Comparative safety of antiepileptic drugs during pregnancy

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ABSTRACT

Objective: To assess the safety of the newer antiepileptic drugs (AEDs) during pregnancy.

Methods: The study population was pregnant women who enrolled in the North American AED Pregnancy Registry between 1997 and 2011. Data on AED use and maternal characteristics were collected through phone interviews at enrollment, at 7 months' gestation, and postpartum. Malformations were confirmed by medical records. The risk of major malformations was calculated among infants exposed to specific AEDs in monotherapy during the first trimester of pregnancy and among an unexposed group. Risk ratios (RRs) and 95% confidence intervals (CIs) were estimated with logistic regression.

Results: The risk of major malformations was 9.3% (30 of 323) for valproate, 5.5% (11 of 199) for phenobarbital, 4.2% (15 of 359) for topiramate, 3.0% (31 of 1.033) for carbamazepine, 2.9% (12 of 416) for phenytoin, 2.4% (11 of 450) for levetiracetam, and 2.0% (31 of 1,562) for lamotrigine. Compared with lamotrigine, the RR was 5.1 (95% CI 3.0–8.5) for valproate, 2.9 (1.4–5.8) for phenobarbital, and 2.2 (1.2–4.0) for topiramate. The proportion of women with epilepsy who had seizures during pregnancy ranged from 23% for valproate to 31% for lamotrigine. Valproate was associated with a higher risk of neural tube defects, hypospadias, cardiac defects, and oral clefts and phenobarbital with a higher risk of cardiac defects and oral clefts; 5 infants exposed to topiramate (1.4%) had a cleft lip.

Conclusions: AEDs such as valproate and phenobarbital were associated with a higher risk of major malformations than newer AEDs such as lamotrigine and levetiracetam. Topiramate was associated with an increased risk of cleft lip compared with that of a reference population. ***Neurology*® 2012;78:1692–1699**

GLOSSARY

AED = antiepileptic drug; **CI** = confidence interval; **RR** = relative risk.

Prenatal exposure to traditional antiepileptic drugs (AEDs) has been associated with an increased risk of congenital malformations and deficits in IQ.[1,2] However, the magnitude of the risks and the specific abnormalities has varied for each drug: it is widely accepted that valproate increases the risk of spina bifida, phenytoin of digit hypoplasia, phenobarbital of oral clefts, and carbamazepine of neural tube defects.[3–5]

Less is known about the safety of newer AEDs during pregnancy.[6] The relatively low risk of specific major malformations together with the few pregnant women exposed to each drug in the population have made it difficult to obtain valid, precise, and timely estimates of the teratogenic effects of recently introduced AEDs. Cohorts of women taking a variety of thera-

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Supplemental Data

CME

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pies with shared indications, enrolled early in pregnancy, and followed throughout gestation and postpartum can be used to assess the relative safety of individual AEDs.

We present the findings in the North American AED Pregnancy Registry. The objective was to estimate the risk of major malformations in infants whose mothers had taken specific AEDs as monotherapy during the first trimester of pregnancy and to assess whether exposure to each AED is associated with an increased risk of specific major malformations.

METHODS

Study design. The North American AED Pregnancy Registry is an ongoing surveillance system of pregnant women who are taking an AED for any reason.[5,7,8] Women self-enrolled by calling a toll-free telephone number. To be eligible, a woman must be pregnant and have taken AEDs at some point during her pregnancy.

Women are interviewed at enrollment, at 7 months' gestation and at 8–12 weeks after the expected date of delivery. The computer-assisted interviews include questions on start and stop dates of each AED taken, dose, frequency, changes in medication, indication, and, if epilepsy, number and type of seizures during pregnancy; demographic characteristics; habits, such as cigarette smoking, alcohol intake, and use of illicit drugs; medical conditions; use of other medications; family history; and results of any prenatal testing.

Study population. Women were eligible for analysis if they had a liveborn infant, a stillborn infant, or a pregnancy terminated because of a fetal abnormality and were ineligible if they had a spontaneous abortion, withdrew from the Registry, or were lost to follow-up. The units of analysis were pregnancies, and malformations in one or more fetuses in twins were considered as one outcome.

Although women are encouraged to enroll before they have had any prenatal testing, they are enrolled throughout pregnancy. Enrollment is considered pure prospective if subjects enroll without having had a nuchal translucency screening test or chorionic villus sampling at 11–13 weeks' gestation, an amniocentesis, maternal serum screening, or an ultrasound after 15 weeks' gestation. The traditional enrollees might have some knowledge of the status of the fetus.

We present below findings for the first trimester monotherapy-exposed groups with 50 or more women eligible for analysis.

Exposure definition. Women were considered exposed if they used any AED, as monotherapy, during the first 4 lunar months after the last menstrual period. Women could have added or switched to different AEDs after the first trimester.

Outcome definitions. The outcomes of interest were major congenital malformations diagnosed before 12 completed weeks after birth. A major malformation was defined as a structural abnormality with surgical, medical, or cosmetic importance.[9] The physical features excluded were minor anomalies, birth marks, deformations, anatomic findings by ultrasound studies in pregnancy that were not identified by the examining pediatrician, complications of prematurity, genetic disorders, and chromosome abnormalities.[9] In the postnatal interview, the mother is asked about the birth status of the infant, including any health problems, and she is asked to sign and return a medical record release form. The infant's doctors are asked to return copies of their examination findings through the first 12 weeks of life. Medical records are requested also from the infant's cardiologist or urologist or other specialist who has evaluated the infant. The written descriptions in the pediatricians' examinations are reviewed by the teratologist (L.B.H.), blinded to exposure status, to determine inclusion or exclusion.

Reference groups. Our primary reference group was women exposed to lamotrigine because it was the most commonly reported AED in the Registry. The rationale for the primary active reference group was 2-fold. First, this comparison responds to the most clinically relevant question: which AED is safest? Second, it minimizes confounding by indication, because most subjects in the groups compared (i.e., specific AEDs vs lamotrigine) will have epilepsy. A secondary internal reference group was pregnant women not taking an AED and without epilepsy who had been recruited, since 2003, among the friends and relatives of AED-exposed participants and followed with the same methodology.

In addition, to estimate the expected risk of specific malformations, we considered an external reference group of 206,224 infants born at Brigham and Women's Hospital in Boston and captured by a surveillance system that used the same inclusion/exclusion criteria for outcome definition, but followed infants only up to 5 days after birth.[10] For analyses using this reference, malformations identified in the Registry after 5 days of life had to be excluded.

Analysis. We evaluated the sociodemographic and clinical characteristics of women exposed to specific drugs. The risk of major congenital malformations in each exposed group was compared with the risk in the internal reference groups. We estimated both crude and adjusted relative risks (RRs) and their 95% confidence intervals (CIs) using multivariate logistic regression. Potential confounders considered included maternal age, race, education, alcohol use, cigarette smoking, periconceptional folic acid supplementation, illicit drug use, chronic diseases (e.g., insulin-dependent diabetes), and calendar year. We added one potential confounder at a time to each model; because RR estimates remained similar, we present the crude RRs as the main analysis. Within women with epilepsy, we compared the risk of seizures during pregnancy among AED-exposed groups.

We conducted a number of sensitivity analyses. To assess the role of indication, we restricted the comparisons to women with epilepsy. To assess the impact of gestational time at enrollment, we restricted the analysis to pure prospective subjects. To assess the accuracy of maternal AED report, we repeated the analyses using only AED use information from medical records.

Standard protocol approvals, registrations, and patient consents. Informed consent is obtained verbally at enrollment. The study has been approved annually by the Human Studies Committee of the Massachusetts General Hospital and Partners HealthCare.

RESULTS

From February 1, 1997, through June 1, 2011, a total of 7,370 AED-exposed and 479 AED-unexposed women (internal comparison group) were enrolled. Of 5,667 women taking an AED as mono-

Table 1 Characteristics of the study subjects either unexposed or exposed to AEDs in monotherapy during the first trimester: North America AED Pregnancy Registry 1997–2011

Categories[a]	Unexposed (n = 442)[b]	Lamotrigine (n = 1,562)	Carbamazepine (n = 1,033)	Levetiracetam (n = 450)	Phenytoin (n = 416)	Topiramate (n = 359)	Valproate (n = 323)	Phenobarbital (n = 199)	Oxcarbazepine (n = 182)	Gabapentin (n = 145)	Zonisamide (n = 90)	Clonazepam (n = 64)
Maternal age, y, mean (SD)	31.5 (4.2)	30.24 (5.0)	29.9 (5.5)	29.6 (5.1)	29.8 (5.3)	28.81 (5.5)	28.6 (6.0)	31.1 (5.2)	30.4 (5.5)	31.12 (5.4)	27.4 (5.5)	33.4 (4.4)
Mother's education, n (%)												
< Grade 12	17 (3.9)	181 (12.6)	81 (16.1)	73 (16.3)	30 (18.4)	98 (28.7)	37 (23.1)	7 (8.2)	21 (11.6)	17 (20.5)	19 (21.1)	0 (0.0)
Junior college graduate (2-y)	59 (13.4)	284 (19.7)	109 (21.7)	100 (22.3)	46 (28.2)	98 (28.7)	46 (28.8)	20 (23.5)	50 (27.6)	18 (21.7)	22 (24.4)	9 (24.3)
College graduate (4-y)	177 (40.2)	582 (40.4)	193 (38.5)	170 (37.9)	56 (34.4)	99 (29.0)	50 (31.3)	32 (37.7)	67 (37.0)	23 (27.7)	32 (35.6)	16 (43.2)
Postcollege	187 (42.5)	393 (27.3)	119 (23.7)	106 (23.6)	31 (19.0)	47 (13.7)	27 (16.9)	26 (30.6)	43 (23.8)	25 (30.1)	17 (18.9)	12 (32.4)
Married, n (%)	417 (94.8)	1,289 (89.5)	414 (83.1)	375 (83.9)	133 (81.6)	252 (73.9)	108 (67.9)	78 (92.9)	155 (85.2)	69 (83.1)	64 (71.1)	27 (73.0)
Mother Caucasian, n (%)	401 (90.9)	1,381 (88.4)	903 (87.4)	377 (83.8)	344 (82.7)	325 (90.5)	277 (85.8)	176 (88.4)	155 (85.2)	136 (93.8)	76 (84.4)	60 (93.8)
Father Caucasian, n (%)	394 (89.3)	1,330 (85.3)	882 (85.6)	366 (81.5)	335 (80.5)	295 (82.2)	258 (80.1)	171 (85.9)	149 (81.9)	124 (85.5)	68 (75.6)	59 (92.2)
Primiparity, n (%)	146 (33.0)	663 (42.5)	374 (36.2)	180 (40.0)	135 (32.5)	151 (42.0)	124 (38.4)	51 (25.6)	81 (44.5)	55 (37.9)	50 (55.6)	25 (39.1)
Folic acid supplement at LMP, n (%)	305 (69.0)	1,229 (78.7)	684 (66.2)	358 (79.6)	232 (55.8)	216 (60.2)	209 (64.7)	126 (63.3)	142 (78.0)	82 (56.6)	57 (63.3)	27 (42.2)
Cigarette smoking, n (%)												
None	414 (93.9)	1,422 (91.2)	904 (87.8)	403 (89.6)	352 (85.0)	297 (82.7)	240 (74.3)	174 (87.4)	168 (92.8)	114 (78.6)	78 (88.6)	47 (73.4)
> None, <[1/2] pack	16 (3.6)	57 (3.7)	48 (4.7)	26 (5.8)	19 (4.6)	20 (5.6)	35 (10.8)	10 (5.0)	5 (2.8)	7 (4.8)	4 (4.6)	5 (7.8)
>[1/2] pack, <1 pack	6 (1.4)	37 (2.4)	27 (2.6)	13 (2.9)	16 (3.9)	22 (6.1)	20 (6.2)	5 (2.5)	5 (2.8)	12 (8.3)	4 (4.6)	5 (7.8)
>1 pack	3 (0.7)	34 (2.2)	41 (4.0)	7 (1.6)	24 (5.8)	15 (4.2)	22 (6.8)	10 (5.0)	2 (1.1)	10 (6.9)	2 (2.3)	6 (9.4)
Yes, but unknown	2 (0.5)	9 (0.6)	10 (1.0)	1 (0.2)	3 (0.7)	5 (1.4)	6 (1.9)	0 (0.0)	1 (0.6)	2 (1.4)	0 (0.0)	1 (1.6)
Alcohol, n (%)												
None	308 (70.0)	1,186 (76.2)	726 (70.4)	347 (77.1)	299 (72.2)	283 (79.1)	222 (68.7)	132 (67.0)	147 (80.8)	102 (70.3)	75 (83.3)	39 (60.9)
Moderate (1–5 drinks/wk)	103 (24.4)	323 (20.8)	265 (25.7)	80 (17.8)	99 (23.9)	62 (17.3)	81 (25.1)	58 (29.4)	29 (15.9)	38 (26.2)	13 (14.4)	23 (35.9)
>5 drinks/wk	20 (4.6)	24 (1.5)	17 (1.7)	16 (3.6)	3 (0.7)	7 (2.0)	8 (2.5)	4 (2.0)	3 (1.7)	1 (0.7)	1 (1.1)	1 (1.6)
Yes, but unknown	9 (2.1)	23 (1.5)	23 (2.2)	7 (1.6)	13 (3.1)	6 (1.7)	12 (3.7)	3 (1.5)	3 (1.7)	4 (2.8)	1 (1.1)	1 (1.6)
Indication epilepsy, n (%)	NA	1,366 (87.5)	1,021 (98.8)	447 (99.3)	416 (100)	302 (84.1)	296 (91.6)	198 (99.5)	179 (98.4)	105 (72.4)	89 (98.9)	19 (29.7)
Age first seizure, y, mean (SD)[c]	NA	17.9 (8.5)	16.6 (8.7)	18.1 (8.7)	18.2 (8.6)	17.09 (8.6)	13.3 (6.3)	14.7 (8.2)	18.8 (9.1)	19.1 (10.0)	13.4 (8.0)	12.4 (6.6)
Seizures during pregnancy, n (%)[c]	NA	424 (31.0)	283 (27.7)	138 (30.9)	113 (27.2)	100 (33.1)	69 (23.3)	40 (20.2)	78 (43.6)	47 (44.8)	21 (23.6)	5 (26.3)

Abbreviations: AED = antiepileptic drug; LMP = last menstrual period.

[a] Numbers in columns might not add to the total because of missing values.

[b] The unexposed internal comparison group were pregnant women, not taking an AED, who were recruited from among the friends and family members of the enrolled women taking an AED.

[c] Among subjects with epilepsy.

Table 2 Risk of major malformations identified among infants who had been exposed to a specific AED in monotherapy during the first trimester and among the internal comparison group of unexposed infants and relative risk of major malformations compared withto both unexposed and lamotrigine groups: North America AED Pregnancy Registry 1997–2011

	Unexposed (n = 442)[b]	Lamotrigine (n = 1,562)	Carbamazepine (n = 1,033)	Phenytoin (n = 416)	Levetiracetam (n = 450)	Topiramate (n = 359)	Valproate (n = 323)	Phenobarbital (n = 199)	Oxcarbazepine (n = 182)	Gabapentin (n = 145)	Zonisamide (n = 90)	Clonazepam (n = 64)
Major congenital malformations[a]												
No. (%)	5 (1.1)	31 (2.0)	31 (3.0)	12 (2.9)	11 (2.4)	15 (4.2)	30 (9.3)	11 (5.5)	4 (2.2)	1 (0.7)	0 (0)	2 (3.1)
95% CI	(0.37–2.6)	(1.4–2.8)	(2.1–4.2)	(1.5–5.0)	(1.2–4.3)	(2.4–6.8)	(6.4–13.0)	(2.8–9.7)	(0.6–5.5)	(0.02–3.8)	(0.0–3.3)	(0.4–10.8)
Unexposed reference												
Relative risk	Reference	1.8	2.7	2.6	2.2	3.8	9.0	5.1	2.0	0.6	NA	2.8
95% CI		(0.7–4.6)	(1.0–7.0)	(0.9–7.4)	(0.8–6.4)	(1.4–10.6)	(3.4–23.3)	(1.8–14.9)	(0.5–7.4)	(0.07–5.2)		(0.5–14.8)
Exposed reference												
Relative risk		Reference	1.5	1.5	1.2	2.2	5.1	2.9	1.1	0.3	NA	1.6
95% CI			(0.9–2.5)	(0.7–2.9)	(0.6–2.5)	(1.2–4.0)	(3.0–8.5)	(1.4–5.8)	(0.4–3.2)	(0.05–2.5)		(0.4–6.8)
Exposed reference restricted to pure prospective participants												
Relative risk		Reference	1.1	1.4	0.8	2.5	4.2	2.5	1.5	0.5	NA	1.3
95% CI			(0.6–2.2)	(0.6–3.4)	(0.3–2.1)	(1.2–5.2)	(2.1–8.3)	(0.9–6.8)	(0.5–4.6)	(0.07–4.1)		(0.2–10.1)

Abbreviations: AED = antiepileptic drug; CI = confidence interval.
[a] Diagnosed during pregnancy or before 12 weeks after birth. Confirmed by review of medical records.
[b] The unexposed internal comparison group were pregnant women not taking an AED, who were recruited from among the friends and family members of the enrolled women taking an AED.

therapy during the first trimester, 4,899 were eligible for analysis (figure e-1 on the *Neurology*® Web site at www.neurology.org). From the unexposed internal comparison group, 442 subjects were eligible for analysis.

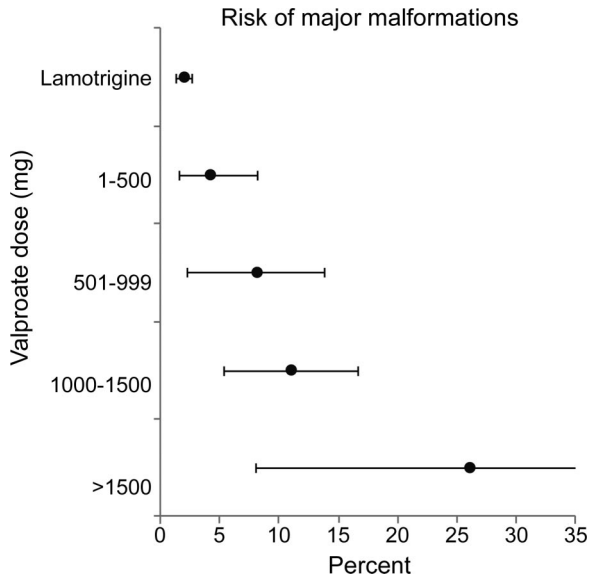
In 2011, the most commonly reported AED monotherapies during the first trimester were lamotrigine, levetiracetam, and topiramate (figure e-2). AEDs were used for epilepsy (92%), mood disorders (6%), migraine (1%), and other conditions. Of note, the AED pregnancy registry does not reflect the indications in the general population because it targets women with epilepsy. Demographic characteristics are presented in table 1.

Major malformations. Compared with lamotrigine, the RR of major malformations was 1.2 (95% CI 0.6–2.5) for levetiracetam and 2.2 (1.2–4.0) for topiramate (table 2). Neither restriction to pure prospective enrollees, nor adjustment for potential confounders, nor restriction to women with epilepsy, nor use of AED information from medical records (data not shown) changed the results significantly. For example, compared with lamotrigine, the RR for topiramate was 2.5 (1.2–5.2) after restriction to pure prospective enrollees, 2.2 (1.2–4.2) after adjustment for potential confounders, 2.4 (1.2–4.6) after restriction to nonsmokers, 3.1 (1.6–5.9) after restriction to women with epilepsy, and 2.2 (1.2–4.1) based on AED information from medical records. Compared with the unexposed reference group, the RR of major malformations was 2.2 (0.8–6.4) for levetiracetam and 3.8 (1.4–10.6) for topiramate.

Dose. The risk of major malformations increased with valproate dose (figure 1); the median average daily dose during the first trimester was 1,000 mg for pregnancies with malformations and 750 mg for those without malformations. There was no apparent dose trend for other AEDs; the median average dose was identical for malformed and nonmalformed infants exposed to phenobarbital (120 mg), topiramate (200 mg), or lamotrigine (300 mg).

Seizures. The proportion of women with epilepsy who reported seizures during pregnancy varied among AEDs (table 1). AED groups with a higher frequency of seizures tended to have a lower risk of major malformations (figure 2). Exclusively within valproate and phenobarbital users, women without seizures during pregnancy had a numerically higher risk of malformations (10.6% and 6.3%, respectively) than women with seizures (7.3% and 2.5%), and such a difference was not explained by AED dose. However, these analyses were based on small numbers and should be considered exploratory.

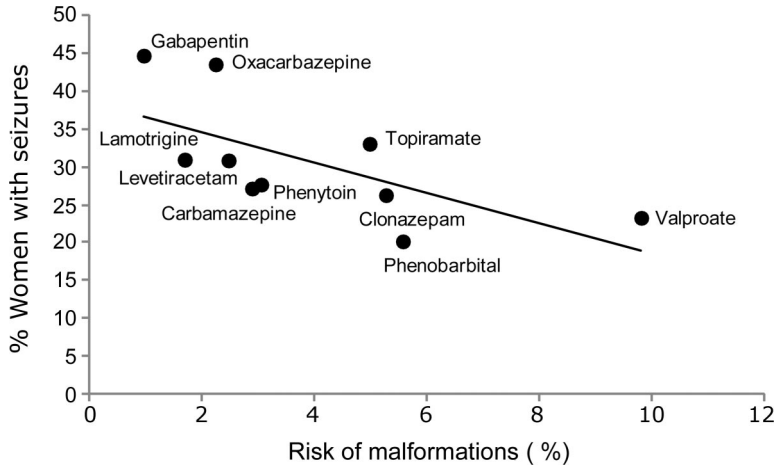
Figure 1 Risk of major malformations by average valproate dose (mg) during the first trimester



North American AED Pregnancy Registry 1997–2011.

Specific malformations. The frequency of specific malformations for each AED is described in tables 3 and e-1. In a comparison of the lower bound of the risk estimates with the risk in the external reference population,[10] valproate was associated with an increased risk of neural tube defects, hypospadias, and cardiovascular malformations, and phenobarbital was associated with a higher risk of cardiovascular malformations. The risk of oral clefts was higher among infants exposed to phenobarbital, valproate, and topiramate. Among the topiramate-exposed infants, there were 5 infants with cleft lip.

Figure 2 Risk of major malformations by proportion of women having at least one seizure during their pregnancy within each antiepileptic drug group among women with epilepsy



North American AED Pregnancy Registry 1997–2011.

DISCUSSION The risk of major malformations overall associated with first-trimester exposure to specific AEDs ranged from 9.3% for valproate to 2.0% for lamotrigine. The risk of oral clefts was more than 10 per 1,000 for infants exposed to phenobarbital, valproate, and topiramate users, which is higher than expected based on any reference population (approximately 1 per 1,000 births).[10]

The teratogenicity of valproic acid is well established.[11] Although the risk of malformations has been shown to be dose dependent,[12–14] low doses (<1,000 mg) seem to be associated with an increased risk.[15] It is widely accepted that first-trimester exposure to valproic acid increases the risk of neural tube defects from approximately 1 per 1,000 to 10 per 1,000 births.[1,12,13,16,17] Some studies have also suggested an association with hypospadias,[1,13,14,16,17] oral clefts,[1,13,16] cardiac septal defects,[1,14,16,17] and limb defects.[1,17] Our findings are consistent with these literature reports. Moreover, prenatal exposure to valproic acid has been associated with neurodevelopmental delay and autism.[18] Despite the overwhelming evidence for fetal toxicity, valproic acid is still prescribed to pregnant women because it is an effective drug in the treatment of idiopathic generalized epilepsy and, specifically, juvenile myoclonic epilepsy.

Previous studies had suggested that other traditional AEDs may increase the risk of malformations 2–3 times. Phenobarbital has been associated with oral clefts and cardiovascular and urogenital defects.[19] Although less common, oral clefts, cardiovascular defects, and urogenital defects have also been reported after phenytoin therapy.[20,21] Exposure to carbamazepine during pregnancy has been associated with cleft palate,[22] neural tube defects,[20,22,23] hypospadias, and cardiovascular defects.[22]

The use of lamotrigine, topiramate, and levetiracetam has increased in the last decade and, therefore, assessing their safety is critical.[6] Studies consistently show a lower risk of malformations overall for lamotrigine than for traditional AEDs,[6,24] and in most studies the risk does not increase with dose.[6,13,25,26] We published a risk of oral clefts of 7.3 per 1,000 among users of lamotrigine monotherapy.[8] With a larger sample size, the estimate is now 4.5 per 1,000 (95% CI 2.0–8.8). Other studies have reported lower risks of oral clefts after first-trimester lamotrigine exposure: 1–2.5 per 1,000.[6,13,26]

For topiramate, based on 359 women exposed in monotherapy during the first trimester, we found a risk of cleft lip of 14 per 1,000. The lower bound of the 95% CI was 5.1 per 1,000, which is still higher than the expected risk in the population. Another registry from the United Kingdom has reported a risk of oral clefts of 29 (95% CI 5–91)[27] per 1,000

Table 3 Prevalence of most common specific malformations diagnosed before 5 days of age among infants exposed to the AED monotherapies most commonly reported in the North America AED Pregnancy Registry 1997–2011 and among an external reference population from Brigham and Women's Hospital in Boston

Major congenital anomaly[a]	Lamotrigine (n = 1,562)	Carbamazepine (n = 1,033)	Phenytoin (n = 416)	Levetiracetam (n = 450)	Topiramate (n = 359)	Valproate (n = 323)	Phenobarbital (n = 199)	External reference, %[b]
Hypospadias[c]								
No. (%)	0	1 (0.19)	0	0	2 (1.1)	5 (3.1)	1 (0.97)	0.04
95% CI		(0.01–0.93)			(0.19–3.6)	(1.1–6.7)	(0.05–4.7)	
Neural tube defects								
No. (%)	2 (0.13)	3 (0.29)	0	1 (0.22)	0	4 (1.2)	0	0.12
95% CI	(0.02–0.42)	(0.07–0.79)		(0.01–1.1)		(0.39–3.0)		
Cardiovascular anomalies								
No. (%)	3 (0.19)	3 (0.29)	4 (0.96)	1 (0.22)	1 (0.28)	8 (2.5)	5 (2.5)	0.33
95% CI	(0.05–0.52)	(0.07–0.79)	(0.31–2.4)	(0.01–1.1)	(0.01–1.4)	(0.12–4.6)	(0.93–5.5)	
Oral clefts								
No. (%)	7 (0.45)	5 (0.48)	2 (0.48)	0	5 (1.4)	4 (1.2)	4 (2.0)	0.11
95% CI	(0.20–0.88)	(0.18–1.1)	(0.08–1.6)		(0.51–3.1)	(0.39–3.0)	(0.64–4.8)	

Abbreviations: AED = antiepileptic drug; CI = confidence interval.
[a] Restricted for malformations diagnosed before 5 days of age, including elective terminations, to be comparable with the external reference population. Confirmed by review of medical records. Some infants had more than one defect.
[b] Prevalence among 206,224 births, including stillbirths and elective terminations surveyed for anomalies at Brigham and Women's Hospital in Boston.
[c] Excludes mild glandular hypospadias. Restricted to male infants.

among 70 topiramate monotherapy users, more than 10 times their background risk. A recent study from Denmark has reported 1 case among 108 women exposed during the first trimester, corresponding to a risk of 9.3 cases (95% CI 0.5–45) per 1,000 compared with 1.7 per 1,000 in their unexposed population.[6]

For levetiracetam, one study found no malformed infants among 39 exposed prenatally to monotherapy,[28] and another reported no malformed infants among 58 exposed during the first trimester.[6] In the current study, the risk of major malformations in 450 infants exposed during the first trimester to levetiracetam monotherapy was 2.4% (95% CI 1.2–4.3%).

A few studies have evaluated the teratogenicity of oxcarbazepine; the numbers of malformations after pregnancy exposure were 1 in 55,[29] 2 in 37,[24] 3 in 130,[30] and 11 in 393,[6] each study having too small a sample to assess the risk for specific malformations. The risk associated with oxcarbazepine monotherapy in the current study was 2.2% (95% CI 0.6–5.5%). Likewise, the risk estimates of major congenital malformations for gabapentin and zonisamide had very wide confidence intervals and, therefore, were uninformative.

The evaluation of the teratogenic effects of AEDs is complicated by the fact that epilepsy itself could potentially increase the risk of birth defects.[31] However, several lines of evidence suggest drug effects: the type of epilepsy and the number of seizures during pregnancy do not appear to affect the risk of malformations.[25,32–35] In addition, the risk of malformations is higher in the offspring of women taking AEDs than in those with untreated epilepsy during pregnancy,[3,32,33] and women with a history of epilepsy but taking no AED do not have an increased risk of having children with major malformations.[36] However, the latter observations might also reflect an effect of disease severity, because epilepsy can seldom remain untreated, and untreated women might not be comparable to women taking AEDs. Comparative safety research methods minimize this bias by comparing different AEDs among women with epilepsy.

In addition to the lamotrigine-exposed reference group, we used 2 unexposed comparison groups, one external and the other internal. It was reassuring to see that there was no qualitative difference in the main conclusions from either of these comparisons. Results were also similar when restricting the sample to pure prospective enrollees, when using evidence of AED prescriptions in medical records, when adjusting for potential confounders, or when restricting the sample to women with epilepsy. The limited role of confounding in the assessment of AED teratogenicity had been reported previously.[6,13,30,37]

More than 70% of the enrolled mothers provided medical records release forms. Medical records were received from the neurologist or psychiatrist who prescribed the AED for 65% of the mothers and from the pediatrician for 59% of the infants. In a

validation study, there was a 99% agreement between the mother's verbal report and the doctors' records for the infants whose mothers had provided permission.[8] However, the sensitivity of maternal report might be lower for women who did not provide permission. The low risk of malformations in this study, relative to that in other reports, is probably due to the strict outcome inclusion criteria.[9] In addition, registries rely on volunteers to participate; this population might have a lower risk of malformations. We can only assume that the teratogenic effects of AEDs would be similar in the population of exposed pregnant women from whom the sample was drawn.

In exploratory analyses, AEDs associated with the largest risk of major malformations in the fetus were also associated with the lowest risk of seizures in the mother. Other studies had suggested a higher frequency of seizures during pregnancy in lamotrigine users than in valproate users.[38] In the absence of randomization, the differences in effectiveness observed among the drugs may be due to the underlying indication. Clinicians might continue valproate or phenobarbital treatment for women of childbearing age when their epilepsy is well controlled and they are reluctant to switch drugs and risk seizure recurrence. Conversely, newer AEDs could have been prescribed to patients whose epilepsy was not responding to traditional drugs. Another important factor is the pharmacokinetic changes during pregnancy due to increased clearance, which may be particularly pronounced for specific AEDs and can increase the risk of seizures. Whatever the explanation might be, it is intriguing that less effective seizure control during pregnancy seemed safer for fetal development.

Most traditional AEDs have been associated with relatively specific defects (i.e., oral clefts, neural tube defects, cardiac defects, and urogenital defects) to different degrees. Whether lamotrigine and topiramate also increase the risk of oral clefts is still under investigation. The etiology of all of these malformations might involve alterations in the fusion of embryonic folds. Embryonic cell adhesion involves cellular communication processes that might share mechanisms with neuronal signaling.[39] Neurotransmitters that participate in embryologic cell-cell interactions may be later involved in synaptic transmission.[40] Because AEDs affect neuronal transmissions through various means, one could speculate that more successful inhibition of neurotransmission might lead to both better seizure control in the mother and stronger alteration of cell-cell adhesion processes in the embryo. This hypothesis would be compatible with the lower risk of seizures during pregnancy found for those AED groups associated with a higher risk of malformations.

Because women with epilepsy often need to continue their AEDs during pregnancy for seizure control, we need to know which AEDs are safer for the mother and the fetus. Overall, traditional AEDs such as valproate and phenobarbital were associated with a higher risk of major malformations in the fetus than newer AEDs like lamotrigine and levetiracetam. The observed association of topiramate with an increased risk of cleft lip was based on small numbers and would need to be confirmed by others.

AUTHOR CONTRIBUTIONS

The authors had substantial contributions to the intellectual content of the paper. Dr. Holmes was responsible for the conception and design of the study and for obtaining funding. Dr. Hernández-Díaz was responsible for the analysis of the data and, together with Dr. Holmes, for the interpretation of data and drafting of the manuscript. C.R. Smith and A. Shen participated in the acquisition of data and provided administrative support. Dr. Mittendorf, Dr. Hauser, and Dr. Yerby supervised the study and provided critical revisions of the manuscript.

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