Biomedical Update:

Depakote: are benefits worth the risks?

A recent study suggests that the anticonvulsant drug divalproex sodium (Depakote), a compound of valproate and valproic acid, may reduce repetitive behaviors in individuals with autism spectrum disorders. However, other research reveals that the drug can cause a wide range of dangerous and sometimes life-threatening side effects.

Eric Hollander and colleagues administered divalproex sodium to 13 autistic individuals in an eight-week, double-blind, placebo-controlled study. The researchers detected a marked drop in repetitive behaviors in treated children, as measured by the Children's Yale-Brown Obsessive Compulsive Scale.

The finding is consistent with a 2001 trial by Hollander et al., which found that divalproex sodium reduced core symptoms of autism as well as mood swings, impulsivity, and aggression. A more recent study of individuals with pervasive developmental disorder by J. A. Hellings and colleagues, however, found no significant difference between subjects taking valproate or a placebo. In the Hellings et al. study, one child developed a spreading skin rash, and two elevated serum ammonia levels (a potential indicator of encephalopathy).

The side effects seen in the Hellings et al. study highlight the fact that valproate or valproic acid (which converts to valproate in the gastrointestinal tract) can have severe adverse effects. Depakote already carries warnings noting that it is linked to potentially fatal pancreatitis and liver failure, and that it can cause severe birth defects in children of women who take the drug while pregnant. Recent studies link the drug to other conditions including:

--*Encephalopathy.* K. S. Thygesen and P. Wolf report two cases in which patients taking valproate experienced rapidly progressing, severe cognitive decline and extrapyramidal symptoms (symptoms involving the nerves and muscles that control movement and coordination). Both patients recovered several weeks after their doctors stopped valproate treatment.

--*Endocrinological problems*. In a review article published in June, A. Verrotti and colleagues note that endocrinological changes caused by valproic acid can lead to menstrual disorders, polycystic ovary syndrome, hyperinsulinism, and marked hormonal alterations, as well as impaired skeletal growth and altered pubertal development. D. N. Black and colleagues recently reported an extreme case of drug-related obesity linked to endocrinological disruption, in which a 34-year-old man died of heart failure after gaining 100 pounds on sodium valproate.

--*Potentially dangerous blood loss*. A review article by B.T. Carney and C. L. Minter found that children with cerebral palsy taking valproate had a significantly increased risk of needing a blood transfusion during a major surgery.

Editor's note: ARI includes Depakene (a brand name for valproic acid) on its parent ratings questionnaire. Not surprisingly, the drug ranks as highly effective in treating seizures. However, it has a better:worse ratio of 1.2 to 1 for behavioral effects, meaning that the number of children who get worse on the drug is about equal to the number who get better. Hardly compelling evidence in favor of adminstering a drug with so many serious adverse effects!

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"Divalproex sodium vs. placebo in the treatment of repetitive behaviours in autism spectrum disorder," E. Hollander, L. Soorya, S. Wasserman, K. Esposito, W. Chaplin, and E. Anagnostou, *International Journal of Neuropsychopharmacology*, August 15, 2005 (epub ahead of publication). Address: Eric Hollander, Department of Psychiatry, Mount Sinai School of Medicine, New York, NY 10029.

—and—

"A double-blind, placebo-controlled study of valproate for aggression in youth with pervasive developmental disorders," J. A. Hellings, M. Weckbaugh, E. J. Nickel, S. E. Cain, J. R. Zarcone, R. M. Reese, S. Hall, D. J. Ermer, L. Y. Tsai, S. R. Schroeder, and E. H. Cook, *Journal of Child and Adolescent Psychopharmacology*, Vol. 15, No. 4, August 2005, 682-92. Address: J. A. Hellings, Department of Psychiatry and Behavioral Sciences, University of Kansas Medical Center, Kansas City, KS 66160, jhelling@kumc.edu.

—and—

"Valproate-caused encephalopathy," K. S. Thygesen and P. Wolf, *Ugeskrift for Laeger*, Vol. 167, No. 40, October 3, 2005, 3793-4. Address: K. S. Thygesen, kristinst@get2net.dk.

—and—

"Endocrine and metabolic changes in epileptic patients receiving valproic acid," A. Verrotti, R. Greco, G. Latini, and F. Chiarelli, *Journal of Pediatric Endocrinology and Metabolism*, Vol. 18, No. 5, May 2005, 423-30. Address: A. Verrotti, Department of Pediatrics, University of Chieti, Italy.

—and—

"Lethal obesity associated with sodium valproate in a brain-injured patient," D. N. Black, R. R. Althoff, K. Daye, and C. A. Pelletier, *Cognitive and Behavioral Neurology*, Vol. 18, No. 2, June 2005, 98-101. Address: D. N. Black, Department of Neurology, University of Vermont, Burlington, VT, dnblack@globalnetisp.net.

—and—

"Is operative blood loss associated with valproic acid? Analysis of bilateral femoral osteotomy in children with total involvement cerebral palsy," B. T. Carney and C. L. Minter, *Journal of Pediatric Orthopedics*, Vol. 25, No. 3, May-June 2005, 283-5. Address: B. T. Carney, Shriners Hospital for Children, 1900 Richmond Road, Lexington, KY 40502-1298.

Doctors routinely ignore "black box" warnings

A "black box" warning label is the Food and Drug Administration's strongest warning about the dangers of a particular drug, and is only one step short of withdrawing the drug from the market. Yet a new study shows that doctors routinely prescribe drugs with "black box" warnings, and frequently fail to conduct the lab tests recommended to reduce the risk of dangerous drug side effects.

Anita Wagner and colleagues analyzed the medical records of nearly 930,000 medical plan enrollees to determine the frequency with which drugs with black box warnings are prescribed, and how well doctors complied with precautions specified for these drugs. The researchers report, "During a 30-month period, more than 40% of enrollees received at least one medication that carried a black box warning that could potentially apply to them." In 49.6% of the cases in which patients received drugs whose black-box warnings called for baseline lab tests, the tests were not ordered. Moreover, 9% of prescriptions were written on the same day as prescriptions for drugs that were dangerous if taken in conjunction with the black-box drug.

We need to be clear about the magnitude of risk that justifies a black box warning," Wagner says, "and the evidence that underlies the recommendations."

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"FDA drug prescribing warnings: is the black box half empty or half full?" A. K. Wagner, K. A. Chan, I. Dashevsky, M. A. Raebel, S. E. Andrade, J. E. Lafata, R. L. Davis, J. H. Gurwitz, S. B. Soumerai, and R. Platt, *Pharmacoepidemiology and Drug Safety*, November 18, 2005 (epub ahead of print publication). Address: Anita Wagner, Department of Ambulatory Care and Prevention, Harvard Medical School and Harvard Pilgrim Health Care, Boston, MA 02215.

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"Doctors not heeding 'black-box' warnings on Rx drugs," Amanda Gardner, *New York Times*, November 18, 2005.

IN MEMORIAM: Liz Birt

The autism world recently lost a champion with the tragic death of Liz Birt. An attorney and the mother of an autistic son, Liz was a tireless advocate for the legal and educational rights of autistic children, and hers was one of the most powerful voices speaking out about the link between autism and mercury. Her courage and dedication helped changed our children's world for the better, and she will be deeply missed.