Tailor Psychotropic Drugs to Reduce Side Effects

BY DAN HURLEY

NEW YORK — A wealth of new data is emerging that will help clinicians anticipate and manage endocrine complications of psychotropic drugs, according to a leading researcher.

"We can't take a gene chip and come up with firm recommendations," said Dr. Harold E. Carlson, who has published widely in the field as professor of medicine and endocrinology at Stony Brook (New York) University Health Sciences Center. But based on new data, he said, "We can think about individualized pharmacotherapy tailored to your patients' needs."

Reduced height and weight in children and adolescents taking stimulants for attention-deficit/hyperactivity disorder (ADHD) has been a concern for years, and the latest data from the Multimodal Treatment of ADHD (MTA) Study suggest that growth deficits of about 1 inch persist after 8 years of treatment (J. Am. Acad. Child Adolesc. Psychiatry 2009;48:484-500.)

"We still do not have published data on the final adult height of children who have been treated continuously from childhood with stimulants," Dr. Carlson said at a psychopharmacology update, sponsored by the American Academy of Child and Adolescent Psychiatry (AACAP). "The MTA study is nearing the point where most of the subjects will reach their final adult type. So far, [co–principal investigator] Jim Swanson tells me they remain about 1 inch shorter than they should otherwise be. They may wind up with a permanent growth deficit."

On the other hand, permanent growth deficits were not observed in a study of atomoxetine (J. Child Adolesc. Psychopharmacol. 2007;17:689-700). In the study of 61 children treated for 5 years, initial slowing of growth was followed by a period of catch-up, such that height was usually normal by the fourth or fifth year.

Individual characteristics of patients can alert clinicians to those who might be at increased risk of reduced growth, Dr. Carlson noted. Prepubertal children have more slowing of growth than do adolescents; boys have more slowing than do girls; and children who are tall or overweight at the inception of treatment are at greater risk of slowed growth than shorter, underweight children.

The bottom line, Dr. Carlson said, is that all children and adolescents need to have their height and weight measured before beginning stimulant treatment.

"Do it yourself, or get it from the pediatrician," he said. "Get the growth charts. And then someone should measure height and weight every 6 to 12 months. If the kid seems to be falling off his or her growth curve, and it's a substantial amount, then I think it's time to speak to the pediatrician and consider referring to a pediatric endocrinologist."

With antipsychotics, 'calculate the child's BMI before you begin treatment, and then monitor it at every visit. Provide counseling on diet and exercise from the start.... Structured programs work best.'

Dr. Carlson urged physicians to use the lowest effective dose, to avoid giving short-acting stimulants just before meals, and to provide high-energy snacks or meals when the appetite is least suppressed.

"Work with the family," he said. "If the kids' last dose is in the late afternoon, try having them give a wonderful bedtime snack."

The opposite metabolic effect—weight gain associated with antipsychotics—has been confirmed in multiple studies cited by Dr. Carlson, including one study (J. Am. Acad. Child Adolesc. Psychiatry 2002;413:337-43) showing that olanzapine and risperidone are both associated with "extreme" weight gain in adolescents. The best defense against such unwanted effects, he said, is a good offense.

"You're going to want to calculate the child's BMI before you begin treatment, and then monitor it at every visit," he said. "Provide counseling on diet and exercise from the start. It's much harder to take it off than to prevent it. Structured programs work best. If weight is progressing quickly, try switching medications to one less associated with weight gain. In resistant cases, pharmaceutical therapies have been used to promote weight loss, such as orlistat or metformin."

Sudden cardiac death is another risk to consider when prescribing stimulant medications for ADHD, Dr. Carlson noted.

Confusion has ensued from the varying recommendations for and against routine ECGs by the American Heart Association, the American Academy of Pediatrics, and the AACAP; however "All three groups agree you need a good cardiac history, a detailed family history, and a careful physical exam," Dr. Carlson said. "All agree an ECG should be performed if the initial valuation suggested increased cardiac risk, but the ECG does not need to be done in the absence of such findings."

Despite the growing consensus, he added, "We're not at the end of the story yet." The fact is, Dr. Carlson pointed out, no firm data have yet established whether or not ADHD medications truly do increase the risk of sudden cardiac death, and if so, by how much.

"Looking at all the data we do have," he said, "it certainly seems like the risk is low, about one death per 100,000 per year."

However, in what Dr. Carlson described as "the earthquake of several months ago," a case-control study found that youths who died of sudden cardiac death were 7.4 times more likely to be taking stimulants for ADHD than were youths who died as passengers in automobile accents (Am. J. Psychiatry 2009;166:992-1001).

"The study had a bunch of flaws, pointed out in editorials and letters since," Dr. Carlson noted. "The FDA has not changed its policy as a result."

With a large study now underway aimed at replicating the data in that 2009 study, Dr. Carlson said, "I would surely hope that with an n of 100,000, we should get a good answer. So stay tuned."

Another endocrine risk reviewed by Dr. Carlson was the stimulation of excess prolactin associated with antipsychotics, a condition that not only stimulates lactation but also can inhibit penile erections, decrease libido, and cause a variety of other adverse effects.

Dr. Carlson cited unpublished data from a study by Dr. Christoph U. Correll, showing that the 3-month incidence of missing at least one menstrual period in 152 female youths varied widely, from 21.7% on olanzapine, and 30% on risperidone, to 2.9% on quetiapine and 8.3% of aripiprazole. Risperidone also had the highest incidence, at 6.3%, associated with galactorrhea in 345 postpubertal youth.

"You need to ask your patients about these potential side effects," Dr. Carlson said. "A lot of teenagers will not volunteer this information. You'll have to drag it out of them little by little. All of these things are sensitive issues in teenagers."

If signs and symptoms of hyperprolactinemia are confirmed by a blood test, switching to a more prolactin-sparing agent, or reducing the dose, are recommended. But, he added, "If you can't stop or switch, you can combine your drug with one that is prolactin neutral or lowering, such as aripiprazole." He cited a paper (Am. J. Psychiatry 2007;164:1404-10) that found that adjunctive aripiprazole treatment reversed hyperprolactinemia in both sexes.

Finally, Dr. Carlson noted that the incidence of polycystic ovary syndrome (PCOS) was found to be 10.5% in bipolar patients taking valproate, compared with 1.4% of those taking any other antipsychotic medication (Biol. Psychiatry 2006;59:1078-86).

With all female bipolar patients, he said, "Ask about their menstrual function," Dr. Carlson recommended. "Ask before starting a drug and then each time you see them. Ask about acne and facial or body hair. They're not going to volunteer this very often."

If symptoms of PCOS emerge, he said: "Arrange for them to get counseling on diet and exercise. You could set them up to see a primary care physician, gynecologist, or endocrinologist. There are treatments besides stopping the drug."

Dr. Carlson disclosed financial relationships with pharmaceutical companies, including Eli Lilly; Janssen L.P.; Ortho-McNeil-Janssen Pharmaceuticals; Otsuka America Pharmaceutical; Bristol-Myers Squibb; Cephalon Inc.; McNeil Pediatrics, a division of McNeil-PPC; and Shire U.S. ■

Psychosis Could Be Linked to Blood-Brain Barrier Disruption

BY SUSAN BIRK

CHICAGO — The inflammatory theory of schizophrenia first put forth more than 100 years ago has scientific validity, a study of 30 psychotic pediatric patients indicates.

The study found significantly elevated serum levels of several inflammatory markers implicated in disruption of the blood-brain barrier (BBB) in psychotic children, compared with controls. The finding provides evidence for a relationship between psychosis, inflammation, and BBB disruption, reported Dr. Tatiana Falcone and the cerebrovascular research team led by Dr. Damir Janigro of Cleveland Clinic in a poster at the annual meeting of the American Academy of Child and Adolescent Psychiatry.

"If our hypothesis is correct, and a causal link between inflammation and psychosis exists, new treatment modalities may be identified to add as a coadjuvant treatment for schizophrenia," Dr. Falcone said in an interview.

"Although there are some studies evaluating anti-inflammatory medications in patients with schizophrenia, the results are confounding. We believe this might be related to the timing of the intervention, with more hope for effectiveness in first-episode psychosis and/or early-onset schizophrenia," she said.

Patients had a diagnosis of acute psychosis on admission to the child and adolescent psychiatric unit at Cleveland Clinic. In the control group, a preliminary interview ruled out psychosis, neurodegenerative disorders, fever, current infection, and current use of antibiotics.

Blood samples were taken from the psychotic children on admission. All subjects underwent serum analysis for several inflammatory markers, including S100-β, a neurotrophic protein; tumor necrosis factor (TNF)–α; interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-8, and IL-10; and C-reactive protein.

The S100-β levels in 85% of the psychotic children exceeded the recognized normal range. The psychiatric patients also had significantly higher levels of IL-1β, TNF-α, IL-5, IL-6, and IL-10 than did controls. "These inflammatory mediators are often directly involved in BBB disruption," Dr. Falcone said. ■