.5	4.3	1.66 (1.59–1.73)	30.1	29.8	1.02 (0.98–1.05)
Bipolar disorder	1.1	1.9	1.76 (1.65–1.87)	14.2	14.8	1.07 (1.02–1.12)
Schizophrenia	0.0	NTSR	0.96 (0.38–2.44)	0.2	NTSR	0.71 (0.39–1.28)
Medical diagnoses (not mutually exclusive)						
Musculoskeletal pain	27.7	49.2	2.29 (2.25–2.33)	37.3	59.6	1.96 (1.90–2.03)
Fibromyalgia	6.6	11.7	1.78 (1.74–1.83)	10.1	20.1	1.76 (1.70–1.83)
Headache	6.8	17.4	2.47 (2.42–2.53)	12.8	28.3	1.96 (1.89–2.03)
Neuropathic pain	6.5	9.9	1.47 (1.43–1.51)	7.4	14.3	1.63 (1.56–1.70)
General anesthesia	5.6	14.4	2.54 (2.48–2.60)	7.1	15.4	1.84 (1.76–1.92)
Other medical diagnosis	5.3	15.4	2.68 (2.62–2.75)	7.1	17.2	1.92 (1.85–2.00)
Number of antepartum hospital admissions before delivery						
0	96.9	90.2	Reference	94.5	86.4	Reference
1	2.8	8.3	2.64 (2.56–2.72)	4.8	10.9	1.81 (1.73–1.90)
≥2	0.3	1.5	3.65 (3.43–3.88)	0.7	2.6	2.27 (2.09–2.47)
Total days admitted antepartum before delivery						
0	96.9	90.2	Reference	94.4	86.3	Reference
1–3	2.0	5.6	2.51 (2.42–2.60)	3.2	6.6	1.72 (1.62–1.83)
≥4	1.1	4.3	3.13 (3.01–3.26)	2.5	7.0	2.06 (1.95–2.18)
Reported substance use based on claims data (not mutually exclusive)						
Opioid misuse	0.0	0.6	–	0.2	2.7	3.14 (2.99–3.30)
Any tobacco use	1.7	4.4	2.36 (2.26–2.45)	4.0	8.8	1.78 (1.69–1.88)
Any alcohol use	0.1	0.2	1.94 (1.56–2.41)	0.4	0.5	1.18 (0.92–1.50)
Any drug use (marijuana, cocaine, amphetamine)	0.9	3.0	2.75 (2.63–2.88)	2.9	8.7	2.13 (2.03–2.24)

ARR = adjusted risk ratio; CDHP = consumer-directed health plan; NTSR = numbers too small to report (<11); POS/POS with cap = point of service or point of service with capitation; PPO/EPO = preferred provider organization or exclusive provider organization.
* Log-binomial models adjusted for the following covariates: maternal age (continuous), region, number of dependent children (categorical: 0, 1, ≥2), and insurance plan type.
† "Other" for U.S. region and insurance plan indicator: *n* = 8626 and *n* = 46 031, respectively.

an MME of 50 or greater per day, there was no difference between women prescribed psychotropics versus those who were not from 2011 to 2015. During the 2 earlier time periods (2000 to 2005 and 2006 to 2010), women coprescribed opioids and psychotropics had a slightly higher risk for MME of 50 or greater per day than those prescribed opioids only (**Supplement Tables 9** and **10**, available at Annals.org).

We examined women coprescribed opioids (n = 9750) with a benzodiazepine (n = 1403 [14.4%]) and gabapentin (n = 385 [4.0%]) from 2011 to 2015 (**Table 3**). Women with a benzodiazepine or gabapentin prescription compared with those without either prescription, respectively, were more likely to have been prescribed 2 or more opioid agents and 30 days of opioids or longer, as well as MME of 90 or greater per day. The cumulative quantity of opioids during pregnancy was 109% greater with versus without benzodiazepines (median cumulative MME, 282 [interquartile range, 108 to 1420] vs. 135 [interquartile range, 75 to 240]) and 730% greater with versus without gabapentin (median cumulative MME, 1037 [interquartile range, 225 to 5741] vs. 125 [interquartile range, 75 to 240]).

Discussion

In this analysis of nearly 1 million pregnancies among U.S. private health insurance beneficiaries with continuous coverage throughout pregnancy from 2001 to 2015, we found that opioids are frequently coprescribed with psychotropic medication in pregnancy and are associated with antepartum hospitalization. A substantial proportion of pregnant women were prescribed opioids at doses that may increase the risk for overdose (MME ≥50/day, 23%) and that exceed currently recommended guidelines (MME ≥90/day, 9%).

We found that both documented substance use and antepartum hospitalization were increased with opioid prescription with and without psychotropic coprescription. This increased risk was higher for opioids alone versus with psychotropic coprescription. Prior population-level analyses have identified maternal characteristics independently associated with opioid and psychotropic prescription during pregnancy (16, 18, 24). Few studies have characterized opioid prescription in the setting of coprescription with psychotropics compared with opioid prescriptions alone with the exception of neonatal abstinence syndrome, in which opioid prescription with psychotropics increases the risk (30% to 60%) and severity (24, 28, 33–35). The limited data on women hospitalized during pregnancy have focused on obstetric and medical indications (36, 37); however, emerging data suggest that psychiatric indications could account for close to one tenth of postpartum readmissions, nearing the frequency of hypertensive complications (38). In the current study, women coprescribed opioids with psychotropics likely had underlying psychiatric conditions and potentially comorbid medical conditions, which may explain the higher frequency and smaller decrease in opioid prescription in this group. In addition, treatment with psychotropics may reflect access and engagement in care, and hence a decreased likelihood of substance use and hospitalization during pregnancy. Finally, the lower risk for antepartum hospitalization with coprescription versus opioids alone may reflect the beneficial effect of psychotropic medication in controlling underlying conditions that might contribute to opioid use.

Our study contributes to the literature by establishing that pregnant women frequently receive opioids at amounts considered "high risk" for overdose (including MME ≥50/day, which doubles the risk, and MME ≥90/day, which is the maximum recommended daily dose, equal to 60 mg of oxycodone) (31, 32). Women with opioid coprescription with psychotropics were slightly more likely to exceed the above thresholds versus those without psychotropics (opioids only) and were

Table 3. High-Risk Opioid Prescribing During Pregnancy, by Coprescription Status (2011–2015)*

Variable	Average MME ≥50/d	Average MME ≥90/d	≥2 Opioid Agents	≥30 Days' Opioid Prescription
Psychotropic prescription				
Participants, *n*	53 525	53 525	53 688	53 656
No (reference), %	19.7	5.2	10.3	6.0
Yes, %	19.6	6.5	22.4	22.2
ARR (95% CI)†	1.00 (0.96–1.05)	1.26 (1.16–1.37)	2.18 (2.08–2.28)	3.63 (3.44–3.83)
Coprescription				
Participants, *n*	9719	9719	9750	9745
Benzodiazepine				
No (reference), %	19.6	6.3	21.3	20.2
Yes, %	19.6	7.2	29.1	33.7
ARR (95% CI)†	0.99 (0.89–1.12)	1.12 (0.91–1.37)	1.38 (1.26–1.51)	1.68 (1.54–1.82)
Gabapentin				
No (reference), %	19.5	6.4	21.5	20.7
Yes, %	23.2	9.4	44.9	57.7
ARR (95% CI)†	1.20 (1.00–1.44)	1.48 (1.07–2.03)	2.07 (1.85–2.33)	2.72 (2.48–2.98)

ARR = adjusted risk ratio; MME = morphine milligram equivalents.
* Analysis restricted to women with an opioid prescription at any time in pregnancy.
† Log-binomal models were used. Relative risk of having the outcome for those with psychotropic coprescription versus those without after adjustment for the following covariates: maternal age, region, insurance plan type, and number of dependent children.

also more likely to have been prescribed multiple opioid agents and for a longer duration of pregnancy. Over time, the proportion of women with MME of 50 or greater and 90 or greater per day decreased, particularly among those coprescribed psychotropics. We also found that gabapentin and benzodiazepines were frequently coprescribed with opioids at a higher dose and were associated with increased opioid duration and multiple opioid agents. Gabapentin and benzodiazepine prescription have both been associated with an increased risk for drug overdose and opioid-related death among U.S. adults prescribed opioids (5, 6) and increasingly among women with pregnancy-associated deaths (7, 8). For this reason, current guidelines recommend that clinicians avoid prescribing benzodiazepines concurrently with opioids whenever possible, and the U.S. Food and Drug Administration has a black box warning highlighting the dangers of using these drugs together (32). Taken together, these results highlight current recommendations that opioids be reserved for pregnant women in whom the benefits clearly outweigh the risks (25, 31, 32).

There are several limitations to note. First, although we identified women at risk for overdose (MME ≥50/day), we could not reliably identify overdose events using these data (39) because many overdose events likely did not take place in the hospital (8). Data capture of overdose events may improve with statewide maternal mortality review committees (15). Second, we could not fully reconcile clinical indications for treatment and opioid and psychotropic prescriptions. For example, many women prescribed an antidepressant did not have an accompanying diagnosis of depression or anxiety and may have been prescribed these medications for non–mood-related conditions. Third, diversion, cost, loss or theft, or nonadherence to prescribed medications were important considerations, and these estimates assumed that all women prescribed medications were taking them as prescribed (18). Fourth, our estimates reflect insurance claims for medications dispensed by an outpatient pharmacy and not whether the medication was actually taken (13, 18, 24, 35) and do not include in-hospital prescriptions, which may have resulted in underestimation of opioid and psychotropic exposure. Fifth, we may have included pregnancies that ended in late second trimester terminations or stillbirths, leading to differential misclassification. Sixth, we estimated the duration of drug exposure for each pregnancy based on an imputed LMP, consistent with prior studies (18). Although this approach generally yields an accurate estimate of gestational age, some degree of misclassification is possible (40). Finally, we used claims data from commercial insurers with variation in participation each year. In addition, although the MarketScan extract captures approximately 25% of deliveries and 50% of deliveries covered by commercial insurance, this cohort was limited to women with continuous enrollment from conception through delivery to assess psychotropic and opioid prescription throughout pregnancy. Thus, generalizability beyond this population may be limited, and results related to frequency of study outcomes across time and geographic regions should be interpreted cautiously.

These results highlight the need for studies aimed at understanding the decision-making process for prescribing opioids with or without psychotropics among pregnant women as well as for integrated obstetric, mental health, and substance use services. Efforts to screen, identify, and treat women for mental health and substance use disorders, including opioids, are endorsed by the American College of Obstetricians and Gynecologists and the CDC (1, 32, 41, 42). However, fewer than 20% of obstetric providers routinely screen for substance use disorders (42). Whether integrated screening and treatment programs that concurrently address pain management, addiction counseling, and mental health services could decrease substance use and antepartum hospitalization during pregnancy and improve obstetric and infant outcomes for this high-risk population remains unknown.

In conclusion, opioids are frequently coprescribed with psychotropic medication in pregnancy. A substantial proportion of privately insured U.S. pregnant women are prescribed opioid doses exceeding current guidelines and at thresholds that may increase the risk for overdose. Judicious evidence-based opioid and psychotropic prescribing in pregnancy and further research to understand indications for using these medications in an era of increasing concern about opioid misuse are needed, which could have a significant impact on maternal and infant outcomes.

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