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Increasing use of atypical antipsychotics and anticonvulsants during pregnancy

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Abstract

Purpose—To quantify maternal use of atypical antipsychotics, typical antipsychotics, anticonvulsants and lithium during pregnancy.

Methods—Tennessee birth and death records were linked to Tennessee Medicaid data to conduct a retrospective cohort study of 296,817 women enrolled in Tennessee Medicaid throughout pregnancy who had a live birth or fetal death from 1985 to 2005.

Results—During the study time period, the adjusted rate of use of any study medication during pregnancy increased from nearly 14 to 31 per 1,000 pregnancies ($\beta = 0.08$, 95% CI = 0.07, 0.09). Significant increases were reported in use of anticonvulsants alone among mothers with pain and other psychiatric disorders, atypical antipsychotics alone among mothers with bipolar disorders, schizophrenia, unipolar depressive disorders, and other psychiatric disorders, and more than one studied medication for mothers with epilepsy, pain disorders, bipolar disorders, unipolar depressive disorders, and other psychiatric disorders. Significant decreases were reported in use of lithium alone and typical antipsychotics alone for all clinically meaningful diagnosis groups.

Conclusions—There was a substantial increase in use of atypical antipsychotics alone, anticonvulsants alone, and medications from multiple studied categories among Tennessee

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Medicaid-insured pregnant women during the study period. Further examination of the maternal and fetal consequences of exposure to these medications during pregnancy is warranted.

Keywords

anticonvulsants; antipsychotics; fetal effects; lithium; pregnancy

Introduction

Antipsychotics, anticonvulsants, and lithium have demonstrated efficacy for several serious psychiatric disorders, including bipolar disorder.^{1–3} Recent studies demonstrate increasing use of some of these medications among patients of all ages, including pregnancy-age and pregnant women.^{4–12} Appropriate use has been shown to reduce the risks associated with untreated maternal psychiatric disorders and of psychiatric symptom relapse due to medication discontinuation.^{13–15} At the same time, pregnancy-related exposure to certain antipsychotics, anticonvulsants and/or lithium may place the developing fetus at risk for birth defects and other adverse outcomes.^{11,12,16–20}

Because of different pharmacologic properties of the various psychotropic drugs, it is possible that they interact in varying ways with the developing fetus. For example, while atypical antipsychotics and typical antipsychotics are both dopamine D2 receptor agonists,²¹ atypical antipsychotics have higher binding affinity for serotonin 5-HT_{2A} receptors.²² In recognition of some of these risks, the U.S. Food and Drug Administration (FDA) recently issued warnings against the use of specific atypical antipsychotics during pregnancy due to the risk of abnormal muscle movements and withdrawal symptoms in newborns,²³ valproic acid due to the risk of neural tube birth defects,²⁴ and topiramate due to the risk of cleft lip and cleft palate birth defects.²⁵

More information is needed on the extent of maternal use of these medications during pregnancy. Thus, we conducted a large, retrospective cohort study in a population of women enrolled in the Tennessee Medicaid program throughout pregnancy to quantify the rates and identify trends over time of maternal use of antipsychotics, anticonvulsants, and lithium during pregnancy.

Methods

Data Sources

The current study was conducted using Tennessee birth, death and fetal death certificates linked to Tennessee Medicaid data. Although the information collected on vital records changes over time, there were no major changes to the method of collection of the key study variables in the study time period. Birth, death and fetal death certificates were used to identify mothers who delivered a live infant or had a fetal death in Tennessee, to estimate conception dates, and to obtain information on maternal age, race, ethnicity, education level, and prior number of pregnancies.^{26,27} We defined the conception date as the date of the last menstrual period (LMP), which was either recorded on the birth certificate or estimated from birth weight using a previously-validated method based on information from births with a known LMP date.^{26,28}

Pregnancies were included in the cohort if the date of delivery or fetal death was between January 1, 1985 and December 31, 2005, and the mother was noted as a Tennessee resident on the birth certificate, excluding pregnancies with missing or invalid information on maternal age. Tennessee Medicaid enrollment files were then used to identify pregnancies in which the mother was enrolled in the Tennessee Medicaid program from 30 days prior to the

LMP date through the date of delivery or fetal death (allowing gaps in enrollment of less than 7 days).

During the 20-year study period (1985 – 2005) there were 1,510,520 pregnancies in Tennessee, of which approximately half were Medicaid-insured events.²⁹ Of those, 296,817 (roughly 40% of Medicaid-eligible pregnancies) met all requirements for inclusion in the study cohort. The majority of excluded pregnancies were excluded because the mother was not enrolled in Tennessee Medicaid 30 days before the conception date. Although we considered relaxing the enrollment criteria from LMP – 30 days through the date of delivery or fetal death to LMP date through date of delivery or fetal death, doing so would have expanded the cohort by fewer than 10,000 total pregnancies and risked misclassifying early fetal exposures; thus, we defined our cohort to maximize accurate classification of maternal medication use.

The number of mothers giving birth who met enrollment criteria increased over time and ranged from 1,323 in 1985 to 19,509 in 2005. The increase in the number of Medicaid-insured pregnancies in Tennessee reflects the introduction in 1994 of TennCare,³⁰ Tennessee's expanded Medicaid program, and mirrors nationwide Medicaid expansions over roughly the same period of time.³¹

Cohort Construction and Variable Definition

Tennessee birth and fetal death certificates were used to define the calendar year of delivery or fetal death as a continuous variable. Tennessee Medicaid pharmacy files, which have been shown to be consistent with patient self-reported medication use,^{28,32,33} were used to classify all cohort qualifying pregnancies according to use of specific prescription medications during pregnancy. Pharmacy files included information about the date a prescription was filled and the number of days of medication supply for all outpatient prescriptions reimbursed by Tennessee Medicaid, including prescriptions filled in pharmacies, purchased over the internet, or filled in other states. A pregnancy was considered exposed if a prescription was filled between the date of the LMP and the date of delivery or fetal death, or if a prescription was filled in the 30 days before the LMP and the days supply extended past the LMP.

Pharmacy files were used to determine whether prescriptions were filled for each of four broad classes of medication: typical antipsychotics, atypical antipsychotics, anticonvulsants and lithium. Typical antipsychotics, which are sometimes referred to as first-generation antipsychotics, included acetophenazine, carphenazine, chlorpromazine hydrochloride, chlorprothixene, droperidol, fluphenazine hydrochloride, haloperidol, loxapine succinate, mesoridazine besylate, molindone hydrochloride, perphenazine, pimozide, piperacetazine, thioridazine, thiothixene hydrochloride, and trifluoperazine hydrochloride.^{34,35} Atypical antipsychotics, which are sometimes referred to as second-generation antipsychotics, included aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone.^{34,35} Anticonvulsant medications included carbamazepine, divalproex, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, and valproate.^{34–42} Phenytoin and phenobarbital, two first generation anticonvulsants, were not included because they are not used for mood stabilization.

For analytic purposes, each pregnancy was classified into mutually exclusive exposure categories according to whether or not a prescription was filled for a medication in any of these four broad categories. Each pregnancy was classified as not exposed to any of the studied medications, exposed to typical antipsychotics alone, exposed to atypical antipsychotics alone, exposed to anticonvulsants alone, exposed to lithium alone, or exposed

to a medication in more than one of these categories. Potential exposures to other types of medications were not classified.

Maternal covariates were defined from Tennessee birth and fetal death certificates and from Tennessee Medicaid claims data. Tennessee birth and fetal death certificates were used to define maternal age at LMP in years, race, Hispanic ethnicity, education level, and prima gravid status. For mothers filling prescriptions for one of the studied medications, we used Tennessee Medicaid claims data from 30 days before to 7 days after the date of the first qualifying prescription for one of the studied medications to define maternal diagnoses associated with the prescription. For other mothers, claims from LMP to the date of delivery or fetal death were used. Definitions for epilepsy, pain disorders, schizophrenia, bipolar disorders, unipolar depressive disorders, and other psychiatric disorders are provided in Table 1.

Analytic Plan

For each medication category studied, Poisson regression models were developed to estimate trends over time (linear test of trend), adjusted rate ratios (aRRs) and 95% confidence intervals (95% CI), and adjusted rate differences (aRDs) and 95% CI, adjusting for maternal age at delivery, race, ethnicity, history of prior pregnancies, education, and maternal diagnosis group. We fit interaction terms for each diagnosis group based on the clinically meaningful indication for each medication category and the calendar year of delivery or fetal death, in addition to the aforementioned covariates.^{43–50} Marginal prediction based on these models was used to estimate the prevalence of maternal medication use per 1,000 pregnancies for each calendar year for use of any studied medication and for individual diagnosis groups.⁵¹

Due to infrequent use of study medications prior to 1995, reference years were 1995 or earlier for all study medication categories except for atypical antipsychotics alone, for which the reference years were 2000 or earlier. Given that there were significant changes to the Tennessee Medicaid program in 1995, we examined whether pregnancies in the cohort before 1995 were significantly different than pregnancies in the cohort after 1995. Pregnancies enrolled before 1995 were more likely to be black and less likely to have at least a high school education, to have diagnosis of unipolar depressive disorder, other psychiatric disorder or pain.

To account for correlation due to mothers with more than one pregnancy during the study period, the robust Huber-White sandwich variance estimator was used to provide correct standard errors and confidence intervals of the estimated rate ratios.⁵² All analyses were complete case analyses and were performed with R version 2.15.1.⁵³ Permission to perform the study was obtained from the Vanderbilt University Institutional Review Board, the State of Tennessee Health Department, and the TennCare Bureau.

Results

During the entire study time period, 5,784 (or 1.9%) of the 296,817 mothers in the study cohort filled at least one prescription during pregnancy for one of the study medications (Table 2).

Anticonvulsants, which were filled by 2,143 mothers, were the most frequently used study medication. Prescriptions from more than one study medication category were filled during pregnancy by 910 mothers, including 414 who filled prescriptions for an anticonvulsant and an atypical antipsychotic medication (45.5% of multiple medication users), 97 (10.7%) who filled prescriptions for lithium and a typical antipsychotic, 95 (10.4%) who filled

prescriptions for a typical antipsychotic and an atypical antipsychotic, 86 (9.5%) who filled prescriptions for a typical antipsychotic and an anticonvulsant, 64 (7.0%) who filled prescriptions for an atypical antipsychotic and lithium, and 44 (4.8%) who filled prescriptions for lithium and an anticonvulsant. Of note, 110 (12.1%) filled prescriptions for medications from three or more categories.

Table 3 shows the characteristics of mothers who filled prescriptions in each studied medication category. Cohort eligible mothers were on average about 25 years of age. A majority was white, non-Hispanic, had at least a high school education, and was not *prima gravid*. Use of medications in each category was more common among white, non-Hispanic, non-*prima gravid* mothers, with at least a high school education.

Adjusting for maternal age at delivery, race, ethnicity, education, number of previous pregnancies and diagnosis, the rate of use of any study medication – either alone or in combination – increased from 13.54 to 31.02 per 1,000 pregnancies (linear test of trend = 0.08, 95% CI = 0.07, 0.09; aRR = 2.29, 95% CI = 2.20, 2.38; aRD = 17.49, 95% CI = 4.41, 30.57) (Table 4). There were significant increases in the use of atypical antipsychotics alone from 1.73 in 2000 and earlier to 16.52 in 2005 per 1,000 pregnancies (linear test of trend = 0.45, 95% CI = 0.43, 0.48; aRR = 9.53, 95% CI = 8.67, 10.47; aRD = 14.79, 95% CI = 6.42, 23.16), anticonvulsants alone from 4.12 in 1995 and earlier to 13.24 in 2005 per 1,000 pregnancies (linear test of trend = 0.12, 95% CI = 0.10, 0.13; aRR = 3.22, 95% CI = 3.01, 3.44; aRD = 9.12, 95% CI = 0.95, 17.29) and medications from multiple studied categories from 1.54 in 1995 and earlier to 5.66 in 2005 per 1,000 pregnancies (linear test of trend = 0.13, 95% CI = 0.11, 0.15; aRR = 3.68, 95% CI = 3.31, 4.10; aRD = 4.12, 95% CI = -1.14, 9.38). There were significant decreases in the use of typical antipsychotics alone from 7.77 in 1995 and earlier to 0.99 in 2005 per 1,000 pregnancies (linear test of trend = -0.21, 95% CI = -0.23, -0.18; aRR = 0.13, 95% CI = 0.11, 0.15; aRD = -6.78, 95% CI = -12.58, -0.98) and lithium alone from 2.11 in 1995 and earlier to 0.46 in 2005 per 1,000 pregnancies (linear test of trend = -0.15, 95% CI = -0.19, -0.11; aRR = 0.22, 95% CI = 0.18, 0.27; aRD = -1.65, 95% CI = -4.79, 1.49).

Table 5 shows the linear trend and 95% CI for each clinically-meaningful diagnosis group for each medication category. Use of anticonvulsants alone decreased significantly among mothers with epilepsy ($\beta = -0.03$, 95% CI = -0.06, -0.00), increased significantly among mothers with pain disorders ($\beta = 0.20$, 95% CI = 0.16, 0.23) and other psychiatric disorders ($\beta = 0.08$, 95% CI = 0.05, 0.11), and did not change significantly among mothers with bipolar disorders ($\beta = 0.00$, 95% CI = -0.05, 0.05). Use of atypical antipsychotics alone increased among mothers with bipolar disorders (0.29, 95% CI = 0.23, 0.35), schizophrenia ($\beta = 0.27$, 95% CI = 0.17, 0.37), unipolar depressive disorders ($\beta = 0.35$, 95% CI = 0.31, 0.39), and other psychiatric disorders ($\beta = 0.35$, 95% CI = 0.31, 0.38). Use of lithium alone decreased among mothers with bipolar disorders ($\beta = -0.22$, 95% CI = -0.27, -0.17), unipolar depressive disorders ($\beta = -0.25$, 95% CI = -0.32, -0.18), and other psychiatric disorders ($\beta = -0.26$, 95% CI = -0.31, -0.21). Use of typical antipsychotics alone decreased among mothers with bipolar disorders ($\beta = -0.17$, 95% CI = -0.25, -0.08), schizophrenia ($\beta = -0.37$, 95% CI = -0.43, -0.32), and other psychiatric disorders ($\beta = 0.26$, 95% CI = -0.29, -0.22).

Use of multiple studied medications increased among mothers with epilepsy ($\beta = 0.20$, 95% CI = 0.05, 0.36), pain disorders ($\beta = 0.18$, 95% CI = 0.11, 0.24), bipolar disorders ($\beta = 0.07$, 95% CI = 0.03, 0.11), unipolar depressive disorders ($\beta = 0.10$, 95% CI = 0.06, 0.15), and other psychiatric disorders ($\beta = 0.09$, 95% CI = 0.06, 0.12), but did not change among mothers with schizophrenia ($\beta = 0.01$, 95% CI = -0.05, 0.06).

Discussion

In the Tennessee Medicaid population, the adjusted rate of use of any study medication during pregnancy increased from nearly 14 to almost 31 per 1,000 pregnancies over the 20-year study period. The use of anticonvulsants alone increased among mothers with pain disorders and other psychiatric disorders but decreased among mothers with epilepsy. The use of atypical antipsychotics alone increased for mothers with bipolar disorders, schizophrenia, unipolar depressive disorders and other psychiatric disorders. Use of lithium alone decreased for mothers with bipolar disorders, unipolar depressive disorders and other psychiatric disorders. The use of typical antipsychotics alone decreased for patients with bipolar disorders, schizophrenia and other psychiatric disorders. The use of multiple studied medications increased among mothers with epilepsy, pain disorders, bipolar disorders, unipolar depressive disorders and other psychiatric disorders. Existing research has demonstrated increasing off-label use of atypical antipsychotics and anticonvulsant medications in the U.S. and case control studies suggest that early fetal exposure to anticonvulsants may be associated with increased risk for birth defects.^{4–12}

The potential benefit of using atypical antipsychotics and anticonvulsants either alone or in combination for some psychiatric conditions during pregnancy is well-established,^{13–15} and the results of the current study may represent improved recognition and treatment of pregnancy-related psychiatric conditions. At the same time, these findings arouse concern because little is known about the potential risk associated with prenatal exposure to certain atypical antipsychotics and because the risk associated with prenatal exposure to several anticonvulsants and with treatment with more than one medication at a time is well-documented.^{16,17,21–25} In conjunction with recent FDA warnings about the risks of use of some of these medications during pregnancy,^{23–25} these results reinforce the need for additional research examining the comparative safety of use of these medications by women during pregnancy.

The current study has some limitations. Although the use of Medicaid pharmacy files has been shown to mitigate methodological concern about selection bias, recall bias, and differential misclassification that are often associated with the retrospective examination of medication use, administrative claims databases do not allow for the classification of medication adherence. Thus, there is no way to determine whether the proportion of mothers taking the medications after filling a prescription changed over time. Additionally, our database only included mothers continuously enrolled in the Tennessee Medicaid program and did not include prescriptions written while a mother may have been in the hospital. Thus, the results may not generalize to other populations. It is important to note, however, that in recent years approximately 50% of mothers giving birth in Tennessee were enrolled in Medicaid at the time of delivery and that nationally approximately one-third of all births were covered by Medicaid.³⁰ Finally, our broad classification of maternal diagnosis did not allow us to examine differences by individual specific psychiatric or pain diagnosis.

In spite of these limitations, our results demonstrate significant changes in the utilization of antipsychotics, anticonvulsants, lithium, and these medications in combination with one another by pregnant Tennessee Medicaid enrollees during the study period. In view of the clinical effectiveness of these medications and relative lack of data regarding potential adverse maternal, fetal and neonatal effects associated with some of the studied drugs and drug combinations, future research examining the potential impact of maternal use of these medications during pregnancy is warranted.

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KEY POINTS

1. Use of atypical antipsychotics and anticonvulsants during pregnancy has increased.
2. Use of typical antipsychotics and lithium during pregnancy has decreased.
3. Further examination of consequences of increasing maternal and fetal exposure to these medications is warranted.

Table 1

Diagnosis group definitions

Diagnosis group	ICD-9 Codes
Epilepsy	345.x [excluding 345.6], 780.39
Pain disorders	053.1, 053.9, 250.60–256.63, 307.81, 336.9, 337.1, 337.2x, 338, 338.2–338.29, 338.3, 338.4, 339.0, 339.0x, 339.2x, 339.4x, 339.8x, 346–346.91, 350.1, 350.2, 350.8, 350.9, 352.1, 353.0, 353.1, 353.2, 353.4, 353.6, 353.8, 353.9, 354.0, 354.1, 354.2, 354.3, 354.4, 354.5, 354.8, 354.9, 355.0, 355.1, 355.2, 355.3, 355.4, 355.5, 355.6, 355.7x, 355.8, 355.9, 356.0, 356.2, 356.8, 356.9, 357.0, 357.1, 357.2, 357.3, 357.5, 357.6, 357.7, 357.8x, 357.9, 388.71, 388.72, 723.1, 723.4, 724.1, 724.4, 729.1, 729.2, 780.96, 782.0, 784, or 957.9
Psychiatric diagnoses	
Schizophrenia	295.xx
Bipolar disorders	296.0x, 296.4x, 296.5x, 296.6x, 296.7x, 296.8x
Unipolar depressive disorders	296.2x, 296.3x, 300.4x, 311.xx
Other psychiatric disorders	290.xx – 294.xx, 296.9x, 297.xx – 299.xx, 300.0x – 300.3x, 300.5x – 300.9x, 301.xx – 319.x

Table 2

Number of pregnancies and number of mothers filling prescriptions for antipsychotics, anticonvulsants and lithium, Tennessee Medicaid, 1985 – 2005.

Calendar Year	# Pregnancies	# Users					Any Studied Medication
		Typical Antipsychotics Alone	Atypical Antipsychotics Alone	Anticonvulsants Alone	Lithium Alone	Medications From Multiple Categories	
All years	296,817	1,149	1,288	2,143	294	910	5,784
1995 and earlier	98,667	591	---	347	79	94	1116
2000 ^a	21,137	52	106	182	18	57	360
2005	19,509	28	268	474	14	190	974

^aFor atypical antipsychotics 2000, is 2000 and earlier

Table 3

Characteristics of mothers filling prescriptions for antipsychotics, anticonvulsants, and lithium during pregnancy, Tennessee Medicaid, 1985–2005.

Variable	n = 296,817	Typical Antipsychotics Alone (n = 1,149)	Atypical Antipsychotics Alone (n = 1,288)	Anticonvulsants Alone (n = 2,143)	Lithium Alone (n = 294)	Multiple (n = 910)	Any (n = 5,784)
Age in Years, Mean (SD)	296,817	26.7 (6.27)	25.5 (6.61)	24.8 (0.56)	25.7 (0.63)	26.9 (0.63)	25.7 (6.07)
Race, n (%)	296,753						
White	156,172	626 (54.48)	902 (70.03)	1735 (80.96)	256 (87.03)	690 (75.91)	4208 (72.78)
Black	138,663	522 (45.43)	377 (29.27)	398 (18.57)	38 (12.97)	209 (22.99)	1544 (26.70)
Other	1,918	1 (0.09)	9 (0.70)	10 (0.47)	0 (0.00)	10 (1.10)	30 (0.52)
Hispanic Ethnicity, n (%)	277,504						
No	274,485	1141 (99.39)	1271 (98.68)	2113 (99.39)	290 (98.30)	900 (98.90)	5714 (99.10)
Yes	3,019	7 (0.61)	17 (1.32)	13 (0.61)	5 (1.70)	10 (1.10)	52 (0.90)
Education, n (%)	295,846						
Less than High School	134,509	559 (49.08)	580 (45.24)	775 (36.38)	107 (36.05)	343 (37.98)	2363 (41.11)
High School or More	161,337	580 (50.92)	702 (54.76)	1355 (63.62)	188 (63.95)	560 (62.02)	3385 (58.89)
Prima gravida, n (%)	295,631						
No	224,713	874 (76.40)	964 (75.91)	1554 (72.86)	214 (72.45)	665 (73.56)	4270 (74.33)
Yes	70,918	270 (23.60)	306 (24.09)	579 (27.14)	81 (27.55)	239 (26.44)	1475 (25.67)
Epilepsy, n (%)	296,817						
No	293,663	1138 (99.04)	1259 (97.75)	1634 (76.25)	293 (99.66)	855 (93.96)	5179 (89.54)
Yes	3,154	11 (0.96)	29 (2.25)	509 (23.75)	1 (0.34)	55 (6.04)	605 (10.46)
Schizophrenia, n (%)	296,817						
No	295,659	853 (74.24)	1166 (90.53)	2132 (99.49)	282 (95.92)	742 (81.54)	5175 (89.47)
Yes	1,158	296 (25.76)	122 (9.47)	11 (0.51)	12 (4.08)	168 (18.46)	609 (10.53)
Bipolar disorder, n (%)	296,817						
No	293,481	1084 (94.34)	1014 (78.73)	1845 (86.09)	147 (50.00)	468 (51.43)	4558 (78.80)
Yes	3,336	65 (5.66)	274 (21.27)	298 (13.91)	147 (50.00)	442 (48.57)	1226 (21.20)
Unipolar depression, n (%)	296,817						
No	275,808	852 (74.15)	620 (48.14)	1721 (80.31)	210 (71.43)	563 (61.87)	3966 (68.57)
Yes	21,009	297 (25.85)	668 (51.86)	422 (19.69)	84 (28.57)	347 (38.13)	1818 (31.43)
Other psychiatric disorder, n (%)	296,817						

Variable	n = 296,817	Typical Antipsychotics Alone (n = 1,149)	Atypical Antipsychotics Alone (n = 1,288)	Anticonvulsants Alone (n = 2,143)	Lithium Alone (n = 294)	Multiple (n = 910)	Any (n = 5,784)
No	239,073	717 (62.40)	562 (43.63)	1505 (70.23)	158 (53.74)	377 (41.43)	3319 (57.38)
Yes	57,744	432 (37.60)	726 (56.37)	638 (29.77)	136 (46.26)	533 (58.57)	2465 (42.62)
Pain diagnosis, n (%)	296,817						
No	243,414	974 (84.77)	1029 (79.89)	1559 (72.75)	269 (91.50)	705 (77.47)	4536 (78.42)
Yes	53,403	175 (15.23)	259 (20.11)	584 (27.25)	25 (8.50)	205 (22.53)	1248 (21.58)

Table 4

Adjusted rate ratio (aRR), adjusted rate difference (aRD) and 95% confidence interval (95% C.I.) for prescribing of antipsychotics, anticonvulsants, and lithium during pregnancy in 2005.

Medication	Year ^d	aRR ^b	(95% CI for aRR)	aRD ^b	(95% CI for aRD)
Typical Antipsychotics Alone	1995	1.00	--	1.00	--
	2005	0.13	(0.11, 0.15)	-6.78	(-12.58, -0.98)
Atypical Antipsychotics Alone	2000	1.00	--	1.00	--
	2005	9.53	(8.67, 10.47)	14.79	(6.42, 23.16)
Anticonvulsants Alone	1995	1.00	--	1.00	--
	2005	3.22	(3.01, 3.44)	9.12	(0.95, 17.29)
Lithium Alone	1995	1.00	--	1.00	--
	2005	0.22	(0.18, 0.27)	-1.65	(-4.79, 1.49)
Medications from Multiple Categories	1995	1.00	--	1.00	--
	2005	3.68	(3.31, 4.10)	4.12	(-1.14, 9.38)
Any Studied Medication	1995	1.00	--	1.00	--
	2005	2.29	(2.20, 2.38)	17.49	(4.41, 30.57)

^aThe reference year is 1995 and earlier for all medication categories except atypical antipsychotics for which it is 2000 and earlier due to infrequent use of studied medications in the earlier years. Although we considered year as a continuous variable, the rate ratios were obtained from the same models and compared 2005 to the reference year.

^bRate ratios and rate differences are adjusted for maternal age, race, ethnicity, education, prima gravida, and diagnosis group.

Table 5

Test for linear trend (95% CI) for each medication category by clinically meaningful diagnosis group

Maternal Diagnosis Group	Test for linear trend (95% CI) <i>(a)</i>				
	Anticonvulsants Alone	Atypical Antipsychotics Alone	Lithium Alone	Typical Antipsychotics Alone	Multiple Studied Medications
Epilepsy	-0.03 (-0.06, -0.00)	--	--	--	0.20 (0.05, 0.36)
Pain	0.20 (0.16, 0.23)	--	--	--	0.18 (0.11, 0.24)
Psychiatric					
Bipolar	0.00 (-0.05, 0.05)	0.29 (0.23, 0.35)	-0.22 (-0.27, -0.17)	-0.17 (-0.25, -0.08)	0.07 (0.03, 0.11)
Schizophrenia	--	0.27 (0.17, 0.37)	--	-0.37 (-0.43, -0.32)	0.01 (-0.05, 0.06)
Unipolar	--	0.35 (0.31, 0.39)	-0.25 (-0.32, -0.18)	--	0.10 (0.06, 0.15)
Other ^(b)	0.08 (0.05, 0.11)	0.35 (0.31, 0.38)	-0.26 (-0.31, -0.21)	-0.26 (-0.29, -0.22)	0.09 (0.06, 0.12)

^(a) The coefficients presented in this table represent the β for calendar year from the Poisson models.

^(b) Other psychiatric diagnoses include ICD-9 Codes 290.xx – 294.xx, 296.9, 297.xx – 299.xx, 300.0x – 300.3x, 300.5x – 300.9x, and 301.xx – 319.x.