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**Valproate Linked to Cognitive Delay, Autism in Children**

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December 13, 2011 (Baltimore, Maryland) — Results from the final segment of the decade-long Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study confirm that fetal exposure to valproate impairs IQ well into childhood.

The US Food and Drug Administration issued a [safety announcement](#) this summer, warning of such concerns. The main study supporting this decision was based on the preliminary work of Kimford Meador, MD, from Emory University in Atlanta, Georgia, and colleagues in the NEAD study ([N Engl J Med. 2009;360:1597-1605](#)).

**Valproate and cognitive delay at age 6**

Although several reports from this cohort have been published previously, the primary outcome for the study, IQ results at age 6 years, was presented here at the American Epilepsy Society (AES) 65th Annual Meeting.

The prospective observational multicenter study, which was conducted in the United States and the United Kingdom, enrolled 310 pregnant women with epilepsy who were receiving antiepileptic drug monotherapy. The purpose was to determine whether differential long-term neurodevelopmental effects exist across 4 commonly used drugs: carbamazepine, lamotrigine, phenytoin, and valproate.

Investigators observed significant cognitive effects with valproate compared with other agents. Child IQ was significantly lower with this antiepileptic drug than with others ( $P = .002$ ).

"The deficits we saw early on continue to age 6," Dr. Meador said. "Children were 8 to 11 IQ points lower."

**Table. Mean IQ at Age 6 Years by Antiepileptic Drug Exposure**

Drug	Adjusted Mean IQs
Carbamazepine	105
Lamotrigine	108
Phenytoin	108
Valproate	97

The effect of valproate exposure was dose dependent ( $r, -.56; P < .001$ ). This was not the case for the other antiepileptic drugs.

"Valproate is a very poor first choice for women of childbearing age," Dr. Meador said. Guidelines on epilepsy in pregnancy developed by the American Academy of Neurology and the AES released in 2009 already suggest that valproate should be avoided during pregnancy if possible.

However, Dr. Meador has a couple of patients with epilepsy who only respond to valproate, for example. "In such instances, the lowest possible dose is indicated."

The investigators are planning to present the results on other cognitive domains this spring at the American Academy of Neurology annual meeting.

"Further investigation is needed to confirm if the verbal impairments seen in the children exposed to valproate in this study occur in a different cohort," Dr. Meador said.

"Research is also needed to determine the cognitive effects of fetal exposure on other antiepileptic drugs and to identify the mechanisms underlying these effects."

The work was awarded the Dreifuss Honor of the AES. "I knew Dr. Fritz Dreifuss from my internship," Dr. Meador said at the meeting. "He was a great researcher and a wonderful person, and this is truly an honor."

### **Valproate and Autism**

[Another study](#) presented at this meeting links prenatal valproate exposure to a higher risk for autism, but the results of the population-based study are preliminary. However, investigators saw a 2.6 times higher relative risk for autism spectrum disorder.

The relative risk for childhood autism was almost 5-fold higher compared with children without prenatal exposure to valproate.

The findings are from several national registries. Investigators led by Jakob Christensen, MD, from Aarhus University in Denmark, looked at 6000 mothers with epilepsy taking valproate 30 days before the day of conception to the day of birth. The investigators then evaluated how many children were born with autism.

Dr. Christensen acknowledged to *Medscape Medical News* that it is unclear whether the increased risk is related to valproate exposure or to the well-known link between epilepsy and autism.

"It's hard to say. We adjusted for psychiatric comorbidity in mothers, but more work remains," he said.

### **Epilepsy and Developmental Delay**

"We don't know whether uncontrolled epilepsy may lead to autism," Masanori Takeoka, MD, from Harvard Medical School in Boston, Massachusetts, said in another news conference at the meeting, "but both tend to feature intellectual disabilities."

Dr. Takeoka is senior investigator of another study [presented at the meeting](#). His team found not only that autism is common in children with epilepsy but also that their seizures are surprisingly photosensitive.

"Systematic screening should be routine for all children seen in epilepsy clinics," Anne Berg, PhD, from Children's Memorial Hospital in Chicago, Illinois, told reporters.

In a [separate study](#), Dr. Berg's team found that despite problems, many children with epilepsy are not evaluated for autism or developmental delay.

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