Anticonvulsant Mood Stabilizer and Lithium Use and Risk of Adverse Pregnancy Outcomes

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ABSTRACT

Objective: To determine the comparative safety of mood stabilizers with respect to risk of preeclampsia, placental abruption, growth restriction, and preterm birth.

Methods: A cohort study was carried out using Medicaid Analytic eXtract data for pregnant women linked to live born infants enrolled from 2000 to 2010. Exposure to lamotrigine, valproate, topiramate, carbamazepine, oxcarbazepine, and lithium during the first 20 weeks of pregnancy was assessed. The reference group did not fill a prescription for an anticonvulsant or lithium during the 3 months prior to conception or the first half of pregnancy. Women who continued mood stabilizer monotherapy after 20 weeks were also compared to those who discontinued. Risk ratios (RRs) and 95% CIs were estimated with propensity score stratification to control for confounding.

Results: Among 1,472,672 pregnancies, 10,575 (0.7%) were exposed to anticonvulsant mood stabilizer or lithium monotherapy and 917 (0.06%) were exposed to polytherapy. In unadjusted analyses, exposure to each specific mood stabilizer and polytherapy was associated with increased risks of all adverse outcomes considered compared to no exposure (RR ranged from 1.15 to 1.56). However, these RR estimates were not meaningfully elevated with adjustment for confounding (0.89 to 1.16). Continuation of mood stabilizers was not associated with an increased risk for any outcomes compared to discontinuation and was associated with a reduced risk of placental abruption and growth restriction.

Conclusions: Anticonvulsant mood stabilizers and lithium are not associated with an increased risk of placenta-mediated complications or preterm birth after accounting for confounding by indication.

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Anticonvulsants have been increasingly used to treat bipolar disorder and other conditions, including migraines and neuropathic pain. While lithium remains an important first-line treatment, the US Food and Drug Administration (FDA) has approved several anticonvulsants for treatment of bipolar disorder, and others are used off-label.[1,2] Prior to the recent update to the FDA's pregnancy risk classification system, many of these medications were categorized as Pregnancy Category C while lithium, carbamazepine, and valproic acid were classified as Category D due to an increased risk of certain congenital malformations.

Teratogenicity is not the only safety concern in pregnancy, however. There is accumulating evidence from studies of pregnant women[3–8] that certain anticonvulsants are associated with reduced birth weight, which might be due to prematurity or growth restriction. Growth restriction is the failure of a fetus to meet its ideal growth potential, which can lead to newborns small for their gestational age (SGA) at birth and may arise from a poorly functioning placenta.[9] Other placenta-mediated pregnancy disorders include preeclampsia, placental abruption, preterm birth, and stillbirth, which as a group have been termed *ischemic placental disease*.[10,11] However, most studies of the safety of anticonvulsant mood stabilizers have been predominated by women with epilepsy. It is challenging to differentiate the effect of mood stabilizers on ischemic placental disease from the effect of epilepsy itself in these studies because some studies, though not all, have shown that epilepsy (treated or not) is associated with an increased risk of preeclampsia,[3,12,13] preterm birth,[3,13,14] low birth weight,[14] and SGA.[15] Hence, it is of interest to study the safety of these medications in populations of women with other indications, including bipolar disorder and pain conditions.

Our objective was to determine the comparative safety of mood stabilizers with respect to risk of preeclampsia, placental abruption, growth restriction, and preterm birth, with a focus on controlling for confounding by indication.

METHODS

Study Population

We identified a cohort of deliveries from 2000 to 2010 linked to live born infants in the Medicaid Analytic eXtract database. This population has been described in detail in a previous publication.[16] Mothers were 12–55 years of age with continuous enrollment from 3 months before pregnancy until 1 month after delivery. Infants were required to be eligible for Medicaid or have a claim in the month after birth to improve the capture of preterm birth codes.

Clinical Points

- Women who use mood stabilizers have an increased risk of placenta-mediated pregnancy complications.
- This study should provide reassurance to clinicians and their patients that mood stabilizer treatment is unlikely to be responsible for this increased risk.
- The teratogenic potential and adverse neurodevelopmental effects of valproate must be taken into consideration when treatment options are weighed during pregnancy.

We used a validated algorithm to estimate the date of the last menstrual period (LMP) based on presence or absence of preterm birth diagnoses.[17] We excluded deliveries with a major congenital malformation from our comparisons, because this is a recognized cause of growth restriction. Malformations were identified by *International Classification of Diseases, Ninth Revision* (*ICD-9*), diagnosis and procedure codes, previously described in detail.[18]

Outcome Definitions

Outcomes were defined based on claims in maternal or infant records after 20 weeks of gestation and were validated based on medical record review.[19,20] Outcomes of interest included SGA birth (a marker of intrauterine growth restriction; *ICD-9* 656.5, 764.0, 764.1, 764.9), preeclampsia (*ICD-9* 642.4–642.7), and placental abruption (*ICD-9* 641.20–641.23). We examined each of these as separate outcomes and together as a composite outcome also including low birth weight at term gestations (< 2,500 g is SGA for births ≥ 37 weeks; *ICD-9* V213). We also assessed preterm birth (*ICD-9* 644.2, 774.2, 776.6, 362.20, 362.22–362.27, 765 excluding 765.20, 765.29), which may be related to impaired placentation. Because preterm birth may be the result of physician intervention, we applied an algorithm to separate spontaneous and medically indicated preterm birth, in which spontaneous preterm births were considered the etiologically relevant subtype, though both subtypes may be relevant.[21]

Exposure Definitions

The exposures of interest were lithium and anticonvulsant medications that are used as mood stabilizers, including lamotrigine, valproate, topiramate, carbamazepine, and oxcarbazepine. Ischemic placental disease is thought to develop, at least in part, in response to impaired placentation in the first half of pregnancy.[10] Therefore, our primary exposure definition was at least 1 dispensed prescription for a mood stabilizer in the first 20 weeks of pregnancy. We further classified exposure into monotherapy, defined as having received no other mood stabilizers (as previously defined) or other anticonvulsants during the first 20 weeks, and polytherapy, defined as having received at least 1 dispensing for 2 or more different mood stabilizers. We compared the monotherapy (specific drugs and pooled together) and polytherapy groups to an unexposed reference group of patients with no dispensing of lithium or any anticonvulsant (including those not used as mood stabilizers) from 3 months before pregnancy until 20 weeks of gestation. We also compared the other monotherapy groups to lamotrigine monotherapy as an active control group.

The outcomes of interest may have heterogeneous etiology, and we could not rule out potential adverse effects of exposures after the first half of pregnancy. Thus, to assess whether the second half of pregnancy is also a sensitive period for these outcomes, we compared those who continued versus discontinued the medication in the second half of pregnancy among those using any mood stabilizer monotherapy (due to limited sample size for specific medications and polytherapy).

Potential Confounders

Potential confounders of interest included indications for mood stabilizers, demographic characteristics (delivery year, geographic region, maternal age, race/ethnicity), risk factors for ischemic placental disease and preterm birth (eg, parity; multifetal gestation; tobacco, alcohol, or drug use; overweight/obesity; hypertension; diabetes),[22–24] chronic comorbid conditions (psychiatric, pain), proxies for health care utilization and severity of chronic illness (eg, number of outpatient visits, hospitalization), and comedication. The complete list of covariates is available upon request and at http://www.harvardpreg.org/publications.html. Most confounders were assessed from claims in the first half of pregnancy and the 3 months prior, with the exception of health care utilization proxies that were assessed before pregnancy to capture patterns before prenatal care initiation. The actual indication for each prescription filled was not known. Potential indications for mood stabilizers were identified based on *ICD-9* codes for epilepsy, bipolar disorder, migraine, and neuropathic pain in maternal claims from 3 months before pregnancy until delivery to maximize sensitivity for these important covariates. For epilepsy, we did not include codes from the delivery hospitalization or 7 days before delivery to avoid misclassifying convulsions due to eclampsia as epilepsy. We also defined a specific algorithm that required at least 2 *ICD-9* codes for epilepsy in the absence of anticonvulsant medications based on existing algorithms, adapted to the pregnancy setting.[25–27]

Statistical Analysis

We used binomial regression with a log-link to estimate the risk ratios (RRs) and 95% CIs for the association between mood stabilizer use and pregnancy complications. To control for confounding, we calculated propensity scores for each exposure/reference comparison using logistic regression models to predict the probability of exposure. To incorporate the propensity scores into our outcome models, we used fine stratification. First, we excluded pregnancies with propensity scores in non-overlapping regions of the propensity score distributions for exposed and unexposed. Then, the exposed population was classified into 50 strata of equal size based

on the distribution of the propensity score, and comparator patients were then weighted according to the number of exposed patients per strata.[28] We also examined the crude association between potential indications and outcomes among the unexposed as another metric to assess the potential for confounding by indication.

We carried out several sensitivity analyses. First, to enhance the probability that those who filled a prescription for mood stabilizer monotherapy in pregnancy were actually taking the medication, we redefined exposure as having refilled the prescription twice in the first 20 weeks of pregnancy. Further, to focus more precisely on the period of placental development, we redefined exposure as having medication supply available from 8 to 18 weeks of gestation.

Since we were concerned about confounding by indication and that patterns of use may be different for different indications, we examined effect modification across the main indication subgroups, epilepsy (most specific definition) and bipolar disorder.

The study was approved by the institutional review board at Brigham and Women's Hospital, and the need for informed consent was waived.

RESULTS

Among linked deliveries that met the enrollment criteria, 51,456 (3.4%) were excluded due to a major congenital malformation. Among the remaining pregnancies, 20,549 (1.4%) were excluded because the women filled a prescription for an anticonvulsant or lithium in the 90 days before LMP but not during pregnancy and were not clearly exposed or unexposed or else used another anticonvulsant in the first 20 weeks of pregnancy and were ineligible for any of the defined exposed groups; 1,440,631 (97.8%) were unexposed, 10,575 (0.7%) were exposed to mood stabilizer monotherapy, and 917 (0.06%) were exposed to polytherapy.

Women taking mood stabilizer monotherapy in the first 20 weeks of pregnancy were more likely to be older, nulliparous, and white compared to nonusers (Table 1). The potential indications for monotherapy were bipolar disorder (39%), migraine (32%), epilepsy (25%), and neuropathic pain (7%). The characteristics of women exposed and unexposed in the first 20 weeks were balanced in the weighted sample after exclusion of 0.2% of monotherapy-exposed women and 1% of the reference group with propensity scores outside of the overlapping distribution and applying propensity score stratification weights. Women who continued monotherapy after 20 weeks were more likely to be teenagers, less likely to have bipolar disorder or migraines, and more likely to have epilepsy. They were also less likely to have some other pain and psychiatric conditions, including depression and anxiety. After weighting according to the propensity score, the covariates were well balanced in the continuer and discontinuer comparison groups. Further exploration of pregnancy characteristics of continuers indicated less discontinuation of atypical antipsychotics and benzodiazepines and lower tobacco, alcohol, and drug use in late pregnancy compared to discontinuers. The observed association between the indications and the outcomes among the unexposed suggested potential for confounding by indication (or associated conditions), with RRs for ischemic placental disease ranging from 1.21 for neuropathic pain to 1.60 for epilepsy, and justified the need for careful adjustment.

Pregnancies exposed to mood stabilizers had an increased risk of ischemic placental disease compared to unexposed pregnancies; the RR was 1.34 (95% CI, 1.27–1.42) for any monotherapy and 1.56 (95% CI, 1.31–1.86) for polytherapy. The RRs for monotherapy with specific mood stabilizers ranged from 1.15 to 1.49 (Table 2). However, after control for confounding, mood stabilizer use was not associated with an increased risk of ischemic placental disease; adjusted RR was 0.97 (95% CI, 0.91–1.04) for any monotherapy and 1.16 (95% CI, 0.93–1.45) for polytherapy. Adjusted RRs for specific mood stabilizers ranged from 0.89 to 1.08. Further, women exposed to valproate, topiramate, carbamazepine, oxcarbazepine, or lithium monotherapy were not at increased risk of ischemic placental disease compared to those on lamotrigine monotherapy in crude or adjusted models.

When each of the placenta-mediated complications was considered individually, crude comparisons indicated that women taking mood stabilizers as monotherapy or polytherapy had an increased risk for each complication compared to unexposed women; RRs ranged from 1.22 to 1.75 (Table 3). However, after control for all measured confounders, mood stabilizer monotherapy overall was not associated with any of the individual outcomes, nor were any of the individual medications (data available upon request and at http://www.harvardpreg.org/publications.html). Only mood stabilizer polytherapy remained associated with an increased risk of preeclampsia (RR = 1.47; 95% CI, 1.09–1.99) and possibly placental abruption (RR = 1.57; 95% CI, 0.93–2.66), albeit the confidence intervals were wide (Table 3).

Women who continued filling prescriptions for mood stabilizer monotherapy in the latter half of pregnancy had no increased risk of ischemic placental disease or preterm birth compared to women who used mood stabilizers exclusively in the first half of pregnancy (ie, discontinued) (Table 4). On the contrary, results suggest a lower risk for placental abruption (RR = 0.57; 95% CI, 0.36–0.90) and SGA (RR = 0.73; 95% CI, 0.55–0.97) for those who continued compared to women who discontinued.

Sensitivity analyses varying the exposure definition confirmed the null associations between mood stabilizer monotherapy and each outcome, with the exception of an increased risk of placental abruption for 8- to 18-week exposure (Figure 1). The analyses stratified by potential indication confirmed null associations between mood stabilizer monotherapy and most outcomes (data available upon request and at http://www.harvardpreg.org/publications.html). Mood stabilizer monotherapy was associated with an increased risk of preeclampsia among women with epilepsy but not bipolar disorder. Mood stabilizer monotherapy and individual anticonvulsant mood stabilizers were associated with an increased risk of placental

Table 1. Selected Characteristics of Mothers Exposed or Not Exposed to Mood Stabilizer Monotherapy[a]

	Crude					Adjusted (Propensity-Score Weighted)				
	Mood Stabilizer Monotherapy (n = 10,575)		No Anticonvulsant or Lithium Use (n = 1,440,631)			Mood Stabilizer Monotherapy (n = 10,557)		No Anticonvulsant or Lithium Use (n = 1,425,671)		
Maternal Characteristic	n	%	n	%	Standard Difference	n	%	n	%	Standard Difference
Age at delivery, y										
≤ 19	2,070	19.6	350,553	24.3	−0.12	2,069	19.6	268,186.5	18.8	0.02
20–29	6,119	57.9	841,460	58.4	−0.01	6,108	57.9	818,651.6	57.4	0.01
30–39	2,246	21.4	229,970	16.0	0.14	2,240	21.2	318,534.8	22.3	−0.03
≥ 40	140	1.3	18,648	1.3	0.00	140	1.3	20,298.1	1.4	−0.01
Race/ethnicity										
White/caucasian	7,459	70.5	568,974	39.5	0.66	7,444	70.5	1,069,639.0	75.0	−0.10
Black/African American	1,715	16.2	487,416	33.8	−0.42	1,714	16.2	199,377.2	14.0	0.06
Hispanic/Latino	569	5.4	217,215	15.1	−0.32	568	5.4	58,106.6	4.1	0.06
Other/unknown	832	7.9	167,026	11.6	−0.13	831	7.9	98,548.3	6.9	0.04
Risk factors for ischemic placental disease										
Multipara	7,006	66.3	1,088,122	75.5	−0.21	6,996	66.3	950,218.7	66.7	−0.01
Multifetal gestation	311	2.9	41,211	2.9	0.00	311	2.9	42,281.4	3.0	0.00
Tobacco use	987	9.3	50,938	3.5	0.24	981	9.3	151,659.4	10.6	−0.04
Alcohol use	286	2.7	8,277	0.6	0.17	284	2.7	45,704.4	3.2	−0.03
Other drug dependence	759	7.2	20,700	1.4	0.29	755	7.2	113,724.8	8.0	−0.03
Asthma	1,071	10.1	66,142	4.6	0.21	1,070	10.1	158,228.8	11.1	−0.03
Hypertension	575	5.4	37,192	2.6	0.15	571	5.4	88,962.3	6.2	−0.04
Diabetes	358	3.4	24,870	1.7	0.11	357	3.4	54,114.9	3.8	−0.02
Overweight/obese	412	3.9	30,349	2.1	0.11	411	3.9	60,833.6	4.3	−0.02
Potential indications for mood stabilizers[b]										
Bipolar disorder	4,153	39.3	16,782	1.2	1.08	4,135	39.2	620,117.7	43.5	−0.09
Epilepsy (specific)	2,008	19.0	858	0.1	0.68	1,990	18.9	151,671.6	10.6	0.23
Epilepsy (sensitive excluding specific)	607	5.7	6,662	0.5	0.31	607	5.8	116,980.7	8.2	−0.10
Migraine/headache	3,356	31.7	157,400	10.9	0.53	3,341	31.7	513,708.3	36.0	−0.09
Neuropathic pain	725	6.9	30,855	2.1	0.23	720	6.8	114,994.0	8.1	−0.05
Other comorbid conditions										
Schizophrenia	306	2.9	2,138	0.1	0.23	304	2.9	47,594.5	3.3	−0.03
Depression	3,300	31.2	91,221	6.3	0.67	3,291	31.2	542,874.5	38.1	−0.15
Anxiety disorder	1,955	18.5	50,750	3.5	0.49	1,947	18.4	315,071.3	22.1	−0.09
Sleep disorder	369	3.5	9,482	0.7	0.20	367	3.5	58,498.2	4.1	−0.03
Back and neck pain	2,250	21.3	126,181	8.8	0.36	2,237	21.2	346,550.7	24.3	−0.07
Arthritis and musculoskeletal pain	2,039	19.3	119,371	8.3	0.32	2,030	19.2	305,168.3	21.4	−0.05
Other psychiatric and pain medication										
Atyptical antipsychotic	2,724	25.8	13,602	0.9	0.78	2,708	25.7	409,680.6	28.7	−0.07
Antidepressant	5,839	55.2	127,606	8.9	1.14	5,821	55.1	947,274.9	66.4	−0.23
Benzodiazepine	2,603	24.6	40,466	2.8	0.67	2,593	24.6	401,177.4	28.1	−0.08
Other hypnotics	1,801	17.0	57,667	4.0	0.43	1,795	17.0	279,594.0	19.6	−0.07
ADHD medication	692	6.5	6,057	0.4	0.34	687	6.5	110,800.9	7.8	−0.05
Opioid	4,548	43.0	312,626	21.7	0.47	4,532	42.9	685,518.7	48.1	−0.10
Triptan	880	8.3	14,118	1.0	0.35	875	8.3	149,125.4	10.5	−0.07
NSAID	2,997	28.3	237,016	16.5	0.29	2,985	28.3	448,988.6	31.5	−0.07
Acetaminophen	4,951	46.8	377,753	26.2	0.44	4,935	46.7	738,569.7	51.8	−0.10
Severity/health care utilization proxies	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
No. of outpatient visits[c]	4.85	7.06	1.77	3.17	0.56	4.84	7.05	5.24	7.96	−0.05
No. of hospitalizations[c]	0.09	0.37	0.04	0.24	0.15	0.09	0.37	0.09	0.35	0.01
No. of emergency department visits[c]	0.64	1.80	0.27	0.76	0.27	0.64	1.80	0.71	1.45	−0.04
No. of distinct medications[c,d]	4.38	3.87	1.62	2.30	0.87	4.37	3.86	4.91	4.24	−0.13
No. of bipolar disorder diagnoses	0.29	0.45	0.01	0.08	0.86	0.29	0.45	0.31	0.46	−0.06
No. of depression diagnoses	0.26	0.44	0.06	0.23	0.59	0.26	0.44	0.32	0.47	−0.13

[a]Covariates defined from LMP – 90 to LMP + 140 unless otherwise indicated. The crude comparison is for the original study sample. The adjusted comparison is after exclusion of pregnancies in the non-overlapping regions of the propensity score distributions and application of propensity score stratification weights to the sample. Use of decimals for n values under "No Anticonvulsant or Lithium Use" for adjusted data is the result of weighting the unexposed mothers.

[b]At least 1 *ICD-9* diagnostic code from LMP – 90 to delivery.

[c]Health care utilization proxy variables defined during LMP – 90 to LMP – 1.

[d]At the generic level, excluding anticonvulsants and lithium.

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, LMP = last menstrual period, LMP + 140 = 140 days after LMP, LMP – 1 = 1 day before LMP, LMP – 90 = 90 days before LMP, NSAID = nonsteroidal anti-inflammatory drug.

Table 2. Risk of Ischemic Placental Disease Associated With Mood Stabilizer Use in the First 20 Weeks of Pregnancy[a]

		Reference: Unexposed		Reference: Lamotrigine	
Variable	Outcome, n (%)	Crude RR (95% CI)	Adjusted RR (95% CI)	Crude RR (95% CI)	Adjusted RR (95% CI)
No anticonvulsant or lithium (n = 1,440,631)	109,744 (7.62)	Reference	Reference		
Mood stabilizer monotherapy (n = 10,575)	1,083 (10.24)	1.34 (1.27–1.42)	0.97 (0.91–1.04)		
Mood stabilizer polytherapy (n = 917)	109 (11.89)	1.56 (1.31–1.86)	1.16 (0.93–1.45)		
Lamotrigine (n = 2,682)	265 (9.88)	1.30 (1.16–1.45)	0.96 (0.84–1.09)	Reference	Reference
Valproate (n = 2,398)	230 (9.59)	1.26 (1.11–1.42)	0.95 (0.83–1.08)	0.97 (0.82–1.15)	0.90 (0.67–1.22)
Topiramate (n = 2,280)	256 (11.23)	1.46 (1.30–1.64)	1.04 (0.92–1.17)	1.13 (0.96–1.33)	0.85 (0.64–1.13)
Carbamazepine (n = 1,232)	140 (11.36)	1.49 (1.27–1.75)	1.08 (0.87–1.34)	1.15 (0.94–1.40)	0.95 (0.68–1.33)
Oxcarbazepine (n = 1,109)	115 (10.37)	1.36 (1.14–1.61)	1.01 (0.84–1.21)	1.05 (0.85–1.29)	0.99 (0.74–1.32)
Lithium (n = 874)	77 (8.81)	1.15 (0.93–1.43)	0.89 (0.72–1.12)	0.89 (0.70–1.14)	0.72 (0.44–1.18)

[a]Adjusted RR estimates adjusted for all potential confounding factors including demographic factors, risk factors for ischemic placental disease and preterm birth, potential indication for mood stabilizer use, other psychiatric and pain diagnoses, other psychiatric and pain medications (LMP – 90 to LMP + 140), and severity of chronic illness/health service utilization proxies by inclusion of propensity score stratification weights.
Abbreviations: LMP = last menstrual period, LMP + 140 = 140 days after LMP, LMP – 90 = 90 days before LMP, RR = risk ratio.

Table 3. Risk of Placental Complications Associated With Mood Stabilizer Monotherapy and Polytherapy in the First 20 Weeks of Pregnancy[a]

	Outcome, n (%)						
				Monotherapy RR (95% CI)		Polytherapy RR (95% CI)	
Complication	Monotherapy (n = 10,575)	Polytherapy (n = 917)	Unexposed Reference (n = 1,440,631)	Crude	Adjusted	Crude	Adjusted
Preeclampsia	530 (5.01)	60 (6.54)	53,634 (3.72)	1.34 (1.23–1.45)	1.02 (0.92–1.14)	1.75 (1.37–2.23)	1.47 (1.09–1.99)
Placental abruption	205 (1.94)	19 (2.07)	20,269 (1.41)	1.38 (1.20–1.58)	1.10 (0.93–1.30)	1.48 (0.95–2.31)	1.57 (0.93–2.66)
Small for gestational age	422 (3.99)	40 (4.36)	41,653 (2.89)	1.38 (1.25–1.51)	0.91 (0.81–1.02)	1.51 (1.11–2.04)	0.90 (0.61–1.33)
Preterm birth	1,580 (14.94)	152 (16.58)	160,604 (11.15)	1.33 (1.27–1.40)	0.96 (0.90–1.01)	1.48 (1.28–1.72)	0.97 (0.80–1.16)
Medically indicated preterm birth	740 (7.00)	68 (7.42)	82,811 (5.75)	1.22 (1.13–1.31)	0.93 (0.85–1.01)	1.29 (1.02–1.62)	0.93 (0.70–1.23)
Spontaneous preterm birth	840 (7.94)	84 (9.16)	77,793 (5.40)	1.46 (1.37–1.56)	0.98 (0.90–1.07)	1.70 (1.38–2.08)	1.00 (0.77–1.31)

[a]Adjusted RR estimates adjusted for all potential confounding factors including demographic factors, risk factors for ischemic placental disease and preterm birth, potential indication for mood stabilizer use, other psychiatric and pain diagnoses, other psychiatric and pain medications (LMP – 90 to LMP + 140), and severity of chronic illness/health service utilization proxies by inclusion of propensity score stratification weights.
Abbreviations: LMP = last menstrual period, LMP + 140 = 140 days after LMP, LMP – 90 = 90 days before LMP, RR = risk ratio.

Table 4. Risk of Placental Complications Associated With Continuation of Mood Stabilizer Monotherapy After 20 Weeks of Pregnancy Compared to Discontinuation During the First 20 Weeks[a]

	Outcome, n (%)		Reference: Discontinuation	
Outcome	Mood Stabilizer Continuation (n = 3,206)	Mood Stabilizer Discontinuation (n = 7,369)	Crude RR (95% CI)	Adjusted RR (95% CI)
Ischemic placental disease	319 (9.95)	764 (10.37)	0.97 (0.85–1.09)	0.87 (0.73–1.03)
Preeclampsia	176 (5.49)	354 (4.80)	1.15 (0.97–1.38)	1.01 (0.78–1.31)
Placental abruption	41 (1.28)	164 (2.23)	0.57 (0.41–0.81)	0.57 (0.36–0.90)
Small for gestational age	122 (3.81)	300 (4.07)	0.93 (0.76–1.15)	0.73 (0.55–0.97)
Preterm birth	509 (15.88)	1,071 (14.53)	1.09 (0.99–1.20)	1.05 (0.91–1.22)
Medically indicated preterm birth	236 (7.36)	504 (6.84)	1.07 (0.92–1.25)	1.02 (0.81–1.27)
Spontaneous preterm birth	273 (8.52)	567 (7.69)	1.11 (0.96–1.27)	1.08 (0.89–1.33)

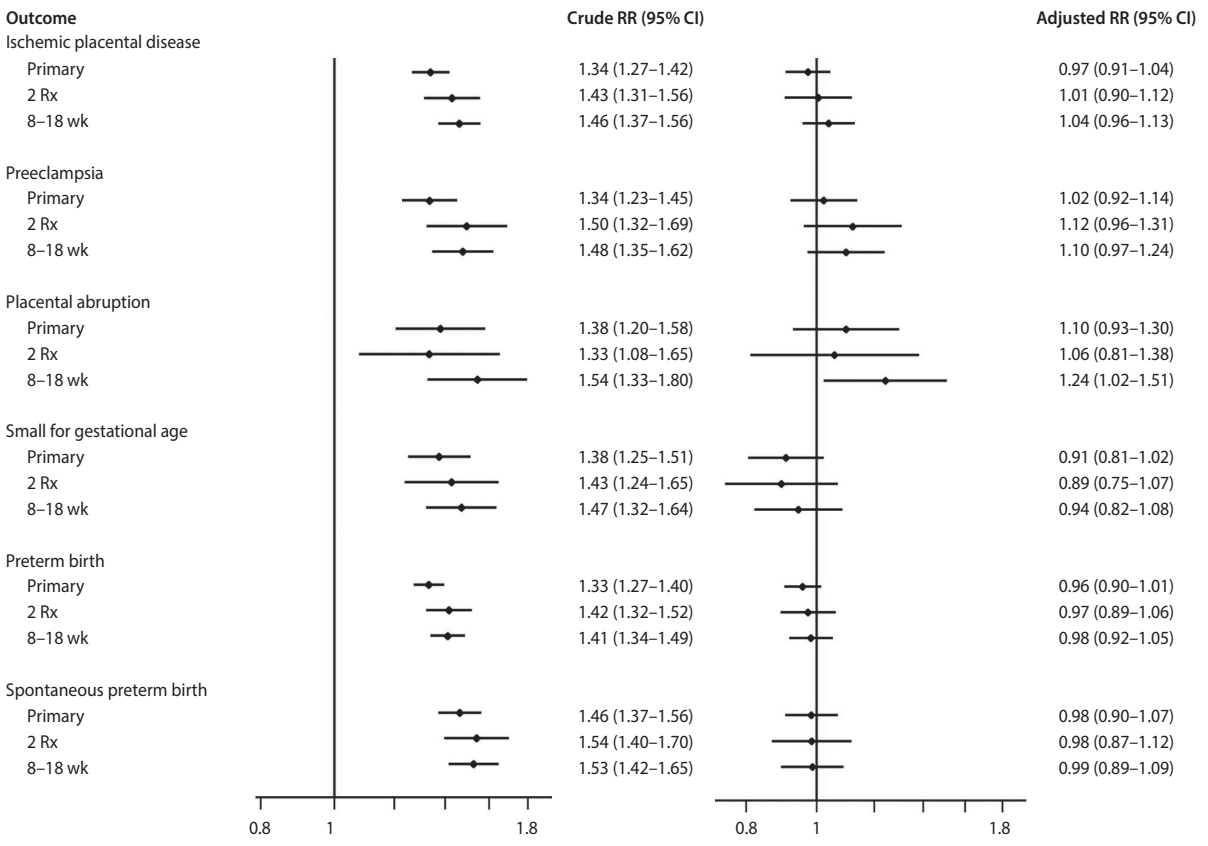
[a]Adjusted RR estimates adjusted for all potential confounding factors including demographic factors, risk factors for ischemic placental disease and preterm birth, potential indication for mood stabilizer use, other psychiatric and pain diagnoses, other psychiatric and pain medications (LMP – 90 to LMP + 140), and severity of chronic illness/health service utilization proxies by inclusion of propensity score stratification weights.
Abbreviations: LMP = last menstrual period, LMP + 140 = 140 days after LMP, LMP – 90 = 90 days before LMP, RR = risk ratio.

abruption and a decreased risk of SGA among women with a bipolar disorder diagnosis but not epilepsy.

DISCUSSION

In a cohort of over 1.5 million women enrolled in US Medicaid, users of anticonvulsant mood stabilizers and lithium dispensed during the period of placentation had an increased risk of placenta-mediated pregnancy complications compared to unexposed. However, the relative risks approached the null after adjustment for indication and other confounding factors. Although women using polytherapy and women with epilepsy using monotherapy had an increased risk of preeclampsia, the largely null results in adjusted analyses suggest that these higher risks may be due to either residual confounding or higher intensity of exposure in women on polytherapy or with epilepsy (including duration and consistency of use, dose, and number of drugs). Further, compared to women who discontinued mood stabilizer monotherapy, women

Figure 1. Sensitivity Analysis Using Alternative Definitions of Exposure[a]



[a]*Primary* was defined as at least 1 dispensed prescription from LMP to LMP + 140, 8–18 wk was defined as having medication supply available from 8 to 18 weeks, and 2 Rx was defined as having at least 2 dispensed prescriptions from LMP to LMP + 140.
Abbreviations: 2 Rx = prescription refilled twice in the first 20 weeks of pregnancy, LMP = last menstrual period, LMP + 140 = 140 days after LMP, RR = risk ratio.

who continued had a lower risk of placental abruption and SGA. This finding may be due to differences in lifestyle factors between those who are adherent and continue on these medications throughout pregnancy and those who are not. This notion is supported by the higher prevalence of drug and alcohol abuse and smoking among those who discontinue treatment. Indeed, there is evidence of increased risk of perinatal complications associated with mental illness and bipolar disorder specifically,[29,30] and there is a high risk of relapse of symptoms of bipolar disorder during pregnancy and postpartum, particularly if treatment is rapidly discontinued.[31] While the potentially increased risks associated with discontinuation would need to be replicated in other studies, overall our results suggest that individual mood stabilizers are not associated with an increased risk of placenta-mediated pregnancy complications.

While there is some conflicting evidence, most studies suggest that women with epilepsy have an increased risk of placenta-mediated complications. Some studies[12,14] suggest that treatment may mitigate risks observed for untreated epilepsy, whereas others[3,13,32] implicate treatment as the cause of elevated risks. Studies within the Medical Birth Registry of Norway[3,32] suggested that women with epilepsy had a modestly (20%–30%) increased risk of preeclampsia, SGA, and preterm birth. Among those who were using an anticonvulsant medication in pregnancy (34%), the risks were higher (60%–70%). However, these women were compared to women without epilepsy and with no anticonvulsant use. A study[12] that compared women with epilepsy and treatment to women with epilepsy and no treatment found no significant differences in risk of preeclampsia, SGA, or preterm birth. The study design and the results are more aligned with our primary results in the cohort overall since the propensity score methods we employed estimated the risk for treated pregnancies compared to untreated pregnancies with similar characteristics, including indication and other risk factors for pregnancy complications. Similar prior evidence comparing treated and untreated illness is lacking for other indications, including bipolar disorder, migraine, and neuropathic pain.

Some studies,[7,33,34] though not all,[35] that focused on safety of anticonvulsant medications irrespective of their indication for use have also concluded that these drugs may increase the risk of preeclampsia, placental abruption, SGA, and preterm birth. Most prior studies of mood stabilizer safety may not have adequately addressed confounding by indication and associated factors; few controlled for concomitant medication use[35] or other indicators of illness severity. While

it is possible that indications in themselves are associated with placental effects, we hypothesized that the higher prevalence of smoking, diabetes, other medication use, or lifestyle-associated factors would be primarily responsible for any increased risks of placenta-mediated complications. In our study, we tried to address concern for confounding by indication by controlling for a wide range of comorbid medical conditions and comedication. In addition, we balanced several indicators of health care utilization and illness severity in the propensity score models, including number of diagnoses of bipolar disorder during the baseline period and number of emergency department visits.

Strengths of the study include the large, diverse study population, which allowed us to investigate individual medications and infrequent outcomes. The US Medicaid population, particularly those eligible before pregnancy, represents a vulnerable population of women with disabilities, low socioeconomic status, young age, and racial minorities. While the incidence of adverse pregnancy outcomes would tend to be higher than in the general population, we assume that the results regarding effects of pharmaceuticals would be transportable to other populations, at least qualitatively.

We defined the study outcomes with an emphasis on specificity and used validated outcome definitions. We incorporated several sensitivity analyses to test the robustness of our findings, including use of an active comparator drug to address confounding by indication. Lamotrigine was an appropriate choice based on the results from the comparison with unexposed pregnancies and prior research suggesting a relatively benign safety profile.[36–38]

One limitation of research using administrative data is that prescriptions dispensed during pregnancy may not have been taken once the pregnancy was known. Our sensitivity analysis redefining exposure based on 2 dispensings during pregnancy confirmed our main findings; however, we could not completely rule out a threshold effect for longer duration of exposure. We did not have information on the actual indication for the medication and inferred the indication from diagnoses observed during baseline and pregnancy. However, some individuals had no diagnosis recorded during this time for a suspected indication for the use of a mood stabilizer. We may also have missed information on important covariates, such as smoking and obesity. However, we very likely controlled to some extent for both indication and missing covariate information by proxy. Our propensity score models included a number of covariates that are correlated with these factors (eg, depression, antidepressant use, diabetes). Finally, we most likely had some misclassification of the start of pregnancy, particularly for preterm births,[17] since we estimated the LMP based on the presence or absence of codes indicating preterm. While this misclassification is less problematic for medications taken chronically, it could be more problematic for medications that are commonly discontinued at the start of pregnancy, eg, valproate, and could result in bias toward the null.

Health professionals caring for women with an indication for mood stabilizer therapy should be aware that these women are at increased risk for placenta-mediated pregnancy complications. However, our results should provide reassurance to doctors and patients that mood stabilizer therapy is unlikely to be responsible for this increased risk. While there were some modest signals, residual confounding may explain these results. The previously suggested effect of mood stabilizers on placentation may have been confounded by the underlying characteristics of women with the indication. Finally, it is still important to consider pregnancy-related use of mood stabilizers, especially valproate, in light of other evidence for teratogenicity including adverse neurodevelopmental effects in exposed children, which were not examined in this study.

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