Antiepileptic drug use by pregnant women enrolled in Florida Medicaid

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ABSTRACT

Objective: The study aims were to investigate secular trends in antiepileptic drug (AED) use in women during pregnancy, and to compare the use of first- and second-generation AEDs.

Methods: Study participants consisted of female Florida Medicaid beneficiaries, older than 15 years, and pregnant within the time period 1999 to 2009. Fifteen AEDs were categorized into first and second generation of AEDs. Continuous use of AEDs was defined as at least 2 consecutive AED prescriptions totaling more than a 30-day supply. Polytherapy was defined as 2 or more AEDs continuously used for at least 30 overlapping days. Annual prevalence was estimated and compared.

Results: We included 2,099 pregnant women who were enrolled in Florida Medicaid from 1999 to 2009 and exposed to AEDs during pregnancy. Although there were fluctuations, overall AED use in the study cohort did not increase from 2000 to 2009 ($\beta \pm$ standard error [SE]: -0.07 ± 0.06 , $p = 0.31$). The use of first-generation AEDs decreased ($\beta \pm$ SE: -6.21 ± 0.47 , $p < 0.0001$), whereas the use of second-generation AEDs increased ($\beta \pm$ SE: 6.27 ± 0.52 , $p < 0.0001$) from 2000 to 2009. AED use in polytherapy did not change through the study period. Valproate use reduced from 23% to 8% in the study population ($\beta \pm$ SE: -1.61 ± 0.36 , $p = 0.0019$), but this decrease was only for women receiving an AED for epilepsy and was not present for other indications.

Conclusion: The second-generation AEDs are replacing first-generation AEDs in both monotherapy and polytherapy. Valproate use has declined for epilepsy but not other indications. Additional changes in AED use are expected in future years. *Neurology*® 2015;84:944-950

GLOSSARY

AED = antiepileptic drug; **FDA** = Food and Drug Administration; **ICD-9-CM** = International Classification of Diseases, Ninth Revision, Clinical Modification; **MA** = minor abnormality; **MCM** = major congenital malformation; **NDC** = National Drug Code.

Previous studies reported a 2- to 3-fold increase in the malformations among offspring with in utero exposure to antiepileptic drugs (AEDs).¹⁻³ The risks have been reported as 3.1% to 9.0% for major congenital malformations (MCMs), 37% for one minor abnormality (MA), and 11% for 2 MAs in offspring with in utero exposure to AEDs.^{2,4} Several studies found that AED polytherapy poses a higher risk of malformation (8.6%) than that of AED monotherapy (4.5%).⁴⁻⁶

The risk of MCMs increases to 4% to 9% after in utero exposure to the first-generation AEDs.^{5,7} The percentage of MCMs was reported as 6.5% for phenobarbital,⁸ 3.7% for phenytoin,⁹ and 2.2% for carbamazepine.¹⁰ Valproate has shown a greater risk (6.2%–20.3%) of MCM,^{9,11-13} which is 7.3-fold higher than that of nonexposed, and 4-fold higher than in those exposed to other AEDs.¹² It has been noted that in utero exposure to valproate was associated with elevated risk of impaired cognitive function for children at 3 years of age,¹⁴ and reduced cognitive abilities in multiple domains for children at 6 years old.¹⁵ These cognitive deficits can occur without MCMs or MAs. For the second-generation AEDs, the risks of MCMs have been reported as 2.0% to 3.7% for lamotrigine,¹⁶⁻¹⁸ 0.7% to 2.4% for levetiracetam,^{18,19} 2.8% for oxcarbazepine,²⁰ and 4.2% to 4.8% for topiramate.^{18,20}

Supplemental data
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Despite the aforementioned concerns of MCMs in AED use, current literature lacks comprehensive, population-based information on AED use trends over time in pregnant women. The aim of this study was to examine the pattern of AED use in pregnant women enrolled in Florida Medicaid.

METHODS Data sources. This study is based on 2 statewide, retrospective, 10-year data sources: Florida Medicaid claims and Florida Birth Vital Statistics from January 1, 1999, to December 31, 2009. Two datasets were linked using the mother's social security number and the child's date of birth.

Florida Birth Vital Statistics at Florida Department of Health collects and manages a statewide birth certificate dataset. Birth time, place, and date for infants, and demographic characteristics for infant, mother, and father are recorded on the birth certificates.

Florida Medicaid covers pregnant women up to 185% federal poverty level.²¹ Florida Medicaid claims, assembled by Florida's Agency for Health Care Administration, provide monthly details on Medicaid eligibility and medical and pharmacy claims for Florida Medicaid fee-for-service beneficiaries. Medical claims from inpatient hospital, outpatient clinics, or emergency rooms include diagnosis codes (*ICD-9-CM*), procedure codes (up to 31 Current Procedural Terminology codes), source of admission, physician type, discharge status, and total amount of charges. Pharmacy claims include National Drug Codes (NDCs) for all dispensed drugs reimbursed by Medicaid. In this study, maternal exposure to study drugs was determined using NDCs from pharmacy claim records, and mother's indications diagnosed during pregnancy were identified using diagnosis codes from medical claims. The operational definitions for all demographic and clinical characteristics are described in table e-1 on the *Neurology*[®] Web site at Neurology.org.

Standard protocol approvals, registrations, and patient consents. This study was approved by the institutional review board of the University of Florida and the Florida Department of Health.

Study population. This study included female Florida Medicaid enrollees who were older than 15 years, took AEDs during pregnancy, delivered a live infant between April 1, 2000, and December 31, 2009, and were enrolled in the Medicaid program as identified by pregnancy status. The study cohort of maternal-baby pairs was generated by linking the Florida Medicaid claims and Florida Birth Vital Statistics.

Exclusion criteria for maternal-infant pairs included mothers with dual eligibility for Medicare, HMO (health maintenance organization), or other private insurance.

Study design. This was a retrospective cohort study. The study index date was the infant's birth date. The AED exposure window was defined as the 9-month pregnancy period after the first day of the last menstrual date. The study period covered January 1, 2000, to December 31, 2009.

Assessment of AED exposure. In this study, exposure to AEDs was determined from Medicaid pharmacy claims using NDCs. AEDs were classified as a group of drugs, including the first-generation AEDs: carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone, and valproate; and the second-generation AEDs: felbamate, gabapentin, lamotrigine,

levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, and zonisamide. Pharmacy claims in Medicaid data have been approved as an accurate source for the assessment of drug exposure.²² The rates of concordance with patient self-reported medication use was high in previous studies.^{22,23}

Information of drug use from Medicaid pharmacy claims included NDC for filled prescription drugs and the number of days for which the drug was supplied.²⁴ As previously mentioned, the birth anomalies are related to dose and time of exposure during pregnancy, MCM associates with teratogen exposure in the first trimester, and MA and low birth weight relate to maternal drug exposure in the third trimester.²⁵ Maternal drug exposure during the entire pregnancy period can affect the combined outcome. The exposure window was thus established as the period of 14 days before the first day of the mother's last menstrual period to the infant's birth date. The drug exposure was defined as any one dose of study drug dispensed during the exposure window, including drugs dispensed before the exposure window with days of supply covering at least 1 day of the exposure window. Adding 14 days before the pregnancy is to account for the conception period and the residual effects of AEDs. Sensitivity study was conducted to examine the effects of different drug exposure windows on the combined outcome.

The mother's last menstrual period was obtained using a multistep algorithm derived from linkages to the healthy start prenatal screen, which contains more accurate information because it is collected during the first trimester of the pregnancy.²⁶ When healthy start information was not available, the last menstrual period date on the birth certificate was used. If these 2 dates were not available (about 13% of last menstrual period date is missing on birth certificates), this information was imputed from clinical estimate.^{27–29} A previous study suggested that the last menstrual period from birth certificates and clinical estimates agreed within less than 2 weeks.³⁰

Continuous use of AEDs was defined as at least 2 consecutive prescriptions for AEDs or totaling more than a 30-day supply. Polytherapy was defined as one or more other AEDs continuously used for at least 30 overlapping days. Annual prevalence was estimated and compared across different drug combinations, including the first- and second-generation AEDs.

Assessment of characteristics of study participants. Demographic characteristics were identified from birth certificates,³¹ whereas comorbidities or comedications during pregnancy were identified using *ICD-9-CM* or NDCs from Medicaid medical claims.³² The operational definitions for all covariates adjusted in data analysis are described in table e-1. The secular trend of AED use was assessed in the overall study cohort, as well as the specific subgroups, such as patients with epilepsy and patients with psychiatric disorder only, defined as bipolar, anxiety, depression, or mental disorder.

Statistical analysis. SAS 9.3 (SAS Institute, Cary, NC) was used for data analyses and modeling, and SigmaPlot 11.0 (Systat Software Inc., San Jose, CA) or Microsoft PowerPoint 2010 14.0 (Microsoft Corp., Redmond, WA) was used for graphs. The secular trend was analyzed using Joinpoint Regression Program version 3.4.3 (National Cancer Institute, Silver Spring, MD).

Descriptive statistics were used to describe the secular trend of AED use from January 2000, the start of the drug exposure period, and the end of the drug exposure period in December 2009. The univariate linear regression slope β and corresponding standard error (SE) were estimated and tested under $H_0: \beta = 0$. Significance level for all tests was set at $p < 0.05$.

Table 1 Demographic and clinical characteristics of study participants

Characteristics	AED users (n = 2,099)
Maternal age at infant birth, y	26.2 ± 5.9
Paternal age at infant birth, y	29.9 ± 8.0
Mother's race	
White	1,150 (55)
Black	358 (17)
Other	588 (28)
Father's race	
White	727 (35)
Black	253 (12)
Other	538 (26)
Mother's education level	
Above high school	738 (35)
Father's education level	
Above high school	493 (23)
Mother's previous adverse pregnancy experience	17 (1)
Mother received prenatal care	1,430 (68)
Mother's total no. of prenatal visits	11.7 ± 17.8
Mother's marital status, yes	734 (35)
Mother's parity	1.3 ± 8.6
Mother's previous gestational diabetes	64 (3)
Mother's previous gestational hypertension	95 (5)
Mother's previous eclampsia	8 (0.4)
Mother's previous preterm	32 (1.5)
Mother's previous cesarean delivery	209 (10)
Epilepsy diagnosis prior or during pregnancy	883 (42)
Anxiety diagnosis prior or during pregnancy	331 (16)
Neural pain diagnosis prior or during pregnancy	73 (3.5)
Bipolar diagnosis prior or during pregnancy	558 (27)
Depression diagnosis prior or during pregnancy	570 (27)
Migraine diagnosis prior or during pregnancy	221 (11)
Mental disorder diagnosis prior or during pregnancy	1,087 (52)
Antipsychotic exposure during pregnancy	252 (12)
Antidepressant exposure during pregnancy	480 (23)
Folic acid use prior or during pregnancy	1,610 (77)
Anxiolytic (including sedatives and hypnotics) exposure during pregnancy	643 (31)
Antihypertensive exposure during pregnancy	13 (0.6)
Hormone use during pregnancy	127 (6)
ACE inhibitor exposure during pregnancy	12 (0.57)
Antineoplastic exposure during pregnancy	10 (0.5)
Antibiotic exposure during pregnancy	924 (44)
Glucocorticoid exposure during pregnancy	77 (4)
NSAID exposure during pregnancy	107 (5)
Antiviral exposure during pregnancy	38 (1.8)

Abbreviations: ACE = angiotensin-converting enzyme; AED = antiepileptic drug; NSAID = nonsteroidal anti-inflammatory drug.

Data are mean ± SD or n (%). Obtained from Florida Birth Vital Statistics and Medicaid claims data.

RESULTS A total of 753,377 pregnant women were identified in the Florida Medicaid program between 2000 and 2009. The final study cohort included 2,099 women exposed to AEDs during pregnancy (table 1).

The percentage of mothers with any AED use during pregnancy over all pregnant women enrolled in Florida Medicaid was calculated for each study year. The secular trends of AED use in the study population from 2000 to 2009 were analyzed and plotted in figure 1. Of the total 753,377 mothers in the Florida Medicaid program, AED exposure in mothers during pregnancy ranged from 1.4 to 3.5 per 1,000 women from the year 2000 to 2009. Despite the observed small fluctuations, AED use in pregnant women enrolled in Florida Medicaid was stabilized from 2000 to 2009 ($\beta \pm \text{SE}$: -0.07 ± 0.06 , $p = 0.31$).

AED exposure was further categorized into 2 groups: first- and second-generation AEDs. As shown in figure 2, the number of pregnant women exposed to first-generation AEDs decreased significantly from 2000 to 2009 ($\beta \pm \text{SE}$: -6.11 ± 0.47 , $p < 0.0001$), and the overall exposure to second-generation AEDs increased ($\beta \pm \text{SE}$: 6.27 ± 0.52 , $p < 0.0001$).

Figure 3, A and B, delineates the secular trends for the most frequently used AEDs in the study population. The dispensing rates of 4 of the most frequently used first-generation AEDs significantly decreased from 2000 to 2009. The use of valproate decreased more slowly than phenytoin ($\beta \pm \text{SE}$: -1.61 ± 0.36 vs -2.97 ± 0.29), but faster than carbamazepine ($\beta \pm \text{SE}$: -1.61 ± 0.36 vs -1.17 ± 0.34) and phenobarbital ($\beta \pm \text{SE}$: -1.61 ± 0.36 vs -1.13 ± 0.24) (figure 3A). As shown in figure 3B, lamotrigine (2.6% in 2000, 30% in 2008, $\beta \pm \text{SE}$: 3.48 ± 0.51 , $p = 0.0001$) and levetiracetam (0% in 2001, 21.7% in 2009, $\beta \pm \text{SE}$: 2.48 ± 0.28 , $p < 0.0001$) are 2 frequently used second-generation AEDs that rapidly increased during the study period. Another frequently used second-generation AED, topiramate, did not significantly change in rate of use through the study period (4.3% in 2000 to 9.4% in 2009; $\beta \pm \text{SE}$: 0.31 ± 0.97 , $p = 0.36$).

Of a total of 2,099 pregnant women exposed to AEDs, more than half were exposed to 2 or more AEDs during pregnancy. The secular trends for AED use in polytherapy or monotherapy did not significantly vary over time (polytherapy was 62% in 2000 and 63% in 2009, $\beta \pm \text{SE}$: 0.35 ± 0.90 , $p = 0.71$). In subgroup analysis, we found that overall AED use did not significantly change either in the patients with epilepsy ($\beta \pm \text{SE}$: 0.28 ± 0.87 , $p = 0.75$) or the patients with psychiatric disorders only ($\beta \pm \text{SE}$: 0.95 ± 0.71 , $p = 0.22$).

Given that valproate has been shown to produce the highest risks of malformations and neurodevelopment,

Figure 1 Percentage of AED use in pregnant women in Florida Medicaid

$\beta = 0.07$, $SE = 0.06$, $p = 0.31$. AED = antiepileptic drug.

specific analyses by indication were conducted. In figure 4, we present the rates of valproate use in the overall study cohort, patients with epilepsy, and patients with psychiatric disorders only. There were significant reductions of valproate use in the overall study cohort ($\beta = -1.61$, $SE = 0.36$, $p = 0.002$) and patients with epilepsy ($\beta = -3.65$, $SE = 0.95$, $p = 0.005$). However, valproate use was not reduced in

patients with psychiatric disorders only ($\beta = 0.67$, $SE = 1.66$, $p = 0.70$).

We further investigated folate use in the study population. Folate use was identified using the NDC for vitamin or active ingredient of folic acid. Of a total of 2,099 pregnant women exposed to AEDs during pregnancy, we identified 1,610 women (77%) who had taken folate before or during pregnancy. There was no significant change in folate use from 2000 to 2009 ($\beta = 0.08$, $SE = 0.39$, $p = 0.83$).

DISCUSSION We investigated the trends of AED use in a cohort of pregnant women in the Florida Medicaid program. Specifically, we examined the secular trends of AED exposure during pregnancy overall as well as in polytherapy and monotherapy.

The results noted in table 1 delineate a profile of the study population. Epilepsy, anxiety, bipolar, depression, migraine, and other mental disorders are common indications for the women exposed to AEDs during pregnancy. In addition, mothers exposed to AEDs during pregnancy were more likely to be unmarried (65% vs 48%) and fewer were of black race (17% vs 23%) compared to the general population of pregnant women with a live birth listed in Florida Medicaid.³³ Figure 1 shows the prevalence of AED use in pregnant women enrolled in Florida Medicaid from 2000 to 2009. AED use was not significantly changed from 2000 to 2009 in the overall study cohort, patients with epilepsy, or patients with psychiatric disorders only. Approximately 0.14% to 0.35% of pregnant women in our study were exposed to AEDs during this time period, which may be slightly lower than what was documented in the general population, 0.2% to 0.5%.^{21,34} Of all prescribed AEDs, the use of polytherapy had no significant reduction from 2000 to 2009 in our study. The percentage of pregnant women with epilepsy receiving polytherapy in our cohort is higher than that of other cohorts.³⁵ A previous study regarding prescribing patterns of AEDs in the United States from 2001 to 2007 concluded that increased AED use in pregnant women was driven by a 5-fold increase in the use of second-generation AEDs.³⁶ Although overall AED use did not increase significantly in our cohort, we did see an increase in use of second-generation AEDs and a reduction of first-generation AEDs during pregnancy.

In our study cohort, carbamazepine, phenytoin, and valproate were the 3 most frequently used AEDs in pregnant women from 2002 to 2004. In 2005, lamotrigine replaced carbamazepine as the most frequently used AED. In 2007, levetiracetam surpassed valproate and became the most frequently used AED next to lamotrigine. Thus, our results showed that the top 2 most frequently used AEDs after 2007 were

Figure 2 Percentage of first- and second-generation AED use from 2000 to 2009

$\beta = -6.21$, $SE = 0.47$, $p < 0.0001$ for first-generation AED use; $\beta = 6.27$, $SE = 0.52$, $p < 0.0001$ for second-generation AED use. AED = antiepileptic drug.

Figure 3 Percentage of most frequently used first- and second-generation AEDs

(A) First-generation AEDs from 2000 to 2009: $\beta = -1.17$, $SE = 0.34$, $p = 0.009$ for carbamazepine use; $\beta = -2.97$, $SE = 0.29$, $p < 0.0001$ for phenytoin use; $\beta = -1.61$, $SE = 0.36$, $p = 0.0019$ for valproate use; and $\beta = -1.13$, $SE = 0.24$, $p = 0.0015$ for phenobarbital use. (B) Second-generation AEDs from 2000 to 2009: $\beta = 3.48$, $SE = 0.51$, $p = 0.0001$ for lamotrigine use; $\beta = 2.48$, $SE = 0.28$, $p < 0.0001$ for levetiracetam use; and $\beta = 0.31$, $SE = 0.97$, $p = 0.36$ for topiramate use. AED = antiepileptic drug.

lamotrigine and levetiracetam, which is similar to the results previously reported from a survey of epilepsy centers.³⁷

It is noted in this study that valproate use decreased significantly from 2000 to 2009 in pregnant women across all treatments. The patterns are coincident with previous studies for AED exposure in women with epilepsy of childbearing age in Florida Medicaid and the North American Epilepsy Registry.^{37,38} Given that several studies during the time period of our study have reported an association of fetal valproate exposure with an increased risk of MCMs and with impairment in children's cognitive function, it is not surprising that valproate use has declined in pregnant women who use AEDs during pregnancy.^{12,39} However, when analyzed by indications, valproate use decreased for epilepsy indications,

but not for nonepilepsy indications, such as bipolar disorder, depression, anxiety, and mental disorders. It seems that neurologists treating epilepsy are more aware or responsive to valproate's teratogenic risks than those treating nonepilepsy indications, which are primarily psychiatric.

Our study population is limited to pregnant women enrolled in the Medicaid program, which comprises persons of lower socioeconomic status than that of the general population or among private insurance holders. Our study spans 10 years, from 2000 to 2009, with more information about secular trends of AED prescribing in pregnant women. Analyses of the secular trends were conducted to disclose the details about the change of AED prescribing patterns over time in pregnant women. The overall insignificant change of AED use appears to be attributable to the rapid increase in use of newer generation AEDs compensating for the reduction of first-generation AEDs. New scientific findings or Food and Drug Administration (FDA) black box warnings on the safety issues of AEDs influence the prescribing patterns of AEDs as well. Given that the FDA issued a black box warning for topiramate related to congenital malformations,⁴⁰ and that new data continue to be collected, we expect to see changes in AED use in pregnant women in future years.

Several limitations should be considered as a consequence of using linked claim data and the nature of the study design. First, this study is based on 2 linked data sources. Unmatched data because of poor quality or missing identifiers were not analyzed. The study population is limited to matched mother-infant pairs with mothers enrolled in the Florida Medicaid program. Therefore, sample size and power are restricted because of relatively rare outcomes and exposures.

Second, Medicaid claim data were used for reimbursement of health care providers. Pharmacy claims only show dispensed prescriptions, thus actual drug use in patients might differ because of drug incompletion and over-the-counter drug use.

Third, AED exposure was defined as any AED use during the overall pregnancy period. Given that a large number of women enrolled in the Medicaid program after they were pregnant, the AED exposure window and length cannot be identified.

Fourth, although birth certificates and medical claims are key data sources for medical epidemiologic research, there are limitations in their validity and reliability.^{31,32}

Our study identified the trends for AED use during pregnancy from 2000 to 2009. Use of second-generation AEDs has increased in pregnant women, while use of first-generation AEDs has declined. Use of the AED with the highest teratogenic risk, valproate, has declined in patients with epilepsy but not

Figure 4 Percentage of valproate use in overall study cohort or patients with different indications

$\beta = -1.61$, $SE = 0.36$, $p = 0.002$ for VPA use in overall study cohort; $\beta = -3.65$, $SE = 0.95$, $p = 0.005$ for VPA use in patients with epilepsy; $\beta = 0.67$, $SE = 1.66$, $p = 0.70$ for VPA use in patients with psychiatric disorders only. AED = antiepileptic drug; VPA = valproate.

in patients using it for other indications. Additional changes in AED use are expected in future years as more information is obtained on relative risks.

AUTHOR CONTRIBUTIONS

Dr. Xuerong Wen: drafting/revising the manuscript for content, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis. Dr. Kimford Meador: drafting/revising the manuscript for content, study concept or design, interpretation of data, obtaining funding. Dr. Abraham Hartzema: drafting/revising the manuscript for content, study concept or design, and interpretation of data.

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DISCLOSURE

X. Wen reports no disclosures relevant to the manuscript. K. Meador serves on the editorial boards of *Neurology*[®], *Behavior & Neurology*, *Epilepsy & Behavior*, *Epilepsy.com*, and the *Journal of Clinical Neurophysiology* and on the professional advisory board for the Epilepsy Foundation; he has received travel support from Sanofi-Aventis, and received research support from GlaxoSmithKline, Eisai Inc., Marinus Pharmaceuticals, Inc., Myriad Genetics, Inc., NeuroPace, Inc., Pfizer, SAM Technology Inc., UCB Pharma, the NIH National Institute of Neurological Disorders and Stroke (2R01-NS38455 [PI], 2U01-NS038455 [multi-PI], 1 R01 NS076665 [consultant]), the PCORI (PCORI 527 [co-PI]), and the Epilepsy Foundation. Dr. Meador has consulted for the Epilepsy Study Consortium, which receives money from multiple pharmaceutical companies (in relation to his work for Eisai, NeuroPace, Novartis, Supernus, Upsher-Smith Laboratories, UCB Pharma, and Vivus Pharmaceuticals). The funds for consulting for the Epilepsy Study Consortium were paid to his university. A. Hartzema has a consultant appointment with Pfizer not related to this study. He also has a senior advisor appointment to the FDA CDRH, and declares that the views expressed here are his personal views and not those of the FDA. Go to Neurology.org for full disclosures.

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Comment: Are we filling knowledge gaps about antiepileptic drugs and pregnancy?

Antiepileptic drugs (AEDs) can be associated with congenital malformations and suboptimal neurodevelopmental outcomes. Avoidance of valproic acid (VPA) is recommended (when possible) for women with epilepsy of childbearing potential based on accumulating evidence over the past decades.¹ The uptake of evidence in practice is usually poor and does not typically occur with traditional dissemination methods.²

Wen et al.³ performed an important study examining secular trends in the use of first- and second-generation AEDs in a vulnerable population, i.e., pregnant Florida women on Medicaid, between 1999 and 2009. Using linked administrative data, the authors report a decrease in the use of first-generation and an increase in the use of second-generation AEDs over time. VPA use decreased from 23% to 8% in women with epilepsy. The proportion of women on folic acid (77%) or on AED polytherapy (60%) did not change over time.

Although the findings are noteworthy, some study limitations must be considered. Most notably, only live births with successful mother–infant matching were included, the extent (dose, duration) of AED or folic exposure is unknown, and administrative health data are not 100% accurate.

Nevertheless, the findings of this study are an important contribution to the literature. The decrease in VPA use over time with an increase in the use of second-generation AEDs (most notably lamotrigine and levetiracetam) are concordant with best practice. Although purely speculative, we have to assume that successful knowledge dissemination is occurring in regards to the appropriate use of AEDs in epilepsy-related pregnancy, at least in this population. It is concerning that the use of VPA in pregnant women with psychiatric conditions (without epilepsy) is not decreasing. Could it be that neurology and epilepsy societies and organizations are more effective at disseminating knowledge about epilepsy care, resulting in higher uptake in practice?

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