Antipsychotics/diabetes link: evidence grows stronger

Evidence continues to mount that both typical and atypical antipsychotic drugs can increase the risk of type II diabetes and other dangerous blood sugar abnormalities. Among the recent findings:

• F. D. Gianfrancesco and colleagues analyzed insurance claims data for psychotic patients treated by several major health plans. Patients with preexisting type II diabetes were excluded.

The researchers report that the diabetes risk of patients taking risperidone (Risperdal) was not significantly different from that for patients not receiving treatment with antipsychotic drugs, "whereas patients receiving other antipsychotics had a significantly greater risk of diabetes than untreated patients." Olanzapine (Zyprexa) increased the risk three-fold, clozapine (Clozaril) more than seven-fold, and conventional antipsychotics two-fold to three-fold. Higher age and greater use of non-antipsychotic psychotropic drugs also increased the risk for diabetes.

• Focusing on schizophrenic patients, J. Ananth et al. performed a Medline search that uncovered 30 case reports of type II diabetes, hyperglycemia, or diabetic ketoacidosis related to clozapine use, and 26 cases linked to olanzapine use. In addition, they found several case studies linking these health problems to quetiapine (Seroquel) or risperidone. While the researchers note that schizophrenics in general appear to have an increased risk of type II diabetes, they say, "The findings that 50 percent of the patients completely improve upon drug discontinuation, and that hyperglycemia [elevated blood sugar] promptly recurs upon reinstitution of the incriminated drug, indicate that this side effect is reversible and is drug related." They note that African-American patients appear to be particularly susceptible to drug-caused type II diabetes.

• D. R. Wilson et al. reviewed records from the Ohio Department of Mental Health and identified patients treated with atypical antipsychotics and also evaluated or treated for type II diabetes. The researchers located 11 cases involving "new-onset, acute, and marked glucose intolerance" developing after treatment with clozapine, olanzapine or quetiapine. Of these, the researchers say, six patients required insulin treatment at least temporarily, and five patients developed diabetic ketoacidosis (a life-threatening condition). Two patients recovered despite ongoing antipsychotic treatment.

• While several studies show at most a weak link between risperidone and the development of type II diabetes, one study suggests that the combination or risperidone and paroxetine (Paxil) can lead to severe weight gain and diabetes. H. Fukui and T. Murai report on two patients who gained no weight while taking risperidone alone (although the drug is linked to marked weight gain in many patients). When given a combination of paroxetine and risperidone, however, the patients gained 14 kilograms and 13.5 kilograms respectively, and one of the patients developed type II diabetes. The researchers say, "We speculate a drug-drug interaction involving inhibition of the cytochrome P450 enzyme."

Christian Shriqui notes that in recent years "there has been a surge of published data, often extracted from large multi-center-controlled clinical trials" that implicates antipsychotics as a risk factor for excessive weight gain, abnormal glucose regulation, and other metabolic side effects. He recommends that patients put on these medications be screened for diabetes risk factors, and that those taking clozapine and olanzapine in particular should receive monthly weight and body mass index monitoring and receive regular fasting plasma glucose and serum lipid tests.

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"Differential effects of risperidone, olanzapine, clozapine, and conventional antipsychotics on type 2 diabetes: findings from a large health plan database," F. D. Gianfrancesco, A. L. Grogg, R. A. Mahmoud, R. H. Wang, and H. A. Nasrallah, *Journal of Clinical Psychiatry*, Vol. 63, No. 10, October 2002, 920-30. Address: F. D. Gianfrancesco, HECON Associates, Mongtomery Village, MD 20886.

—and—

"Atypical antipsychotic drug use and diabetes," J. Ananth, R. Venkatesh, K. Burgoyne, and S. Gunatilake, *Psychotherapy and Psychosomatics*, Vol. 71, No. 5, Sept.-Oct. 2002, 244-54. Address: J. Ananth, Harbor-UCLA Medical Center, 1000 W. Carson Street, Torrance, CA 90502.

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"New-onset diabetes and ketoacidosis with atypical antipsychotics," D. R. Wilson, L. D'Souza, N. Sarkar, M. Newton, and C. Hammond, *Schizophrenia Research*, Vol. 59, No. 1, January 2003, 1-6. Address: D. R. Wilson, Department of Psychiatry, Creighton University School of Medicine, Omaha, NE 68178.

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"Severe weight gain induced by combination treatment with risperidone and paroxetine," H. Fukui and T. Murai, *Clinical Neuropharmacology*, Vol. 25, No. 5, September-October 2002, 269-71. Address not listed.

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"Atypical antipsychotics," Christian L. Shriqui, *Canadian Journal of CME*, July 2002, 65-80. Address: Christian Shriqui, Centre Hospitalier Universitaire de Quebec, Pavillon CHUL, Ste. Foy, Quebec, Canada.

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Risperidone: benefits ... and side effects

While recent research indicates that risperidone (Risperdal) is more effective than most psychotropic drugs in reducing autistic symptoms, increasing concerns are being raised about its side effects. As reported in earlier issues of ARRI (see 16/1, 15/4, 14/1) risperidone is linked to extreme weight gain in many individuals, and can also cause tardive dyskinesia (a movement disorder) and heart rhythm abnormalities in some cases. New research also raises concerns about the drug's potential cardiovascular risks, and about its potential for causing major depression.

McCracken study positive, but questions raised

The most recent positive findings about risperidone's behavior effects were reported by James T. McCracken and colleagues. In an eight-week multi-site, randomized, double-blind trial, the researchers administered risperidone (dose range 0.5 to 3.5 mg/day) to 49 autistic children between the ages of 5 and 17, while giving a placebo to 52 children. Outcome measures included scores on the Irritability subscale of the Aberrant Behavior Checklist, and ratings on the Clinical Global Impressions-Improvement (CGI-I) scale.

The researchers report, "The rate of a positive response, defined as at least a 25 percent decrease in the irritability score and a rating of much improved or very much improved on the CGI-I scale, was 69 percent in the risperidone group and 12 percent in the placebo group." According to the National Institute of Mental Health, which funded the study, "This is the largest positive effect by a medication ever observed in children with autism."

Doctors commenting on the McCracken et al. study, however, have raised concerns about the study's findings. Louis Sandler notes, for instance, "Over an eight-week period, the treatment group had documented weight gains of about 6 pounds. The article indicates that increased 'fatigue, drowsiness, dizziness, and drooling' occurred at significant rates. One has to wonder whether the increased drowsiness and dizziness in the children was just one of the many unaccounted-for variables that lessened their 'irritability.'"

In addition, Guy Valiquette notes that risperidone often causes hypoprolactinemia, which can lead over the long term to osteoporosis. "As an endocrinologist with a large component of my practice devoted to persons with developmental disabilities," he says, "I see many 20-year-old and 30-year-old adults with [low] scores for bone mineral density." And Ricardo Munarriz et al. comment that "conspicuously absent from the side effect profile was risperidone-associated priapism," a condition involving painful per-

continued on page 7