NEJM Resident 360

Literature

Clinical Pearls & Morning Reports

Autism and Prenatal Exposure to Antiseizure Medication

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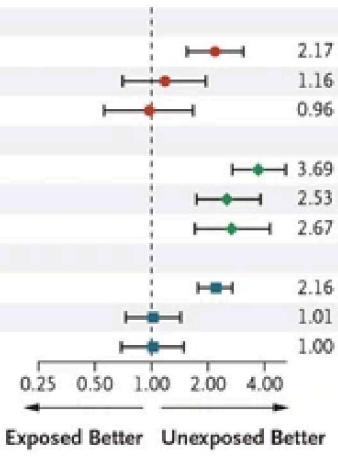
Medication and Cohort	Analysis	Exposed	Unexposed	Cumulative Incidence at 8 Yr of Age		Hazard Ratio (95% CI)
				Exposed	Unexposed	
		no. of cases/total no.		*percent*		
Topiramate						
Full cohort	Crude	32/2469	24,947/4,199,796	4.75	1.89	2.17 (1.54–3.07)
Epilepsy cohort	Crude	17/1030	102/8,815	6.15	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)



In this study, was topiramate exposure during the second half of pregnancy associated with an increased risk of autism spectrum disorder?

Most women with epilepsy receive treatment with antiseizure medication throughout pregnancy. Hernández-Díaz et al. conducted a study that used two population-based United States health care utilization databases to examine the association between topiramate treatment during the second half of pregnancy and risk of autism spectrum disorder among offspring. Valproate- and lamotrigine-exposed pregnancies were used as positive and negative controls, respectively. Read the NEJM Original Article here.

Clinical Pearls

Q: Does in utero exposure to valproate pose a risk to the fetus when used at low doses?

A: Given the well-known strong teratogenic and neurotoxic effects of valproate on the fetus, 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. 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.

Q: What is known about the safety of lamotrigine during pregnancy?

A: In addition to the teratogenic effects of valproate, maternal use of the drug during pregnancy has been associated with decreased neurocognitive function in children, and increased risks of autism spectrum disorder and attention deficit–hyperactivity disorder. In contrast, studies, with few exceptions, have generally not linked maternal lamotrigine use with adverse neurodevelopmental outcomes. Data to inform neurodevelopmental outcomes in children exposed to topiramate in utero have been limited and mixed. 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.

Morning Report Questions

Q: In this study, was topiramate exposure during the second half of pregnancy associated with an increased risk of autism spectrum disorder?

A: In this 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. 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. 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).

Q: What were some of the limitations of this study?

A: 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. 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.

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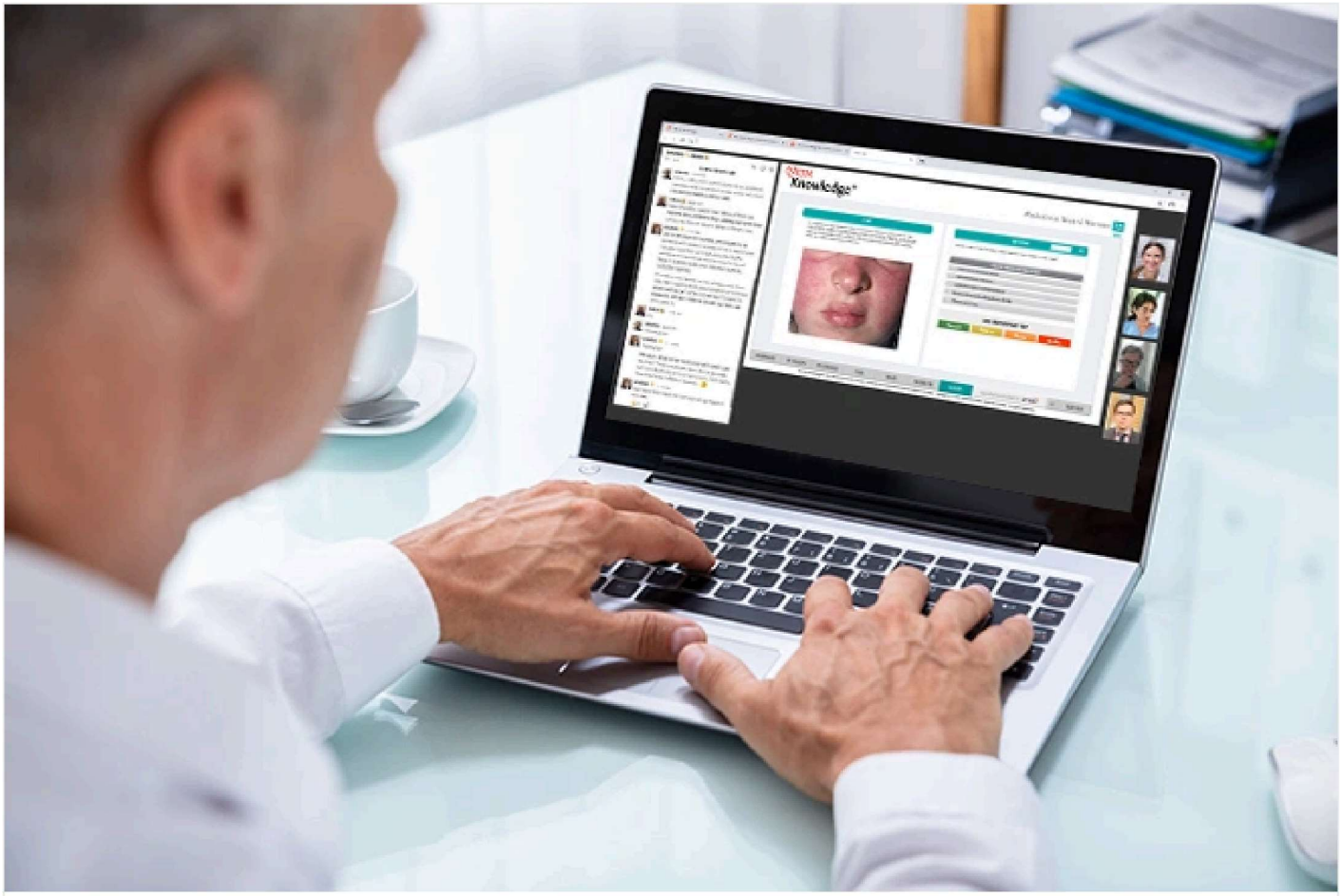

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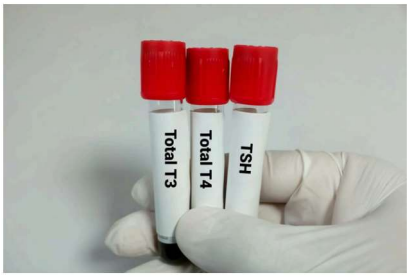

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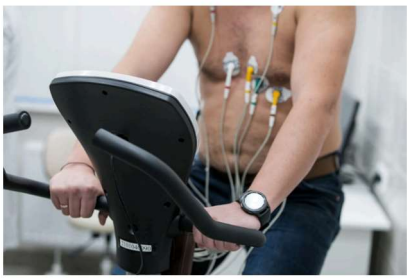

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