Antipsychotic Drugs Spur Metabolic Changes

BY BETSY BATES

FROM THE ANNUAL MEETING OF THE AMERICAN PSYCHIATRIC ASSOCIATION

NEW ORLEANS — Worrisome and clinically measurable metabolic changes can be seen in just 12 weeks among children and adolescents who received antipsychotic medications in a National Institutes of Health–sponsored study, prompting serious concern among clinicians who learned of the results at the meeting.

The results struck at the heart of a troubling dichotomy: an explosion of prescriptions of antipsychotic medications for children, but little evidence in real-world practice that young patients are being routinely screened for metabolic changes that have the potential to shorten life expectancy.

The ongoing Metabolic Effects of Antipsychotics in Children study has already enrolled more than 140 children aged 7-18 years who were already slated to be placed on antipsychotics in the community.

Investigators closely monitored changes over 3 months in body fat using dual-energy x-ray absorptiometry (DXA) and insulin sensitivity using gold-standard methods, as well as tracking clinically available measures such as body mass index (BMI) percentile, and plasma glucose and lipids.

Body fat percentages rose in "not all, but certainly the majority of these children and youth," said Dr. John W. Newcomer, professor of psychiatry and medicine and Director of the Center for Clinical Studies at Washington University in St. Louis.

Mean increases were highly variable among children and adolescents taking antipsychotic medications, but have averaged almost 3 kilos, or 6.5 pounds, "of body fat, not just weight," in just 12 weeks, he said.

Some variance was seen in mean percent body fat accrual depending on which antipsychotic medication the children and adolescents received in the randomized open-label study, with olanzapine linked to a roughly 5% increase; aripiprazole, about a 1% increase; and risperidone falling somewhere in the middle at about 3%.

However, box plots revealed "substantial overlap" in the results, showing that each individual child's metabolic response to a given drug is somewhat unpredictable.

"You can find kids who take any one of these medications and potentially get a substantial increase in body fat, and you can also find kids who take any one of these agents who actually have very little change in body fat, although some medications are associated with a higher risk of substantial increase," Dr. Newcomer said.

Increases in BMI percentiles were "substantial" as well, and closely paralleled more sophisticated measures of body fat, such as DXA.

"The good news is, it's pretty easy to track the changes in adiposity," said Dr. Newcomer in an interview following the meeting.

"We used very fancy and expensive measures of body fat, but what pediatricians have in the front of every kid's chart (the BMI percentage table) does a darned good job of not only lining up where the child is at the baseline screen, but also in tracking changes over time."

In a similar vein, the study found that simple blood cholesterol profiles—especially triglycerides and HDL—did a "halfway decent job" of estimating insulin sensitivity at baseline and then tracking changes through the early months of therapy, Dr. Newcomer added.

"The point is … don't wait a year to check the labs," he said. "Don't not look."

What is troubling to many is the fact that many clinicians indeed are not looking.

A Medicaid claims data study published earlier this year found that glucose screening was performed in just 31.6% and lipid testing in just 13.4% of 5,370 children aged 6-17 years prescribed antipsychotic drugs from July 1, 2004, to June 30, 2006 (Arch. Pediatr. Adolesc. Med. 2010;164:344-51).

Dr. Newcomer, a coauthor on the Medicaid claims research, said a growing number of "very eye-opening studies" about the enduring impact of childhood metabolic dysregulation and obesity should make clinicians weigh risks and consequences carefully when choosing drugs to prescribe for childhood schizophrenia, and perhaps even more so for use in disruptive behavior disorders and other nonpsychotic diagnoses.

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"I have certainly learned that there are children at the end of the road of clinical options who are either not going to be in school or unable to participate without some heroic treatment measures, such as low-dose antipsychotic treatment, to help them to re-engage in education," he said.

At the same time, relatively brief pharmacologic interventions for children who do not have schizophrenia or bipolar disorder should leave "a metabolic footprint … as modest as possible," he said.

The Washington University study extended body weight findings from the nonrandomized SATIETY study published last year (JAMA 2009;302:1765-73), in which 272 4- to 19-year-olds prescribed antipsychotic drugs gained from a mean 4.4 kg (aripiprazole) to 8.5 kg (olanzapine) in a median of just 10.8 weeks on medication.

At the APA scientific session where interim data were released from the MEAC study, one audience member rose to call the findings "catastrophic."

"What you're showing us is very, very scary," he told Dr. Newcomer, who replied that the metabolic impacts of other classes of drugs widely used in children, including benzodiazepines and high-dose antidepressants, are also potentially concerning.

"We're having this policy debate under a streetlamp as though second-generation antipsychotics are the only drugs that cause weight gain," Dr. Newcomer said. "Let's not kid ourselves."

One alternative raised at the session was intensive behavioral modification, such as a year-long, school-based program for disruptive children described by Dr. Jacob Venter, of Wellesley, Mass., and his colleagues at the same APA scientific session.

Dr. Newcomer pointed to the University of Arizona behavioral study as an example of how nonpharmacologic interventions can produce "some good results," even among children with severe behavioral dysregulation.

"The problem is, I don't know about your town, but in St. Louis, there is a 6-month waiting list to see a child psychiatrist," he told the audience.

By the time they can be seen, "These families are in great distress and sometimes aren't terribly interested in taking those referrals for behavioral treatments, either because they already tried some therapy or because they seek rapid change," he said.

Families want the quick responses they associate with medication, and when a trial of behavioral modification is suggested as a starting place, "We can't give it away."

As for trying to reduce prescribing of antipsychotic medications to children, particularly among those who do not have symptoms consistent with bipolar disorder or schizophrenia, Dr. Newcomer, who also chairs Missouri's Drug Utilization Review Board, was somewhat skeptical about the potential to substantially reduce that clinical practice.

"Like it or not, that horse is out of the barn. The clinical benefits can be obvious to parents, children, and their doctors, so there will continue to be interest in this therapeutic approach, even as we fully elaborate the risks. This is happening all over the country. The rates of prescriptions are going up. The off-label use is tremendous, suggesting a lot of unmet need," he said.

Indeed, a series of studies conducted by a team led by Dr. Mark Olfson at Columbia University, New York, has found that prescribing of antipsychotic medications by psychiatrists and primary care physicians has skyrocketed in the United States since the mid-1990s, with treatment of disruptive behavior disorders, including attention-deficit/hyperactivity disorder, playing a significant role in the increase.

In one recent example, Dr. Olfson reported that antipsychotic use by 2- to 5-year-olds covered by private insurance rose from 0.78 per 1,000 to 1.59 per 1,000 from 1999 to 2007. Less than half of the children in the study had received a mental health assessment, a psychotherapy visit, or a consultation with a psychiatrist.

Antipsychotic medication was prescribed in more than 1.2 million outpatient office visits by children in 2002, up from 201,000 in 1993, Dr. Olfson reported (Arch. Gen. Psychiatry 2006;63:679-85). Diagnoses of disruptive behavior disorders (37.8%), mood disorders (31.8%), pervasive developmental disorders or mental retardation (17.3%), and psychotic disorders (14.2%) accounted for most of those visits. ■

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Dr. John W. Newcomer says that mean increases "of body fat, not just weight" averaged 6 lbs in just 12 weeks.

Disclosures: *Dr. Newcomer disclosed that he has served as a consultant to several pharmaceutical companies but reported no relevant financial conflicts of interest associated with his study.*