



## **Risk of Birth Defects Found in 2 Epilepsy Drugs Data show rates as high as five times the norm. But stopping treatment can be complicated.**

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December 8, 2004

A new analysis of two drugs widely used to control epilepsy, manage bipolar disorder and alleviate migraines shows up to a five-fold increase in the risk of major birth defects, researchers said Tuesday.

Both drugs already carry warnings against use by pregnant women, but the risk had not been quantified, said Dr. Martha J. Morrell of Stanford University.

"This is the first time we have had real information to give our patients," she said.

One of the drugs, phenobarbital, has been declining in popularity. The second, valproic acid, should not be the first choice of treatment for young women who could get pregnant, said Dr. Kimford Meador of the University of Florida.

That's already the recommendation in England, he said, "and in my opinion, that should be the approach here."

Solving the problem is not as straightforward as banning use of the drugs, however, because in some cases one of them may provide the only way to control a person's seizures.

"Seizures can kill the mother, especially during pregnancy," Meador said. "They can also kill the child. Convulsions can also impair the child's cognition."

Whenever possible, newer drugs such as lamotrigine should be prescribed, Morrell said. Although physicians have not enrolled enough women using lamotrigine (sold under the brand name Lamictal) to be sure of its safety, she said, the numbers so far are "very compelling and reassuring."

An estimated 56 million prescriptions for anticonvulsants were filled in the United States in the last year. An estimated 12 million to 15 million of them were to women of childbearing age, said Dr. Gregory Barkley of Wayne State University, chairman of the Epilepsy Foundation's Professional Advisory Board.

"The risk extends to a broad proportion of the population," he said.

The physicians spoke in a telephone briefing from a New Orleans meeting of the American Epilepsy Society.

The doctors cautioned that women taking the drugs should not quit suddenly, because that could trigger seizures. Instead, they should consult with their physicians, who can gradually switch them to a safer drug.

"Stopping abruptly can be dangerous," Barkley said.

And there are still a large number of anticonvulsants for which no information on safety is available, Barkley said. Some of the drugs "are also used in combinations, and there may be some that should be avoided," he said. "We don't have any information on that yet."

The problem is that none of the drugs was tested in pregnant women in the clinical trials used for Food and Drug Administration approval. To have done so would have been unethical when it was not clear that the drugs were effective.

There have been hints for years that there are problems with some of the drugs. "The question is, is it safe to take them during pregnancy?" Morrell said. "The answer has been, well, we don't exactly know. We've been making decisions based on poor data."

In an effort to get better data, five registries were established between 1992 and 1999. The registries enroll pregnant women taking the drugs and monitor the outcomes.

Dr. Lewis Holmes of Harvard University heads the North American registry, which has enrolled about 4,000 women. Preliminary data, he said Tuesday, indicate that 10.7% of infants born to women taking valproic acid had a major birth defect, compared with a rate of about 2% in the general population. The rate was 6.5% among women taking phenobarbital.

The major birth defects include heart problems, cleft palate, and skeletal and kidney defects.

Several ongoing studies are also looking at the development of children whose mothers took valproic acid while they were pregnant. One study in Britain has found that the children, on average, have an IQ that is 10 points lower than that of children whose mothers did not take the drug.

The North American registry has not enrolled enough women to determine the safety of other drugs, and Holmes is seeking volunteers.

Women who are taking the anticonvulsants and who are pregnant can participate by calling (888) 233-2334 early in the pregnancy. All information collected in the study is confidential, he said.