

Supplementary Materials

eMethods. Confounding bias correction using National Health and Nutrition Examination Survey (NHANES) data.

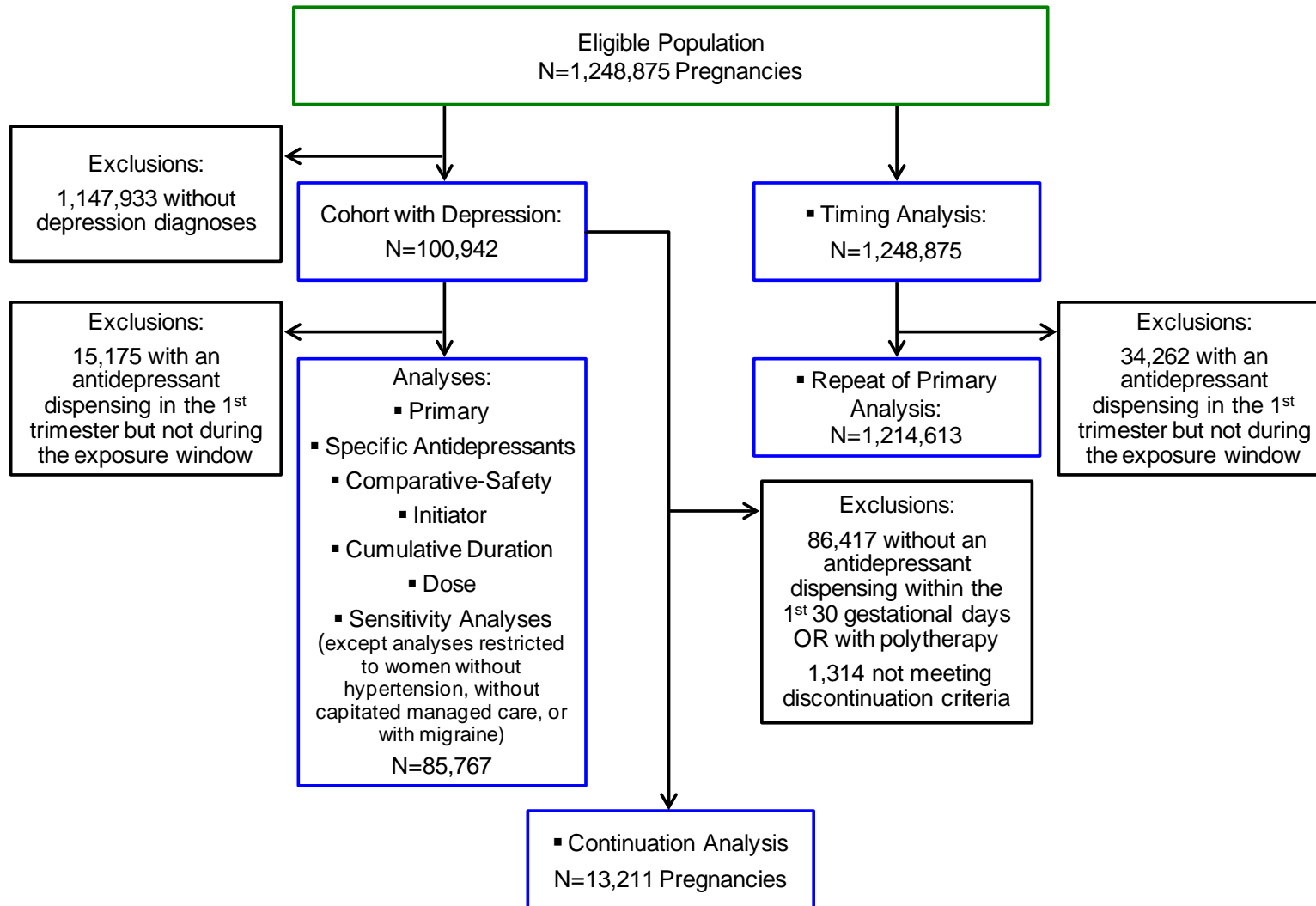
Because obesity and smoking are poorly measured by healthcare utilization data, we conducted a sensitivity analysis¹⁻² to correct the SSRI, SNRI, tricyclic and bupropion monotherapy RRs for residual confounding by these factors. The bias corrected RRs are estimated using the original RR, the confounder-outcome RR, the prevalence of the confounder among the reference group and the prevalence of the confounder among the exposed.

We assumed the obesity-preeclampsia RR was 3.0,³ and we assumed the smoking-preeclampsia RR was 0.7.⁴ We used 1999-2010 NHANES data among women ages 12-55 (N=15,736) to obtain prevalence estimates accounting for the complex sampling design.⁵ Women ages 20 and older who reported any current smoking and women ages 12-19 who reported any smoking in the past 30 days were classified as smokers, and women with body mass index (BMI) ≥ 30 kg/mg² were classified as obese. We estimated the prevalence of the confounders among women who reported no antidepressant use (unexposed) and among women who reported using antidepressants by class (exposed). Due to small sample size, we were unable to examine the confounder prevalence by antidepressant class among women with depression.

We calculated the obesity and smoking corrected RRs for the primary analysis using the prevalence estimates for the unexposed as the referent prevalence. Then we

calculated the bias corrected RRs for the comparative safety analysis using the prevalence estimates for the women who reported using SSRIs as the referent prevalence.

eFigure1. Study population overview.



eAppendix. Classification of antidepressant dose according to Goodman & Gilman's Usual Dose.⁶

Antidepressants	Dose (mg/day) Levels		
	Low	Medium	High
SSRIs			
Citalopram	<20	≥20 and ≤30	>30
Escitalopram	<10	≥10 and ≤15	>15
Fluoxetine	<20	≥20 and ≤30	>30
Fluvoxamine	<100	≥100 and ≤150	>150
Paroxetine	<20	≥20 and ≤30	>30
Sertraline	<100	≥100 and ≤125	>125
SNRIs			
Venlafaxine	<75	≥75 and ≤150	>150
Duloxetine	<80	≥80 and ≤90	>90
Tricyclics			
Amoxapine	<200	≥200 and ≤250	>250
Desipramine	<100	≥100 and ≤150	>150
Maprotiline	<100	≥100 and ≤125	>125
Nortriptyline	<75	≥75 and ≤112.5	>112.5
Amitriptyline	<100	≥100 and ≤150	>150
Clomipramine	<100	≥100 and ≤150	>150
Doxepin	<100	≥100 and ≤150	>150
Imipramine	<100	≥100 and ≤150	>150
Bupropion	<200	≥200 and ≤250	>250
Other Antidepressants			
Mirtazapine	<15	≥15 and ≤30	>30
Nefazodone	<200	≥200 and ≤300	>300
Trazodone	<150	≥150 and ≤175	>175

Abbreviations: mg, milligram; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

eTable 1. Relative risks and 95% confidence intervals comparing the risk for preeclampsia between women with and without antidepressant exposure by class and cumulative exposure duration level;^a restricted to women with depression. Medicaid Analytic eXtract, 2000-2007.

Monotherapy Exposure Group	N Total	Women with Preeclampsia		Delivery Year Adjusted		Fully Adjusted	
		N	%	RR	(95% CI)	RR	(95% CI)
SSRI							
Long	4586	267	5.8	1.08	(0.96, 1.22)	1.05	(0.93, 1.19)
Medium	7782	416	5.4	0.99	(0.89, 1.09)	0.98	(0.89, 1.09)
Short	6632	350	5.3	0.98	(0.88, 1.09)	0.99	(0.89, 1.10)
SNRI							
Long	507	48	9.5	1.71	(1.31, 2.24)	1.64	(1.25, 2.16)
Medium	407	41	10.1	1.83	(1.37, 2.45)	1.75	(1.31, 2.34)
Short	302	18	6.0	1.09	(0.70, 1.70)	1.01	(0.64, 1.57)
Tricyclic							
Long ^b	-	-	15.3	2.81	(1.72, 4.58)	2.31	(1.43, 3.75)
Medium	147	13	8.8	1.66	(0.99, 2.79)	1.27	(0.76, 2.12)
Short	209	21	10.1	1.88	(1.26, 2.81)	1.63	(1.09, 2.44)
Bupropion							
Long	423	26	6.2	1.11	(0.77, 1.62)	1.05	(0.72, 1.52)
Medium	987	56	5.7	1.02	(0.79, 1.32)	1.01	(0.78, 1.31)
Short	1212	71	5.9	1.07	(0.85, 1.34)	1.12	(0.89, 1.40)
Unexposed	59219	3215	5.4	Reference		Reference	

Abbreviations: CI, confidence interval; RR, relative risk; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

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, and number of baseline outpatient visits.

^aCumulative exposure duration levels, short ≤ 30 , medium 31-90, and long >90 class-specific antidepressant days supply that overlapped with the exposure window (135 days long).

^bCell sizes are too small for display per the Centers for Medicare and Medicaid Services cell size suppression policy.

eTable 2. Relative risks and 95% confidence intervals comparing the risk for preeclampsia between women with and without antidepressant exposure by class and dose;^a restricted to women with depression. Medicaid Analytic eXtract, 2000-2007.

Monotherapy Exposure Group	N Total	Women with Preeclampsia		Delivery Year Adjusted		Fully Adjusted	
		N	%	RR	95% CI	RR	95% CI
SSRI							
High	2726	171	6.3	1.15	(0.99, 1.33)	1.10	(0.95, 1.28)
Medium	11361	614	5.4	1.00	(0.92, 1.09)	1.00	(0.91, 1.09)
Low	4913	248	5.1	0.93	(0.82, 1.06)	0.95	(0.84, 1.08)
SNRI							
High ^b	-	-	11.9	2.18	(1.14, 4.18)	1.98	(1.08, 3.64)
Medium	910	84	9.2	1.68	(1.37, 2.06)	1.63	(1.32, 2.00)
Low	239	15	6.3	1.14	(0.70, 1.85)	1.01	(0.63, 1.64)
Tricyclic							
Medium or High ^b	-	-	10.3	1.91	(0.76, 4.80)	1.38	(0.57, 3.33)
Low	402	43	10.7	1.99	(1.50, 2.64)	1.66	(1.25, 2.20)
Bupropion							
Medium or High	424	24	5.7	1.01	(0.69, 1.49)	1.01	(0.68, 1.50)
Low	2198	129	5.9	1.07	(0.90, 1.27)	1.07	(0.90, 1.28)
Other							
Medium or High	324	17	5.3	0.99	(0.63, 1.57)	0.80	(0.51, 1.25)
Low	323	12	3.7	0.68	(0.39, 1.20)	0.61	(0.35, 1.06)
Unexposed	59219	3215	5.4	Reference		Reference	

Abbreviations: CI, confidence interval; RR, relative risk; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

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, and number of baseline outpatient visits.

^aDose levels were defined according to Goodman & Gilman's Usual Dose (mg/day):⁶ low < lowest usual dose, medium ≤ the midpoint of the usual dose range, high > the midpoint of the usual dose range.

^bCell sizes are too small for display per the Centers for Medicare and Medicaid Services cell size suppression policy.

eTable 3. Relative risks and 95% confidence intervals for outcome sensitivity analyses: changing the outcome definition and correcting for outcome misclassification;⁷ restricted to women with depression. Medicaid Analytic eXtract, 2000-2007.

Sensitivity Analysis (Exposure Group)	N Total	Women with Preeclampsia		Fully Adjusted RR or OR ^a (95% CI)	
		N	%		
Outcome: Inpatient Preeclampsia					
SSRI Monotherapy	19000	658	3.5	1.03	(0.94, 1.13)
SNRI Monotherapy	1216	67	5.5	1.57	(1.24, 1.99)
Tricyclic Monotherapy	441	29	6.6	1.60	(1.12, 2.27)
Bupropion Monotherapy	2622	92	3.5	1.04	(0.85, 1.29)
Other Monotherapy	647	17	2.6	0.66	(0.42, 1.04)
Polytherapy	2622	105	4.0	1.02	(0.84, 1.25)
Unexposed	59219	2071	3.5	Reference	
Outcome: Severe Preeclampsia/Eclampsia					
SSRI Monotherapy	19000	321	1.7	1.03	(0.91, 1.18)
SNRI Monotherapy	1216	34	2.8	1.59	(1.12, 2.24)
Tricyclic Monotherapy	441	14	3.2	1.56	(0.92, 2.64)
Bupropion Monotherapy	2622	34	1.3	0.79	(0.56, 1.12)
Other Monotherapy	647	11	1.7	0.84	(0.46, 1.52)
Polytherapy	2622	54	2.1	1.05	(0.79, 1.39)
Unexposed	59219	976	1.7	Reference	
Misclassification Correction: Any Preeclampsia					
SSRI Monotherapy	19000	1003	5.4	1.00	(0.91, 1.09)
SNRI Monotherapy	1216	107	8.8	2.16	(1.38, 3.37)
Tricyclic Monotherapy	441	47	10.7	2.14	(1.49, 3.01)
Bupropion Monotherapy	2622	153	5.8	1.09	(0.89, 1.37)
Other Monotherapy	647	29	4.5	0.67	(0.42, 1.06)
Polytherapy	2622	169	6.5	1.12	(0.93, 1.37)
Unexposed	59219	3215	5.4	Reference	
Misclassification Correction: Inpatient Preeclampsia					
SSRI Monotherapy	19000	658	3.5	1.03	(0.92, 1.14)
SNRI Monotherapy	1216	67	5.5	1.71	(1.31, 2.26)
Tricyclic Monotherapy	441	29	6.6	1.85	(1.20, 2.96)
Bupropion Monotherapy	2622	92	3.5	1.06	(0.83, 1.34)

Other Monotherapy	647	17	2.6	0.66	(0.40, 1.15)
Polytherapy	2622	105	4.0	1.08	(0.85, 1.37)
Unexposed	59219	2071	3.5	Reference	

Abbreviations: CI, confidence interval; RR, relative risk; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor. 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, and number of baseline outpatient visits.

^aOR, odds ratios were estimated for the outcome misclassification correction analyses.

eTable 4. Confounding bias corrected¹⁻² relative risks comparing the risk for preeclampsia between women with and without antidepressant exposure by class and between women by antidepressant class.

Monotherapy Exposure Group	Prevalence of Obesity Among Exposed (%)	Prevalence of Smoking Among Exposed (%)	Primary Analysis Bias Corrected RR ^{a,b}	Comparative Safety Bias Corrected RR ^{a,c}
SSRI	40.0	33.7	0.90	-
SNRI	49.2	41.9	1.29	1.44
Tricyclic	44.6	41.4	1.44	1.60
Bupropion	35.8	30.2	1.00	1.12

Abbreviations: RR, relative risk; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

^aAssumes the obesity-preeclampsia relative risk is 3.0 and the smoking-preeclampsia relative risk is 0.7.³⁻⁴

^bThe referent prevalence of obesity is 28.7% and the referent prevalence of smoking is 22.0%, i.e., the prevalence among women who reported no antidepressant use, for this analysis.

^cThe referent prevalence of the confounders is the prevalence of the confounders among women exposed to SSRIs for this analysis.

eTable 5. High-dimensional propensity score analysis.^a Odds ratios (OR) and 95% confidence intervals (CI) adjusted for deciles of propensity score, comparing the risk for preeclampsia among women with and without antidepressant exposure by class; restricted to women with depression. Medicaid Analytic eXtract, 2000-2007.

Monotherapy Exposure Group	N Total	Women with Preeclampsia		Covariates in Propensity Score Model					
				Delivery Year		Investigator-Defined ^b		Investigator-Defined ^b and Empirically Defined	
				N	%	OR	(95% CI)	OR	(95% CI)
SSRI	15874	826	5.2	1.00	(0.93, 1.08)	1.03	(0.95, 1.12)	1.03	(0.95, 1.12)
SNRI	836	64	7.7	1.65	(1.34, 2.02)	1.69	(1.34, 2.13)	1.52	(1.17, 1.98)
Tricyclic	269	23	8.6	2.10	(1.54, 2.86)	1.66	(1.14, 2.40)	1.39	(0.90, 2.15)
Unexposed ^c				Reference		Reference		Reference	

Abbreviations: SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

^aWomen with the highest and lowest 2.5% of the propensity score are excluded from the analyses.

^bInvestigator-defined covariates: 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, and number of baseline outpatient visits.

^cThe unexposed group varied for each analysis.

eTable 6. Relative risks and 95% confidence intervals for sensitivity analyses: changing the depression and exposure definitions, and accounting for within-state instead of within-woman correlations; restricted to women with depression. Medicaid Analytic eXtract, 2000-2007.

Sensitivity Analysis (Exposure Group)	N Total	Women with Preeclampsia		Fully Adjusted	
		N	%	RR	(95% CI)
Depression: Specific ICD-9 Codes					
SSRI Monotherapy	14049	756	5.4	0.97	(0.89, 1.06)
SNRI Monotherapy	897	89	9.9	1.67	(1.36, 2.05)
Tricyclic Monotherapy	264	26	9.9	1.44	(1.00, 2.06)
Bupropion Monotherapy	1932	106	5.5	1.00	(0.83, 1.22)
Other Monotherapy	434	21	4.8	0.74	(0.49, 1.11)
Polytherapy	2026	133	6.6	1.00	(0.84, 1.20)
Unexposed	32155	1754	5.5	Reference	
Exposure: Shortened Window					
SSRI Monotherapy	10714	606	5.7	1.05	(0.96, 1.15)
SNRI Monotherapy	938	84	9.0	1.59	(1.29, 1.96)
Tricyclic Monotherapy	257	26	10.1	1.59	(1.10, 2.29)
Bupropion Monotherapy	1553	101	6.5	1.20	(0.99, 1.45)
Other Monotherapy	461	18	3.9	0.63	(0.40, 0.99)
Polytherapy	1183	82	6.9	1.05	(0.84, 1.31)
Unexposed	48874	2635	5.4	Reference	
Accounting for Within-State Correlations					
SSRI Monotherapy	19000	1033	5.4	0.99	(0.93, 1.06)
SNRI Monotherapy	1216	107	8.8	1.48	(1.26, 1.74)
Tricyclic Monotherapy	441	47	10.7	1.57	(1.26, 1.97)
Bupropion Monotherapy	2622	153	5.8	1.05	(0.90, 1.22)
Other Monotherapy	647	29	4.5	0.71	(0.51, 0.98)
Polytherapy	2622	169	6.5	1.01	(0.86, 1.18)
Unexposed	59219	3215	5.4	Reference	

Abbreviations: CI, confidence interval; ICD-9, *International Classification of Diseases*, Ninth Revision; RR, relative risk; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

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, and number of baseline outpatient visits.

eTable 7. Relative risks and 95% confidence intervals for additional adjustments; restricted to women with depression. Medicaid Analytic eXtract, 2000-2007.

Exposure Group	N Total	Women with Preeclampsia		Additionally Adjusted for Pre-baseline Information ^a		Additionally Adjusted for Hypertension ^b	
		N	%	RR	(95% CI)	RR	(95% CI)
SSRI							
Monotherapy	19000	1033	5.4	1.00	(0.93, 1.07)	1.00	(0.93, 1.07)
SNRI							
Monotherapy	1216	107	8.8	1.50	(1.25, 1.81)	1.56	(1.30, 1.87)
Tricyclic							
Monotherapy	441	47	10.7	1.56	(1.19, 2.05)	1.49	(1.13, 1.96)
Bupropion							
Monotherapy	2622	153	5.8	1.06	(0.91, 1.25)	1.06	(0.90, 1.24)
Other							
Monotherapy	647	29	4.5	0.70	(0.50, 1.00)	0.70	(0.50, 1.00)
Polytherapy	2622	169	6.5	1.01	(0.86, 1.17)	1.01	(0.87, 1.18)
Unexposed	59219	3215	5.4	Reference		Reference	

Abbreviations: CI, confidence interval; RR, relative risk; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

^aAdjusted for: delivery year, age, race/ethnicity, multiparity, multiple gestation, number of outpatient depression diagnoses, number of inpatient depression diagnoses, mental disorder complicating pregnancy, anticonvulsant dispensing, benzodiazepine dispensing, number of baseline prescription drugs, and number of baseline outpatient visits, *and diabetes (no antidiabetic dispensing and no diabetes diagnosis, antidiabetic dispensing and diabetes diagnosis, antidiabetic dispensing and diabetes diagnosis), pain-related diagnosis, and sleep disorder including information prior to the last menstrual period.*

^bAdjusted for: 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 hypertension (no antihypertensive dispensing and no hypertension diagnosis, no antihypertensive dispensing and hypertension diagnosis, antihypertensive dispensing and no hypertension diagnosis, antihypertensive dispensing and hypertension diagnosis).*

eTable 8. Relative risks and 95% confidence intervals for additional restrictions among women with depression, unless otherwise noted. Medicaid Analytic eXtract, 2000-2007.

Restrictions (Exposure Group)	N Total	Women with Preeclampsia		Fully Adjusted	
		N	%	RR	(95% CI)
Restricted to Women Without Antihypertensives or Hypertension					
SSRI Monotherapy	18114	888	4.9	1.00	(0.93, 1.08)
SNRI Monotherapy	1147	92	8.0	1.55	(1.27, 1.90)
Tricyclic Monotherapy	381	36	9.5	1.72	(1.26, 2.34)
Bupropion Monotherapy	2501	136	5.4	1.11	(0.94, 1.32)
Other Monotherapy	606	23	3.8	0.70	(0.47, 1.04)
Polytherapy	2426	128	5.3	0.98	(0.82, 1.17)
Unexposed	57650	2929	5.1	Reference	
Restricted to Women With a Migraine Diagnosis^a					
SSRI Monotherapy	2191	158	7.2	1.13	(0.95, 1.35)
SNRI Monotherapy	163	16	9.8	1.51	(0.94, 2.41)
Tricyclic Monotherapy	416	41	9.9	1.46	(1.08, 1.95)
Bupropion Monotherapy	334	22	6.6	1.06	(0.71, 1.59)
Other Monotherapy ^b	-	-	6.6	0.97	(0.46, 2.05)
Polytherapy	399	36	9.0	1.30	(0.93, 1.80)
Unexposed	18196	1171	6.4	Reference	
Restricted to Women Not Enrolled in Capitated Managed Care Plans					
SSRI Monotherapy	11881	707	6.0	1.01	(0.92, 1.10)
SNRI Monotherapy	793	69	8.7	1.41	(1.12, 1.77)
Tricyclic Monotherapy	293	33	11.3	1.57	(1.13, 2.17)
Bupropion Monotherapy	1663	95	5.7	0.96	(0.79, 1.18)
Other Monotherapy	384	16	4.2	0.61	(0.38, 0.97)
Polytherapy	1630	111	6.8	0.98	(0.81, 1.18)
Unexposed	32725	1910	5.8	Reference	
Restricted to Non-White Women					
SSRI Monotherapy	5319	326	6.1	0.97	(0.86, 1.09)
SNRI Monotherapy	250	23	9.2	1.29	(0.86, 1.93)
Tricyclic Monotherapy	153	13	8.4	1.12	(0.67, 1.85)
Unexposed	27971	1697	6.1	Reference	
Restricted to White Women					
SSRI Monotherapy	13681	707	5.2	1.02	(0.93, 1.12)
SNRI Monotherapy	966	84	8.7	1.59	(1.29, 1.96)
Tricyclic Monotherapy	286	34	11.9	2.04	(1.49, 2.80)
Unexposed	31248	1518	4.9	Reference	
Restricted to Women Age <30					
SSRI Monotherapy	14637	741	5.1	1.04	(0.95, 1.13)
SNRI Monotherapy	858	59	6.9	1.33	(1.03, 1.71)

Tricyclic Monotherapy	293	25	8.5	1.52	(1.04, 2.21)
Unexposed	49714	2566	5.2		Reference
Restricted to Women Age $\geq 30^c$					
SSRI Monotherapy	4363	292	6.7	0.92	(0.80, 1.05)
SNRI Monotherapy	358	48	13.4	1.76	(1.32, 2.33)
Tricyclic Monotherapy	148	22	14.9	1.73	(1.16, 2.59)
Unexposed	9505	649	6.8		Reference
Restricted to White Women Age ≥ 30					
SSRI Monotherapy	2942	200	6.8	1.02	(0.85, 1.21)
SNRI Monotherapy	270	38	14.1	1.98	(1.43, 2.73)
Tricyclic Monotherapy	92	12	13.0	1.74	(1.01, 3.01)
Unexposed	4503	276	6.1		Reference

Abbreviations: CI, confidence interval; RR, relative risk; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

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, and number of baseline outpatient visits.

^aIncludes women with and without depression.

^bCell sizes are too small for display per the Centers for Medicare and Medicaid Services cell size suppression policy.

^cAdjusted for age with linear and quadratic terms.

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