Adderall, Ritalin, Seroquel: new reports warn of dangers

New warnings are being raised about the dangers of two drugs often given to autistic children, and one of these drugs is now banned by the Canadian government.

In February, Health Canada, the Canadian drug regulatory agency, instructed Shire bioChem, the manufacturer of Adderall XR, to withdraw the drug from the Canadian market "due to safety information concerning the association of sudden deaths, heart-related deaths, and strokes in children and adults taking usual recommended doses of Adderall and Adderall XR." (The quick release version of Adderall has never been sold in Canada.)

The decision by Health Canada was based on a review of safety information provided by Shire. The review revealed 20 international reports of sudden death in patients taking either form of Adderall. "These deaths," Health Canada stated, "were not associated with overdose, misuse, or abuse." Fourteen of the fatalities occurred in children.

Also in February, researchers in Texas reported that every one of 12 young study subjects taking Ritalin (methylphenidate) for a brief time exhibited a dramatic increase in levels of chromosome abnormalities. Such abnormalities are linked to an increased risk of cancer.

Randa El-Zein et al. looked for three types of chromosome abnormalities in their subjects' peripheral blood lymphocytes before and three months after the children began taking a typical dose of Ritalin. They say, "In all participants, treatment induced a significant 3, 4.3 and 2.4-fold increase in chromosome aberrations, sister chromatid exchanges and micronuclei frequencies, respectively."

These findings, they say require further investigation, "especially in view of the well-documented relationship between elevated frequencies of chromosome aberrations and increased cancer risk."

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"Health Canada suspends the market authorization of Adderall XR®, a drug prescribed for Attention Deficit Hyperactivity Disorder (ADHD) in children," Health Canada advisory, February 9, 2005, http://www.hc-sc.gc.ca/english/protection/warnings/2005/2005_01.html.

—and—

"Cytogenetic effects in children treated with methylphenidate," Randa El-Zein, Sherif Abdel-Rahman, Matthew Hay, Mirtha Lopez, Melissa Bondy, Debra Morris, and Marvin Legator, *Cancer Letters*, February 2005 (epub ahead of print publication). Address: Marvin Legator, Department of Preventive Medicine and Community Health, University of Texas Medical Branch, 2.102 Ewing Hall. Galveston, TX 77555-1110.

Atypical antispychotics again linked to severe side effects

Research continues to link atypical antipsychotic drugs to metabolic changes that can put patients at risk for Type 2 diabetes, stroke, or heart disease.

In one recent investigation, B. L. Lambert and colleagues conducted a case-control study of Medi-Cal claims involving schizophrenic patients who developed hyperlipidemia while taking an antipsychotic drug. Hyperlipidemia, an excess of fats in the bloodstream, is a powerful risk factor for coronary artery disease.

The researchers found that compared with patients taking older antipsychotic drugs, patients taking olanzapine (Zyprexa) were significantly more likely to develop hyperlipidemia. Clozapine (Clozaril) was also associated with an increased risk of hyperlipidemia, although not as strongly as olanzapine.

Another study links atypical psychotics to insulin resistance, a dangerous condition in which muscle, fat, and liver cells cannot use insulin properly. Insulin resistance eventually results in excess glucose in the bloodstream and puts individuals at risk for Type 2 diabetes and cardiovascular disease.

Mark Riddle and colleagues evaluated 11 overweight children who experienced large weight gain while taking olanzapine, quetiapine (Seroquel) or risperidone (Risperdal). Weight gain is a common side effect of these drugs.

The researchers found that all six children taking moderate or high doses of one of the drugs, and three of five children taking low doses, showed evidence of insulin resistance. This evidence included high blood pressure, elevated levels of triglycerides, low levels of "good" cholesterol, and increased levels of protein in the urine.

"The insulin resistance seen in these children was greater than what would be expected from weight gain alone," said lead study author Mark Riddle, "suggesting there is a factor distinct from excess weight that directly induces insulin resistance."

The new research adds to evidence linking atypical antipsychotics to potentially dangerous metabolic changes (see ARRI 18/2, 16/4).

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"Association between antipsychotic treatment and hyperlipidemia among California Medicaid patients with schizophrenia," B. L. Lambert, K. Y. Chang, E. Tafesse, and W. Carson, *Journal of Clinical Psychopharmacology*, Vol. 25, No. 1, February 2005, 12-18. Address: B. L. Lambert, Department of Pharmacy Administration, University of Illinois at Chicago, Chicago, IL 60612-7231, lambertb@uic.edu.

—and—

"Antipsychotic drugs linked to insulin resistance in children," news release, Johns Hopkins Medical Institutions, October 20, 2004. Study reported at the annual meeting of the American Academy of Child and Adolescent Psychiatry, Washington, D.C., October 19-24, 2004.

Popular ear-infection drug implicated in autism

A new study suggests a link between autism and the use of Augmentin, an antibiotic frequently prescribed for children's ear infections.

Joan Fallon performed detailed case reviews of 206 autistic children under the age of three. "A significant commonality was discerned," she says, "that being the level of chronic otitis media." Children in the study had experienced an average of nearly 10 bouts of otitis media (ear infection), and had received an average of 12 courses of antibiotics. The group as a whole had been administered 893 courses of Augmentin, with 362 of them being given to children under the age of one.

Fallon notes that the manufacturing process for Augmentin (a combination of amoxicillin and potassium clavulanate) involves the fermentation of clavulanic acid. This process involves large amounts of urea/ammonia, and Fallon suggests that residual ammonia in Augmentin could cause urea poisoning.

Hallmarks of urea poisoning, she notes, include neurotoxic effects on brain tissue and corrosive effects on the digestive tract. Symptoms include abdominal colic, bloating, diarrhea, tremor, impaired coordination, weakness, poor appetite, and other signs often seen in neurological toxicity. In addition, urea poisoning can cause damage to the secretory cells of the small intestine. Autistic children, Fallon notes, also exhibit both neurological and digestive symptoms.

Fallon also cites a study showing that low-birth-weight, preterm babies cannot clear clavulanate (given with ticarcillin in the study) quickly from their systems. Since Augmentin is known to be toxic to the liver, she says, "the fact that prolongation in [this group of infants] occurred is significant."

Fallon notes that Augmentin is one of the most widely prescribed drugs for children, and that its introduction in the 1980s as a treatment for childhood illnesses coincided with the rise in cases of autism. "It is imperative," she says, "that further research be undertaken to determine if a subset of children are at risk for neurotoxicity due to the use of clavulanate or clavulanic acid in pharmaceutical preparations—especially Augmentin."

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"Could one of the most widely prescribed antibiotics amoxicillin/clavulanate 'Augmentin™' be a risk factor for autism?," Joan Fallon, *Medical Hypotheses*, Vol. 64, 2005, 312-15. Address: Joan Fallon, 1234 Central Avenue, Suite 1B, Yonkers, NY 10704, joanfallon@aol.com.

—and—

"Commonly prescribed antibiotic implicated in autism," *eMediaWire*, January 31, 2005.