Antidepressant Use and Risk for Preeclampsia

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Background: Prior studies suggest that women who use antidepressants during pregnancy have an increased risk for preeclampsia, yet the comparative safety of specific antidepressants remains unclear. US nationwide Medicaid Analytic eXtract (MAX) data have not been used to study medication safety during pregnancy.

Methods: We identified 100,942 pregnant women with depression from 2000 to 2007 MAX data. We used pharmacy dispensing records to ascertain exposure to selective serotonin reuptake inhibitor (SSRI), serotonin–norepenephrine reuptake inhibitor (SNRI), tricyclic, bupropion, other antidepressant monotherapy or polytherapy, and specific antidepressants, during the second trimester and first half of the third trimester. Relative risks (RRs) and 95% confidence intervals (CIs) were adjusted for delivery year, preeclampsia risk factors, depression severity proxies, other antidepressant indications, other medications, and healthcare utilization.

Results: The risk of preeclampsia was 5.4% among women with depression and no antidepressant exposure. Compared with these women, the risk for preeclampsia was higher among those receiving SNRI (RR: 1.52, 95% CI = 1.26–1.83) and tricyclic monotherapy (RR: 1.62, 95% CI = 1.23–2.12), but not SSRI monotherapy (RR: 1.00, 95% CI = 0.93–1.07) or other antidepressants. Compared with women receiving SSRI monotherapy, preeclampsia risk was higher among women with SNRI (RR: 1.54, 95% CI = 1.28–1.86) and tricyclic (RR: 1.64, 95% CI = 1.25–2.16) monotherapy. None of the specific SSRIs was associated with preeclampsia. The RR with venlafaxine was 1.57 (95% CI = 1.29–1.91) and with amitriptyline 1.72 (95% CI = 1.24–2.40).

Conclusions: In this population, SNRIs and tricyclics were associated with a higher risk of preeclampsia than SSRIs.

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Preeclampsia can seriously compromise maternal and offspring health.[1] It causes intrauterine growth restriction and is a major cause of medically indicated preterm delivery.[1,2] Current evidence suggests an association between antidepressant use during pregnancy and preeclampsia,[3–6] although it is unclear if pharmacotherapy affects the risk of preeclampsia independently of mood disorders.[7–9] Previous studies of selective serotonin reuptake inhibitors (SSRIs), the most commonly used antidepressants during pregnancy,[10] and risk for preeclampsia have reported varying degrees of association. The first study reported a 3.2-fold increase in risk of preeclampsia among SSRI users (95% confidence interval [CI] = 1.9–5.3),[3] whereas in two subsequent studies, the increases in risks were more moderate (1.2- to 1.6-fold).[5,6] The evidence is more limited for non-SSRI antidepressants, although serotonin–norepinephrine reuptake inhibitor (SNRI) and tricyclic antidepressants were associated with preeclampsia in one study.[5]

Findings from these studies were challenged on the basis of potential confounding by indication, insufficient size to provide precise estimates, assess non-SSRIs, or conduct subgroup analyses, and whether the results could be replicated in other populations. Using healthcare utilization data from the Medicaid Analytic eXtract (MAX), we investigated the association between specific antidepressants used during mid-pregnancy and preeclampsia. To reduce the potential for confounding by underlying mood disorders, only women with depression diagnoses were included in the study population. The large cohort of over 100,000 pregnancies produced stable estimates and permitted us to conduct novel analyses, such as estimating the comparative safety of specific antidepressants during pregnancy, and stratifying analyses within subgroups defined by age and race. Our evaluation of antidepressants

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and preeclampsia was conducted within a racially diverse and indigent population typically neglected in volunteer-based studies.

METHODS

Eligible Population

The pregnancy cohort was identified from 2000 to 2007 MAX data as previously described.[11,12] Briefly, Medicaid enrollment information was linked to inpatient and outpatient procedures and diagnoses, and to outpatient pharmacy dispensing data using the state and Medicaid identification number. Women with delivery-related diagnoses and procedures were identified, and live-born infants were linked to these women by matching state, Medicaid Case Number, and maternal delivery dates with infant date of birth. The date of last menstrual period (LMP) was assigned to be 245 days before the infant's date of birth for pregnancies that were preterm by maternal or infant International Classification of Diseases, Ninth Revision (ICD-9), codes (644.0, 644.2, and 765.x), and 270 days before the infant's date of birth for all other pregnancies. This validated algorithm accurately classified gestational age at delivery within 2 weeks for 75% of preterm and nearly all term deliveries in a similar database.[13] To ensure healthcare claim completeness, we excluded women who did not meet Medicaid enrollment and eligibility criteria from 1 month before the LMP month until the month after the delivery month. There were 1,248,875 pregnancies from 1,072,352 women in the eligible population. This project was approved by Brigham and Women's Hospital and Harvard School of Public Health Institutional Review Boards, and a data use agreement was approved by Centers for Medicare and Medicaid Services.

Depression

We restricted the cohort to 100,942 women with a depression diagnosis for the main analyses (eFigure 1, http://links.lww.com/EDE/A697, illustrates the number of women available for each analysis). We defined depression as any inpatient or outpatient ICD-9 code for 296.x, 300.x, 309.x, or 311.x between the LMP and 225 gestational days, that is, the end of the exposure window described below. The positive predictive value (PPV) for depression defined with these three-digit codes was 77% in another healthcare utilization database.[14] Although this definition also includes codes for anxiety, which is associated with preeclampsia,[7,9] and bipolar disorder, it should identify more women with depression than a four-digit definition with higher specificity for depression.

Outcome

We defined preeclampsia as any inpatient or outpatient ICD-9 code for preeclampsia or eclampsia (642.4x–642.7x) after 140 gestational days[15] and within 30 days after the delivery date (Figure 1). We assessed outcome validity by reviewing delivery hospital medical records for a sample of 183 women. There was no evidence of differential misclassification by antidepressant exposure. The PPV was 66% overall (95% CI: 59–73%) and 92% for inpatient preeclampsia (95% CI = 86–96%). These estimates are conservative, as we did not have outpatient medical records, that is, some unconfirmed cases could be true cases that were diagnosed outside the delivery hospitalization. In outcome sensitivity analyses, we considered only inpatient and severe preeclampsia/eclampsia (separately), and we corrected odds ratios for overall and inpatient preeclampsia misclassification using sensitivities and specificities that were plausible based on the PPVs.[16]

Exposure

The primary exposure window was from 90 to 225 gestational days, that is, the second trimester through the end of the first half of the third trimester. We selected this window because previous studies reported that there is an increased risk for preeclampsia among women exposed to antidepressants after the first trimester.[3] Women were classified as exposed if they had an antidepressant dispensed during the exposure window, and as unexposed (the reference group for the primary analysis) if there was no antidepressant dispensed between the LMP and the end of the window. To avoid reverse causation bias, women were classified as unexposed if their first preeclampsia diagnosis occurred before their first antidepressant was dispensed during the exposure window (64 women). Women who received only one antidepressant class during the window were classified as having either SSRI, SNRI, tricyclic, bupropion, or other antidepressant (mirtazapine, nefazodone, trazodone) monotherapy. Women who received more than one class, because of concomitant or sequential exposure to multiple classes, were classified as having polytherapy with an SSRI and another class or non-SSRIs. The 34,262 women who received antidepressants only during the first trimester but not during the exposure window, including 15,175 women with depression, were excluded from the primary analysis.

The primary analysis compared risk for preeclampsia between exposed women (according to antidepressant class) and unexposed women. In five subsequent analyses, we varied the exposure definition or reference group while maintaining the same exposure window. First, among women in the monotherapy groups, we compared specific antidepressants, if there were at least 100 women with depression exposed to a given medication, with no antidepressant exposure. Second, in a comparative safety analysis, we compared other exposure groups to the SSRI monotherapy group. Third, in an initiator versus unexposed analysis, we classified women with no antidepressant dispensed during the first trimester but with antidepressants dispensed during the exposure window as initiators. Fourth, in a cumulative duration analysis, we classified women within each monotherapy group by the amount of class-specific antidepressant days supply that overlapped with

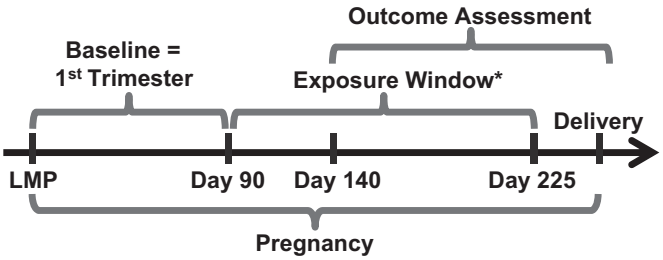

FIGURE 1. Study timeline. *Women who have their first exposure window antidepressant dispensing after their first preeclampsia diagnosis are classified as unexposed.

the exposure window (135 days): short ≤30, medium 31–90, and long >90 duration versus unexposed. Finally, in a dose analysis, we categorized women within each monotherapy group according to the highest antidepressant dose dispensed during the exposure window and compared them with unexposed women. Dose levels were defined according to Goodman & Gilman's usual dose (mg/day):[17] low < lowest usual dose, medium ≤ the midpoint of the usual dose range, high > the midpoint of the usual dose range (eAppendix, http://links.lww.com/EDE/A697). Because of small numbers, medium and high doses were combined for tricylic, bupropion, and other monotherapy.

To test the robustness of the exposure window definition, we did a timing analysis in which exposure was defined as an antidepressant dispensed within 30-day intervals throughout gestation; unexposed women had no antidepressant dispensed between the LMP and the end of each interval. Women who had an antidepressant dispensed within the first 30 gestational days were eligible for a continuation/discontinuation analysis. Women with additional dispensings during the exposure window were classified as continuers, women with no dispensings beyond the first 30 gestational days until the end of the exposure window and no days supply that extended into the exposure window were classified as discontinuers, and all other women were excluded.

Covariates

Information on other medication use and comorbidities was obtained during the baseline period (the first trimester) with the exception of depression and other antidepressant indications, which was obtained from the LMP until the end of the exposure window (ie, 225 gestational days). Potential confounders included risk factors for preeclampsia: age (quadratic spline), race/ethnicity (white, black, Hispanic, Asian or Pacific Islander, other, or unknown), primiparity (multiparae defined using adult with dependent children as the Medicaid eligibility type),[11] multiple gestation, and diabetes (diagnosis and no antidiabetic dispensing, no diagnosis and dispensing, diagnosis and dispensing); proxies of depression severity: number of outpatient (0, 1, 2–4, 5–9, ≥10) and inpatient (0, 1, ≥2) depression diagnoses between the LMP and 225 gestational days; other antidepressant indications: mental disorders complicating pregnancy (ICD-9 code 648.4x), pain-related diagnosis (chronic and generalized pain, irritable bowel syndrome, gastrointestinal ulcer, inflammatory bowel disease, lupus, rheumatoid arthritis, headache, migraine, myalgia), and sleep disorder; other psychotropic medication: anticonvulsant and benzodiazepine dispensings; and general markers of comorbidity: number of distinct prescription drugs excluding antidepressants dispensed (quadratic spline) and number of outpatient visits (quadratic spline) during the baseline.[18]

Statistical Analysis

We used generalized estimating equations to estimate relative risks (RRs) for preeclampsia along with their corresponding 95% CIs.[19] Models were adjusted for delivery year, and robust variances were utilized to account for correlations among women with multiple pregnancies.[19] Models were additionally adjusted for preeclampsia risk factors and for depression severity proxies, other indications, other medications, and healthcare utilization. All polytherapy groups were collapsed after the primary analysis because results were similar across polytherapy groups, which were small. We tested for multiplicative modification of the SSRI, SNRI, and tricyclic relations by age (≥30), race/ethnicity (white and nonwhite), and multiparity because our cohort is younger and more racially diverse than cohorts from previous studies[3–6] and a high proportion of women are multiparous. We also tested for additive effect modification using the relative excess risk of interaction (RERI).[20]

Sensitivity Analysis

We performed several sensitivity analyses to evaluate the robustness of the primary results. First, we corrected RRs for confounding[21,22] by obesity and smoking using estimates from the National Health and Nutrition Examination Survey (NHANES) (eMethods, http://links.lww.com/EDE/A697). Then, we utilized high-dimensional propensity score methods to empirically identify and adjust for additional confounders.[23,24] We excluded 2.5% of women on both extremes of the propensity score distribution and adjusted logistic regression models for deciles of the score, which was estimated from investigator-defined covariates and 200 empirically identified variables. We implemented a depression definition using specific depression diagnosis codes that did not include bipolar and anxiety disorders (ICD-9 codes: 296.2x–296.3x, 296.9, 300.4x, 309.0x–309.1x, 309.28, 311.x). To determine if the primary results could be attenuated because of the classification of women with a preeclampsia diagnosis before antidepressant exposure as unexposed, we restricted the end of the exposure window to 140 gestational days. We accounted for correlations within states rather than within women. We also adjusted for diabetes, antidiabetic drug dispensings, sleep disorders, and pain-related diagnosis by using additional information from before the LMP. Baseline hypertension may be an intermediate between some antidepressants and preeclampsia because certain antidepressants can elevate blood

pressure[25,26] and hypertension is a risk factor for preeclampsia.[27] Consequently, we accounted for hypertension in sensitivity analyses by adjustment and restriction. We restricted to women with migraine, regardless of depression, to further reduce the potential for confounding by migraine.[28–30] Finally, we restricted to women not enrolled in capitated managed-care plans to reduce the potential for exposure misclassification (women in these plans may have incomplete information).[31]

RESULTS

Within the source population, 7.8% of women had at least one antidepressant dispensed during pregnancy and 4.6% had at least one dispensed during the exposure window. Among women with depression, 42.5% had at least one dispensed during pregnancy and 26.3% had at least one dispensed during the window. Compared with unexposed women with depression, women with depression and antidepressant exposure were more often older, white, and multiparous, and were more likely to have other antidepressant indications, use other psychotropic medications, and have higher levels of healthcare utilization (Table 1). Baseline characteristics were more homogeneous among exposure groups, although women in the tricyclic group were more likely to have hypertension, pain-related diagnoses, and sleep disorders than women in other groups.

Risk of preeclampsia was 4.7% among women without depression and without antidepressant exposure. Among women with depression, the risk of preeclampsia was 5.4% for women without antidepressant therapy and 5.4% in the SSRI, 8.8% in the SNRI, and 10.7% in the tricyclic–monotherapy groups. Compared with unexposed women, women in the SNRI monotherapy group had an adjusted RR of 1.52 (95% CI = 1.26–1.83) and 1.62 (1.23–2.12) in the tricyclic–monotherapy group. There was no association for the SSRI monotherapy (RR: 1.00; 95% CI = 0.93–1.07) or other antidepressant groups, including the polytherapy groups. Covariate adjustment attenuated the relative associations for SNRI and tricyclic–monotherapy and several polytherapy groups (Table 2). There was no substantially increased risk for preeclampsia in any of the specific SSRI antidepressants considered (Table 3). Venlafaxine was associated with a 1.57-fold increased risk for preeclampsia (1.29–1.91) and the RR for amitriptyline was 1.72 (1.24–2.40). Compared with women with SSRI monotherapy, the RR of preeclampsia was 1.54 for women with SNRI monotherapy (1.28–1.86), 1.64 for tricyclic monotherapy (1.25–2.16), and 1.08 for bupropion monotherapy (0.92–1.28).

When the primary analysis was repeated to include both women with and without depression, the associations changed slightly; the RR for preeclampsia was 1.05 for SSRI (1.00–1.10), 1.53 for SNRI (1.33–1.76), and 1.38 (1.18–1.60) for tricyclic–monotherapy groups. Among women with and without depression, the RRs for preeclampsia adjusted for delivery year were fairly stable during the first 8 months of pregnancy for SSRIs, bupropion, and other antidepressants (Figure 2). The RRs increased after the first month of pregnancy for SNRI and tricyclic therapies.

When we considered monotherapy initiators, the RR for preeclampsia was 1.03 (0.89–1.20) for the SSRI, 1.26 (0.68–2.33) for the SNRI, and 1.77 (0.89–3.53) for the tricyclic groups, compared with the unexposed group. Comparing continuers to discontinuers, the RR for preeclampsia was 1.21 (1.02–1.45) for SSRI, 1.61 (1.04–2.47) for SNRI, and 1.59 (0.66–3.88) for tricyclic monotherapies (Table 4).

The median antidepressant days supply during the exposure window was 55 for SSRI, 77 for SNRI, 33 for tricyclic, 35 for bupropion, and 39 for other antidepressant monotherapy groups. The RR was 1.45 (1.13–1.87) for women exposed to at least 130 days of SSRI monotherapy, but only 3.8% of SSRI monotherapy users had a duration this long. Among women with SNRI monotherapy, only women with high or medium cumulative duration had an increased risk for preeclampsia, compared with unexposed women, whereas women at any level in the tricyclic–monotherapy group had an increased risk for preeclampsia (eTable 1, http://links.lww.com/EDE/A697).

None of the levels of SSRI dose were associated with preeclampsia. In contrast, low SNRI doses were not associated with preeclampsia whereas higher doses were associated, and any tricyclic dose was associated (eTable 2, http://links.lww.com/EDE/A697).

Considering outcome misclassification, the risk of preeclampsia among women with depression and without antidepressant exposure could be as low as 3.6%. After correcting for outcome misclassification, the SNRI and tricyclic associations increased. However, when restricting the outcome definition to preeclampsia identified through inpatient codes or severe preeclampsia/eclampsia codes, results did not change meaningfully (eTable 3, http://links.lww.com/EDE/A697).

After correcting the primary RRs for obesity and smoking using NHANES estimates, all RRs shifted downward: 0.90 for SSRIs, 1.29 for SNRIs, and 1.44 for tricyclics (eTable 4, http://links.lww.com/EDE/A697). After correcting the comparative safety RRs for obesity and smoking, RRs shifted downward slightly: 1.44 for SNRIs and 1.60 for tricyclics. Only the tricyclic association was attenuated (RR: 1.39, 95% CI = 0.90–2.15) in the high-dimensional propensity score analysis compared with the primary analysis (eTable 5, http://links.lww.com/EDE/A697). Results from the other sensitivity analyses (eTables 6–8, http://links.lww.com/EDE/A697) did not differ substantially from the primary analysis. The RRs ranged from 0.97 to 1.13 for SSRIs, 1.41 to 1.67 for SNRIs, and 1.44 to 1.72 for tricyclics.

Multiplicative effect modification was borderline statistically significant for SNRI exposure by age ($P = 0.06$) and for tricyclic exposure by race ($P = 0.05$). The SNRI RR was highest among women at least 30 years old, and the tricyclic

TABLE 1. Cohort Characteristics by Exposure Group, Restricted to Women with Depression: Medicaid Analytic eXtract, 2000–2007

Cohort Characteristics	Unexposed N = 59,219	SSRI Monotherapy N = 19,000	SNRI Monotherapy N = 1,216	Tricyclic Monotherapy N = 441	Bupropion Monotherapy N = 2,622	Other Monotherapy N = 647	Polytherapy N = 2,622
Birth year; No. (%)							
2000–2002	12,366 (21)	3,671 (19)	136 (11)	105 (24)	356 (14)	161 (25)	452 (17)
2003–2004	17,152 (29)	6,549 (34)	408 (34)	149 (34)	716 (27)	195 (30)	898 (34)
2005–2007	29,701 (50)	8,780 (46)	672 (55)	187 (42)	1,550 (59)	291 (45)	1,272 (49)
Age (years); median (IQ range)	23 (8)	25 (8)	26 (9)	26 (10)	25 (8)	26 (10)	27 (9)
Race/ethnicity; No. (%)							
White	31,248 (53)	13,681 (72)	966 (79)	286 (65)	1,993 (76)	435 (67)	1,901 (73)
Black	15,698 (27)	2,619 (14)	98 (8)	91 (21)	335 (13)	117 (18)	353 (14)
Hispanic	8,118 (14)	1,492 (8)	72 (6)	36 (8)	151 (6)	45 (7)	167 (6)
Other	4,155 (7)	1,208 (6)	80 (7)	28 (6)	143 (5)	50 (8)	201 (8)
Multiparous; No. (%)	39,319 (66)	14,780 (78)	950 (78)	347 (79)	2,076 (79)	465 (72)	2,019 (77)
Multiple gestation; No. (%)	1,159 (2.0)	376 (2.0)	26 (2.1)	12 (2.7)	48 (1.8)	12 (1.9)	47 (1.8)
Diabetes diagnosis or antidiabetic dispensing; No. (%)	1,097 (1.9)	468 (2.5)	36 (3.0)	15 (3.4)	60 (2.3)	16 (2.5)	91 (3.5)
Hypertension diagnosis or antihypertensive dispensing; No. (%)	1,569 (3)	886 (5)	69 (6)	60 (14)	121 (5)	41 (6)	196 (8)
Inpatient depression diagnosis;[a] No. (%)	2,969 (5)	1,879 (10)	104 (9)	41 (9)	208 (8)	108 (17)	330 (13)
Number of outpatient depression diagnoses;[a] median (IQ range)	2 (4)	2 (5)	3 (6)	2 (4)	2 (5)	3 (6)	4 (6)
Other antidepressant indications;[a] No. (%)							
Mental health disorder complicating pregnancy	5,390 (9)	3,303 (17)	117 (15)	75 (17)	427 (16)	143 (22)	584 (22)
Pain-related diagnosis	7,799 (13)	3,540 (19)	263 (22)	179 (41)	459 (18)	144 (22)	674 (26)
Sleep disorder	595 (1)	440 (2)	38 (3)	32 (7)	74 (3)	30 (5)	105 (4)
Other psychotropic medication use; No. (%)							
Anticonvulsants	1,563 (3)	1,240 (7)	156 (13)	47 (11)	180 (7)	87 (14)	335 (13)
Benzodiazepines	3,193 (5)	2,736 (14)	294 (24)	117 (27)	313 (12)	185 (27)	678 (26)
Number of baseline prescription drugs excluding antidepressants; median (IQ range)	2 (4)	3 (4)	3 (4)	4 (5)	3 (4)	4 (5)	4 (5)
Number of outpatient visits; median (IQ range)	8 (6)	8 (6)	9 (7)	9 (6)	8 (6)	9 (7)	9 (7)

IQ indicates interquartile.
[a]Diagnosis during the first 225 gestational days (ie, during the baseline and exposure window).

RR was highest among white women (eTable 8, http://links.lww.com/EDE/A697). There was evidence of additive effect modification of SNRI exposure by age (RERI = 0.89 [0.15–1.63] for ages ≥30) and of tricyclic exposure by race (RERI = 0.76 [0.04–1.48] for white women). There was no evidence of effect modification by parity.

DISCUSSION

Women who used SNRIs or tricyclics during mid-pregnancy had an approximately 1.5-fold increased risk of preeclampsia when compared with women who did not use antidepressants, as well as with women who used SSRIs. Unlike previous studies,[3,5,6] we did not find an increased risk

TABLE 2. RRs and 95% CIs Comparing the Risk for Preeclampsia Between Women With and Without Antidepressant Exposure by Class, Restricted to Women With Depression: Medicaid Analytic eXtract, 2000–2007

		Women with Preeclampsia		Delivery Year Adjusted[a]		Preeclampsia Risk Factor Adjusted[b]		Fully Adjusted[c]	
Exposure Group	**N**	**No.**	**%**	**RR**	**(95% CI)**	**RR**	**(95% CI)**	**RR**	**(95% CI)**
Monotherapy									
SSRI	19,000	1,033	5	1.01	(0.94–1.08)	1.05	(0.98–1.13)	1.00	(0.93–1.07)
SNRI	1,216	107	9	1.60	(1.34–1.92)	1.64	(1.37–1.97)	1.52	(1.26–1.83)
Tricyclic	441	47	11	1.97	(1.50–2.58)	1.88	(1.43–2.47)	1.62	(1.23–2.12)
Bupropion	2,622	153	6	1.06	(0.90–1.24)	1.12	(0.95–1.31)	1.06	(0.91–1.25)
Other	647	29	5	0.84	(0.59–1.19)	0.80	(0.56–1.13)	0.71	(0.50–1.00)
Polytherapy									
SSRI and SNRI	290	18	6	1.12	(0.72–1.76)	1.13	(0.73–1.76)	1.02	(0.66–1.58)
SSRI and tricyclic	322	26	8	1.49	(1.02–2.16)	1.42	(0.98–2.05)	1.16	(0.81–1.67)
SSRI and bupropion	788	51	6	1.19	(0.91–1.55)	1.18	(0.91–1.54)	1.07	(0.82–1.40)
SSRI and other	891	53	6	1.09	(0.84–1.42)	1.01	(0.78–1.32)	0.93	(0.71–1.21)
Non-SSRI combinations	331	21	6	1.14	(0.75–1.73)	1.10	(0.72–1.67)	0.96	(0.63–1.45)
Unexposed	59,219	3,215	5	Reference		Reference		Reference	

[a]Delivery year adjustment (2000–2001, 2002, 2003, 2004, 2005, 2006, 2007).
[b]Preeclampsia risk factor adjustment: delivery year adjustment and age, race, multiparity, multiple gestation, and diabetes.
[c]Full adjustment: preeclampsia risk factor adjustment and number of outpatient depression diagnoses, number of inpatient depression diagnoses, mental disorder complicating pregnancy, pain-related diagnosis, sleep disorder, anticonvulsant dispensing, benzodiazepine dispensing, number of baseline prescription drugs, and number of baseline outpatient visits.

TABLE 3. RRs and 95% CIs Comparing the Risk for Preeclampsia Between Women in the Monotherapy Exposure Groups With Specific Antidepressant Exposures and Women Without Antidepressant Exposure, Restricted to Women With Depression: Medicaid Analytic eXtract, 2000–2007

		Women with Preeclampsia		Delivery Year Adjusted		Fully Adjusted[a]	
Exposure Group (Specific Antidepressant)	**N**	**No.**	**%**	**RR**	**(95% CI)**	**RR**	**(95% CI)**
SSRI monotherapy							
Sertraline	7,143	398	6	1.03	(0.93–1.13)	1.03	(0.93–1.14)
Fluoxetine	5,650	299	5	0.98	(0.88–1.10)	0.97	(0.87–1.09)
Paroxetine	3,517	183	5	0.99	(0.85–1.14)	0.99	(0.86–1.15)
Escitalopram	1,936	125	6	1.15	(0.97–1.37)	1.14	(0.96–1.36)
Citalopram	1,680	91	5	1.02	(0.83–1.24)	1.01	(0.82–1.23)
SNRI monotherapy							
Venalfaxine	1,113	100	9	1.64	(1.36–1.98)	1.57	(1.29–1.91)
Duloxetine[b]			7	1.13	(0.55–2.30)	0.89	(0.43–1.83)
Tricyclic monotherapy							
Amitriptyline	271	31	11	2.09	(1.49–2.92)	1.72	(1.24–2.40)
Other monotherapy							
Trazodone	339	14	4	0.76	(0.45–1.27)	0.63	(0.38–1.05)
Mirtazapine	253	14	6	1.05	(0.63–1.74)	0.81	(0.50–1.34)
Unexposed	59,219	3,215	5	Reference		Reference	

[a]Full adjustment: delivery year, age, race/ethnicity, multiparity, multiple gestation, diabetes, number of outpatient depression diagnoses, number of inpatient depression diagnoses, mental disorder complicating pregnancy, pain-related diagnosis, sleep disorder, anticonvulsant dispensing, benzodiazepine dispensing, number of baseline prescription drugs, number of baseline outpatient visits, and other specific antidepressants used during the exposure window including those listed above and desipramine, doxepin, imipramine, nortriptyline, maprotiline, and nefazodone.
[b]Cell sizes are too small for display per the Centers for Medicare and Medicaid Services cell size suppression policy.

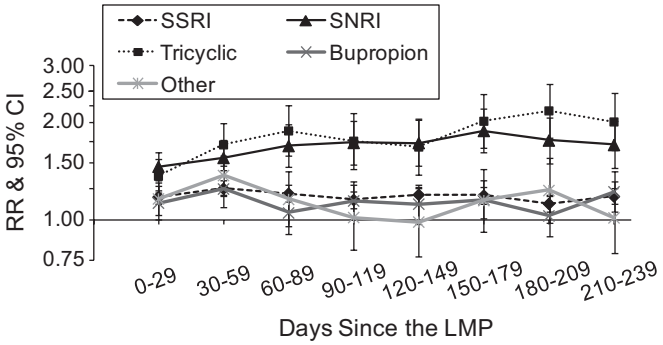

FIGURE 2. Timing analysis; unrestricted cohort. Medicaid Analytic eXtract, 2000–2007. RRs and 95% CIs comparing the risk for preeclampsia in women with dispensings for SSRIs, SNRIs, tricyclics, bupropion, or other antidepressants in 30-day intervals throughout pregnancy versus women with no claims for any antidepressants from the start of pregnancy until the end of the interval of interest.

of preeclampsia among women who used SSRIs during mid-pregnancy compared with women who did not use antidepressants; none of the SSRIs was associated with preeclampsia. The SNRI velafaxine and the tricyclic amitriptyline were associated with preeclampsia.

In the primary analysis, we compared women who used antidepressants during mid-pregnancy with women who did not use antidepressants. We also compared non-SSRI with SSRI users, initiators with noninitiators, and continuers with discontinuers. The comparative safety analysis addressed the question: is preeclampsia risk higher for women who use SNRIs or tricyclics than for SSRI users? This analysis may reduce confounding through the use of an active comparator group more similar with respect to unmeasured confounders than unexposed women. Again, the estimates suggested a moderate increased risk among women who used SNRIs or tricyclics, compared with SSRI users. The initiator analysis addressed an unambiguous question: does preeclampsia risk increase for women who initiate antidepressants during mid-pregnancy? Furthermore, this type of analysis precludes adjustment for covariates that are affected by prior treatment.[32] The estimates suggested a moderate increased risk among tricyclic initiators and a mild increased risk for SNRI initiators. The continuation/discontinuation analysis also addressed a well-defined and clinically relevant question: among women who use antidepressants early in pregnancy, does preeclampsia risk increase for women who continue using their medications? This analysis may reduce confounding through comparator groups that are more similar than unexposed women. The estimates suggested a moderate increased risk among women who continued SNRI or tricyclic treatments. The null finding for SSRIs in the primary analysis and the slightly increased risk for the SSRI continuers in the continuation/discontinuation

TABLE 4. RRs and 95% CIs Comparing the Risk for Preeclampsia Between Continuers and Discontinuers, Restricted to Women with Depression and Antidepressant Dispensings During the First 30 Gestational Days: Medicaid Analytic eXtract, 2000–2007

		Women with Preeclampsia		Delivery Year Adjusted[a]		Fully Adjusted[b]	
Exposure Group	**N**	**No.**	**%**	**RR**	**(95% CI)**	**RR**	**(95% CI)**
SSRI monotherapy							
Continuer	5,215	303	6	1.21	(1.03–1.44)	1.21	(1.02–1.45)
Discontinuer	4,661	222	5		Reference		Reference
SNRI monotherapy							
Continuer	541	46	9	1.57	(1.03–2.38)	1.61	(1.04–2.47)
Discontinuer	714	37	5		Reference		Reference
Tricyclic monotherapy							
Continuer[c]			11	1.66	(0.81–3.38)	1.59	(0.66–3.88)
Discontinuer	313	21	7		Reference		Reference
Bupropion monotherapy							
Continuer	360	21	6	1.20	(0.71–2.05)	1.10	(0.64–1.91)
Discontinuer	691	33	5		Reference		Reference
Other monotherapy							
Continuer[c]			6	1.32	(0.64–2.75)	1.18	(0.53–2.64)
Discontinuer	489	24	5		Reference		Reference

Continuers are women who have dispensings during the exposure window; discontinuers are women with no dispensings beyond the first 30 gestational days until the end of the exposure window and no days supply extending into the exposure window.

[a]Delivery year adjustment: 2000–2002, 2003–2004, 2005–2007.

[b]Full adjustment: delivery year, quadratic age, race/ethnicity (white, black, Hispanic, other/unknown), multiparity, diabetes diagnosis or antidiabetic dispensing, number of outpatient depression diagnoses (0, 1, ≥2), any inpatient depression diagnoses, mental disorder complicating pregnancy, pain-related diagnosis, anticonvulsant dispensing, benzodiazepine dispensing, number of baseline prescription drugs, and number of outpatient visits.

[c]Cell sizes are too small for display per the Centers for Medicare and Medicaid Services cell size suppression policy.

analysis results may reflect differences across the analytic cohorts used in these two analyses.

SSRIs, SNRIs, and tricyclics inhibit serotonin transporters or both serotonin and norepinephrine transporters and augment extracellular concentrations of these monoamines.[33] Serotonin and norepinephrine induce uterine, placental, and umbilical vasoconstriction in in vitro studies.[34–39] Antidepressant-mediated vasoconstriction could lead to uteroplacental underperfusion and ischemia, a biologic pathway that may be common to preeclampsia and certain etiologies of preterm delivery.[40] However, there are few data regarding the impact of antidepressants on uterine and umbilical blood flow in pregnant women.[41,42] Alternatively, depression has been hypothesized to cause preeclampsia through increased hypothalamic-pituitary-adrenal activity, systemic inflammation, and vasoconstriction.[7–9,30]

We tried to reduce confounding by depression through restriction, traditional and high-dimensional propensity score model adjustment, and comparative safety and continuation/discontinuation analyses. Although the associations persisted through all analyses, we could not rule out confounding by depression severity, or unmeasured lifestyle factors associated with depression severity, as noncausal explanations of our results even in the analyses with active comparators. Adjustment for factors that may be correlated with depression severity attenuated the associations slightly, and further adjustment could have moved the RRs closer to the null.

Although we controlled for confounding by other antidepressant indications, results could nevertheless reflect residual confounding by unrecorded indications. Tricyclics are often used for indications other than depression.[43] Confounding by migraine in particular is a concern because tricyclics are prescribed for migraine prophylaxis,[44] and migraine is associated with preeclampsia.[28–30] Because the tricyclic association was attenuated when restricting to women with migraine, the primary analysis may reflect some residual confounding by misclassified migraine.

In our data, we were unable to measure obesity, which is strongly and positively associated with preeclampsia,[45] and smoking, which is negatively associated.[46] Based on external adjustment, it seems unlikely that residual confounding by these factors could explain our results entirely. Had we been able to adjust for body mass index, our results may have been attenuated only slightly. Moreover, adjustment for body mass index and smoking did not change the SSRI and preeclampsia association in one study with this information.[3]

Another potential limitation is exposure misclassification. We have assumed that women were taking medications around the days indicated by pharmacy records.[47] Missing pharmacy claims are another source of exposure misclassification. We expect that both sources of misclassification are nondifferential (given the prospective recording of prescription information) and would tend to bias the results toward the null, which is problematic for a safety study and for the SSRI result in particular. However, it was reassuring that the results did not change when we excluded all women enrolled in capitated plans, which may report incomplete claims information,[31] or when we considered various exposure windows. Furthermore, the SSRI association was null for the SSRI long-cumulative-duration exposure group, which contained women dispensed multiple antidepressant prescriptions during mid-pregnancy.

Outcome misclassification is another concern because it could also bias the associations downward. Results did not change when we focused on inpatient preeclampsia, which had high PPV in MAX based on medical record review. Correcting the inpatient preeclampsia RRs for outcome misclassification strengthened the SNRI and tricyclic associations.

We did not confirm the positive association between SSRIs and preeclampsia reported in the previous studies, and the magnitude of the SNRI and tricyclic relations were smaller in this study. There are several possible explanations for these differences. First, incomplete claims information, resulting in nondifferential exposure and outcome misclassification, could partially explain why our results were attenuated. Second, lower adherence or dose in this population could contribute to the attenuation. Third, random variability may have been at play in earlier studies; our SSRI estimate was stable with over 1000 exposed cases, whereas there were many fewer exposed cases in previous studies.[3,6] Fourth, we may have better adjustment for underlying disorders; we were able to adjust for mood disorder and mood disorder severity, which attenuated results. Finally, the discrepant results may be attributed to differences in study population that affect the baseline risk of preeclampsia and the effect of antidepressants. Women in this cohort have low socioeconomic status and are younger and less likely to be white than in the previous study cohorts.[3,5,6] Moreover, differences in the distribution of potential effect modifiers among the cohorts would result in dissimilar population average associations. When we restricted the cohort to white women at least 30 years old, the magnitude of the SNRI association was the same as previously reported from the British Columbia cohort, which had median age of 30 and comprised primarily white women.[5]

This was the first study of an exposure–outcome relation within a nationwide Medicaid cohort. The results from this study may not generalize to all populations; nevertheless, they are relevant considering that over 40% of pregnant women in the United States are enrolled in Medicaid.[48] We have demonstrated that pregnancy cohorts carefully identified from MAX can be used to evaluate pharmaceutical safety. The large study size allowed us to evaluate five different classes of antidepressants, several specific antidepressants, and antidepressant initiation and discontinuation while restricting analyses to women with depression. The diverse and large cohort also permitted us to identify age and race as potential effect modifiers.

In this Medicaid population, SNRI and tricyclic use during mid-pregnancy were associated with a higher risk of

preeclampsia than SSRIs. We could not rule out the possibility that results from any of the analyses reflect residual confounding by unmeasured lifestyle factors, other antidepressant indications, or depression severity. After taking into account the uncertainty from random variability and biases, our best estimate for the RR of preeclampsia is around 0.9–1.1 for SSRIs, 1.3–1.7 for SNRIs, and 1.4–1.9 for tricyclics. Further biologic research is needed to elucidate the potential role that SNRI and tricyclic antidepressants may play in the development of preeclampsia.

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