OBSTETRICS

Association between buprenorphine dose and outcomes among pregnant persons with opioid use disorder

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BACKGROUND: Opioid use disorder contributes to maternal morbidity and mortality in the United States. Little is known about how the patterns of buprenorphine dose and duration throughout pregnancy may affect neonatal and postpartum outcomes.

OBJECTIVE: To determine the associations between trajectories of buprenorphine utilization and dose during pregnancy on maternal and neonatal health outcomes.

STUDY DESIGN: Retrospective cohort study among 2925 pregnant persons with opioid use disorder, followed from the estimated start date of pregnancy through 90 days after delivery. We used administrative healthcare data from Medicaid-enrolled individuals to assess buprenorphine dose and use and maternal (postpartum buprenorphine continuation and overdose) and neonatal (low birthweight, neonatal abstinence syndrome (NAS)) outcomes. Group-based trajectory modelling was used to identify trajectories of buprenorphine dose and use during pregnancy. Weighted multivariable logistic regression assessed the association between buprenorphine trajectories and outcomes.

RESULTS: We identified 8 trajectories of buprenorphine utilization and dose during pregnancy. Regression analyses found that high doses of buprenorphine and a longer duration of buprenorphine use during pregnancy was associated with higher odds of postpartum buprenorphine continuation and reduced rates of overdose. Higher doses and longer duration of buprenorphine treatment were not associated with an increase in NAS or term low birth weight, relative to moderate or low doses or shorter treatment duration.

CONCLUSION: A longer duration and higher dose of buprenorphine treatment during pregnancy were associated with improved odds of postpartum buprenorphine continuation and were not associated with adverse neonatal outcomes.

Key words: buprenorphine, low birthweight, neonatal abstinence syndrome, opioid use disorders, overdose, pharmacoepidemiology, postpartum care, substance use disorders

Introduction

Opioid use disorder (OUD) is a major contributor to adverse pregnancy outcomes in the United States.[1] The use of medications for opioid use disorder (MOUD), buprenorphine and methadone, is critical for reducing the risk of overdose, improving pregnancy outcomes, and is the recommended, evidence-based treatment approach for pregnant persons with OUD.[2,3] In an evaluation of over 13,000 pregnancies with OUD, MOUD use was associated with a 57% decline in overdose and a 25% decline in preterm birth rates.[4]

Buprenorphine is the most commonly used medication for pregnant persons with OUD due to its ability to be prescribed by any licensed provider, availability across clinical settings, and improved neonatal outcomes compared to methadone and nonprescribed opioid use.[4–6] Despite these advantages, many persons with OUD who initiate buprenorphine in pregnancy discontinue treatment or have varying levels of medication adherence.[6–8] Subtherapeutic buprenorphine dosing in pregnancy may contribute to buprenorphine treatment discontinuation among pregnant persons with OUD. Pregnancy is associated with profound physiologic changes including alterations in blood volume, renal clearance, and hepatic metabolism which can significantly impact the pharmacokinetics of drugs.[9] As such, many drugs require unique dosing considerations to achieve therapeutic effects during pregnancy.[10] In pharmacokinetic studies among pregnant persons with OUD, plasma concentrations of buprenorphine are significantly reduced during pregnancy, compared to concentrations after delivery, and these changes are most pronounced in the third trimester.[11–13]

Prior research evaluating the relationship between alternative, pregnancy-specific buprenorphine dosing regimens and outcomes has been limited. In an evaluation of dosing patterns in a small observational cohort, findings suggested that dividing a patient's total daily dose into a more frequent dosing interval (eg, three- or four-times daily) may improve buprenorphine adherence during pregnancy.[11] However, despite the importance of dose to the therapeutic effectiveness of medications, the effects of an increased total daily buprenorphine dose and the consistency of buprenorphine dosing during pregnancy on maternal and neonatal outcomes has not been evaluated. As such, the objectives of this study were to understand the real-world patterns of buprenorphine dosing in pregnant populations and the relationships between dose, longitudinal patterns of dosing, and outcomes during pregnancy.

Materials and methods

In this study, we sought to test 2 hypotheses: 1) there will be significant

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AJOG at a Glance

Why was this study conducted?

To determine the associations between buprenorphine dose, utilization, and maternal and neonatal health outcomes.

Key findings?

Among a cohort of nearly 3000 persons with opioid use disorder, we identified 8 distinct trajectories of buprenorphine dose and utilization in pregnancy. A longer duration of use of buprenorphine throughout pregnancy, including at higher doses, was associated with higher postpartum treatment retention and fewer overdoses. Odds of low birthweight and neonatal abstinence syndrome did not differ by buprenorphine dose in pregnancy.

What does this add to what is known?

Findings support the need for a personalized approach to dosing including dose escalations during pregnancy to improve outcomes for persons with opioid use disorder.

variation in longitudinal patterns or "trajectories" of buprenorphine dose and use in pregnancy among persons with OUD; and 2) a higher dose and/or longer duration of buprenorphine use in pregnancy will not be associated with adverse maternal or neonatal outcomes.

Study population and dataset

For this analysis, we utilized administrative healthcare data from the Pennsylvania Medicaid program. Medicaid data include a census of healthcare utilization information on enrollees, including demographic information, inpatient and outpatient care, and outpatient prescription fill records including medication dose. We identified Medicaid-enrolled females ages 15 to 50 years who had a live birth from January 1, 2009 and September 30, 2019, who had diagnosis of OUD (ICD-9: 304.0X, 305.5X, 304.7X; ICD-10: F11.XXX) at any point during their pregnancy.[2,3] The pregnancy period was calculated according to the obstetrical estimate of gestational age at delivery and live births were identified using the date of delivery in inpatient records.[14] Since this analysis was designed to evaluate the broadest possible number of buprenorphine use patterns during pregnancy, we included patients who had ≥2 prescription fills for buprenorphine and did not have any methadone use in pregnancy or postpartum. Finally, we matched data on maternal-child dyads using a family identifier in the Pennsylvania Medicaid enrollment records, the date of delivery among persons with a live birth delivery, and the date of birth among one or more infants (depending on singleton or multiple births). We obtained a high (94%) match rate using this method.[15] Because we sought to follow individuals longitudinally to prospectively assess buprenorphine use and outcomes, we included those who were continuously enrolled in Medicaid coverage from the estimated pregnancy start through 90 days postpartum and who were not dually enrolled in Medicare coverage. Because of this inclusion criterion, we did not include those who had a fatal overdose. Our unit of analysis was the pregnant person, and infant's birth outcomes were linked to maternal records. Supplemental Table 1 describes the codes used to create each variable. This study was determined to be exempt from review by the University of Pittsburgh Institutional Review Board because it involved the use of secondary de-identified data (#22090080).

Buprenorphine dose and use trajectories

Our primary exposure of interest was the longitudinal pattern or trajectory of a patient's buprenorphine use during pregnancy, encompassing time-varying differences in the duration of use and dose, identified using group-based trajectory modelling. Group-based trajectory modeling was used to identify groups with distinct patterns of buprenorphine use and dose within the study cohort.[16] Using this method, we first calculated a standardized daily dose of buprenorphine for each patient in our study based on the dispensed dose, the date the medication was dispensed, and the days-supply of all buprenorphine fills during pregnancy. We next applied group-based trajectory models (censored normal distributions), with the standardized daily dose as the outcome, to categorize different profiles of buprenorphine use and dose in pregnancy. These trajectory models were constructed with a flexible functional form, and we examined from the second through the fifth polynomial function of time (ie, week or month 1 to X). From these results, we selected the trajectories based on Nagin's criteria: the observed proportion of group assignment close to the estimated proportion of group assignments, average posterior probabilities of group assignment >0.7, and odds of correct classification >5.[17] Supplemental Table 2 shows additional details about our group-based trajectory models and comparison of model fit.

Outcomes

We evaluated the effect of buprenorphine dose and duration of use trajectories on 4 outcomes: postpartum buprenorphine continuation, overdose, term (≥37 weeks at delivery) low birthweight (ie, birthweight ≤2500 g at delivery), and neonatal abstinence syndrome (NAS). Postpartum buprenorphine continuation was categorized as a binary measure defined using the proportion of days' covered (PDC) algorithm,[18] which calculates the number of days where a patient has a supply of buprenorphine relative to the 90 day postpartum period. Consistent with prior research, high (versus low) adherence was defined as a PDC of ≥0.80.[19] Term low birth weight was defined as having a birthweight of ≤2500 g at birth among those at ≥37 weeks gestation at delivery. NAS was defined as having a

diagnosis of NAS during the birth hospitalization. Infant outcomes were calculated using inpatient data during their birth hospitalization. Due to a lack of overdose events to statistically model that outcome, likely because our inclusion criteria required buprenorphine use among all patients, we reported unadjusted descriptive findings regarding the occurrence of overdose across trajectory groups.

Covariates

Covariates associated with buprenorphine use and pregnancy outcomes were included. These covariates were as follows: age at the date of delivery; race and ethnicity (categorized as non-Hispanic white, non-Hispanic Black, non-Hispanic other races, or Hispanic); residence in an urban vs rural county; number of buprenorphine prescribers and number of buprenorphine prescriptions; indicators of mental health disorders; indicators of tobacco and/or other co-occurring substance use disorders; indicators of HIV or HCV infection; and any use of gabapentinoids or SSRI/SNRIs (which might be associated both with OUD and with NAS). Covariates were non-time-varying and were measured during pregnancy. We also controlled for the year of delivery and indicator of enrollment in each Medicaid-managed care plan to account for time trends in buprenorphine coverage and treatment.

Statistical analysis

Because the distribution of covariates differed across the trajectory groups and could influence buprenorphine treatment patterns, we calculated inverse probability of treatment (IPT) weights to reduce bias from confounding in estimating the association between buprenorphine trajectories and outcomes. Specifically, we fit multivariable logistic regression models where the outcome was a patient's likelihood of being in a particular trajectory group, and the independent variables included all covariates previously mentioned. A standardized weight was then constructed for each patient based on the ratio of the probability that they were in a particular trajectory group and the probability that they were in that trajectory condition based on observed characteristics. The distribution of the stabilized weights had a mean of 1.0 and ranged from 0.18 to 9.73. Supplemental Figure shows the distribution of stabilized weights within each trajectory group, and Supplemental Table 3 shows the absolute standardized mean differences (SMD) in study variables before and after weighting. As shown, after weighting, the SMD were well below 0.1. We then fit 3 IPT weighted multivariable logistic regression models where the group trajectory of buprenorphine use in pregnancy was the exposure of interest and the outcomes were binary measures of high adherence to buprenorphine postpartum, term low birthweight, and diagnosis of NAS during the birth hospitalization. Results are presented as adjusted odds ratios (aORs) with accompanying 95% confidence intervals (CI).

Results

Study cohort characteristics

The study cohort included 2925 patients with a diagnosis of OUD in pregnancy. Descriptive characteristics are shown in Table 1. The mean age at delivery was

TABLE 1
Characteristics of Medicaid-enrolled pregnant patients with opioid use disorder who used buprenorphine during pregnancy, 2009-2019[a]

Characteristic	Overall n=2925
Mean age (±SD, y)	29 (±4.6)
Race/ethnicity	
Non-Hispanic Black	119 (4.0)
Non-Hispanic White	2712 (92.7)
Hispanic	60 (2.0)
Non-Hispanic other races[b]	34 (1.2)
County of residence[c]	
Rural	715 (24.4)
Urban	2180 (74.5)
Mental health condition	
Anxiety	1206 (41.2)
Depression or other mood disorder	1366 (46.7)
Bipolar disorder, schizophrenia, or other psychotic disorder	48 (1.6)
Co-occurring, nonopioid substance use disorders	
Alcohol	187 (6.4)
Tobacco	1967 (67.3)
Simulant (amphetamine, cocaine), cannabis, or sedative use disorder	1414 (48.3)
Co-occurring medication use	
SSRI/SNRIs	688 (23.5)
Gabapentinoids	396 (13.5)
Co-occurring infectious disease diagnoses	
HCV	784 (26.8)
HIV	<10 (<1)

[a] Unless otherwise specified; [b] Other races include American Indian/Alaska Native, American Indian, Asian, Native Hawaiian/Pacific Islander, multiple races, or race not disclosed; [c] 1% of patients missing county of residence.

29 years (SD: 4.6); 93% of patients identified as white, 4% identified as Black, and 2% as Hispanic/Latinx; and most (75%) resided in urban counties. The prevalence of mood and anxiety disorders exceeded 40%, 27% were diagnosed with Hepatitis C infection in pregnancy, and <1% were diagnosed with HIV infection in pregnancy. Use of other nonopioid substances was common, with 68% identified with tobacco use, 7% with alcohol use, and 48% with the use of other nonopioid substances (including cannabis, amphetamines, cocaine, and others). Nearly a quarter of patients (24%) had prescribed SSRI/SNRI medications, and 14% had prescribed gabapentinoids in pregnancy.

Trajectories of buprenorphine dose and use

An 8-group trajectory model met our statistical criteria (Figure). These trajectories were then categorized into 3 groups based on similarities in utilization patterns: group A - pre-pregnancy, consistent buprenorphine use, group B - buprenorphine initiation during pregnancy, and group C - buprenorphine discontinuation during pregnancy. Among patients who initiated buprenorphine prior to pregnancy and had consistent buprenorphine use throughout pregnancy (group A) (panel A, 45% of the cohort), 3 distinct trajectories emerged by dose: high dose (mean daily dose 22.35 mg, SD ±0.81 mg), moderate dose (mean daily dose 14.76 mg, SD±0.52 mg), and low dose (mean daily dose 6.97 mg, SD ±1.58 mg). Among patients who initiated buprenorphine during pregnancy (group B) (panel B, 40% of the cohort), 3 distinct trajectories emerged by both trimester of initiation and dose: second trimester, moderate dose initiation (mean daily dose 10.58 mg, SD ±6.40 mg), third trimester, moderate dose initiation (mean daily dose 5.98 mg, SD ±6.47 mg), third trimester, low dose initiation (mean daily dose 1.46 mg, SD ±1.92). Among patients with prepregnancy use, but who discontinued buprenorphine during pregnancy (group C) (panel C, 15% of the cohort), 2 distinct trajectories emerged by both trimester of discontinuation and dose: first trimester, low dose discontinuation (mean daily dose 2.24 mg, SD ±3.54 mg) and second trimester, moderate dose discontinuation (mean daily dose 6.80 mg, SD ±5.26 mg).

Table 2 shows descriptive characteristics relevant to buprenorphine use among patients within each trajectory group. Group A had the greatest number of days with buprenorphine use (202−271 days) and buprenorphine prescription fills (17−18 fills) in pregnancy. In contrast, group C had the fewest number of days with buprenorphine use (52−130 days) and buprenorphine prescription fills (6−10 fills). Patients in all buprenorphine trajectory groups had similar utilization of outpatient visits, emergency department visits, and inpatient stays.

Associations of buprenorphine trajectory with outcomes

Unadjusted outcomes overall and by trajectory group are shown in Table 3, and results from weighted multivariable regression models are presented in Table 4. Relative to patients with prepregnancy and the consistent use of high doses of buprenorphine during pregnancy (Group A, high dose), patients who used lower doses of buprenorphine later in pregnancy, or who discontinued buprenorphine use had a significantly lower odds of postpartum buprenorphine continuation. For instance, those who initiated treatment in the second trimester had a 45% reduced odds (aOR: 0.55; 95% CI: 0.41, 0.73) of buprenorphine continuation at 90-days postpartum relative to the reference group. In contrast, those who consistently used buprenorphine at moderate doses had a 81% increased odds (aOR: 1.81; 95% CI: 1.09, 2.98) of buprenorphine continuation at 90-days postpartum. Weighted multivariable regression models identified no statistically significant association between the trajectory of buprenorphine use in pregnancy and the odds of term low birthweight. For instance, those with consistent use of higher doses of buprenorphine did not have a statistically different odds of having a low birthweight infant relative to those with consistent use of lower doses (aOR: 0.65; 95% CI: 0.28, 1.50). Likewise, there were no statistically significant differences in the odds of NAS between groups who used different buprenorphine doses in pregnancy and who continued to use buprenorphine at delivery. However, patients who discontinued buprenorphine use in pregnancy had a significantly lower odds of NAS (first trimester discontinuation aOR: 0.64, 95% CI: 0.46, 0.89 and second trimester discontinuation aOR: 0.55, 95% CI: 0.39, 0.79), relative to those with consistent use of buprenorphine during pregnancy and at delivery.

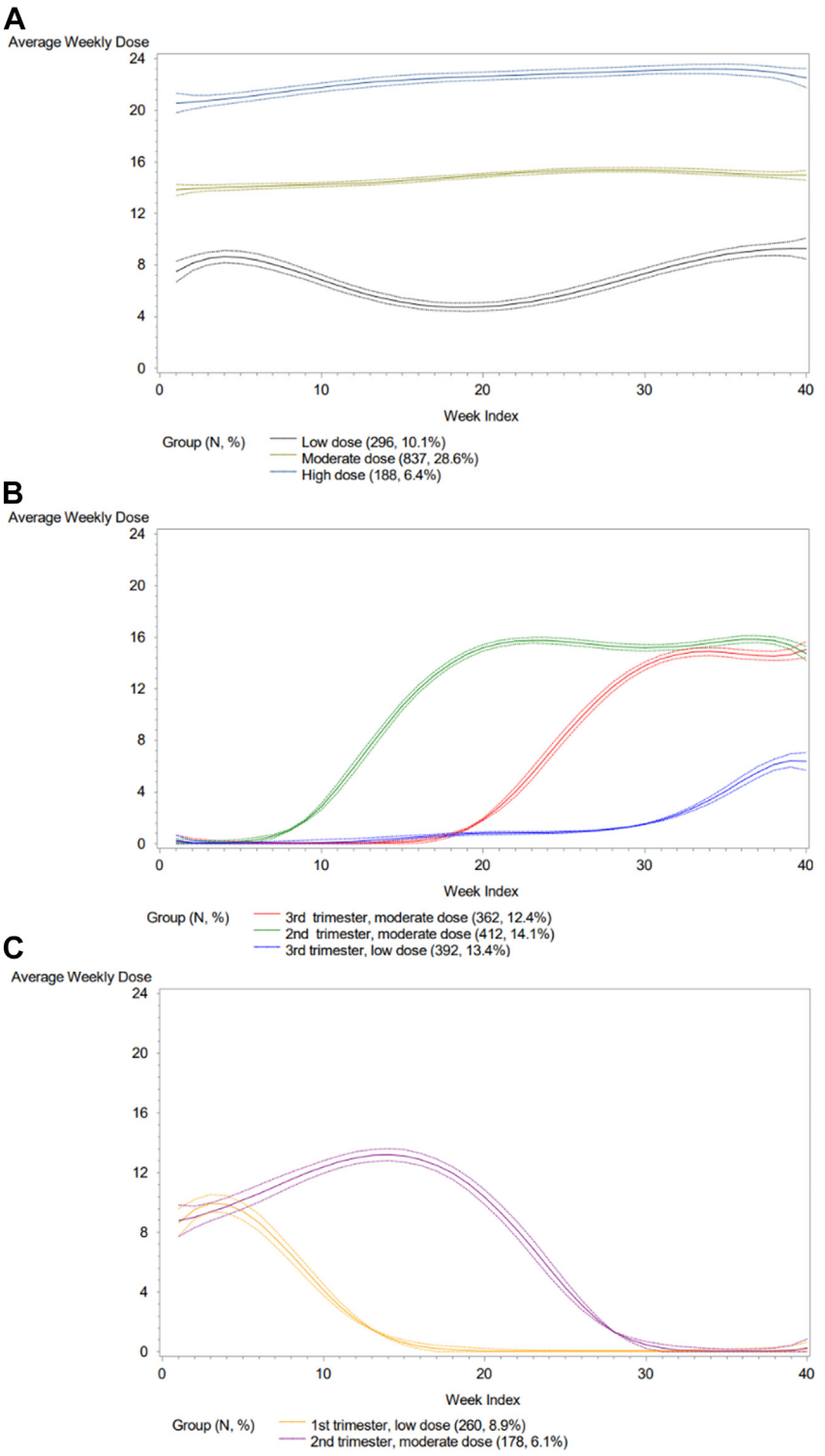
Table 5 shows IPT-weighted descriptive rates of nonfatal overdose events across pregnancy and for the first 90 days postpartum. Patients who discontinued buprenorphine use (18.3 per 1000) or had a later initiation of buprenorphine (21.9 per 1000) in pregnancy had a higher rate of nonfatal overdose in pregnancy and postpartum, relative to those with consistent buprenorphine use during pregnancy (6.9 per 1000).

Comment

Principal findings

In this study of pregnant patients with OUD in a large state Medicaid program, we identified 8 distinct longitudinal patterns or group-based trajectories of buprenorphine dose and duration of use during pregnancy. These groups included those with pre-pregnancy and consistent buprenorphine use during pregnancy, buprenorphine initiation during pregnancy, and buprenorphine discontinuation during pregnancy, with variation in dose within each of those trajectories. Trajectories with a more consistent use of buprenorphine and higher doses in pregnancy were associated with increased odds of continued buprenorphine use in the first 90 days postpartum, relative to trajectories with lower doses or when buprenorphine was discontinued during pregnancy. Overdose during pregnancy and postpartum was also more frequent among trajectories with lower doses or when buprenorphine was discontinued during pregnancy. There were no substantial differences in the odds of term low

FIGURE
Group-based trajectories of buprenorphine dose and duration during pregnancy



A–C, Group-based trajectories of buprenorphine dose and duration of use during pregnancy among Medicaid-enrolled patients with opioid use disorder. Data from 2925 persons enrolled in Pennsylvania Medicaid from 2009 to 2019. Group-based trajectories were modeled with a flexible functional form and the best fit was chosen based on model fit statistics as well as clinical relevance. As shown in Figure, among patients with prepregnancy buprenorphine use and who consistently used buprenorphine throughout pregnancy (Group A, Panel **A**), 3 trajectories were identified: high dose (mean daily dose (MDD) 22.35 mg), moderate dose (MDD 14.76 mg), low dose (MDD 6.97 mg). Among patients who initiated buprenorphine during pregnancy (group B, panel **B**), 3 trajectories were identified: first trimester, moderate dose initiation (MDD 10.58 mg), second trimester, moderate dose initiation (MDD 5.98 mg), and third trimester, low dose initiation (MDD 1.46 mg). Among patients with prepregnancy buprenorphine use, but who discontinued buprenorphine use during pregnancy, 2 trajectories were identified: first trimester, low dose discontinuation (MDD 2.24 mg), second trimester, moderate dose discontinuation (MDD 6.80 mg).

birthweight and NAS when higher versus moderate or low doses of buprenorphine were used during pregnancy.

Results in the context of what is known

Consistent with prior research showing that buprenorphine reduces the risk of overdose in pregnancy and the postpartum period,[20] our findings demonstrate that buprenorphine use during pregnancy is associated with fewer overdose events. Despite this, approximately 15% of patients in our cohort discontinued buprenorphine during pregnancy. While the reasons for discontinuation are unclear and unable to be discerned from administrative data, buprenorphine discontinuation has been observed in other studies of pregnant and postpartum patients.[21] Internal and external stigma, patient and provider misconceptions, influence from family and friends, and fear of child welfare involvement have all been identified as factors preventing many patients from continuing MOUD use during pregnancy.[22] Further, illicitly manufactured fentanyl, which is 30 to 50 times more potent than heroin, has emerged as the predominant opioid in the unregulated US drug supply.[23] Because fentanyl is a high potency opioid, buprenorphine, a partial opioid agonist, may not effectively mitigate opioid cravings and withdrawal for many persons with a history of fentanyl use.

TABLE 2
Weighted descriptive characteristics related to buprenorphine use among Medicaid-enrolled pregnant patients with opioid use disorder, by buprenorphine trajectory group

Characteristic	Pre-pregnancy, consistent buprenorphine use during pregnancy (group A)			Buprenorphine initiation during pregnancy (group B)			Buprenorphine discontinuation during pregnancy (group C)	
	High dose	Moderate dose	Low dose	2nd trimester, moderate dose	3rd trimester, moderate dose	3rd trimester, low dose	1st trimester, low dose	2nd trimester, moderate dose
Unweighted N	188	837	296	412	362	392	260	178
Weighted N[a]	186	840	295	413	364	390	254	179
Buprenorphine utilization, mean (SD)								
No. buprenorphine prescriptions during pregnancy	18.5 (9.1)	18.5 (9.1)	17.7 (14.2)	15.1 (7.2)	10.7 (5.7)	5.6 (3.5)	5.9 (4.0)	10.0 (5.8)
No. days with buprenorphine use in pregnancy[b]	271.2 (13.4)	260.2 (24.5)	202.1 (63.1)	185.4 (28.6)	115.0 (27.9)	49.1 (31.7)	52.4 (26.3)	130.1 (40.4)
Other healthcare utilization, mean (SD)								
No. outpatient visits	22 (18)	27 (17)	26 (15)	26 (16)	23 (16)	19 (14)	21 (16)	22 (16)
No. emergency department visits	3 (3)	3 (3)	3 (3)	4 (3)	3 (3)	4 (4)	4 (3)	3 (2)
No. inpatient stays[c]	3 (2)	3 (5)	3 (3)	4 (3)	3 (3)	5 (6)	4 (6)	4 (3)

[a] Weighted according to the inverse probability of treatment of being in a particular trajectory; weights are predicted probabilities based on a logistic regression model including the following covariates: age at the date of delivery; race and ethnicity (categorized as non-Hispanic white, non-Hispanic Black, non-Hispanic other races, or Hispanic); number of buprenorphine prescribers and number of buprenorphine prescriptions; indicators of mental health disorders; indicators of tobacco and/or other co-occurring substance use disorders; indicators of HIV or HCV infection; and any use of gabapentinoids or SSRI/SNRIs; [b] Sum of the days' supply of all fills buprenorphine prescriptions in pregnancy; [c] Including delivery stay and any other inpatient stays in pregnancy through 90 days postpartum.

The discontinuation of buprenorphine during pregnancy was associated with a reduced odds of NAS diagnosis. Because our study used administrative healthcare claims data, we relied on diagnostic coding versus clinical assessments to identify NAS cases. This may have introduced identification bias, as the infants of parents who were prescribed buprenorphine during their delivery hospitalization (versus parents without MOUD use at delivery) may have been more likely to be observed and diagnosed with NAS after delivery. Further, because we observed similar rates of term low birthweight and healthcare utilization patterns among trajectory groups, differences in NAS diagnosis rates are not likely attributable to confounding by these factors. This finding should also be placed in context of prior research that demonstrates that discontinuing MOUD use during pregnancy is associated with an increase in adverse outcomes including overdose.[24]

In addition to dose, prepregnancy, consistent buprenorphine use during pregnancy was associated with improved outcomes compared to individuals who initiated buprenorphine in the second and third trimesters. These findings are consistent with prior research demonstrating that a longer duration of MOUD use is associated with improved pregnancy-associated outcomes including a reduced risk of preterm birth and an increased rate of postpartum MOUD continuation.[2] Individuals who initiate buprenorphine later in pregnancy may be in an earlier stage of their recovery which may also have contributed to the differences in the outcomes observed. Regardless, these findings indicate that efforts to improve MOUD access and use during pregnancy should focus on initiating MOUD as early as possible during pregnancy for persons who do not initiate MOUD prior to conception.

Clinical implications

Our results indicate that while buprenorphine dosing is highly variable across pregnancy, higher doses are associated with improvements in continuation rates and a decreased frequency of overdose.

TABLE 3
Unadjusted outcomes among Medicaid-enrolled pregnant patients with opioid use disorder, by buprenorphine trajectory group

Characteristic	Postpartum buprenorphine continuation[a]	Low birthweight[b]	Neonatal abstinence syndrome[c]
All groups, n (%)	1565 (53.5)	187 (6.4)	1948 (66.6)
Group A, n (%)			
High dose, n=188	158 (85.0)	<11 (–)[d]	119 (63.3)
Moderate dose, n=837	610 (72.3)	61 (7.2)	604 (72.2)
Low dose, n=296	174 (58.8)	16 (5.4)	200 (67.6)
Group B, n (%)			
2nd trimester, moderate dose, n=412	248 (60.2)	19 (4.6)	288 (70.0)
3rd trimester, moderate dose, n=362	211 (58.3)	22 (6.1)	238 (65.7)
3rd trimester, low dose, n=392	136 (34.7)	31 (7.9)	246 (62.8)
Group C, n (%)			
1st trimester, low dose, n=260	13 (0.05)	20 (7.7)	155 (59.6)
2nd trimester, moderate dose, n=178	15 (0.08)	<11 (–)[d]	98 (55.0)

Group A=pre-pregnancy, consistent buprenorphine use in pregnancy, group B=buprenorphine initiation in pregnancy, group C=buprenorphine discontinuation in pregnancy.

[a] Indicates >80% of days covered with buprenorphine in 90 days after delivery; [b] Indicates <2500 g at gestational age of ≥37 weeks; [c] Diagnosis of NAS during birth hospitalization; [d] N and % not shown due to small sample size.

Consistent with clinical guidelines recommending a person-centered approach to buprenorphine treatment in pregnancy, providers should utilize a shared decision-making approach when considering buprenorphine dose changes in pregnancy as the dose required to mitigate clinical symptoms may differ for each patient.[25] Clinical decision-making should incorporate an individual's prior experiences, prior illicit opioid use patterns (eg, fentanyl), and a review of clinical symptoms (eg, increased symptoms of opioid withdrawal and/or opioid cravings) each trimester to determine the

TABLE 4
Weighted, multivariable association between buprenorphine trajectories and outcomes among Medicaid-enrolled pregnant patients with opioid use disorder

Characteristic	Postpartum buprenorphine continuation aOR (95% CI)	Low birthweight aOR (95% CI)	Neonatal abstinence syndrome, aOR (95% CI)
Group A			
High dose	*Ref*	*Ref*	*Ref*
Moderate dose	1.81 (1.09, 2.98)	0.65 (0.28, 1.50)	0.82 (0.56, 1.19)
Low dose	0.50 (0.37, 0.68)	0.65 (0.36, 1.18)	0.90 (0.66, 1.23)
Group B			
2nd trimester, moderate dose	0.56 (0.43, 0.73)	0.57 (0.32, 1.00)	0.93 (0.70,1.24)
3rd trimester, moderate dose	0.55 (0.41, 0.73)	0.89 (0.52, 1.53)	0.81 (0.60,1.10)
3rd trimester, low dose	0.21 (0.15, 0.29)	1.23 (0.67, 2.26)	0.87 (0.64, 1.18)
Group C			
1st trimester, low dose	0.03 (0.01, 0.07)	1.16 (0.56, 2.40)	0.64 (0.46, 0.89)
2nd trimester, moderate dose	0.04 (0.02, 0.07)	0.70 (0.33, 1.47)	0.55 (0.39, 0.79)

Group A=pre-pregnancy, consistent buprenorphine use in pregnancy, group B=buprenorphine initiation in pregnancy, group C=buprenorphine discontinuation in pregnancy.

From weighted multivariable logistic regression models including unweighted n=2925 pregnant patients with opioid use disorder. Weights were derived according to the inverse probability of treatment of being in a particular trajectory; weights are predicted probabilities based on a logistic regression model including the following covariates: age at the date of delivery; race and ethnicity (categorized as non-Hispanic white, non-Hispanic Black, non-Hispanic other races, or Hispanic); number of buprenorphine prescribers and number of buprenorphine prescriptions; indicators of mental health disorders; indicators of tobacco and/or other co-occurring substance use disorders; indicators of HIV or HCV infection; and any use of gabapentinoids or SSRI/SNRIs.

TABLE 5
Weighted rates of overdose among Medicaid-enrolled pregnant patients with opioid use disorder, by buprenorphine trajectory categories

Characteristic	Prepregnancy, consistent buprenorphine use during pregnancy, n=1321 (group A)	Buprenorphine initiation during pregnancy, n=1167 (group B)	Buprenorphine discontinuation during pregnancy, n=433 (group C)
Overdose in pregnancy, rate per 1000	4.1	18.0	17.0
Overdose in 90 d postpartum, rate per 1000	2.8	3.9	1.3
Any overdose, rate per 1000	6.9	21.9	18.3

Weights were derived according to the inverse probability of treatment of being in a particular trajectory; weights are predicted probabilities based on a logistic regression model including the following covariates: age at the date of delivery; race and ethnicity (categorized as non-Hispanic white, non-Hispanic Black, non-Hispanic other races, or Hispanic); number of buprenorphine prescribers and number of buprenorphine prescriptions; indicators of mental health disorders; indicators of tobacco and/or other co-occurring substance use disorders; indicators of HIV or HCV infection; and any use of gabapentinoids or SSRI/SNRIs.

need for a change or increase in dose. Our findings also provide reassurance for providers and patients that dosing strategies can be adjusted without adverse effects on neonatal outcomes.

Research implications

Our findings complement a rapidly expanding evidence base demonstrating that MOUD is a critical component of treatment for pregnant persons with OUD by reducing the risk overdose and other adverse maternal and child health outcomes. However, findings from this study take a closer look at MOUD utilization patterns (eg, dose, continuation, timing of initiation) to understand how use patterns may differ within a population and how those differences influence health outcomes. Further research is necessary to understand how different drug exposures influence buprenorphine dosing and use patterns especially in the fentanyl age. Additional research is also necessary to understand factors that influence methadone dose and utilization patterns as well as how methadone versus buprenorphine dose and use patterns compare. Finally, qualitative and mixed-methods research approaches are also needed to understand patient-reported factors that influence MOUD use and dose during pregnancy.

Strengths and limitations

The primary strength of this study is the use of real-world, population-level data to understand distinct trajectories of buprenorphine use in pregnancy and the association of these trajectories with health outcomes during pregnancy and for 90-days postpartum. Because Medicaid is the largest single payer for obstetric care among persons with OUD, our data were well-suited to address this question. Despite these strengths, our study has certain limitations. First, we lacked statistical power to study overdose events in adjusted models; however, descriptive statistics suggest that longer duration and higher dose of buprenorphine in pregnancy is associated with lower overdose rates. Relatedly, we did not study fatal overdose events due to our study goal of evaluating outcomes throughout pregnancy and postpartum. Second, because this is an observational study, we cannot make any claims of causality about the observed associations between buprenorphine trajectories in pregnancy and outcomes. Third, study data are from a relatively homogenous population in one state, meaning that the buprenorphine trajectories we identified may not generalize to other states with different population characteristics or MOUD access. Fourth, due to data structure, we were not able to assess continual measures of birthweight or gestational age, so we reported a more limited birth outcome of low birthweight among term gestations. Finally, the study data spans 2009 to 2019 and does not overlap with the predominance of fentanyl in the US opioid supply. As such, the buprenorphine dose and continuation patterns we observed may differ in the context of current illicit opioid use patterns.

Conclusions

In this population-based study of Medicaid-enrolled pregnant patients with OUD, we identified 8 distinct trajectories of buprenorphine dose and duration of use in pregnancy. Generally, a longer duration of use and a higher dose of buprenorphine were associated with improved odds of continuing buprenorphine postpartum, less frequent overdose events, and were not associated with adverse neonatal outcomes. These results reiterate the importance of MOUD use during pregnancy to mitigate adverse outcomes associated with the opioid crisis. ■

GLOSSARY

aOR adjusted odds ratio
CI confidence interval
IPT inverse probability of treatment
MOUD medications for opioid use disorder
NAS neonatal abstinence syndrome
OUD opioid use disorder
PDC proportion of days' covered
SMD standardized mean difference

Acknowledgments

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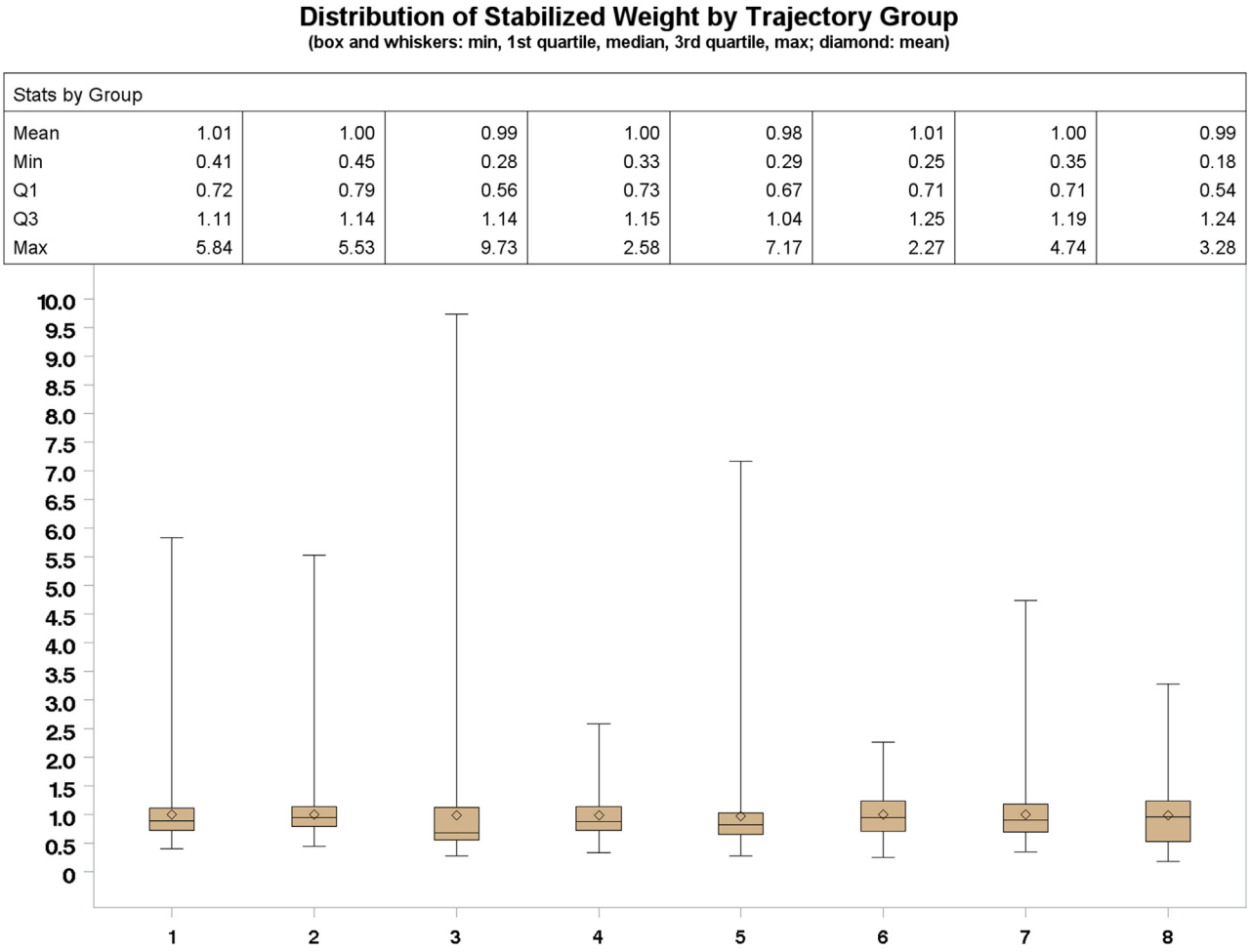
SUPPLEMENTAL FIGURE

Distribution of stabilized weights, by trajectory group



Boxes represent the first quartile, median, and third quartile; diamonds represent the mean; whiskers show the minimum and maximum values. Stabilized inverse probability of treatment weights were calculated within each buprenorphine trajectory group among Medicaid-enrolled persons with an opioid use disorder in pregnancy. Weights were based on models including the following: age at the date of delivery; patient race and ethnicity (categorized as non-Hispanic white, non-Hispanic Black, non-Hispanic other races, or Hispanic); number of buprenorphine prescribers and number of buprenorphine prescriptions; indicators of mental health disorders; indicators of tobacco and/or other co-occurring substance use disorders; indicators of HIV or HCV infection; any use of gabapentinoids or SSRI/SNRIs; year of delivery; and enrollment in a Medicaid managed care plan. Covariates were non-time-varying and were measured during pregnancy.

SUPPLEMENTAL TABLE 1

Diagnosis and procedure codes used to create study variables

Variable description	Data files	Definition
Cohort: females ages 15 −50 y with a date of delivery between January 1, 2009 and September 30, 2019	Enrollment files and inpatient and outpatient claims	- Any ICD-9-CM diagnosis starting in ('650', 'V27', 'V3') and any ICD-10-CM diagnosis starting in ('O80', 'O82', 'Z370', 'Z371', 'Z372', 'Z373', 'Z374', 'Z375', 'Z376', 'Z377', 'Z380', 'Z383', 'Z386') from inpatient, outpatient files OR - Any procedure code in (59400, 59409, 59410, 59510, 59514, 59515, 59610, 59612, 59614, 59618, 59620, 59622) from inpatient, outpatient files - Any ICD-9 diagnosis starting in ('640', '641', '642', '643', '645', '646', '647', '648', '649', '651', '652', '653', '654','655','658','659','660','661', '662','663','664','665','668','669', '671','673','674','675','676','678','679') OR in: ('642', '646', '647', '648', '649', '654', '665', '666', '667', '668', '669', '671', '673', '674', '675', '676', '679') OR diagnosis starting in: ('7681') - Any surgical procedure codes: ('72','73','740','741','742','744','7499') - Those with any diagnosis indicating stillbirth (ICD-9: '630', '631', '632', '633', '634', '635', '636', '637', '639', '6564', '7680', '7681', V271', 'V274', 'V277' or ICD-10: 'Z371','Z374','Z377') were excluded.
Opioid use disorder (OUD) in pregnancy	Inpatient and outpatient claims	- Any of the following diagnosis codes in any diagnosis field: ICD-10: 'F11.x' ICD-9: '3040', '3047', '3055' - For those with multiple deliveries but only one with OUD diagnosis, only the delivery with OUD diagnosis in pregnancy was retained for the analysis.
Encounters for buprenorphine in pregnancy and postpartum	Outpatient, pharmacy, and National Drug Codes (NDC)	- All outpatient claims with HCPCS code (PROC_CODE) for methadone administration: 'H0020', 'J1230' - Exclude those with methadone treatment in pregnancy - Then, all pharmacy claims with a National Drug Code (NDC) for buprenorphine formulation for the treatment of OUD were scanned. The list of NDCs for the OUD medications is lengthy and can be provided upon request.
Any prescription of gabapentins or SSRI in pregnancy	Pharmacy claims and NDC	- The lists of NDCs for gabapentins and SSRI are lengthy and can be provided upon request.
Term low birthweight (LBW)	Inpatient and outpatient claims	Term low birth weight (<2500 g at birth among those at ≥ 37 wk gestation) - Any diagnosis of low birth weight in infant's record within 28 d from DOB: ICD-9: '76401' — '76408' or '76411' — '76418' or '76421' — '76428' or '76491' — '76498' or '76501' — '76508' or '76511' — '76518' or ICD-10: 'P070', 'P071' - APR-DRGs of ('0588', '0589', '0591', '0593', '0602', '0603', '0607', '0608', '0609', '0611', '0612', '0613', '0614', '0621', '0622', '0623', '0625', '0626')
Neonatal abstinence syndrome (NAS)	Inpatient and outpatient claims	- During the birth episode, any diagnosis of ICD-9: '7795', or ICD-10: 'P961' - Exclude those with diagnoses in: (ICD-9: '76501', '76502', '76503', '76504', '76505', '7707', '7721', '7797', '7775', '7776', ICD-10: 'P070', 'P0714', 'P0715', 'P270', 'P271', 'P278', 'P520', 'P521', 'P522', 'P523', 'P912', 'P77', 'P780') from the definition of NAS
Overdose in pregnancy (excluding date of delivery) and any overdose in 90 d postpartum (including date of delivery)	Inpatient and outpatient claims	- Any ICD-9 diagnosis in '96500', '96501', '96502', '96509' 'E8500', 'E8501', 'E8502' - Any ICD-10 diagnosis in T400X1A, T400X1D, T400X1S, T400X2A, T400X2D, T400X2S, T400X3A, T400X3D, T400X3S, T400X4A, T400X4D, T400X4S, T401X1A, T401X1D, T401X1S, T401X2A, T401X2D, T401X2S, T401X3A, T401X3D, T401X3S, T401X4A, T401X4D, T401X4S, T402X1A, T402X1D, T402X1S, T402X2A, T402X2D, T402X2S, T402X3A, T402X3D, T402X3S, T402X4A, T402X4D, T402X4S, T403X1A, T403X1D, T403X1S, T403X2A, T403X2D, T403X2S, T403X3A, T403X3D, T403X3S, T403X4A, T403X4D, T403X4S, T404X1A, T404X1D, T404X1S, T404X2A, T404X2D, T404X2S, T404X3A, T404X3D, T404X3S, T404X4A, T404X4D, T404X4S, T40601A, T40601D, T40601S, T40602A, T40602D, T40602S, T40603A, T40603D, T40603S, T40604A, T40604D, T40604S, T40691A, T40691D, T40691S, T40692A, T40692D, T40692S, T40693A, T40693D, T40693S, T40694A, T40694D, T40694S

(continued)

SUPPLEMENTAL TABLE 1

Diagnosis and procedure codes used to create study variables *(continued)*

Variable description	Data files	Definition
Human immunodeficiency virus (HIV) in pregnancy Hepatitis C virus (HCV) in pregnancy	Inpatient and outpatient claims	- HIV: ICD-9: '042', '07953', 'V08'; ICD-10: 'O987', 'B20', 'Z21' - HCV: ICD-9: '07041', '07044', '07051', '07054', 'V0262', '07070', '07071'; ICD-10: 'B182', 'B192', 'B171'
Mental health conditions and substance use disorders (SUD) other than OUD	Inpatient and outpatient claims	- Anxiety disorder: ICD-9: '29384', '30000', '30001', '30002', '30009', '30010', '30020', '30021', '30022', '30023', '30029', '3003', '3005', '30089', '3009', '3080', '3081', '3082', '3083', '3084', '3089', '30981', '3130', '3131', '31321', '31322', '3133', '31382', '31383' ICD-10: 'F064', 'F4000', 'F4001', 'F4002', 'F4010', 'F4011', 'F40210', 'F40218', 'F40220', 'F40228', 'F40230', 'F40231', 'F40232', 'F40233', 'F40240', 'F40241', 'F40242', 'F40243', 'F40248', 'F40290', 'F40291', 'F40298', 'F408', 'F409', 'F410', 'F411', 'F413', 'F418', 'F419', 'F42', 'F430', 'F4310', 'F4311', 'F4312', 'F449', 'F458', 'F488', 'F489', 'F938', 'F99', 'R452', 'R455', 'R456', 'R457' - Mood disorder: ICD-9: '29383', '29600', '29601', '29602', '29603', '29604', '29605', '29606', '29610', '29611', '29612', '29613', '29614', '29615', '29616', '29620', '29621', '29622', '29623', '29624', '29625', '29626', '29630', '29631', '29632', '29633', '29634', '29635', '29636', '29640', '29641', '29642', '29643', '29644', '29645', '29646', '29650', '29651', '29652', '29653', '29654', '29655', '29656', '29660', '29661', '29662', '29663', '29664', '29665', '29666', '2967', '29680', '29681', '29682', '29689', '29690', '29699', '3004', '311' ICD-10: 'F320', 'F321', 'F322', 'F323', 'F324', 'F325', 'F329', 'F330', 'F331', 'F332', 'F333', 'F3340', 'F3341', 'F3342', 'F339', 'F341', 'F3010', 'F3011', 'F3012', 'F3013', 'F302', 'F303', 'F304', 'F308', 'F309', 'F310', 'F3110', 'F3111', 'F3112', 'F3113', 'F312', 'F3130', 'F3131', 'F3132', 'F314', 'F315', 'F3160', 'F3161', 'F3162', 'F3163', 'F3164', 'F3170', 'F3171', 'F3172', 'F3173', 'F3174', 'F3175', 'F3176', 'F3177', 'F3178', 'F3181', 'F3189', 'F319', 'F328', 'F338', 'F348', 'F349', 'F39', 'F0630' - Others: ICD-9: '29381', '29382', '29500', '29501', '29502', '29503', '29504', '29505', '29510', '29511', '29512', '29513', '29514', '29515', '29520', '29521', '29522', '29523', '29524', '29525', '29530', '29531', '29532', '29533', '29534', '29535', '29540', '29541', '29542', '29543', '29544', '29545', '29550', '29551', '29552', '29553', '29554', '29555', '29560', '29561', '29562', '29563', '29564', '29565', '29570', '29571', '29572', '29573', '29574', '29575', '29580', '29581', '29582', '29583', '29584', '29585', '29590', '29591', '29592', '29593', '29594', '29595', '2970', '2971', '2972', '2973', '2978', '2979', '2980', '2981', '2982', '2983', '2984', '2988', '2989' - ICD-10 'F060', 'F062', 'F200', 'F201', 'F202', 'F203', 'F205', 'F2081', 'F2089', 'F209', 'F22', 'F23', 'F24', 'F250', 'F251', 'F258', 'F259', 'F28', 'F29', 'F323', 'F333', 'F4489' - Tobacco use disorders: IDC-9: '3051', '64900', '64901', '64902', '64903', '64904', 'V1582' ICD-10: 'F17', 'Z720', 'O9933', 'Z87891' - Alcohol use disorders: ICD-9: '30390', '30391', '30392', '30393', '30500', '30501', '30502' ICD-10: 'F1010 ', 'F10120', 'F10121', 'F10129', 'F1014 ', 'F10150', 'F10151', 'F10159', 'F10180', 'F10181', 'F10182', 'F10188', 'F1019 ', 'F1020 ', 'F1021 ', 'F10220', 'F10221', 'F10229', 'F10230', 'F10231', 'F10232', 'F10239', 'F1024 ', 'F10250', 'F10251', 'F10259', 'F1026 ', 'F1027 ', 'F10280', 'F10281', 'F10282', 'F10288', 'F1029 ', 'F10920', 'F10921', 'F10929', 'F1094 ', 'F10950', 'F10951', 'F10959', 'F1096 ', 'F1097 ', 'F10980', 'F10981', 'F10982', 'F10988', 'F1099 '

(continued)

SUPPLEMENTAL TABLE 1

Diagnosis and procedure codes used to create study variables *(continued)*

Variable description	Data files	Definition
		- Other SUD: ICD-9: '30430', '30431', '30432', '30433', '30520', '30521', '30522', '30410', '30411', '30412', '30413', '30540', '30541', '30542', '30420', '30421', '30422', '30423', '30560', '30561', '30562', '30450', '30451', '30452', '30453', '30530', '30531', '30532', '30460', '30461', '30462', '30480', '30481', '30482', '30490', '30491', '30492', '30463', '30483', '30493', '30580', '30581', '30582', '30590', '30591', '30592', '30440', '30441', '30442', '30443', '30570', '30571', '30572' ICD-10: 'F1210 ', 'F12120', 'F12121', 'F12122', 'F12129', 'F12150', 'F12151', 'F12159', 'F12180', 'F12188', 'F1219 ', 'F1220 ', 'F1221 ', 'F12220', 'F12221', 'F12222', 'F12229', 'F12250', 'F12251', 'F12259', 'F12280', 'F12288', 'F1229 ', 'F1290 ', 'F12920', 'F12921', 'F12922', 'F12929', 'F12950', 'F12951', 'F12959', 'F12980', 'F12988', 'F1299 ', 'F1310 ', 'F13120', 'F13121', 'F13129', 'F1314 ', 'F13150', 'F13151', 'F13159', 'F13180', 'F13181', 'F13182', 'F13188', 'F1319 ', 'F1320 ', 'F1321 ', 'F13220', 'F13221', 'F13229', 'F13230', 'F13231', 'F13232', 'F13239', 'F1324 ', 'F13250', 'F13251', 'F13259', 'F1326 ', 'F1327 ', 'F13280', 'F13281', 'F13282', 'F13288', 'F1329 ', 'F1390 ', 'F13920', 'F13921', 'F13929', 'F13930', 'F13931', 'F13932', 'F13939', 'F1394 ', 'F13950', 'F13951', 'F13959', 'F1396 ', 'F1397 ', 'F13980', 'F13981', 'F13982', 'F13988', 'F1399 ', 'F1410 ', 'F14120', 'F14121', 'F14122', 'F14129', 'F1414 ', 'F14150', 'F14151', 'F14159', 'F14180', 'F14181', 'F14182', 'F14188', 'F1419 ', 'F1420 ', 'F1421 ', 'F14220', 'F14221', 'F14222', 'F14229', 'F1423 ', 'F1424 ', 'F14250', 'F14251', 'F14259', 'F14280', 'F14281', 'F14282', 'F14288', 'F1429 ', 'F1490 ', 'F14920', 'F14921', 'F14922', 'F14929', 'F1494 ', 'F14950', 'F14951', 'F14959', 'F14980', 'F14981', 'F14982', 'F14988', 'F1499 ', 'F1610 ', 'F16120', 'F16121', 'F16122', 'F16129', 'F1614 ', 'F16150', 'F16151', 'F16159', 'F16180', 'F16183', 'F16188', 'F1619 ', 'F1620 ', 'F1621 ', 'F16220', 'F16221', 'F16229', 'F1624 ', 'F16250', 'F16251', 'F16259', 'F16280', 'F16283', 'F16288', 'F1629 ', 'F1690 ', 'F16920', 'F16921', 'F16929', 'F1694 ', 'F16950', 'F16951', 'F16959', 'F16980', 'F16983', 'F16988', 'F1699 ', 'F1810 ', 'F18120', 'F18121', 'F18129', 'F1814 ', 'F18150', 'F18151', 'F18159', 'F1817 ', 'F18180', 'F18188', 'F1819 ', 'F1820 ', 'F1821 ', 'F18220', 'F18221', 'F18229', 'F1824 ', 'F18250', 'F18251', 'F18259', 'F1827 ', 'F18280', 'F18288', 'F1829 ', 'F1890 ', 'F18920', 'F18921', 'F18929', 'F1894 ', 'F18950', 'F18951', 'F18959', 'F1897 ', 'F18980', 'F18988', 'F1899 ', 'F1910 ', 'F19120', 'F19121', 'F19122', 'F19129', 'F1914 ', 'F19150', 'F19151', 'F19159', 'F1916 ', 'F1917 ', 'F19180', 'F19181', 'F19182', 'F19188', 'F1919 ', 'F1920 ', 'F1921 ', 'F19220', 'F19221', 'F19222', 'F19229', 'F19230', 'F19231', 'F19232', 'F19239', 'F1924 ', 'F19250', 'F19251', 'F19259', 'F1926 ', 'F1927 ', 'F19280', 'F19281', 'F19282', 'F19288', 'F1929 ', 'F1990 ', 'F19920', 'F19921', 'F19922', 'F19929', 'F19930', 'F19931', 'F19932', 'F19939', 'F1994 ', 'F19950', 'F19951', 'F19959', 'F1996 ', 'F1997', 'F19980', 'F19981', 'F19982', 'F19988', 'F1999 ', 'F550 ', 'F551 ', 'F552 ', 'F553 ', 'F554 ', 'F558 '

SUPPLEMENTAL TABLE 2

Group-based trajectory model fit and selection statistics

				Nagin's criteria		
Total # of groups estimated	BIC	Group	Est. Proportion of group assignment, %	Observed proportion of group assignment, %	Avg. Posterior probability	Odds correct classification
2	−305,366.37	1	45.62	45.54	0.9938	192.17
		2	54.38	54.46	0.9933	124.51
3	−292,331.30	1	24.79	24.72	0.9891	274.79
		2	28.70	28.82	0.9856	169.53
		3	46.51	46.46	0.9962	301.38
4	−288,479.21	1	22.98	22.94	0.9918	407.28
		2	27.75	27.90	0.9868	194.15
		3	40.74	40.65	0.9916	172.78
		4	8.54	8.51	0.9805	539.32
5	−281,074.58	1	20.09	20.07	0.9917	472.87
		2	18.50	18.56	0.9852	293.36
		3	18.75	18.74	0.9929	606.28
		4	34.40	34.32	0.9922	242.29
		5	8.25	8.31	0.9779	492.72
6	−276,730.48	1	20.43	20.48	0.9913	446.24
		2	17.15	17.13	0.9884	411.64
		3	13.45	13.47	0.9802	318.62
		4	11.89	11.97	0.9895	695.33
		5	30.36	30.26	0.9904	235.64
		6	6.71	6.70	0.9790	647.84
7	−273,668.36	1	19.90	19.97	0.9875	316.76
		2	16.46	16.44	0.9887	444.29
		3	10.25	10.26	0.9816	468.21
		4	11.02	11.01	0.9886	700.58
		5	29.39	29.40	0.9895	227.04
		6	6.44	6.39	0.9928	1997.37
		7	6.54	6.53	0.9799	695.46
8	−269,962.74	1	12.39	12.38	0.9870	538.20
		2	14.08	14.09	0.9869	458.58
		3	13.47	13.40	0.9899	630.06
		4	10.09	10.12	0.9799	434.13
		5	8.87	8.89	0.9886	893.42
		6	6.14	6.09	0.9962	3986.17
		7	28.44	28.62	0.9871	193.13
		8	6.53	6.43	0.9886	1239.28

(continued)

SUPPLEMENTAL TABLE 2
Group-based trajectory model fit and selection statistics *(continued)*

Total # of groups estimated	BIC	Group	Nagin's criteria: Est. Proportion of group assignment, %	Nagin's criteria: Observed proportion of group assignment, %	Nagin's criteria: Avg. Posterior probability	Nagin's criteria: Odds correct classification
9	−268,525.60	1	13.29	13.16	0.9924	846.50
		2	12.34	12.31	0.9870	538.16
		3	13.73	13.78	0.9844	395.40
		4	8.23	8.34	0.9817	597.91
		5	9.97	10.05	0.9784	409.64
		6	4.45	4.41	0.9894	2014.02
		7	27.61	27.59	0.9909	284.77
		8	3.97	3.90	0.9950	4771.71
		9	6.42	6.46	0.9805	730.66

SUPPLEMENTAL TABLE 3
Standardized mean differences (SMD) characteristics of each variable, pre-, and post-weighting

Characteristic	Pre-weighting: Mean	Pre-weighting: Min	Pre-weighting: Max	Post-weighting: Mean	Post-weighting: Min	Post-weighting: Max
Demographic characteristics						
Age at delivery, y	0.160	0.029	0.301	0.017	0.006	0.035
Race/ethnicity	0.105	0.056	0.158	0.024	0.003	0.036
Medicaid managed care plan enrollment	0.066	0.020	0.138	0.028	0.001	0.057
Urban/Rural residence at delivery	0.101	0.005	0.234	0.024	0.003	0.058
Buprenorphine use						
No. of buprenorphine prescribers	0.280	0.101	0.475	0.054	0.007	0.127
Mental health disorders						
Anxiety disorder	0.043	0.009	0.088	*N/A*		
Mood disorder	0.090	0.005	0.193	0.024	0.006	0.054
Schizophrenia/other psychotic disorders	0.032	0.001	0.061	*N/A*		
Co-occurring substance use disorders						
Tobacco use disorder	0.097	0.003	0.176	0.033	<.0001	0.081
Alcohol use disorder	0.056	0.015	0.114	0.024	0.001	0.050
Other substance use disorders	0.101	0.010	0.177	0.012	0.003	0.022
Infectious diseases						
HIV	0.069	0.001	0.117	0.037	0.004	0.077
HCV	0.064	0.016	0.125	0.020	0.003	0.043
Proportion days covered with other prescriptions						
Gabapentinoids	0.109	0.010	0.226	0.020	0.001	0.040
SSRIs/SNRIs	0.110	0.030	0.238	0.015	0.001	0.035