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Risk of Autism after Prenatal Topiramate, Valproate, or Lamotrigine Exposure

Sonia Hernández-Díaz, M.D., Dr.P.H., Loreen Straub, M.D., Brian T. Bateman, M.D., Yanmin Zhu, Ph.D., Helen Mogun, M.S., Katherine L. Wisner, M.D., Kathryn J. Gray, M.D., Ph.D., Barry Lester, Ph.D., Christopher J. McDougle, M.D., Elyse DiCesare, B.A., Page B. Pennell, M.D., and Krista F. Huybrechts, Ph.D.

ABSTRACT

BACKGROUND

Maternal use of valproate during pregnancy has been associated with an increased risk of neurodevelopmental disorders in children. Although most studies of other antiseizure medications have not shown increased risks of these disorders, there are limited and conflicting data regarding the risk of autism spectrum disorder associated with maternal topiramate use.

METHODS

We identified a population-based cohort of pregnant women and their children within two health care utilization databases in the United States, with data from 2000 through 2020. Exposure to specific antiseizure medications was defined on the basis of prescription fills from gestational week 19 until delivery. Children who had been exposed to topiramate during the second half of pregnancy were compared with those unexposed to any antiseizure medication during pregnancy with respect to the risk of autism spectrum disorder. Valproate was used as a positive control, and lamotrigine was used as a negative control.

RESULTS

The estimated cumulative incidence of autism spectrum disorder at 8 years of age was 1.9% for the full population of children who had not been exposed to antiseizure medication (4,199,796 children). With restriction to children born to mothers with epilepsy, the incidence was 4.2% with no exposure to antiseizure medication (8815 children), 6.2% with exposure to topiramate (1030 children), 10.5% with exposure to valproate (800 children), and 4.1% with exposure to lamotrigine (4205 children). Propensity score–adjusted hazard ratios in a comparison with no exposure to antiseizure medication were 0.96 (95% confidence interval [CI], 0.56 to 1.65) for exposure to topiramate, 2.67 (95% CI, 1.69 to 4.20) for exposure to valproate, and 1.00 (95% CI, 0.69 to 1.46) for exposure to lamotrigine.

CONCLUSIONS

The incidence of autism spectrum disorder was higher among children prenatally exposed to the studied antiseizure medications than in the general population. However, after adjustment for indication and other confounders, the association was substantially attenuated for topiramate and lamotrigine, whereas an increased risk remained for valproate. (Funded by the National Institute of Mental Health.)

From the Department of Epidemiology, Harvard T.H. Chan School of Public Health (S.H.-D.), the Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School (L.S., Y.Z., H.M., E.D., K.F.H.), the Division of Maternal–Fetal Medicine, Department of Obstetrics and Gynecology, Brigham and Women's Hospital (K.J.G.), and the Department of Psychiatry, Harvard Medical School (C.J.M.), Boston, and the Lurie Center for Autism, Massachusetts General Hospital, Lexington (C.J.M.) — all in Massachusetts; the Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, CA (B.T.B.); the Asher Center for the Study and Treatment of Depressive Disorders, Department of Psychiatry and Behavioral Sciences, and the Department of Obstetrics and Gynecology, Feinberg School of Medicine, Northwestern University, Chicago (K.L.W.); the Center for the Study of Children at Risk, Departments of Psychiatry and Pediatrics, Alpert Medical School of Brown University, and Women and Infants Hospital, Providence, RI (B.L.); and the Department of Neurology, University of Pittsburgh School of Medicine, Pittsburgh (P.B.P.). Dr. Hernández-Díaz can be contacted at shernan@hsph.harvard.edu or at the Department of Epidemiology, Harvard T.H. Chan School of Public Health, 677 Huntington Ave., Boston, MA 02115.

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Most women with epilepsy receive treatment with antiseizure medication throughout pregnancy.[1] However, valproate and, to a lesser degree, other traditional antiseizure medications (e.g., phenobarbital and carbamazepine) are known teratogens.[2] Among the antiseizure medications approved within the past 25 years, most (e.g., lamotrigine) do not appear to substantially affect the risk of malformations, with the exception of topiramate, which is associated with an increased risk of oral clefts.[3]

In addition to the teratogenic effects of valproate, maternal use of the drug during pregnancy has been associated with decreased neurocognitive function in children,[4-18] and increased risks of autism spectrum disorder[17,19-22] and attention deficit–hyperactivity disorder (ADHD).[11,20,23] In contrast, studies, with few exceptions,[6,8] have generally not linked maternal lamotrigine use with adverse neurodevelopmental outcomes.[12-20,24,25] Data to inform neurodevelopmental outcomes in children exposed to topiramate in utero have been limited and mixed.[8,9,16,24,26,27] A recent Nordic study showed an increased risk of autism spectrum disorder after prenatal exposure to topiramate on the basis of a small number of cases in exposed children.[17] Further evaluation of the risk of autism spectrum disorder among children with prenatal exposure to topiramate is needed to inform its safety for women with epilepsy or other potential indications, including bipolar disorder, migraine, and weight loss.

We used two population-based U.S. health care utilization databases to study the association between topiramate treatment during pregnancy and risk of autism spectrum disorder among offspring. Valproate- and lamotrigine-exposed pregnancies were used as positive and negative controls, respectively.

Methods

Data Sources

We identified pregnancy cohorts nested in the Medicaid Analytic eXtract–Transformed Medicaid Statistical Information System Analytic Files (MAX-TAF) from 2000 through 2018, which include data on health care use for Medicaid beneficiaries nationwide, and the Merative MarketScan Commercial Claims and Encounters Database (referred to hereafter as MarketScan) from 2003 through 2020, which includes data on commercial health insurance.[28,29] Both data sources contain information on demographic characteristics, diagnoses, and procedures received during inpatient, outpatient, or emergency department visits, as well as dispensed outpatient prescription medications. The study design is summarized in Figure S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. The study was approved by the institutional review board at Brigham and Women's Hospital, which waived the need for informed consent.

Study Population

The study population comprised persons of female sex and any gender identity 12 through 55 years of age (referred to hereafter as women), linked with their liveborn children, and who had insurance coverage from at least 3 months before the date of the estimated last menstrual period to 1 month after delivery. For primary analyses, the cohort was further restricted to women with epilepsy, the main indication for the antiseizure medications considered (see the Supplementary Appendix for details on the algorithm used to define epilepsy). Children with chromosomal anomalies were excluded under the assumption that the cause of potential neurodevelopmental disorders in these children is unlikely to be related to maternal use of antiseizure medications. Children with major congenital malformations were excluded in sensitivity analyses given the potential for shared etiologic pathways between anatomical and neurologic anomalies.[5]

Exposure Groups

The primary exposure group included women with at least one dispensing for topiramate (or valproate or lamotrigine as positive and negative controls, respectively) during the second half of pregnancy (defined as week 19 of gestation to delivery), which is a period of substantial synaptogenesis.[30,31] The unexposed reference group included women without any dispensing of antiseizure medication between 90 days before the last menstrual period and delivery (i.e., presumed inactive or pharmaco-

logically untreated epilepsy). To address exposure misclassification, one sensitivity analysis required at least two dispensings during the exposure window, because women who refill a prescription for antiseizure medication may be more likely to have taken the medication than those who do not refill the medication, and another required a dispensing in the third trimester, which is the peak synaptogenesis period.[30,31]

Several secondary analyses were conducted. To account for concomitant use of more than one antiseizure medication, we defined exposure as monotherapy if the mothers had filled prescriptions for only the specific antiseizure medication of interest but no other antiseizure medications during the exposure window. To evaluate dose response, we defined low daily doses as less than 200 mg for topiramate, less than 1000 mg for valproate, and less than 300 mg for lamotrigine, on the basis of the first dispensing of the drug of interest during the assessment period. Alternative assessments with respect to high or low dose were included in sensitivity analyses. These cutoff points reflect the median dose for patients with epilepsy (Table S1). To evaluate alternative etiologically relevant windows for fetal vulnerability, we considered exposures during the first half of pregnancy (defined as last menstrual period through 18 weeks after last menstrual period) irrespective of exposure thereafter, exposure only during the first half of pregnancy but not afterward, and exposure only during the second half of pregnancy but not earlier. To further improve the comparability of the treatment strategies, we used lamotrigine monotherapy as the active reference group because previous studies supported overall safety with respect to neurodevelopment and because it is a commonly prescribed antiseizure medication in women of reproductive age. We used the full cohort for this comparative safety analysis (i.e., no restriction with respect to epilepsy status) to improve precision and adjusted for possible indications for topiramate and lamotrigine. To assess the generalizability of the results to antiseizure-medication use for nonepilepsy indications, we restricted the population to women without a recorded epilepsy diagnosis and adjusted for other indications.

OUTCOME

Clinical diagnoses of autism spectrum disorder were ascertained with the use of a validated claims-based algorithm that requires at least two visits with codes for autism spectrum disorder at or after the age of 1 year. This algorithm has a positive predictive value of 94%.[32]

COVARIATES

We identified a broad list of potential confounders, including demographic characteristics, maternal mental health and neurologic conditions other than epilepsy (e.g., bipolar disorder, depression, anxiety, and migraine), other potential indications (e.g., weight loss), concomitant medications, lifestyle factors, maternal coexisting conditions, and health care use. A full list of covariates and their assessment periods is provided in Table S2.

STATISTICAL ANALYSIS

Descriptive statistics were calculated for all covariates according to exposure group with the use of means and standard deviations for continuous variables and counts and percentages for categorical variables and compared between groups with the use of standardized mean differences. Children were followed from birth until the end of enrollment, diagnosis of autism spectrum disorder, the end of the study period, or death, whichever occurred first. Crude and weighted cumulative incidence of diagnosis of autism spectrum disorder at 8 years of age was estimated for each exposure group with the use of the Kaplan–Meier method. Cox proportional-hazard models were used to calculate crude and weighted hazard ratios, overall and at each year of age. Propensity score overlap weighting was used to adjust for measured baseline confounders when each antiseizure medication was compared with the reference group.[33] An analysis to adjust for censoring bias was conducted with the use of inverse-probability weights constructed with measured baseline covariates. Weighted 95% confidence intervals were calculated with the use of robust standard errors. Data from each data source were combined by pooling at the individual level and accounting for the data source in the propensity-score models. All analyses were conducted with the use of SAS software, version 9.4 (SAS Institute), and R software.

Table 1. Selected Patient Characteristics among Topiramate-Exposed Pregnancies (Second Half of Pregnancy) as Compared with Unexposed Pregnancies, According to Study Cohort.*

Characteristic	Full Cohort				Epilepsy-Restricted Cohort			
	MAX-TAF		MarketScan		MAX-TAF		MarketScan	
	Exposure to Topiramate (N=1750)	No Exposure to ASM (N=2,433,177)	Exposure to Topiramate (N=719)	No Exposure to ASM (N=1,766,619)	Exposure to Topiramate (N=730)	No Exposure to ASM (N=7245)	Exposure to Topiramate (N=300)	No Exposure to ASM (N=1570)
Age — yr	27.3±6.1	25.1±6.0	31.6±4.7	31.6±4.6	26.1±5.8	24.5±5.4	30.6±4.7	30.4±4.8
Race or ethnic group — no. (%)†								
Asian or other Pacific Islander	18 (1.0)	85,863 (3.5)	NA	NA	<11‡	74 (1.0)	NA	NA
Black	341 (19.5)	740,613 (30.4)	NA	NA	145 (19.9)	2139 (29.5)	NA	NA
Hispanic or Latino	189 (10.8)	505,728 (20.8)	NA	NA	84 (11.5)	963 (13.3)	NA	NA
Unknown or other	73 (4.2)	132,824 (5.5)	NA	NA	—§	340 (4.7)	NA	NA
White	1129 (64.5)	968,149 (39.8)	NA	NA	461 (63.2)	3729 (51.5)	NA	NA
Mental health or developmental conditions — no. (%)								
Anxiety	416 (23.8)	154,631 (6.4)	103 (14.3)	89,865 (5.1)	131 (17.9)	1489 (20.6)	24 (8.0)	237 (15.1)
Bipolar disorder	304 (17.4)	47,692 (2.0)	33 (4.6)	6,104 (0.3)	81 (11.1)	610 (8.4)	6 (2.0)	41 (2.6)
Depression	512 (29.3)	211,025 (8.7)	140 (19.5)	90,744 (5.1)	174 (23.8)	1660 (22.9)	43 (14.3)	223 (14.2)
Epilepsy	730 (41.7)	7,245 (0.3)	300 (41.7)	1,570 (0.1)	730 (100)	7245 (100)	300 (100)	1570 (100)
ADHD	76 (4.3)	23,018 (0.9)	21 (2.9)	12,894 (0.7)	18 (2.5)	191 (2.6)	3 (1.0)	37 (2.4)
Markers of health care use								
No. of mental health diagnoses	1.7±2.7	0.4±1.2	0.8±1.8	0.2±0.8	1.3±2.4	1.3±2.5	0.4±1.3	0.7±1.7
No. of outpatient visits	15.0±15.7	7.9±8.1	12.6±9.3	8.4±6.9	14.5±12.7	11.9±12.5	11.5±7.0	12.2±9.2
Lifestyle behaviors — no. (%)								
Tobacco use	305 (17.4)	232,074 (9.5)	19 (2.6)	24,365 (1.4)	105 (14.4)	1475 (20.4)	7 (2.3)	92 (5.9)
Substance use disorder	202 (11.5)	116,622 (4.8)	21 (2.9)	6,361 (0.4)	70 (9.6)	1007 (13.9)	9 (3.0)	40 (2.5)
Prescription medications — no. (%)								
Antidepressants	769 (43.9)	211,467 (8.7)	272 (37.8)	135,677 (7.7)	223 (30.5)	1452 (20.0)	62 (20.7)	259 (16.5)

Antipsychotics	282 (16.1)	47,822 (2.0)	31 (4.3)	8,484 (0.5)	74 (10.1)	430 (5.9)	5 (1.7)	38 (2.4)
Anxiolytics, hypnotics, or sedatives	310 (17.7)	113,323 (4.7)	90 (12.5)	35,952 (2.0)	86 (11.8)	742 (10.2)	19 (6.3)	83 (5.3)
Barbiturates	208 (11.9)	37,099 (1.5)	106 (14.7)	28,997 (1.6)	54 (7.4)	299 (4.1)	20 (6.7)	54 (3.4)
Benzodiazepines	448 (25.6)	73,675 (3.0)	135 (18.8)	66,721 (3.8)	129 (17.7)	760 (10.5)	37 (12.3)	152 (9.7)
Opioids	897 (51.3)	503,836 (20.7)	264 (36.7)	173,324 (9.8)	303 (41.5)	2514 (34.7)	78 (26.0)	290 (18.5)
Psychostimulants	85 (4.9)	20,802 (0.9)	37 (5.1)	19,981 (1.1)	13 (1.8)	131 (1.8)	6 (2.0)	40 (2.5)

* Plus–minus values are means ±SD. Data were derived from the Medicaid Analytic eXtract–Transformed Medicaid Statistical Information System Analytic Files (MAX-TAF) and the Merative MarketScan Commercial Claims and Encounters Database (MarketScan). ADHD denotes attention deficit–hyperactivity disorder, ASM antiseizure medication, and NA not available.
† Race or ethnic group was determined on the basis of data that had been collected and coded from Medicaid applications and submitted to the Centers for Medicare and Medicaid Services (CMS) by individual states.
‡ The number was suppressed in the MAX-TAF database owing to the cell-suppression policy of the CMS.
§ The number was suppressed to avoid back-calculation.

RESULTS

DESCRIPTION OF STUDY POPULATION

Among 4,292,539 eligible pregnancies, 2469 had at least one dispensation during the second half of pregnancy for topiramate, 1392 for valproate, and 8464 for lamotrigine; 4,199,796 did not have dispensations for any antiseizure medications in the 90 days before and during pregnancy (Fig. S2). As compared with unexposed mothers, mothers exposed to topiramate had a higher frequency of epilepsy, bipolar disorder, migraine, neuropathic pain, anxiety, depression, and ADHD. They were also more likely than unexposed mothers to be White (MAX-TAF population), to have received a diagnosis of diabetes or obesity, to use tobacco or have alcohol use disorder or substance use disorder, and to use antidepressants, anxiolytic agents, or opioids; they also had more frequent health care use. The characteristics were more similar to those of the lamotrigine reference group, although the distribution of neurologic and mental health diagnoses still differed.

Among 28,952 women with a recorded epilepsy diagnosis, 1030 had at least one dispensation during the second half of pregnancy for topiramate, 800 for valproate, and 4205 for lamotrigine; 8815 did not have dispensations for any antiseizure medications in the 90 days before and during pregnancy. Among women with epilepsy, characteristics were more balanced across groups even before weighting on the basis of propensity scores (Table 1 and Tables S3, S4, and S5).

The median follow-up was 2 years. Of the more than 4.2 million children eligible at birth, more than 400,000 were followed for at least 8 years.

INCIDENCE OF AUTISM SPECTRUM DISORDER

The cumulative incidence of autism spectrum disorder at 8 years of age among children not exposed to antiseizure medication was 1.89% (95% confidence interval [CI], 1.87 to 1.92) in the full population, in which the incidence of autism spectrum disorder appeared to be higher for all antiseizure medications considered relative to the unexposed group. On restriction of the population to mothers with epilepsy, the cumulative incidence curves largely overlapped, except for children exposed to valproate, who had

a higher incidence of autism spectrum disorder (Fig. S3). Within the group with maternal epilepsy, the crude cumulative incidence of autism spectrum disorder at 8 years of age was 4.21% (95% CI, 3.27 to 5.16) with no exposure to antiseizure medication, 6.15% (95% CI, 2.98 to 9.31) with exposure to topiramate, 10.51% (95% CI, 6.78 to 14.24) with exposure to valproate, and 4.08% (95% CI, 2.75 to 5.41) with exposure to lamotrigine.

PRIMARY COMPARISONS

The weighted cumulative incidence curves for each comparison are presented in Figure 1. Within the group with maternal epilepsy, the weighted average hazard ratios as compared with no exposure to antiseizure medication were 0.96 (95% CI, 0.56 to 1.65) with exposure to topiramate, 2.67 (95% CI, 1.69 to 4.20) with exposure to valproate, and 1.00 (95% CI, 0.69 to 1.46) with exposure to lamotrigine (Fig. 2). The hazard ratios at each year of age are shown in Figure S4.

SECONDARY ANALYSES

Weighted hazard ratios for topiramate were consistent with no substantive increase in risk with monotherapy, with lower and higher doses, and with exposures early in pregnancy with or without discontinuation (Fig. 3 and Table S6). Similar results were found for lamotrigine. Results were also similar when analyses were restricted to a population without an epilepsy diagnosis after adjustment for nonepilepsy indications and other covariates, although the confidence intervals were wider (Table S7). As compared with no exposure to antiseizure medication, hazard ratios associated with in utero valproate exposure appeared to be higher with the use of higher (rather than lower) doses and lower for exposure only early (rather than late) in pregnancy, although estimates were imprecise. Analyses with alternative assessments with respect to high or low dose yielded similar results (Fig. S5). As compared with lamotrigine monotherapy, the adjusted hazard ratios were 1.22 (95% CI, 0.76 to 1.98) for topiramate and 1.79 (95% CI, 1.12 to 2.87) for valproate.

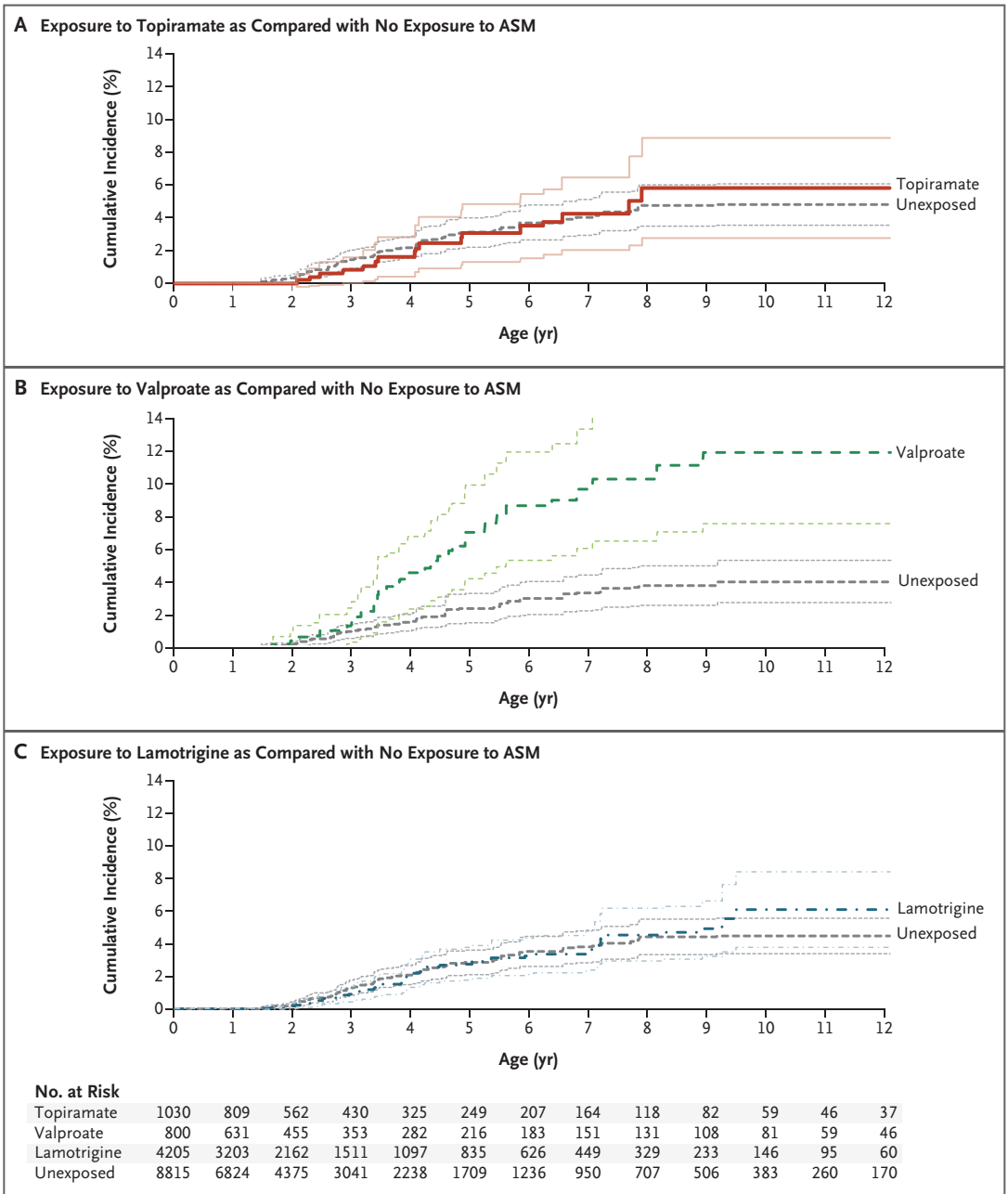
SENSITIVITY ANALYSES

Findings for topiramate, valproate, and lamotrigine were materially unchanged in sensitivity analyses limited to women with more than one dispensing late in pregnancy or a dispensing in the third trimester. Analyses that applied censoring weights or excluded children with major congenital malformations (Fig. 3) also yielded similar results, as did post hoc analyses weighting the population to the unexposed group (Table S8).

DISCUSSION

In a large U.S. nationwide cohort of mother–child dyads, the incidence of autism spectrum disorder was higher among children exposed to topiramate in the second half of pregnancy than in the general population of children without in utero exposure to antiseizure medication, but not relative to other children born to women with epilepsy. Overall, results suggest no substantially increased risk of autism spectrum disorder after prenatal exposure to either topiramate or lamotrigine (the negative control group) and a dose-dependent increased risk of autism spectrum disorder associated with prenatal valproate exposure (the positive control group).

Given the well-known strong teratogenic and neurotoxic effects of valproate on the fetus,[4-18] use during pregnancy is restricted to exceptional circumstances. There is a dose-dependent relationship between valproate and both malformations and cognitive impairment in children, but risks of these adverse outcomes are increased even with the use of low doses of valproate.[10-18,27] Topiramate is generally not considered to be a favorable alternative to valproate in pregnancy owing to increased risks of oral clefts and small size for gestational age.[3,34] Although there are fewer data to inform risks of adverse neurodevelopmental outcomes after maternal topiramate use, concern was raised by a recent Nordic register-based study showing that prenatal topiramate exposure was associated with an increased risk of autism spectrum disorder (adjusted hazard ratio, 2.8; 95% CI, 1.4 to 5.7).[17] This association appeared to be stronger with doses of 100 mg or more. Of the 246 mothers with epilepsy who were prescribed topiramate after the last menstrual period, too few had prescriptions beyond the first trimester to estimate the effects of late-pregnancy use (probably the etiologically relevant exposure window for neurodevelopmental disorders). Although there are some



No. at Risk

Topiramate	1030	809	562	430	325	249	207	164	118	82	59	46	37
Valproate	800	631	455	353	282	216	183	151	131	108	81	59	46
Lamotrigine	4205	3203	2162	1511	1097	835	626	449	329	233	146	95	60
Unexposed	8815	6824	4375	3041	2238	1709	1236	950	707	506	383	260	170

Figure 1. Autism Spectrum Disorder in Children with Prenatal Exposure to Topiramate, Valproate, or Lamotrigine as Compared with Those with No Exposure to Antiseizure Medication (ASM) within the Epilepsy-Restricted Cohort.

Propensity score overlap weighting was used to calculate cumulative incidence. The lighter curves represent 95% confidence intervals.

differences in characteristics between the Nordic cohort and our cohort (Table S9), these would not be expected to explain differences between the Nordic study and our study in risks of autism spectrum disorder associated with topiramate, particularly given that risks associated with valproate and lamotrigine were similar in the two studies.

Our study combined two nationwide maternal–child cohorts with public or commercial health insurance to obtain a representative sample of the U.S. population (Table S10), considered exposures that extended into the second half of pregnancy, and controlled for confounding by maternal indication for antiseizure medication. Limitations of our study should be noted. Despite the large number of pregnancies, a substantial proportion of children were lost to follow-up by 8 years of age. However, the size of the cohort remained large, and analyses that accounted for censoring by observed covariates did not affect the estimates, which makes selection bias unlikely. Prescriptions filled were used as a proxy for actual medication use, which could bias effect estimates toward the null. However, the results of sensitivity analyses that required two fills of an antiseizure medication during the exposure window were consistent with the main results. In addition, the lack of long-term follow-up and the relatively small number of cases of autism spectrum disorder resulted in wide confidence intervals, with hazard ratios for autism spectrum disorder associated with topiramate use (vs. no use of antiseizure medication) in pregnant women with epilepsy ranging from a 44% lower risk to a 65% higher risk.

At least part of the crude association between antiseizure medications and autism spectrum disorder is due to confounding by indication. In previous studies, the risk of neurodevelopmental disorders among the offspring was consistently larger in the subpopulations of women with epilepsy.[15,17,19] In our study, epilepsy was also associated with an elevated risk of diagnosis of autism spectrum disorder among the children, and the risk was elevated across antiseizure medications. Controlling for the indication for use of antiseizure medication and adjusting for other measured confounders shifted hazard-ratio estimates to the null for topiramate and lamotrigine, whereas an increased risk for valproate remained. Some residual confounding is possible — for example, by factors for which we did not have data (e.g., maternal epilepsy type and maternal IQ) or for which data may have been misclassified (e.g., mental health status, alcohol intake, and substance use disorder). However, because correcting for these factors would tend to move the hazard ratios downward, residual confounding would not explain the results for topiramate. In addition, in clinical studies that included adjustment for maternal IQ and epilepsy type, children with prenatal exposure to valproate still had lower IQ scores

Medication and Cohort	Analysis	Exposed	Unexposed	Cumulative Incidence at 8 Yr of Age		Hazard Ratio (95% CI)
				Exposed	Unexposed	
		no. of cases/total no.		*percent*		
Topiramate						
Full cohort	Crude	32/2469	24,947/4,199,796	4.75	1.89	2.17 (1.54–3.07)
Epilepsy cohort	Crude	17/1030	102/8,815	6.15	4.21	1.16 (0.70–1.94)
Epilepsy cohort	PS-weighted	17/1030	102/8,815	5.81	4.77	0.96 (0.56–1.65)
Valproate						
Full cohort	Crude	38/1392	24,947/4,199,796	6.83	1.89	3.69 (2.68–5.07)
Epilepsy cohort	Crude	32/800	102/8,815	10.51	4.21	2.53 (1.70–3.78)
Epilepsy cohort	PS-weighted	32/800	102/8,815	10.31	3.81	2.67 (1.69–4.20)
Lamotrigine						
Full cohort	Crude	93/8464	24,947/4,199,796	3.65	1.89	2.16 (1.76–2.64)
Epilepsy cohort	Crude	50/4205	102/8,815	4.08	4.21	1.01 (0.72–1.41)
Epilepsy cohort	PS-weighted	50/4205	102/8,815	4.55	4.41	1.00 (0.69–1.46)

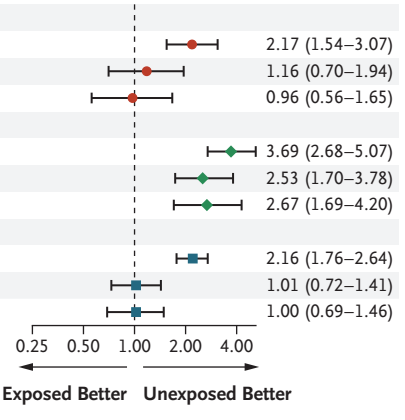


Figure 2. Autism Spectrum Disorder in Children with Prenatal Exposure to Topiramate, Valproate, or Lamotrigine as Compared with Those with No Exposure to ASM, According to Cohort and Type of Analysis.

PS denotes propensity score.

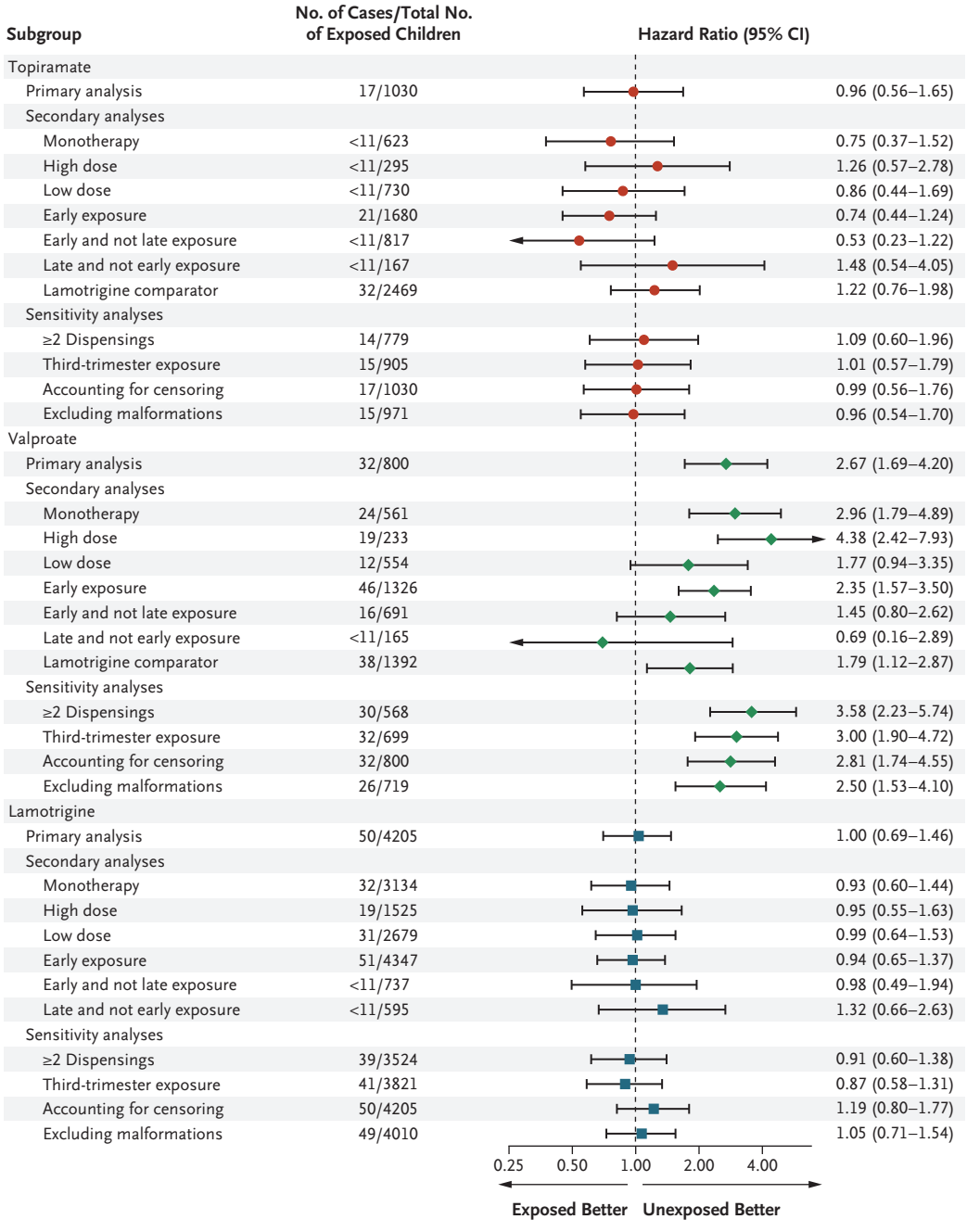


Figure 3. Primary, Secondary, and Sensitivity Analyses of Autism Spectrum Disorder in Children with Prenatal Exposure to Topiramate, Valproate, or Lamotrigine as Compared with Those with No Exposure to ASM within the Epilepsy-Restricted Cohort.

Propensity score overlap weighting was used to calculate hazard ratios. Arrows indicate that the confidence interval extends past the graphed area. Early exposure was defined as prescriptions filled before 19 weeks' gestation, and late exposure was defined as prescriptions filled at 19 weeks' gestation or later. Cutoff points to define high as compared with low daily dose were based on the median dose of the first prescription for the drug of interest dispensed to patients with epilepsy during the assessment period. The cutoff points were 200 mg for topiramate, 1000 mg for valproate, and 300 mg for lamotrigine.

than unexposed children[12,13] and had more autistic traits.[17,19,22] Differential risks among antiseizure medications may be explained by confounding by characteristics associated with both the choice of antiseizure medication and the risk of neurodevelopmental disorders in the child. For example, valproate is more often used for generalized epilepsy and tends to be used by women of childbearing potential only if their epilepsy is refractory to other antiseizure medications. However, neither maternal epilepsy type[5,10,12,13,18,35] nor seizure type and frequency[10,12,13,18] have been associated with poorer child development in most studies, although there are some exceptions.[5,7]

The reasons for the higher risk of neurodevelopmental disorders among children when the mother has an indication for treatment with antiseizure medications are not well delineated. Explanations may include shared genetic disposition for the maternal neuropsychiatric indication and the child's disorder, an effect of maternal illness during childhood on the child's development, or differential surveillance or diagnosis of neurodevelopmental disorders when the mother used antiseizure medications during pregnancy and the assessments are unblinded. Valproate may interfere with neurotransmission critical for cell migration and differentiation or may induce neuronal apoptosis during the synaptogenesis period.[36,37] Prenatal exposure to traditional antiseizure medications has been associated with reduced brain volume, which provides an anatomical basis for the cognitive impairments.[38] Moreover, the effects of antiseizure medication on neurotransmitters that are used by embryonic cells during organogenesis may also play a role in the cause of structural malformations.[39] A common causal mechanism for teratogenicity and fetal neurotoxicity would explain why valproate carries the strongest risks for both. It would also predict some neurotoxic effects for topiramate, given its lower teratogenic potential.[3] However, topiramate was not associated with increased neuronal apoptosis in rodents.[40]

In this large cohort study, the incidence of autism spectrum disorder was higher among children prenatally exposed to the studied antiseizure medications than in the general population. However, after adjustment for indication, the association was substantially attenuated for topiramate and lamotrigine, whereas a dose-dependent increased risk remained for valproate.

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