Children on Atypical Antipsychotics Gain Weight

Study of 272 subjects shows link to lipid and glucose abnormalities as well as hypertension.

BY MARY ANN MOON

Children and adolescents rapidly gain substantial weight on a short course of the atypical antipsychotic medications aripiprazole, olanzapine, quetiapine, and risperidone, according to researchers.

Up to 36% of patients in a study of 272 children and adolescents transitioned to overweight or obese status within 11 weeks, and many showed significant abnormalities in lipid profiles and metabolic measures, said Dr. Christoph U. Correll of Zucker Hillside Hospital, Glen Oaks, N.Y., and his associates.

They studied the cardiometabolic effects of atypical antipsychotic agents because they are "commonly and increasingly prescribed to children and adolescents in the United States as first-line treatment for psychotic disorders, bipolar disorder," and a widening variety of nonpsychotic mental disorders.

Yet they have been linked to weight gain, hypertension, lipid abnormalities, and glucose abnormalities that are a particular concern during development "because they predict adult obesity, the metabolic syndrome, cardiovascular morbidity, and malignancy," the researchers wrote.

Until now, investigators have been unable to tease out the cardiometabolic effects of atypical antipsychotics in children because the agents have been studied only in subjects already exposed to a variety of other antipsychotic medications.

In an editorial accompanying the report, Dr. Christopher K. Varley and Dr. Jon McClellan of Seattle Children's Hospital observed that "the development of clinically significant hyperlipidemias and insulin resistance after only 12 weeks of treatment portends severe long-term metabolic and cardiovascular sequelae."

These results "challenge the widespread use of atypical antipsychotic medications in youth," they added.

When first introduced, atypicals were widely touted as more effective and safer than older neuroleptic agents, which eased physician reticence about prescribing these medications for young patients, they wrote. Before this, traditional antipsychotic medications were far less commonly prescribed for disruptive behavioral disorders (JAMA 2009;302:1811-2).

Much of the data supporting the use of these agents has been provided by industry-sponsored research. "Medical treatment should be dictated by empirical data rather than by anecdote, assumptions, or marketing strategies," they wrote.

Dr. Correll and his colleagues assessed patients aged 4-19 years who were naive to previous antipsychotic therapy and were participating in a cohort study of pediatric psychotic, mood, or aggressive spectrum disorders. For comparison, they assessed a control group of 15 similar participants who either refused or immediately discontinued atypical antipsychotic agents.

In all, 10%-36% of patients, depending on which agent they were taking, gained enough weight to shift into overweight or obese status.

After a median of 11 weeks, all four drugs were associated with weight gain: an average of 8.5 kg for the 45 patients on olanzapine, 6.1 kg for the 36 patients on quetiapine, 5.3 kg for the 135 patients on risperidone, and 4.4 kg for the 41 patients on aripiprazole. More than half the children gained more than 7% of their total body weight.

All the drugs significantly increased fat mass and waist circumference. In all, 10%-36% of patients, depending on which agent they were taking, gained enough weight to shift into overweight or obese status.

Lipid and metabolic abnormalities were not consistent across all four medications. Olanzapine and quetiapine significantly worsened total cholesterol, triglyceride, non–HDL cholesterol, and other lipid measures, while risperidone significantly raised triglycerides. Quetiapine and olanzapine raised the rates of hyperglycemia and metabolic syndrome.

Olanzapine in particular had the largest weight effects, "and also significantly worsened all glucose and lipid parameters, except HDL cholesterol, which is more related to physical activity," the investigators said (JAMA 2009;302:1765-73).

In contrast, the control group showed no such changes, indicating that these alterations could not be attributed to the psychiatric disorder itself or to other aspects of treatment.

"In view of poor physical health outcomes and suboptimal metabolic monitoring in the severely mentally ill, the benefits of second-generation antipsychotic medications must be balanced against their cardiometabolic risks through a careful assessment of the indications for their use, consideration of lower-risk alternatives, and proactive adverse effect monitoring and management," Dr. Correll and his associates said.

Dr. Correll reported being a consultant or receiving honoraria from AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly & Co., Intra-Cellular Therapeutics, Medicure, OrthoMcNeill-Janssen, Otsuka, Organon, Pfizer, Schering-Plough, Solvay, Supernus, Vanda, and Wyeth, and serving on the speakers bureau of AstraZeneca, Bristol-Myers Squibb/Otsuka, and Pfizer.

Dr. Varley and Dr. McClellan reported no conflicts. ■

Two Novel Obesity Drugs Show Promise in Phase III Trials

BY HEIDI SPLETE

WASHINGTON — Two novel weight loss drugs led to significant losses in overweight and obese adults, according to the findings from two phase III, placebo-controlled trials that were presented at the annual meeting of the Obesity Society.

The drugs are not yet approved by the Food and Drug Administration. If approved, they will provide additional options for the treatment of obesity.

In one study, Dr. Caroline Apovian of Boston University Medical Center presented results of the Contrave Obesity Research II (COR-II) study, a phase III, double-blind trial of 1,496 adults with an average age of 44 years and an average body mass index of 36 kg/m^2.

The study involved Orexigen Therapeutics Inc.'s combination naltrexone SR/bupropion SR combination therapy (Contrave).

Participants were randomized to a single daily oral dose of the combination drug NB32 (32 mg naltrexone/360 mg bupropion) or a placebo.

After 28 weeks, 56% of the treatment group participants achieved at least a 5% weight loss—the study's primary outcome measure—compared with 18% of the placebo group. A 10% weight loss was achieved by 27% of the treatment group and 7% of the placebo group; 15% loss was achieved by 10% and 2% of the groups, respectively. Baseline demographics were similar between the treatment and placebo groups.

After 28 weeks, participants were rerandomized to a combination drug including 48 mg naltrexone and 360 mg bupropion (NB48).

"This was a chance to see if there was a higher dose needed," Dr. Apovian said, but at 56 weeks, there was no significant change in weight loss with NB48 compared with NB32.

Patients in the treatment group reported significant decreases in food cravings compared with baseline, she said.

Approximately half of the patients in the drug and placebo groups discontinued the study, but discontinuation because of adverse events was low. Nausea, the most common adverse event, was mild or moderate in most cases, "and occurred mostly in the first 4 weeks," Dr. Apovian said.

After 28 weeks, 56% of the treatment group achieved at least a 5% weight loss—the study's primary outcome measure—compared with 18% of the placebo group.

The combination drug seemed to be well tolerated, and the safety profile was consistent with previous data on the two drugs when used separately, she added.

Dr. Apovian is on the advisory board of Orexigen and has received financial support from other pharmaceutical companies, including Eli Lilly & Co. and Amgen. Orexigen intends to submit the drug for FDA approval in the first half of 2010, according to a company statement.

Dr. Lee Kaplan of Harvard University in Cambridge, Mass., presented results of a study of lorcaserin, a selective 5HT2C agonist designed to promote weight loss without the cardiovascular side effects that are associated with nonspecific 5HT agonists.

The randomized, double-blind, placebo-controlled phase III study enrolled 4,008 patients aged 18-65 years for 52 weeks. The study involved patients with a BMI of 27-45 kg/m^2 with and without at least one comorbid condition. The average age was 44 years, average BMI was 36 kg/m^2, and 80% were female. Baseline demographics were similar between the treatment and placebo groups.

Overall, the intent-to-treat analysis showed that a 5% weight loss was achieved by 47% of participants who took 10 mg lorcaserin twice daily, by 40% of those who took 10 mg lorcaserin once daily, and by 25% of those who took a placebo, said Dr. Kaplan, who is also director of the Massachusetts General Hospital weight center in Boston.

Patients in the twice-daily, once-daily, and placebo groups who completed the study according to the protocol lost an average of 7.7 kg, 6.5 kg, and 3.9 kg, respectively.

The most common adverse events were headache, fatigue, dizziness, and nausea, each of which occurred in less than 5% of patients.

Patients with FDA-defined valvulopathy were included in the study, and the lorcaserin was not associated with increased valvulopathy during the study, Dr. Kaplan added.

Dr. Kaplan has received financial support from lorcaserin's manufacturer, Arena Pharmaceuticals, among other pharmaceutical companies.

Lorcaserin has not yet been approved by the FDA. ■