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Trends in the use of antiepileptic drugs (AEDs) among pregnant women in the U.S., 2001-2007: a Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP) study

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Abstract

Background—Little is known about the extent of antiepileptic drug (AED) use in pregnancy, particularly for newer agents. Our objective was to assess whether AED use has increased among pregnant women in the U.S., 2001-2007.

Methods—We analyzed data from the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP) database, 1 January 2001 to 31 December 2007. We identified live-born

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deliveries among women, aged 15-45 years on delivery date, who were members of MEPREP health plans (N = 585,615 deliveries). Pregnancy exposure to AEDs, determined through outpatient pharmacy dispensing files. Older AEDs were available for clinical use before 1993; other agents were considered newer AEDs. Information on sociodemographic and medical/reproductive factors was obtained from linked birth certificate files. Maternal diagnoses were identified based on ICD-9 codes.

Results—Prevalence of AED use during pregnancy increased between 2001 (15.7 per 1,000 deliveries) and 2007 (21.9 per 1,000 deliveries), driven primarily by a five-fold increase in the use of newer AEDs. Thirteen percent of AED-exposed deliveries involved a combination of two or more AEDs. Psychiatric disorders were the most prevalent diagnoses, followed by epileptic and pain disorders, among AED users regardless of AED type, year of conception or gestational period.

Conclusions—AED use during pregnancy increased between 2001 and 2007, driven by a five-fold increase in the use of newer AEDs. Nearly one in eight AED-exposed deliveries involved the concomitant use of more than one AED. Additional investigations of the reproductive safety of newer AEDs may be needed.

Keywords

pregnancy; anticonvulsant; antiepileptic drugs; drug utilization; prescription practices

Introduction

With the development of newer antiepileptic drugs (AEDs) and the expansion of therapeutic indications for many of these agents,¹ there has been increasing use of AEDs on a population basis, including among women of childbearing potential. However, little is known about the extent of AED use in pregnancy, particularly for newer agents. Due to the severity of the underlying conditions for which AEDs are often prescribed, many mothers may elect to receive ongoing drug treatment during pregnancy. Other mothers may be inadvertently exposed to these medications due to unplanned pregnancies.

Studies of AED prescribing in pregnant women outside of the U.S.^{2, 3} have documented reduced prescribing of valproate and other older AEDs between 1999 and 2007, with concurrent increases in the prescribing of the newer AED, lamotrigine. This likely reflects clinician concerns about the risk of major congenital malformations associated with valproate, although the reproductive risks with other AEDs are far less certain. These pregnancy registry-based studies, however, focused on women with epilepsy and considered only a small number of individual AEDs. There are limited population-based data describing the use of AEDs in pregnant women in the U.S.

Prevalence estimates of AED use in pregnancy are still needed, particularly for more recently approved drugs. While available data suggest the lamotrigine may have a favorable reproductive safety profile,⁴⁻⁸ other newer AEDs may also be perceived as safer than older AEDs in pregnancy in spite of very limited reproductive safety data.^{9, 10} This may result in increases in AED prescribing for non-epileptic disorders, and in the use of AED combination therapy, an important consideration given recent evidence of greater congenital malformation risk with valproate-containing combination therapy relative to monotherapy.¹¹ Our objective was to assess whether AED use has increased among pregnant women in the U.S. between 2001 and 2007 within a cohort of 585,615 deliveries drawn from eleven commercial and Medicaid health plans with considerable geographic and sociodemographic diversity.

Methods

Data source

The study used data from the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP).¹² MEPREP is a collaborative effort between the U.S. Food & Drug Administration (FDA) and researchers from Vanderbilt University, the HMO Research Network, and Kaiser Permanente Northern and Southern California that uses administrative health plan data linked to other clinical data sources to enable the study of medication use and outcomes in pregnancy.¹² Encompassed within these three contract sites are 11 health plan-affiliated research institutions (see Acknowledgements) that provide access to health plan data of approximately 12 million current enrollees within nine states, covering geographically and demographically diverse populations using a wide array of medical care delivery models.

To support multi-site studies of medication use during pregnancy, the research institutions have extracted information on maternal and infant enrollment, demographics, outpatient pharmacy dispensings, and outpatient and inpatient health care encounters from their administrative, claims, and clinical data systems. Health plan data have been linked with birth certificate data obtained from the state departments of public health, which includes information on sociodemographic, medical and reproductive factors, such as gestational age, race/ethnicity, and parity.

Linkages between these data sources permit the identification of pregnant women who delivered a live born infant, their medication exposures, clinical diagnoses, gestational periods, and additional clinical and demographic information. All data have been transformed into de-identified, standardized data sets for each of the participating sites.

Study cohort

The source population for this study included 585,615 live-born deliveries that occurred between 01 January 2001 and 31 December 2007. Eligible women were between 15-45 years of age on the date of delivery, and were members of their respective health plans, with pharmacy benefits, from 180 days before pregnancy through their date of delivery. Brief administrative gaps of 45 days or less in enrollment or pharmacy benefits were allowed.

Measures

Gestational periods for 94.5% of deliveries were defined using the last menstrual period (LMP) or gestational age information recorded in the birth certificates. We developed a multi-stage algorithm to identify the trimesters of pregnancy. When LMP data was available in the birth certificate file, we used the first day of the LMP as the first day of the first trimester ("day zero"). We defined the first trimester as days 0-90, the second trimester as days 91-180, and the third trimester as day 181 through delivery. If the LMP was missing or had an improbable value, day zero was defined as the date of delivery minus the gestational age based on clinical or obstetric estimates. The pre-pregnancy period was defined as the day before the LMP date and the 60 days prior to the LMP. The method of assigning day zero in birth certificates was consistent with the approach used by the National Center for Health Statistics of the Centers for Disease Control and Prevention.¹³ The birth certificate LMP has been validated previously by one of the participating health plans.¹⁴

When gestational age information was missing from the birth certificates, we estimated the trimesters using the delivery date and specific International Classification, 9th Revision, Clinical Modification (ICD-9-CM) codes recorded in the health plan claims data. The algorithm assumed day zero as the date of delivery minus 270 days if there was no ICD-9-

CM code for preterm birth; as the date of delivery minus 245 days if there was a code for preterm birth of unspecified gestational age; and as the date of delivery minus the upper limit of the gestational age range if there was a code for preterm birth with a specified range, e.g., the date of delivery minus 224 days for deliveries with an ICD-9-CM code 765.26 ("31 to 32 weeks of gestation"). These approaches have also been previously validated.^{15, 16}

Annual cohorts that met study inclusion criteria were identified for the study period based on their date of delivery. Prevalence of AED use was calculated for each calendar year, and for each gestational period. The 60-day pre-pregnancy period was used to estimate the prevalence of AED use before pregnancy.

The primary outcome was maternal AED use (Table 1), determined from MEPREP pharmacy files. Pharmacy data files included the medication name, prescription fill date, and the quantity and number of days supply. The days of supply dispensed and quantity dispensed were used to estimate the days of exposure represented by a prescription. If a prescription for a study medication contained 10 tablets but was said to represent 30 days of use, we allocated 30 days of exposure to account for pill splitting or sporadic use. If the days supply from a prescription dispensed during a given trimester carried over into the subsequent trimester, this was considered to be exposure during both trimesters. AEDs approved for clinical use in the U.S. before 1993 were classified as older AEDs. The rest were classified as newer AEDs (Table 1).¹⁷ AEDs were classified according to individual drug for the most commonly used agents. Concomitant AED use was also ascertained. Long-acting benzodiazepines were included as study drugs based on their occasional use as second-line or adjunctive options for long-term management of some chronic or refractory epilepsies,¹⁸⁻²⁰ and the likelihood of substantial use by pregnant women for other therapeutic indications.²¹⁻²³ Only generic designations for study medications were used.

Maternal diagnoses were identified in electronic records of medical care encounters using ICD-9 codes (Table e-1) associated with any claim beginning 180 days prior to the beginning of pregnancy and ending on the delivery date. The following diagnosis groups were identified: any epilepsy, any psychiatric disorder, any pain disorder, any neuromuscular disorder, and any sleep disorder. The pain disorder category included neuropathic pain, specific headache syndromes, and other forms of chronic pain (including fibromyalgia syndrome).

Ethics approval

Approval for this study was granted by the Institutional Review Boards at each participating site, the U.S. FDA Research in Human Subjects Committee, and the state departments of health, where applicable.

Statistical methods

Prevalence was defined as the number of deliveries for which AEDs were used per 1,000 qualifying deliveries in a given category. Prevalence rates were calculated for use of any older or newer AED during the period 60 days before LMP through delivery using all cohort deliveries as the denominator. Descriptive statistics were used to describe the overall prevalence of AED use, and AED use prevalence according to birth year, therapeutic diagnosis, and gestational period. The frequency of AED exposure by maternal diagnosis (a proxy for therapeutic indication), individual drug, year of conception, and gestational period (identified using the definitions provided earlier) was calculated using only AED-exposed deliveries as the denominator. Maternal and infant characteristics of deliveries from both AED-exposed and unexposed were summarized using descriptive statistics.

Results

There were 585,615 qualifying deliveries in the study cohort (Table 2). The majority of cohort members were between the ages of 18-39 years. Approximately 2% ($n = 11,611$) of 585,615 qualifying deliveries included at least one prescription for an AED during pregnancy (from 60 days prior to the LMP through the date of delivery) and were considered AED users. Of the 11,611 AED users, 9,001 (77.5%) were exposed to older AEDs and 3,515 (30.3%) were exposed to newer AEDs. The prevalence of AED use increased between 2001 (15.7 per 1,000 deliveries) and 2007 (21.9 per 1,000 deliveries) (Figure 1), driven by a five-fold increase in the use of newer AEDs; the use of older AEDs remained relatively unchanged. The proportion of newer AED-exposed deliveries rose steadily between 2001 and 2003, followed by a sharper increase in prescribing prevalence between 2003 and 2005. The prevalence of newer AED use among AED-exposed deliveries between 2005 and 2007 was four times the prescribing prevalence of newer AEDs observed in 2001.

The majority of AED users were Caucasian and had a high school or lower level education, while most AED non-users had a level of education above high school graduate (Table 2). Most qualifying deliveries were singleton, full-term, vaginal deliveries of normal birth weight infants. AED users had a higher proportion of moderate pre-term deliveries (32-36 weeks gestation, 13.1% vs. 8.8%) and low birth weight infants (1,500-2,499 g, 10.0% vs. 5.6%) than non-users, while the proportions of post-term deliveries, very- or extremely pre-term deliveries, and very low birth weight infants were comparable in AED users and non-users.

A diagnosis representing a potential treatment indication was identified for approximately 80% of AED-exposed deliveries, the most prevalent of which were psychiatric, pain and epileptic disorders (Table 3). Between 2000-2007, the frequency of AED use temporally associated with specific conditions among all deliveries increased from 0.8 to 1.2% for psychiatric diagnoses and from 0.3 to 0.7% for pain disorders, but remained relatively unchanged for other diagnosis groups (Table 4). Psychiatric disorders were the most common diagnoses, followed by epilepsy and pain disorders, regardless of AED type (older vs. newer), year of conception (Table 4), or gestational period (Table 5). Of the deliveries in which AEDs were used in all three trimesters, the most prevalent diagnoses were epileptic and psychiatric disorders (Table 5).

The most commonly used drugs were older AEDs, particularly benzodiazepines, valproic acid derivatives, carbamazepine and phenytoin (Table e-2). The overall prescribing prevalence of these drugs (any time during pregnancy excluding the pre-pregnancy period) was 0.9%, 0.2%, 0.15% and 0.1%, respectively, for all 585,615 deliveries in the cohort. Over half of older AED-exposed deliveries involved benzodiazepines (Table e-3). The most commonly used newer AEDs were gabapentin, lamotrigine, topiramate, oxcarbazepine, and levetiracetam. Approximately 13% of AED-exposed deliveries (excluding the pre-pregnancy period) involved use of AED combinations, which consisted primarily of concomitant use of older and newer drugs (Table e-2).

AED use during all three trimesters occurred in approximately one-fourth (2,586/10,135) of deliveries with any AED exposure during pregnancy, excluding the pre-pregnancy period (Table e-2). A smaller proportion of such deliveries were accounted for by AED exposure in only the first- (16.1% [1,631/10,135]), second- (2.9% [296/10,135]) or third trimesters (5.6% [563/10,135]). Only 14.6% (1,476/10,135) of deliveries with any AED exposure during pregnancy involved exposure only during the pre-pregnancy period.

Discussion

To our knowledge, this is the first report of AED prescribing patterns in a large and sociodemographically diverse cohort of pregnant women in the U.S. AED use during pregnancy increased between 2001 and 2007. This trend was driven by a 4-fold increase in newer AED use in pregnancy. By contrast, the prevalence of older AED use remained relatively unchanged. Psychiatric diagnoses were the most prevalent diagnoses among women prescribed AEDs, followed by pain disorders and epilepsy. There was increasing use of AEDs in pregnant women with diagnoses for psychiatric and pain disorders during the study period, with no such increases for other diagnosis groups including epilepsy.

Available data on ante-partum AED use come from pregnancy registries maintained outside of the U.S. A recent European and International Registry of Antiepileptic Drugs in Pregnancy (EURAP) report documented increases in newer AED use between 1999 and 2005, although older AEDs were the most commonly prescribed drugs.² The proportion of lamotrigine users increased sharply from ~10% prior to 2001 to ~30% after 2003. In the Australian Register of Antiepileptic Drugs in Pregnancy, increased prescribing of newer AEDs occurred between 1999 and 2007,³ while the use of older AEDs decreased. Although we did not see decreases in the use of older AEDs among pregnant women, we observed similar increases in newer AED use. These trends may be partially explained by the availability of congenital malformation and neurodevelopmental risk data for valproate and some other older AEDs^{5, 24-26} and recent pregnancy registry data showing low congenital malformation risk with lamotrigine,^{5-7, 27} although reproductive risk data are extremely limited for other newer AEDs.²⁸

Variation in AED prescribing frequencies between our study and prior research may reflect differences in methodological approach. Results of the registry studies^{2,3} apply to women who enrolled voluntarily in each registry and were active AED users. AED prescribing prevalence for the broader population of pregnant women, including those with diagnoses other than epilepsy, cannot be easily extrapolated from registry studies. Results from registry studies are also difficult to compare with those of our cohort, which consisted of all deliveries among enrollees in the health plans that contributed data to MEPREP.

Prior studies focused on women with epilepsy, an important limitation given the broad range of indications for many AEDs.¹ For several non-epilepsy indications, AEDs are first-line therapeutic options. For others, AEDs are important adjuncts--or valuable alternatives--to standard treatment. Our study included therapeutic diagnoses for which AEDs are commonly prescribed. Approximately 80% of AED users in our cohort had one or more of these diagnoses. Consistent with data from non-pregnant populations,²⁹⁻³³ psychiatric disorders, epilepsy, and pain syndromes were the most prevalent diagnostic groups. When AEDs were used throughout pregnancy, the most prevalent diagnoses were epilepsy and psychiatric disorders, which may be based on mounting evidence that, for many patients with epilepsy or psychiatric diagnoses such as bipolar disorder, the risk of maternal-fetal harm may be increased if effective pharmacotherapy is discontinued during pregnancy.³⁴⁻³⁶

In the last decade, the use of AED combinations for difficult-to-treat epilepsy and bipolar disorders has increased substantially;^{37, 38} however, the prevalence of AED combination therapy during pregnancy is relatively unknown. The proportion of enrollees from the Australian pregnancy registry study that were prescribed AED combination therapy ranged from 21-34%.²⁵ In our study, approximately 13% of AED-exposed deliveries involved AED combination therapy during pregnancy. Higher prevalence of AED combination therapy in the registry study may be partially explained by differences in cohort membership (voluntary registrants vs. all qualifying deliveries from a defined population). Furthermore,

neurologists were the referral source for 60% of pregnancies in the Australian registry; thus, pregnant women with monotherapy-resistant epilepsy may have been over-represented. These findings are important given recent data suggesting an increased risk of congenital malformations with exposure to AED combinations *in utero*, although this may be restricted to combinations that include valproate.^{11, 39}

To our knowledge, this is the first large-scale, population-based prevalence study of AED use in pregnancy to be undertaken in the U.S., and the first to use linked administrative health plan databases as the data source. Our approach has several advantages. The data source for this study consists of multiple linked administrative health plan databases from all major regions in the U.S.,⁴⁰ thus ensuring a large cohort with substantial sociodemographic diversity. Robust data linkages allowed us to efficiently identify a very large number of deliveries that qualified for cohort inclusion and, for each of these deliveries, ascertain maternal and infant demographic and clinical data, determine gestational period dates, and identify maternal medical and mental health diagnoses without having to rely on subject recall.⁴⁰ Computerized pharmacy records, used to define AED exposure in our study, are not subject to information bias⁴¹ and have high concordance with patient self-report of medication use.⁴²

There are limitations to consider. First, complete data from all MEPREP sites was available only through the end of 2007. AEDs approved for use in the U.S. after 2006 could not be included. Second, AED exposure was determined from prescription records and cannot directly account for patient adherence. Third, diagnoses representing potential AED indications were based on administrative and claims data without secondary confirmation (such as a review of medical charts) that a specific AED was prescribed for the claims-based diagnosis. Fourth, we did not describe specific diagnoses for which individual AEDs may have been prescribed. This may be less-problematic for some drugs, such as phenytoin, for which therapeutic indications are largely limited to epilepsy; however, this does not apply to the majority of AEDs, which have a broader profile of major therapeutic indications. Finally, we did not classify AED combination therapies according to individual drugs.

In conclusion, there was growing use of newer AEDs during the study period, although use of older drugs was still substantial. A small but clinically significant proportion of deliveries were exposed to AED combinations. Psychiatric, epileptic, and pain disorders were the chief diagnoses recorded for these women. The data source used for this study will be crucial for tracking AED prescribing patterns and identifying key determinants of AED use in pregnant women, and for conducting future large-scale studies of adverse maternal-fetal outcomes related to AED use in pregnancy.

Table e-1. ICD-9 diagnosis and procedure codes used to determine clinical diagnos(es) for cohort members, MEPREP 2001-2007

Table e-2. Frequency of individual antiepileptic drug (AED) use and AED combination therapy during pregnancy, MEPREP 2001-2007^{a,b}

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Antiepileptic drug use by year of delivery^a

^aThere were a total of 585,615 deliveries during the study period (2001, N = 79,625; 2002, N = 83,665; 2003, N = 84,033; 2004, N = 83,013; 2005, N = 83,262; 2006, N = 85,721; 2007, N = 86,296). Proportions were calculated using the number of deliveries in each antiepileptic drug (AED) use category as the numerator and the total number of deliveries in a given delivery year as the denominator.

Table 1Study drugs (alphabetically arranged)^{a,b}

Drug name	Category ^c
Acetazolamide	Older antiepileptic drug
Carbamazepine	Older antiepileptic drug
Clonazepam	Older antiepileptic drug
Clorazepate	Older antiepileptic drug
Diazepam	Older antiepileptic drug
Divalproex sodium	Older antiepileptic drug
Ethosuximide	Older antiepileptic drug
Ethotoin	Older antiepileptic drug
Felbamate	Newer antiepileptic drug
Gabapentin	Newer antiepileptic drug
Lamotrigine	Newer antiepileptic drug
Levetiracetam	Newer antiepileptic drug
Mephenytoin	Older antiepileptic drug
Metharbital	Older antiepileptic drug
Methsuximide	Older antiepileptic drug
Oxcarbazepine	Newer antiepileptic drug
Phenobarbital	Older antiepileptic drug
Phenytoin	Older antiepileptic drug
Pregabalin	Newer antiepileptic drug
Primidone	Older antiepileptic drug
Tiagabine	Newer antiepileptic drug
Topiramate	Newer antiepileptic drug
Valproic acid	Older antiepileptic drug
Zonisamide	Newer antiepileptic drug

^a Study drugs include antiepileptic drugs that were commercially available during the years of observation 2001-2007 from MEPREP data files. Excluded from this list are fosphenytoin, lorazepam, paramethadione, phenacemide, phenisuximide, sodium valproate, and trimethadione.

^b Antiepileptic drugs that became commercially available after 2007 (eslicarbazepine, vigabatrin, lacosamide) were not included.

^c Drugs available for clinical use prior to 1993 are referred to as older antiepileptic drugs. The rest are referred to as newer antiepileptic drugs.

Table 2

Cohort demographic characteristics, by antiepileptic drug (AED) use (60 days prior to pregnancy through date of delivery)

	No AED use	Any AED use	Older AED use	Newer AED use
	No. (%)	No. (%)	No. (%)	No. (%)
Total (number of deliveries) ^a	574,004 (100.0)	11,611 (100.0)	9,001 (100.0)	3,515 (100.0)
Maternal age at delivery, years				
< 18	19,400 (3.4)	303 (2.6)	165 (1.8)	153 (4.4)
18-24	147,841 (25.8)	3,395 (29.2)	2,474 (27.5)	1,221 (34.7)
25-29	146,924 (25.6)	2,922 (25.2)	2,238 (24.9)	950 (27.0)
30-34	154,793 (27.0)	2,666 (23.0)	2,163 (24.0)	695 (19.8)
35-39	85,348 (14.9)	1,788 (15.4)	1,503 (16.7)	390 (11.1)
40-44	19,173 (3.3)	516 (4.4)	439 (4.9)	103 (2.9)
45-49	525 (0.1)	21 (0.2)	19 (0.2)	<5 (0.1)
Maternal race/ethnicity				
Hispanic	125,214 (21.8)	1,157 (10.0)	968 (10.8)	257 (7.3)
Non-Hispanic				
Caucasian	258,691 (45.1)	8,134 (70.1)	6,187 (68.7)	2,658 (75.6)
African-American	90,388 (15.8)	1,160 (10.0)	867 (9.6)	362 (10.3)
Asian-American	55,525 (9.7)	356 (3.1)	323 (3.6)	43 (1.2)
Native American	1,438 (0.3)	56 (0.5)	43 (0.5)	18 (0.5)
Other/multiple	20,969 (3.7)	359 (3.1)	303 (3.4)	76 (2.2)
Unknown	21,779 (3.8)	389 (3.4)	310 (3.4)	101 (2.9)
Maternal education, yrs.				
< 12 years	241,951 (42.2)	6,259 (53.9)	4,676 (52.0)	2,153 (61.3)
> 12 years	301,022 (52.4)	4,857 (41.8)	3,932 (43.7)	1,234 (35.1)
Unknown	31,031 (5.4)	495 (4.3)	393 (4.4)	128 (3.6)
Maternal marital status				
Married	151,804 (26.4)	4,040 (34.8)	3,106 (34.5)	1,260 (35.9)
Not married	104,848 (18.3)	3,580 (30.8)	2,497 (27.7)	1,456 (41.4)
Other or unknown	317,352 (55.3)	3,991 (34.4)	3,398 (37.8)	799 (22.7)
Maternal gravidity				
1	166,606 (29.0)	2,957 (25.5)	2,255 (25.1)	920 (26.2)
2	170,026 (29.6)	3,053 (26.3)	2,413 (26.8)	884 (25.2)
3+	215,314 (37.5)	5,188 (44.7)	4,019 (44.7)	1,586 (45.1)
Unknown	22,058 (3.8)	413 (3.6)	314 (3.5)	125 (3.6)
Mode of delivery				
Cesarean section	139,479 (24.3)	3,717 (32.0)	2,890 (32.1)	1,147 (32.6)
Vaginal delivery	413,940 (72.1)	7,543 (65.0)	5,840 (64.9)	2,266 (64.5)

	No AED use	Any AED use	Older AED use	Newer AED use
	No. (%)	No. (%)	No. (%)	No. (%)
Unknown	20,585 (3.6)	351 (3.0)	271 (3.0)	102 (2.9)
Duration of gestation (wks.)				
42+	10,640 (1.9)	141 (1.2)	117 (1.3)	35 (1.0)
37-42	503,146 (87.7)	9,694 (83.5)	7,489 (83.2)	2,943 (83.7)
32-36	50,489 (8.8)	1,517 (13.1)	1,179 (13.1)	461 (13.1)
28-31	6,062 (1.1)	169 (1.5)	139 (1.5)	43 (1.2)
< 28	3,667 (0.6)	90 (0.8)	77 (0.9)	33 (0.9)
Infant plurality				
Single	518,406 (90.3)	10,452 (90.0)	8,027 (89.2)	3,285 (93.5)
Twin	9,147 (1.6)	369 (3.2)	332 (3.7)	46 (1.3)
Triplet	316 (0.1)	17 (0.1)	14 (0.2)	<5 (0.1)
Quadruplet	18 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	46,117 (8.0)	773 (6.7)	628 (7.0)	181 (5.2)
Infant birth weight (g) ^b				
> 4,000 (high birth weight)	56,938 (9.9)	882 (7.6)	711 (7.9)	231 (6.6)
2,500-4,000 (normal birth weight)	457,171 (79.7)	8,975 (77.3)	6,926 (77.0)	2,745 (78.1)
1,500-2,499 (low birth weight)	32,283 (5.6)	1,165 (10.0)	893 (9.9)	366 (10.4)
< 1,500 (very low birth weight)	7,196 (1.3)	219 (1.9)	183 (2.0)	65 (1.9)
Unknown	20,416 (3.6)	370 (3.2)	288 (3.2)	108 (3.1)
Infant sex ^b				
Female	269,816 (47.0)	5,468 (47.1)	4,238 (47.1)	1,652 (47.0)
Male	283,138 (49.3)	5,778 (49.8)	4,473 (49.7)	1,766 (50.2)
Unknown	18,628 (3.2)	331 (2.9)	260 (2.9)	92 (2.6)
Other	2,422 (0.4)	34 (0.3)	30 (0.3)	5 (0.1)

^aProportions were calculated using the N value for each cell as the numerator and the total N value for each column (number of deliveries) as the denominator.

^bWill add up to the number of infants.

Table 3Clinical diagnoses for cohort members, MEPREP 2001-2007^a

Diagnoses ^b	Any AED use	Older AED use	Newer AED use
	N (%)	N (%)	N (%)
Total	11,611 (100.0)	9,001 (100.0)	3,515 (100.0)
Psychiatric disorder, any	5,566 (47.9)	4,024 (44.7)	2,115 (60.2)
Pain disorder, any	2,578 (22.2)	1,795 (19.9)	1,044 (29.7)
Epilepsy, any	2,405 (20.7)	1,909 (21.2)	869 (24.7)
Sleep disorder, any	655 (5.6)	499 (5.5)	299 (8.5)
Neuromuscular disorder, any	240 (2.1)	184 (2.0)	96 (2.7)
No indication from listing	2,309 (19.9)	1,900 (21.1)	452 (12.9)

^aThere were a total of 585,615 deliveries during the study period. Proportions were calculated using the N value for each cell as the numerator and the total number of deliveries involving any (n = 11,611), older (n = 9,001) or newer (n = 3,515) antiepileptic drug (AED) use (60 days prior to pregnancy through date of delivery) during the study period as the denominator.

^bDiagnoses were derived from ICD-9 and procedure codes for medical care encounters occurring 180 days before pregnancy through the date of delivery (see Table e-1). Diagnosis categories are not mutually-exclusive (e.g., are non-hierarchical); thus, for example, encounters with ICD-9 or procedure codes consistent with a psychiatric disorder and a seizure disorder would be classified twice—once as a psychiatric disorder, and once as a seizure disorder. Percentage values may therefore not equal 100%.

Clinical diagnoses of women who used AEDs during pregnancy (180 days prior to pregnancy through date of delivery), by year of conception^{a,b,c}

Table 4

Year of conception	2000 (n = 59,238)	2001 (n = 83,174)	2002 (n = 84,016)	2003 (n = 82,556)	2004 (n = 83,462)	2005 (n = 85,137)	2006 (n = 86,356)	2007 (n = 21,675)
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Any epilepsy	227 (0.4)	323 (0.4)	340 (0.4)	333 (0.4)	378 (0.5)	408 (0.5)	381 (0.4)	72 (0.3)
Any psychiatric	452 (0.8)	678 (0.8)	730 (0.9)	905 (1.1)	1092 (1.3)	1046 (1.2)	957 (1.1)	265 (1.2)
Any pain	187 (0.3)	329 (0.4)	365 (0.4)	422 (0.5)	537 (0.7)	456 (0.5)	459 (0.5)	145 (0.7)
Any neuromusc.	25 (<0.1)	24 (<0.1)	30 (<0.1)	32 (<0.1)	44 (<0.1)	39 (<0.1)	52 (<0.1)	12 (<0.1)
Any sleep	50 (0.1)	82 (0.1)	93 (0.1)	118 (0.1)	143 (0.2)	103 (0.1)	105 (0.1)	40 (0.2)
Other	274 (0.5)	343 (0.4)	381 (0.5)	402 (0.5)	436 (0.5)	500 (0.6)	544 (0.6)	142 (0.7)

^aThere were a total of 585,615 deliveries among cohort members who delivered a live-born infant between 2001-2007. Data for consecutive years of conception (2000-2007)—not years of delivery—are presented in this table. Note therefore that the smaller n-value in 2007 (n=21,675) represents deliveries in which the year of conception and year of delivery were both 2007.

^bProportions were calculated using the N value for each cell as the numerator and the total number of deliveries during the study period (n = 585,615) as the denominator.

^cN-values represent the number of deliveries in each category for each year of conception.

Table 5
Antiepileptic drug indication by gestational period, 2001–2007, inpatient or outpatient encounters^a

	Pre-pregnancy only ^b	Any time during pregnancy (excluding pre-pregnancy period)	All three trimesters ^c	First trimester only ^d	Second trimester only ^d	Third trimester only ^f
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Total	1,476 (100.0)	10,135 (100.0)	2,586 (100.0)	1,631 (100.0)	296 (100.0)	563 (100.0)
Any epilepsy						
All AEDs	57 (3.9)	2,405 (23.7)	1,481 (57.3)	83 (5.1)	33 (11.1)	143 (25.4)
Older AEDs	46 (3.1)	1,909 (18.8)	1,113 (43.0)	72 (4.4)	31 (10.5)	119 (21.1)
Newer AEDs	23 (1.6)	869 (8.6)	448 (17.3)	45 (2.8)	14 (4.7)	63 (11.2)
Any psychiatric						
All AEDs	560 (37.9)	5,566 (54.9)	1,286 (49.7)	749 (45.9)	126 (42.6)	276 (49.0)
Older AEDs	479 (32.5)	4,024 (39.7)	898 (34.7)	572 (35.1)	102 (34.5)	219 (38.9)
Newer AEDs	149 (10.1)	2,115 (20.9)	440 (17.0)	270 (16.6)	40 (13.5)	107 (19.0)
Any pain						
All AEDs	322 (21.8)	2,578 (25.4)	576 (22.8)	402 (24.6)	65 (22.0)	141 (25.0)
Older AEDs	281 (19.0)	1,795 (17.7)	405 (15.7)	294 (18.0)	54 (18.2)	117 (20.8)
Newer AEDs	82 (5.6)	1,044 (10.3)	195 (7.5)	146 (9.0)	22 (7.4)	53 (9.4)
Any neuromuscular						
All AEDs	21 (1.4)	240 (2.4)	82 (3.2)	28 (1.7)	<5 (1.0)	13 (2.3)
Older AEDs	19 (1.3)	184 (1.8)	58 (2.2)	26 (1.6)	<5 (0.7)	9 (1.6)
Newer AEDs	<5 (0.2)	96 (0.9)	25 (1.0)	10 (0.6)	0 (0.0)	5 (0.9)
Any sleep						
All AEDs	79 (5.4)	655 (6.6)	163 (6.3)	86 (5.3)	14 (4.7)	32 (5.7)
Older AEDs	71 (4.8)	499 (4.9)	116 (4.5)	68 (4.2)	10 (3.4)	29 (5.2)
Newer AEDs	16 (1.1)	229 (2.3)	50 (1.9)	26 (1.6)	5 (1.7)	11 (2.0)

^aThere were a total of 585,615 deliveries during the study period. Proportions were calculated using the N value for each cell as the numerator and the total of deliveries involving any antiepileptic drug (AED) drug use in the cohort by gestational period (e.g., n = 10,135 for any use during pregnancy, excluding the pre-pregnancy period) as the denominator. Drug exposures are not mutually exclusive; thus, individually reported proportions for a given category may not equal 100%.

b_j Defined as the day before the last menstrual period (LMP) date and the prior 60 days.

c_j Encompasses the time window beginning on the LMP date and ending on the date of delivery.

d_j Defined as the LMP date and the following 90 days.

e_j Defined as post-LMP days 91-180.

f_j Defined as post-LMP days 181 through date of delivery.