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Adherence trajectories of buprenorphine therapy among pregnant women in a large state Medicaid program in the United States

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Abstract

Purpose: Little is known about the longitudinal patterns of buprenorphine adherence among pregnant women with opioid use disorder, especially when late initiation, nonadherence, or early discontinuation of buprenorphine during pregnancy may increase the risk of adverse outcomes. We aimed to identify distinct trajectories of buprenorphine use during pregnancy, and factors associated with these trajectories in Medicaid-enrolled pregnant women.

Methods: A retrospective cohort study included 2361 Pennsylvania Medicaid enrollees aged 15 to 46 having buprenorphine therapy during pregnancy and a live birth between 2008 and 2015. We used group-based trajectory models to identify buprenorphine use patterns in the 40 weeks prior to delivery and 12 weeks postdelivery. Multivariable multinomial logistic regression models were used to identify factors associated with specific trajectories.

Results: Six distinct trajectories were identified. Four groups initiated buprenorphine during the first trimester of the pregnancy (early initiators): 31.6% with persistently high adherence, 15.1% with moderate-to-high adherence, 10.5% with declining adherence, and 16.7% with early discontinuation. Two groups did not initiate buprenorphine until midsecond or third trimester (late initiators): 13.5% had moderate-to-high adherence and 12.6% had low-to-moderate adherence. Factors significantly associated with late initiation and discontinuation were younger age, non-white race, residents of rural counties, fewer outpatient visits, more frequent emergency department visits and hospitalizations, and lower buprenorphine daily dose.

Conclusions: Six buprenorphine treatment trajectories during pregnancy were identified in this population-based Medicaid cohort, with 25% of women initiating buprenorphine late during pregnancy. Understanding trajectories of buprenorphine use and factors associated with discontinuation/nonadherence may guide integration of behavioral treatment with obstetrical/ gynecological care to improve buprenorphine treatment during pregnancy.

Keywords

adherence; buprenorphine; group-based trajectory models; Medicaid; opioid use disorder; pharmacoepidemiology; pregnant; trajectory

1 | INTRODUCTION

In the last 2 decades, opioid use disorder (OUD) and overdose deaths among reproductive-aged and pregnant women have increased dramatically in the United States.[1] Pregnant women with OUD have an increased risk of adverse maternal, obstetric, and neonatal outcomes (eg, preterm birth, fetal growth restriction).[2,3] Opioid agonist therapy has been shown to reduce illicit drug use and the risk of infection and improve adherence to prenatal care, maternal nutrition, and infant birth weight.[4]

Methadone has been the standard therapy for pregnant women with OUD for over 40 years. Emerging evidence supports buprenorphine (without naloxone) as an alternative first-line therapeutic option in pregnancy.[5] A multicenter, randomized controlled trial demonstrated that buprenorphine-exposed infants had a shorter length of hospital stays, shorter treatment durations for neonatal abstinence syndrome (NAS), and a lower cumulative morphine dose to treat NAS compared to methadone-exposed newborns.[5] Other advantages of buprenorphine over methadone for pregnant women include a lower risk of overdose and fewer drug interactions.[6]

Little evidence exists on longitudinal utilization and adherence patterns of buprenorphine therapy during the pregnancy and postpartum periods among pregnant women with OUD. Typical measures of adherence (eg, average over a year period) or simple criteria of discontinuation (eg, with a gap 30 days) do not capture all clinically relevant measures of

buprenorphine use such as the timing and dynamic patterns of treatment initiation, nonadherence, and discontinuation during pregnancy. Group-based trajectory models with intuitive graphical results can leverage the dynamic nature of buprenorphine use and identify subgroups with similar change over time.[7-9] In our prior work of 10 945 Pennsylvania Medicaid beneficiaries newly initiating buprenorphine,[8] we successfully identified 6 distinct treatment trajectories during the first year of treatment using group-based trajectory models and examined their association with subsequent health outcomes. For example, refilling buprenorphine intermittently was associated with a 24% higher risk of emergency department (ED) visits. Yet, our prior work largely focused on nonpregnant beneficiaries and did not examine timing of initiation and discontinuation patterns of buprenorphine during pregnancy and postdelivery. Therefore, we aimed to identify distinct longitudinal utilization and adherence trajectories of buprenorphine treatment and associated factors among pregnant women with OUD in Pennsylvania Medicaid program. Given that substantial numbers of pregnant women with OUD are Medicaid eligible and Medicaid is the largest funder of substance use disorder treatment services,[10,11] our findings may shed light on patterns of buprenorphine therapy among pregnant women with OUD and factors associated with late initiation, nonadherence, or early discontinuation for target interventions (eg, case management).

2 | METHODS

2.1 | Data sources

In this retrospective longitudinal analysis, we used Pennsylvania Medicaid administrative claims data of all fee-for-service and managed care enrollees from January 2008 through September 2015. Pennsylvania Medicaid ranks the fourth largest of 50 US states by expenditure and the seventh by enrollment (~3 million enrollees annually).[12] The datasets capture eligibility and enrollment information, and all health care services reimbursed by Medicaid including outpatient, inpatient, and professional services as well as prescription drugs. This study of deidentified data was deemed human subjects exempt from review by the University of Pittsburgh Institutional Review Board.

2.2 | Study cohort

Eligible cohort included women aged 15 to 46 years, receiving buprenorphine prescriptions during pregnancy either for sublingual buprenorphine or for buprenorphine/naloxone combination products in generic or proprietary formulations. We excluded women who were dually eligible for Medicare because their prescription drug utilization was not captured in the Medicaid data. We excluded patients who only used intravenous or transdermal buprenorphine formulations, which are approved by the US Food and Drug Administration for pain and not for OUD. Among the 2582 women who received   1 buprenorphine prescription, we excluded 221 women who also received methadone during pregnancy (168 switching from buprenorphine to methadone, 15 using methadone prior to buprenorphine, and 38 switching between methadone and buprenorphine for multiple times) to avoid misclassification of treatment switching as nonadherence or discontinuation of OUD treatment. Global reimbursement for methadone in Medicaid also imposes a challenge on measuring adherence to methadone in claims data.

We identified each patient's delivery dates and their birth outcomes, and excluded those who only had induced/spontaneous abortions (Appendix Figure S1). According to the US National Committee for Quality Assurance (NCQA)'s quality measures of prenatal and postpartum care, we used 280 days prior to the delivery date as the estimated conception date.[13] Patients were required to have continuous Medicaid enrollment during the first trimester (ie, 176 to 280 days prior to delivery) and 43 days prior to delivery and 12 weeks after delivery to obtain information on predictor variables and allow for complete follow-up. [13] The 12-week postdelivery period was chosen because pregnant women in Pennsylvania Medicaid, like many other states, have coverage until 12 weeks after delivery, and this window was considered as clinically reasonable for a postpartum visit (which is recommended at 6 weeks). We followed each patient's prescription buprenorphine fills from the estimated conception date through 12 weeks following the delivery date. When women (n = 407) had multiple pregnancy episodes with buprenorphine treatment during the study period, only the first episode was included in the analysis. The final analytic sample included 2361 women.

2.3 | Outcome variable: trajectories of buprenorphine refill patterns

Our primary outcome of interest was membership in a distinct trajectory of buprenorphine use based on a longitudinal analysis of the days covered with buprenorphine during pregnancy and 12 weeks postdelivery.[7-9,14] Our analyses proceeded in 2 steps.

First, based on dispensing date and days supplied, we created daily flags if the day was covered with buprenorphine starting from the estimated conception date to 12 weeks postdelivery, to establish buprenorphine treatment trajectories.[15,16] When a dispensing occurred before the previous dispensing should have run out, utilization of the refill was assumed to begin the day after the end of the previous dispensing.

Second, group-based trajectory models can identify differential patterns of individual change over time and characterize subgroups more likely to follow certain trajectories.[17,18] We estimated group-based trajectory models using longitudinal binary daily flags as the outcome variable (ie, covered vs not covered with buprenorphine), and the time variable was days since the estimated conception date (1-365). In each model, we used the most flexible functional form of time to allow the trajectories to emerge from the data. Output of trajectory models includes estimated probabilities of group membership for each individual, and estimated trajectory curves over time.[17,18] We selected the final model based on a combination of (1) the Bayesian information criterion (BIC), wherein the largest value indicates the best-fitting model, (2) an estimated proportion of each trajectory group that was sufficiently large (>0.05), and (3) application of Nagin's criteria to assess final model adequacy.[19] The Nagin's criteria of a well-performed trajectory model includes an average posterior probability 0.7 for all groups, odds correct classification 5.0 for all groups, estimated probability of membership in each group close to the proportion of sample assigned to each group, and narrow confidence intervals.[19] These models were estimated using STATA 14.0 (Stata-Corp LP, College Station, TX) and the TRAJ macro (free download at http://www.andrew.cmu.edu/user/bjones).

2.4 | Factors associated with different buprenorphine trajectories

After determining the most appropriate trajectory models, we compared the patient characteristics across identified trajectories with X^2 test and analysis of variance, as appropriate. We then examined the association between the membership in a trajectory group and the factors that were significantly different across trajectories from univariate analyses using a multivariable multinomial logistic regression model. We reported adjusted odds ratios (ORs) with 95% confidence intervals (CI). Statistical significance was defined as 2-tailed $P < .05$.

Based on prior studies of buprenorphine therapy for OUD and medication adherence,[8,20-31] we examined the following patient-level factors: sociodemographic factors including age, race/ethnicity (white vs non-white), type of health plan (fee-for-service or managed care), and eligibility category (pregnancy vs temporary assistance for the needy families [TANF] and other categories). Based on the classification from the National Center for Health Statistics 2010 Rural-Urban County Continuum, we also included an urbanicity measure of enrollees' county of residence (metropolitan vs nonmetropolitan; https://www.ers.usda.gov/data-products/rural-urban-commuting-area-codes/documentation/) because access to care may vary by urbanicity. Health status factors were measured during pregnancy and included diagnosis of OUD, other nonopioid drug use disorder, alcohol use disorder, mental health disorders, tobacco use, adverse pregnancy history (ie, preterm labor/delivery, other high-risk pregnancy), and history of prior methadone treatment any time between 2008 and prior to pregnancy (see supplement Table S1 for the detailed diagnosis and procedure codes).

Health service use factors included any inpatient utilization, number of emergency department (ED) visits, number of outpatient visits, number of other prescriptions with unique ingredients (as a proxy measure of disease and medication complexity), and number of unique prescribers for nonbuprenorphine prescriptions. We also calculated buprenorphine average daily dose (mg/day), maximum increase in buprenorphine dose (mg), number of unique buprenorphine prescribers, and average proportion of days covered (PDC) from estimated conception date to 12 weeks postdelivery. Finally, we measured whether patients received any behavioral counseling as proxy of quality of care for their OUD during the pregnancy.[32] We also examined whether women received any drug urine tests during pregnancy although false positive results from urine drug testing raise concerns regarding negative consequences (eg, accusation of child abuse/neglect by state laws).[33]

2.5 | Sensitivity and post hoc analyses

Women with OUD eligible for Medicaid due to pregnancy may have either no or a very short look-back period prior to the estimated conception date during which factors prior to pregnancy can be measured. This limited our ability to assess the prediction accuracy that was possible before observing any follow-up and to avoid factors such as changes in patient health status that may themselves be consequences of the use (or nonuse) of buprenorphine. Therefore, we conducted an additional sensitivity analysis excluding health service use factors from our final model to ensure the robustness of our findings. Results from the sensitivity analyses were similar to the main findings (supplemental Table S5). Furthermore, we were unable to examine the association between the identified trajectories and relevant

clinical outcomes including prenatal care visits (unmeasurable due to being paid via global payment with delivery), neonatal outcomes (without linkage between maternal and infant records), and long-term maternal outcomes (loss of Medicaid eligibility after 12 weeks postdelivery prior to Medicaid expansion in 2015). We conducted a post hoc analysis to examine proportions of all-cause ED visits and hospitalization between 85 days and 1 year postdelivery across trajectories.

3 | RESULTS

3.1 | Trajectories of buprenorphine refill patterns

Among 2361 pregnant women filling buprenorphine prescriptions, the overall average PDC was 59% (SD 31%) from the estimated conception date through 12 weeks postdelivery, with considerable between-enrollee and within-enrollee variability. According to a combination of BIC value (BIC = −303 412.82), estimated group proportions, and Nagin's criteria, a model with 6 distinct trajectories for buprenorphine use performed optimally and was selected as the final model (supplement Tables S2 and S3).[17]

Figure 1 illustrates the predicted probability of each trajectory of days of covered with buprenorphine from the estimated conception date to 12 weeks postdelivery. Four of the 6 groups (73.6% of the cohort) initiated buprenorphine during the first trimester of pregnancy (ie, early initiators); however, there were distinct groups with respect to the adherence level. Specifically, one-third (n = 747, 31.6% of total cohort, 95% CI = 29.8%-33.5%) were early initiators with persistently high adherence, 15.1% (95% CI = 13.7%-16.6%) with moderate-to-high adherence, 10.5% (95% CI = 9.3%-11.8%) with declining adherence over time, and 16.7% (95% CI = 15.1%-18.1%) with early discontinuation of buprenorphine (ie, before third trimester). The remaining 2 trajectories did not initiate buprenorphine until midsecond trimester or third trimester (ie, late initiators) but with different adherence levels: 13.5% (95% CI = 12.1%-14.9%) having moderate-to-high adherence and 12.6% (95% CI = 11.2%-13.9%) having low-to-moderate adherence.

The overall mean age was 27.8 (SD 4.6) years (Table 1). The majority of patients were white (95%) and in a managed care plan (88%), and resided in metropolitan counties (75%). Almost 90% of women were eligible for Medicaid through TANF or other eligibility groups, and the remaining were eligible through their pregnancy. Nearly 80% of women had at least 1 claim with a diagnosis of OUD in pregnancy. Comorbid nonopioid drug use disorders (72.8%), alcohol use disorder (4.6%), mental health disorders (40.4%), and tobacco use (68.0%) were also prevalent. Eighteen percent of women had an adverse pregnancy history. Two-thirds of women had received medication-assisted therapy prior to their pregnancy (buprenorphine = 55.9%, methadone = 2.5%, buprenorphine and methadone = 7.8%).

Table 1 shows a descriptive comparison of characteristics by buprenorphine trajectory. Compared to early initiators with persistently high adherence, late initiators regardless of their adherence level of buprenorphine were slightly younger (27.0-27.6 vs 28.5 years), more likely to be eligible for Medicaid through pregnancy (12.8%-16.7% vs 6.6%), less likely to live in metropolitan counties (67.6%-69.5% vs 79.0%), and had more frequent diagnoses of comorbid alcohol use disorders (5.4%-7.9% vs 4.8%). Compared to early

initiators with persistently high adherence, early initiators with declining adherence or early discontinuation were less likely to be white (89.1%-92.3% vs 96.3%), have OUD diagnoses (66.7%-71.4% vs 81.4%), other nonopioid drug use disorders (61.6%-68.2% vs 77.1%), and tobacco use (60.8%-63.3% vs 68.7%). All of these differences were statistically significant ($P<.01$).

3.2 | Patterns of health service use, buprenorphine therapy, and quality of care

In Table 2, compared to early initiators with persistently high adherence, late initiators or early initiators with declining adherence or early discontinuation had a higher hospitalization rate (9.1%-14.8% vs 6.7%, $P<.001$) during pregnancy. Early initiators with declining adherence or early discontinuation or late initiators with low-to-moderate adherence also had fewer outpatient visits (9.5-9.9 vs 11.3, $P<.0001$). Compared to early initiators with persistently high adherence, the other 5 trajectory groups, on average, used a lower buprenorphine daily dose (14.7-16.5 vs 17.6 mg/day, $P<.0001$). Overall, 30% to 40% of women received behavioral counseling, and 67% to 77% had a urine drug test during pregnancy.

3.3 | Factors associated with specific buprenorphine trajectories: multivariable multinomial logistic regression

Figure 2 and supplement Table S4 show the factors associated with specific trajectories from the multivariable multinomial logistic regression model, using the early initiators with persistently high adherence trajectory group as the reference group compared with the other 5 groups individually. For example, compared to early initiators with persistently high adherence, significant factors that increase odds of being as early initiators with early discontinuation were younger age (OR = 0.94, 95% CI = 0.91-0.97), non-white race (OR = 2.16, 95% CI = 1.22-3.82), and having no diagnosis of OUD coded (OR = 0.59, 95% CI = 0.42-0.84). History of other substance use disorders were also associated with odds of being in the group of early initiators with early discontinuation (OR = 0.72, 95% CI = 0.53-0.99 for other nonopioid drug use disorders and OR = 0.32, 95% CI = 0.14-0.73 for alcohol use disorder). Higher hospitalizations during pregnancy were also associated more commonly in the group of early initiators with early discontinuation (OR = 2.14, 95% CI = 1.34-3.44). Women who lived in nonmetropolitan counties had a 50% to 59% higher odds to be late initiators (with moderate-to-high adherence: OR = 1.59, 95% CI = 1.12-2.25; with low-to-moderate adherence: OR = 1.50, 95% CI = 1.04-2.15).

Late initiators with low-to-moderate adherence also were more likely to have more frequent hospitalizations (OR = 2.49, 95% CI = 1.50-4.15). Women who had prior buprenorphine therapy prior to their pregnancy were less likely to have suboptimal adherence or premature discontinuation of buprenorphine therapy (varied from early initiators with declining adherence: OR = 0.41 [95% CI = 0.21-64] to late initiators with moderate-to-high adherence: OR = 0.04 [95% CI = 0.03-0.06]). Enrollees having higher buprenorphine daily dose during pregnancy were less likely to have poor adherence or discontinue early (varied from late initiators with low-to-moderate adherence: OR = 0.92 [95% CI = 0.90-0.95] to early initiators with declining adherence: OR = 0.95 [95% CI = 0.92-0.98]).

3.4 | Post hoc analysis: proportions of all-cause ED visits and/or hospitalization across identified trajectories

As shown in Table 3, late initiators with low-to-moderate adherence (37.2 per 100 person years) and early initiators with early discontinuation (37.4 per 100 person years) appear to have higher risk of all-cause hospitalization/ED visits between 85 days and 1 year post-delivery compared to early initiators with persistently high adherence (26.9 per 100 person years) and other trajectory groups (28.5-29.5 per 100 person years; $P < .0001$).

4 | DISCUSSION

Our study yielded 3 important insights into buprenorphine treatment among pregnant women with OUD in a large state Medicaid program. First, we identified 6 distinct trajectories of buprenorphine treatment throughout pregnancy and until 12 weeks postpartum. This variability in use patterns may arise from a variety of factors including barriers to obtaining OUD treatment among pregnant women such as lack of available buprenorphine treatment providers, patient nonadherence to treatment, and/or physician discontinuation of treatment. Second, despite nearly 75% of women initiating buprenorphine early (during the first trimester), over one-third of these early initiators had poor refill adherence or discontinued buprenorphine therapy early (ie, before third trimester). Third, we found marked differences across the trajectory groups in terms of characteristics that may be used by health systems for targeting interventions: for example, residence in rural, underserved areas and the presence of polysubstance use.

The major strength of our study is the use of a group-based trajectory model to examine longitudinal buprenorphine refill patterns over time, rather than using a single adherence measure (eg, average proportion of days covered during pregnancy) or an arbitrary cutpoint for discontinuation (eg, a gap in treatment for 30 days). Single adherence measures may not reflect different levels and patterns of engagement in treatment over time, which are influenced by different patient, provider, and access to care factors. For example, a patient consistently refilling early in treatment and then discontinuing could have the same proportion of days covered as a patient who refills intermittently throughout the entire pregnancy.[7,9] Therefore, trajectory models provide the understanding of heterogeneity in buprenorphine therapy among pregnant women with OUD and may target different interventions to women with different barriers and needs.[8]

Two findings related to the timing of treatment initiation and discontinuation are worth noting. First, one-quarter of women were late initiators and did not initiate treatment until the second trimester (ie, 13.5% with moderate-to-high adherence and 12.6% with low-to-moderate adherence). Second, 16.7% of our cohort discontinued treatment before the third trimester (ie, early initiators with early discontinuation). Potential explanations both for late initiation and for early discontinuation of buprenorphine therapy include unplanned pregnancies and delayed prenatal care presentation,[34] fear of being reported to the police based on state policies,[35] disbelief in the efficacy of care, and a study population with a baseline high risk for nonadherence to medications.[25,34,36-38] Given that premature discontinuation of buprenorphine may elevate the risk of relapse to opioid use and adverse obstetric and neonatal outcomes,[3,4] Medicaid programs might consider investing in

programs that offer woman-centered services tailored to patient needs and patient risk profiles to boost patient adherence and improve retention rates, especially among early initiators with early discontinuation and late initia-tors with low-to-moderate adherence.[39,40]

Several factors were identified that could be used to target patients at high risk of late initiation or early buprenorphine discontinuation including younger age, racial/ethnic minority groups, rural residency, lack of OUD diagnoses, nonopioid substance use disorder, and alcohol use disorder during pregnancy. In addition, late initiators (regardless of their adherence levels) and early initiators with early discontinuation had more inpatient visits and a lower mean buprenorphine daily dose during pregnancy. Given an increase in apparent clearance of buprenorphine during pregnancy, dose escalation of buprenorphine is suggested.[41] Clinicians may consider split dosing in patients complaining of discomfort and craving in the afternoon/evening to prevent relapse.[42,43] Approximately 40% of our cohort had comorbid mental health disorders. Psychosocial treatment is recommended, and several meta-analyses showed the safety of selective serotonin reuptake inhibitors (SSRIs) in pregnancy (except paroxetine with an increased risk of cardiac defects).[44]

Our study has several limitations. First, our study relied on administrative billing data that lacked laboratory results and sociobehavioral information. In the absence of data on timing of conception calculated from the last menstrual period, we applied the delivery date algorithm (ie, 280 days prior to the delivery date) that was used in the US NCQA's quality measures of prenatal and postpartum care.[13] In a validation study of the conception date,[45] applying the delivery date-based algorithm to examine prescription drug exposure in the first trimester for women without preterm births or pregnancy complications was accurate (sensitivity ~92% and specificity ~98%). Nevertheless, the sensitivity for the delivery date algorithm among women with preterm deliveries was low (66%).[45] Women with preterm deliveries may be misclassified as late initiators, although the extent to which this would bias our estimates is unknown. Potential unmeasured confounders also cannot be ruled out from our observational study. Second, similar to all claims-based measures of adherence, it is unknown whether the dispensed drugs were actually consumed by the patients. Third, the US Food and Drug Administration labeled sublingual buprenorphine for treating OUD and not for pain. However, 20% of the study cohort had no OUD diagnosis recorded. It may be that physicians are either not billing Medicaid for OUD treatment while the pharmacy is concurrently billing Medicaid for the prescription or are providing buprenorphine for off-label indications. Fourth, although we were unable to study the association between these trajectories and relevant clinical outcomes including number of prenatal care visits, neonate outcomes, and long-term maternal outcomes, our post hoc analysis showed that early initiators with early discontinuation and late initiators with low-to-moderate adherence had higher proportions of all-cause hospitalization/ED visits between 85 days and 1 year postdelivery compared to other trajectory groups. However, prior to Medicaid expansion in 2015, over a quarter of pregnant women with OUD eligible for Medicaid due to pregnancy may have lost their Medicaid eligibility after 12 weeks postdelivery. Future studies using a prospective design or data that capture longer and more complete data post-delivery are thus warranted.[44] Fifth, women completing withdrawal or detoxification therapy may be misclassified as nonadherent or as discontinuing buprenorphine. However, both the Substance Abuse and Mental Health Services Administration (SAMHSA) and American

Congress of Obstetricians and Gynecologists (ACOG) do not recommend withdrawal or detoxification therapy due to an increased risk of relapse to illicit drugs, preterm labor, fetal distress, and pregnancy loss.[33,44] Finally, findings derived from the Pennsylvania Medicaid population may not be generalizable to other Medicaid populations with a different demographic profile or programmatic features.[46,47] Nevertheless, Pennsylvania is 1 of the largest Medicaid programs by expenditures and monthly enrollment. The features of demographics (except lower Hispanic population) and health care utilization in Pennsylvania Medicaid are similar to those seen in other state Medicaid programs.[48]

Pregnancy is a transformative state (both biologically and socially) that may provide a "window of opportunity" for OUD treatment and provide enormous potential for behavioral changes for this vulnerable population.[49] Our study showed 6 unique trajectories of longitudinal buprenorphine refills among pregnant Medicaid-enrolled women in Pennsylvania. These trajectories and associated factors may be further used to develop more targeted interventions to improve care and health outcomes among pregnant women with OUD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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KEY POINTS

- Six buprenorphine treatment trajectories with different adherence levels were identified among pregnant Medicaid beneficiaries.

- A quarter of pregnant women did not initiate buprenorphine until midsecond or third trimester.

- Factors significantly associated with late initiation and discontinuation were younger age, non-white race, residents of rural counties, having fewer outpatient visits, more frequent emergency department visits and hospitalizations, and lower buprenorphine daily dose.

- Understanding distinct buprenorphine trajectories and associated factors may better guide buprenorphine treatment, integrate behavioral treatment with obstetrical/gynecology care, and target interventions among pregnant women.
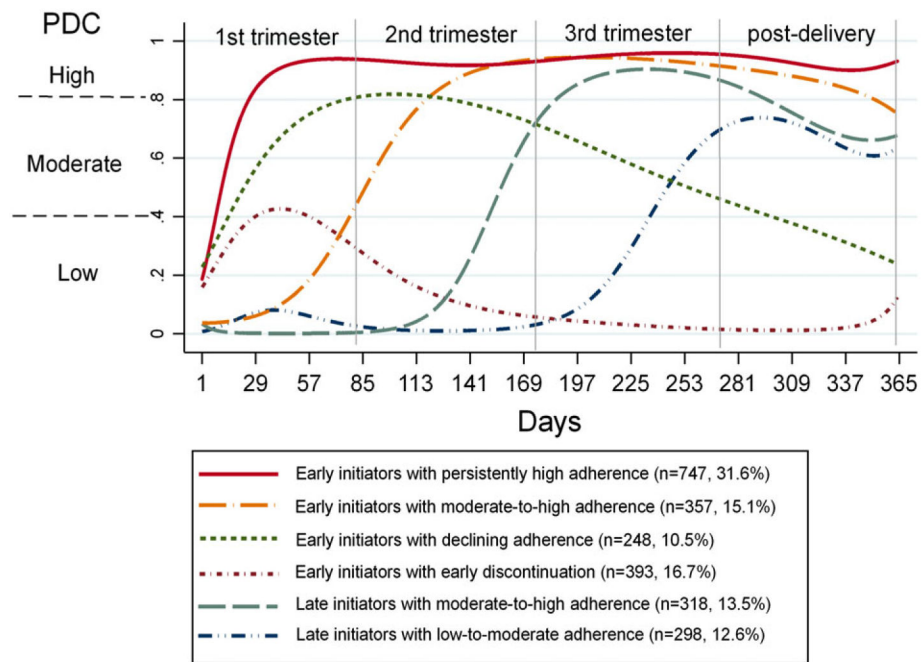
FIGURE 1.

Trajectories of buprenorphine use during pregnancy and 12 weeks postdelivery. PDC, proportion of days covered with buprenorphine [Colour figure can be viewed at wileyonlinelibrary.com]

FIGURE 2.

Factors associated with specific trajectories from multivariable multinomial logistic regression model (reference group: early initiators with persistently high adherence). MAT: medical assisted therapy; OUD: opioid use disorder; SUD: substance use disorders; TANF, temporary assistance for the needy families. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1

Characteristics of pregnant Medicaid enrollees filling buprenorphine prescriptions overall and by trajectory group: 2008 to 2015 (N = 2361)

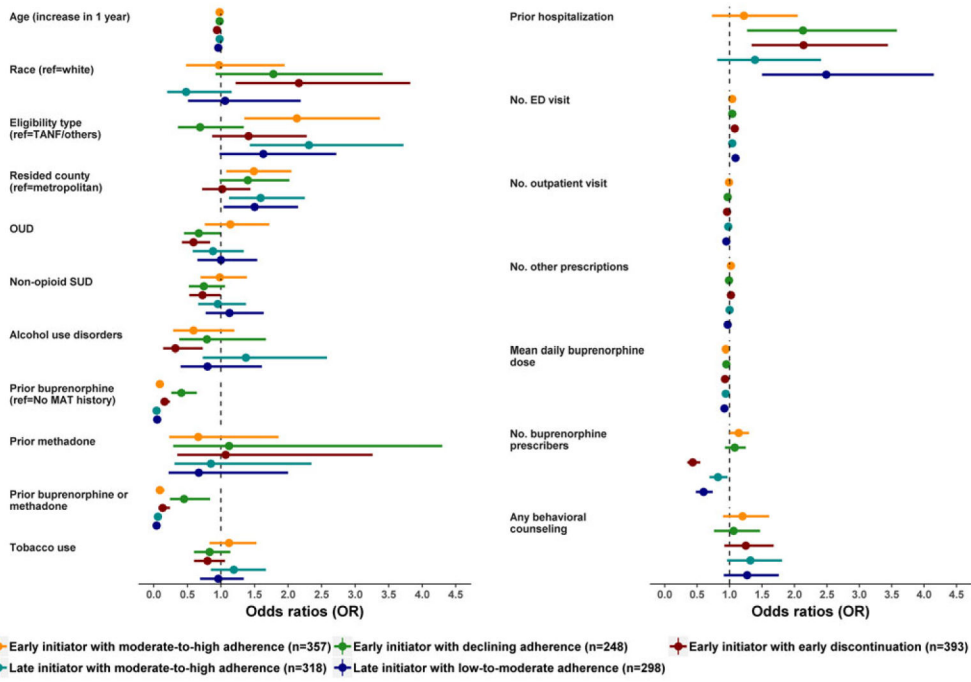| Characteristics	Overall (n = 2361)	Trajectory Group						
		Early Initiators with				Late Initiators with		
		Persistently High Adherence (n = 747)	Moderate-to-High Adherence (n = 357)	Declining Adherence (n = 248)	Early Discontinuation (n = 393)	Moderate-to-High Adherence (n = 318)	Low-to-Moderate Adherence (n = 298)	
Sociodemographic								
Age, mean (SD) [†]	27.8 (4.6)	28.5 (4.5)	27.7 (4.8)	27.9 (4.3)	27.2 (4.8)	27.6 (4.6)	27.0 (4.3)	
Race, % [†]								
White	94.5	96.3	95.8	92.3	89.1	97.5	94.3	
Non-white	5.5	3.8	4.2	7.7	10.9	2.5	5.7	
Health plan type, % [*]								
Fee-for-service	11.9	10.4	10.6	9.3	11.7	14.2	17.5	
Managed care	88.1	89.6	89.4	90.7	88.3	85.9	82.6	
Type of Medicaid eligibility, % [†]								
Pregnancy	10.1	6.6	13.5	4.8	9.9	16.7	12.8	
TANF and others	89.9	93.4	86.6	95.2	90.1	83.3	87.3	
Resided county, % [†]								
Metropolitan	74.5	79.0	69.2	73.8	80.7	67.6	69.5	
Nonmetropolitan	24.7	20.8	30.3	24.6	18.6	31.5	29.2	
Health status during pregnancy								
OUD, % [***]	79.9	81.4	89.6	71.4	66.7	83.3	85.6	
Other nonopioid drug use disorders [a], % [†]	72.8	77.1	77.0	68.2	61.6	73.3	74.8	
Alcohol use disorders, % [*]	4.6	4.8	3.6	4.0	2.3	7.9	5.4	
Mental health disorders [b], %	40.4	40.8	39.8	40.3	41.2	42.8	36.6	
Tobacco use, % [**]	68.0	68.7	72.8	63.3	60.8	73.3	68.5	
Adverse pregnant history [c], %	17.8	19.7	18.8	15.3	16.3	16.4	17.1	

Medication-assisted therapy history prior to pregnancy, % [†]

| | | Trajectory Group | | | | | | |
| | | Early Initiators with | | | | Late Initiators with | |
Characteristics	Overall (n = 2361)	Persistently High Adherence (n = 747)	Moderate-to-High Adherence (n = 357)	Declining Adherence (n = 248)	Early Discontinuation (n = 393)	Moderate-to-High Adherence (n = 318)	Low-to-Moderate Adherence (n = 298)
Buprenorphine	55.9	80.3	43.4	69.8	56.0	26.1	29.9
Methadone	2.5	0.8	3.4	1.6	2.5	5.0	3.4
Buprenorphine and methadone	7.8	11.5	6.7	10.9	4.8	5.4	3.4
None	33.9	7.4	46.5	17.7	36.6	63.5	63.4

Abbreviations: OUD, opioid use disorders; TANF, temporary assistance for the needy families.

Comparison between 6 trajectory groups:

*
P < .05.

**
P < .01.

***
P < .001.

†
P < .0001.

a
Includes diagnosis of dependence on illicit substances other than opioids (cocaine, cannabis, amphetamine, hallucinogen, other sedatives and other substances) or a diagnosis of "antepartum drug dependence," "maternal drug dependence at delivery," or "postpartum drug dependence" (see supplemental Table S1).

b
Mental health disorders include major depression disorder, bipolar disorder, and schizophrenia (see supplemental Table S1).

c
Adverse pregnancy history includes diagnosis of history of preterm labor or delivery, or other high-risk pregnancy.

TABLE 2

Patterns of health service use, buprenorphine use, and quality of care during pregnancy of enrollees receiving buprenorphine therapy by trajectory group (N = 2361)

	Early Initiators with				Late Initiators with	
	Persistently High Adherence (n = 747)	Moderate-to-High Adherence (n = 357)	Declining Adherence (n = 248)	Early Discontinuation (n = 393)	Moderate-to-High Adherence (n = 318)	Low-to-Moderate Adherence (n = 298)
Health service use during pregnancy						
Any hospitalizations, n (%) ***	50 (6.7)	30 (8.4)	29 (11.7)	50 (12.7)	29 (9.1)	44 (14.8)
No. of ED, mean (SD) **	2.3 (3.3)	3.0 (4.2)	2.5 (3.9)	3.3 (6.1)	2.8 (4.8)	3.1 (6.3)
No. of outpatient visits, mean (SD) †	11.3 (8.7)	12.3 (8.9)	9.5 (8.5)	9.5 (9.1)	11.7 (9)	9.9 (7.4)
Number of other prescriptions [a], mean (SD) *	6.3 (4.2)	6.7 (5.1)	6.1 (4.3)	6.6 (5.3)	6.2 (4.7)	5.6 (4.7)
Number of unique prescribers for other prescriptions, mean (SD)	3.0 (1.9)	3.2 (2.3)	3.0 (2.0)	3.0 (2.4)	2.8 (2.1)	2.8 (2.4)
Buprenorphine treatment patterns						
Mean daily dose (mg/day) during first trimester, (SD) †	17.4 (5.5)	13.3 (7.5)	16.6 (5.9)	12.6 (8.5)	NA [c]	NA [c]
Mean daily dose (mg/day) during pregnancy, (SD) †	17.6 (5.5)	15.7 (5)	16.5 (5.8)	15.5 (6.2)	15.3 (5.2)	14.7 (5.5)
No. of unique buprenorphine prescribers [b], mean (SD) †	1.7 (1.0)	1.8 (1.1)	1.7 (1.1)	1.2 (0.5)	1.5 (0.8)	1.3 (0.7)
PDC during the pregnancy and postdelivery, mean (SD) †	0.92 (0.06)	0.73 (0.09)	0.59 (0.14)	0.13 (0.10)	0.50 (0.11)	0.29 (0.12)
Quality of care during pregnancy						
Any behavioral counseling, % *	33.6	39.8	31.5	32.3	40.6	37.9
Any urine drug test, %	73.6	76.5	73.4	66.7	71.7	70.5

Abbreviations: NA, not available; PDC, proportion of days covered.

Comparison between 6 trajectory groups:

*
$P < .05$.

**
$P < .01$.

***
$P < .001$.

†
$P < .0001$.

[a] With unique drug ingredients.

[b]Six hundred thirteen unique prescribers who wrote at least 1 buprenorphine prescription to the women in our study cohort (21.4% of buprenorphine claims had missing prescriber information).

[c]The average dose of buprenorphine during the first trimester was not applicable for women who were later initiators.

TABLE 3

Proportions of all-cause emergency department visits and/or hospitalization between 85 days and 1 year post-delivery across trajectories: a post hoc analysis

Trajectory Groups (n)[a]		All-Cause Emergency Department Visits/ Hospitalization, per 100 Person Years[*]
Early initiators with	Persistently high adherence (n = 747)	26.9
	Moderate-to-high adherence (n = 357)	28.5
	Declining adherence (n = 248)	29.5
	Early discontinuation (n = 393)	37.4
Late initiators with	Moderate-to-high adherence (n = 318)	28.6
	Low-to-moderate adherence (n = 298)	37.2

Abbreviations: ED, emergency department; PDC, proportion of days covered.

[a] Four groups initiated buprenorphine during the first trimester of the pregnancy (early initiators): 31.6% with persistently high adherence (ie, persistently having a high PDC >0.8), 15.1% with moderate-to-high adherence (ie, initiating with a moderate PDC between 0.4 and 0.8 and increasing to a high PDC >0.8), 10.5% with declining adherence (ie, initiating with a moderate PDC but declining overtime to a low PDC <0.4), and 16.7% with early discontinuation (ie, initiating with a low PDC and discontinued before the third trimester). Two groups did not initiate buprenorphine until midsecond or third trimester (late initiators): 13.5% had moderate-to-high adherence (initiating with a moderate PDC, increasing to a high PDC in the third trimester and then decreasing to a moderate PDC postdelivery), 12.6% had low-to-moderate adherence (initiating with a low PDC and increasing to a moderate PDC).

[*] $P < .0001$ for the comparison across 6 groups.