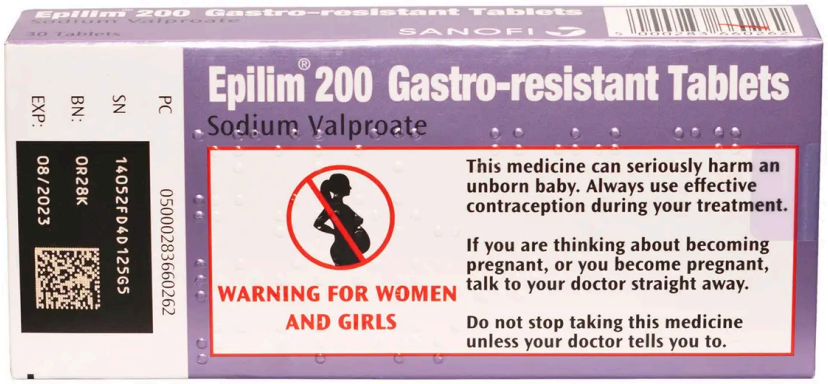
Use of These Epilepsy Meds During Pregnancy Linked to Child's Autism

— Valproate not the only one associated with neurodevelopmental disorders

by Michal Ruprecht, Editorial Intern, MedPage Today
June 1, 2022



Children exposed prenatally to antiseizure medications were at greater risk of autism spectrum disorders (ASD) and intellectual disability (ID), according to a population-based cohort study.

By approximately age 8 years, children were two to four times more likely to be diagnosed with these neurodevelopmental disorders if their mothers had taken topiramate or valproate monotherapy during pregnancy. Exposure to levetiracetam-carbamazepine or lamotrigine-topiramate duotherapy was associated with similar risk as

well, reported Marte-Helene Bjørk, MD, PhD, of Haukeland University Hospital in Norway, and colleagues in *JAMA Neurology*.

Bjørk's group suggested that topiramate does not appear to be a safe alternative to valproate. "Women of reproductive age who are prescribed topiramate should be informed of the potential risks, and these should be weighed against the benefits and available treatment options."

Exposure to other antiseizure medications like oxcarbazepine, carbamazepine, and clonazepam was associated with no increase in neurodevelopmental disorders among children of mothers with epilepsy.

These findings largely fit with what has been seen in prior registries.

Valproate has been associated with one of the highest risks for congenital malformation and neurodevelopmental problems among the seizure medications, whereas levetiracetam and lamotrigine have had some of the best safety data to date, noted Page Pennell, MD, chair of the Department of Neurology at the University of Pittsburgh School of Medicine, in an interview with *MedPage Today*.

Overall, though, physicians are still "flying completely blind" when it comes to safety of most epilepsy drugs in pregnancy, lamented Kimford Meador, MD, of Stanford University School of Medicine and its Neuroscience Health Center in Palo Alto, California.

Beyond the few known to be dangerous and the several that appear fairly safe, "for the other 30-something drugs, we don't know," he said.

"When you're in the clinic and you have a woman come in and she's burned through those first few drugs -- they either didn't work or she got a rash on lamotrigine, she got depressed with levetiracetam, which happens -- and she's got primary generalized epilepsy, you don't know where to go next," said Meador. "There is no data, except maybe avoid valproate if you can."

Women with epilepsy usually require antiseizure medication during their pregnancy. Currently, about 0.5% of pregnant women use antiseizure medications, according to a study from 2020.

Yet the real number is unknown because there is no national reporting system in place in the U.S., Meador noted. Manufacturers are not required to do testing for children's outcomes, nor is there enough funding to look at the underlying mechanisms linking these medications and neurodevelopment in the child.

Some regulatory agencies like the European Medicines Agency recommended clinicians stop prescribing valproate -- a drug on the World Health Organization's list of essential medicines -- to women of childbearing age in 2014. FDA requires valproate labeling to include a warning against use during pregnancy.

Last month, the producer of valproate was required to pay nearly €500,000 in damages to a French family with a child suffering from valproate-associated ASD.

"With regulatory warnings cautioning against valproate use in women of childbearing potential, safety data are urgently needed for alternative treatment options," Bjørk and colleagues emphasized.

Because there was no observed adverse neurodevelopment with levetiracetam-lamotrigine use in their study, they suggested future research focus on this duotherapy to learn more about its safety and efficacy during pregnancy.

The investigators used data from the Nordic register-based study of antiepileptic drugs in pregnancy (SCAN-AED), which includes data from Denmark, Finland, Iceland, Norway, and Sweden collected from 1996 to 2017. Children were diagnosed with ASD and ID according to ICD-10 codes.

Nearly 4.5 million children participated in the study and 48.7% were girls. Median age was 8 years.

Children whose mothers filled prescriptions for antiseizure medication from 90 days before the last menstrual period to birth comprised 0.6% of the cohort and were compared against unexposed controls.

Neurodevelopmental risk increased with higher antiseizure medication dosage, the investigators reported.

Study results generally remained the same when authors expanded the exposed cohort to include children of women who filled their prescription within 2 years of pregnancy, but not within the 90 days prior to their last menstruation.

Bjørk and coauthors said that their inability to gather data on paternal and other family history was a limitation of the study.

"Epidemiological, clinical, and preclinical studies support our results," they maintained. "Previous nationwide register studies have shown similar strength associations between valproate use during pregnancy and ASD and ID."

Michal Ruprecht is a medical student based in Michigan. He is a former reporting intern for MedPage Today. Follow

Disclosures

The study was funded by a grant from NordForsk and the Research Council of Norway. Bjørk disclosed relationships (fees, grant support, or other) with Valproate, Eisai, Novartis Norway, Jazz Pharmaceuticals, Angelini Pharma, Teva, and Lilly.

Pennell disclosed no relevant relationships with industry.

Meador has received research support from the NIH and Eisai. The Epilepsy Study Consortium pays Meador's university for his research consultant time related to Eisai, GW Pharmaceuticals, NeuroPace, Novartis, Supernus, Upsher-Smith Laboratories, UCB Pharma, and Vivus Pharmaceuticals.

Primary Source

JAMA Neurology

Source Reference: *Bjørk MH, et al "Association of prenatal exposure to antiseizure medication with risk of autism and intellectual disability" JAMA Neurol 2022; DOI: 10.1001/jamaneurol.2022.1269.*

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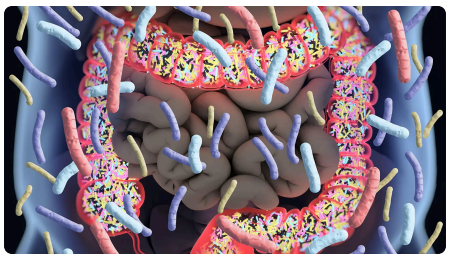

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