Additional Data Link Valproate Use to Birth Defects

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BOSTON — Two new data sets reinforce the recommendation to avoid valproate as a first-line therapy for any indication in women of childbearing years.

The findings, presented at the annual meeting of the American Academy of Neurology, strengthen evidence of a link between valproate and major congenital malformations as well as impaired cognitive development of children exposed in utero.

"Not only our study, but nine other studies on valproate's anatomical and behavioral effects, have shown similar signals of poor outcome with this drug," Dr. Kimford J Meador said. "The drug should not be a first-line therapy for any indication in women of childbearing age. At the very minimum, women need to be aware of these risks if they are going to take this drug. We need to remember that half of U.S. pregnancies are unplanned."

Dr. Meador, the Melvin Greer Professor of Neurology and director of the epilepsy program at the University of Florida, Gainesville, presented interim data from the ongoing Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study for which investigators enrolled 185 children whose mothers took carbamazepine (48), lamotrigine (66), phenytoin (42), or valproate (29) for epilepsy during pregnancy.

Dr. Meador presented data on patients' mental development at age 2 years; the prospective study will follow the cohort to age 6. Mean IQ scores based on the Mental Development Index (MDI) from the Bayley Scale were lowest for children in the valproate group (81), Dr. Meador said. A score below 85 is considered to be below normal limits. Mean scores in the other groups were 94 for lamotrigine, 95 for phenytoin, and 96 for carbamazepine.

In addition, he said, the percentage of children in the valproate group with an MDI of less than 70 (correlating with mental retardation) was 24%, about double that seen in any of the other groups (carbamazepine, 13%; lamotrigine, 11%; and phenytoin, 12%).

The study also found an inverse relationship between maternal valproate blood levels during pregnancy and MDI scores in the children, Dr. Meador noted. All of the valproate relationships remained constant even after maternal IQ—an important driver of childhood IQ—maternal epilepsy type, and past medical history were controlled for.

The mechanism of brain injury in the valproate group is probably third-trimester neuronal apoptosis, Dr. Meador said in an interview. "We think it's similar to what's seen in fetal alcohol syndrome, and the apoptosis appears to occur at a relatively lower dose than it would with other drugs, such as phenytoin. I think that's why we see such an increased signal."

NEAD only includes children of women with epilepsy—the group that accounts for the smallest proportion of valproate prescriptions, he added. "Most of the prescriptions are written for other things. … [Fewer] than half are for epilepsy."

In the third quarter of 2006, about 16% of women of childbearing age with epilepsy were taking the drug, making it the fourth leading antiepileptic in the United States for this group. Valproate sales jumped 28% last year, an increase "that has to include some portion of women of childbearing age," Dr. Meador said.

The second study, GlaxoSmithKline's lamotrigine pregnancy registry, found that valproate in conjunction with lamotrigine significantly increases the risk of a major birth defect. The company produces lamotrigine. The registry, now in its 14th year, has prospectively enrolled 2,400 pregnancies occurring in 32 countries. There are known outcome data on 1,539 pregnancies, said Marianne Cunnington, Ph.D., of GlaxoSmithKline.

The risk of a major birth defect in the 908 first-trimester exposures to lamotrigine only was 2.9%, similar to the background population risk of 2%-3%. The risk associated with nonvalproate polytherapy was 2.6%. But when lamotrigine polytherapy included valproate, the risk of a major congenital malformation jumped to more than 11%. "We have a signal for an increased risk for polytherapy including valproate," she said, although "it's unclear whether valproate is responsible for this increased risk."

Dr. Meador noted, however, that six other studies have concluded that valproate significantly increases the risk of birth defects. "Each of these studies has different cohorts, but [investigators] all found similar rates." ■