

# Conduct Disorder a Red Flag in ADHD Patients

BY BETSY BATES

LOS ANGELES — Early conduct disorder in children with attention-deficit/hyperactivity disorder (ADHD) predicts substance use disorders in adolescence and early adulthood, according to researchers who conducted a long-term prospective study on 778 children.

"I'm a child psychiatrist. I treat kids and work with families. I'd like to know in 10-year-olds, whom do I worry about?" said Dr. Timothy E. Wilens, a pediatric psychopharmacologist at Massachusetts General Hospital in Boston and lead investigator of a 10-year, prospective study of 361 children with ADHD and 417 matched controls.

Children aged 10-11 years and their families underwent extensive interviews, and at periodic intervals over the subsequent decade, culminating in a follow-up evaluation when subjects were in their early 20s.

His overall hypothesis—that ADHD in school-age children would confer an elevated risk of later substance use—was supported, with significant hazard ratios for any substance use of 2.15; alcohol use or dependence, 2.19; drug use or drug dependence, 4.12; and cigarette smoking, 3.21.

As expected, conduct disorder in a child with ADHD "solidly" and independently predicted substance use (hazard ratio, 5.26), including alcohol use or dependence (2.85), drug use or dependence (2.36), and cigarette smoking (2.74).

"We know conduct disorder is big," he said at the annual meeting of the American Academy of Addiction Psychiatry.

"What you may not know is that you can identify it in a 10-year-old pretty clearly, and if you see it in a 10-

year-old, you know you're going to have a problem in adolescence."

What failed to materialize in the study was a hypothesized link to other independent risk factors for eventual substance use in children with ADHD.

Early difficulties with socialization, family environ-

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**Major Finding:** School-age children with ADHD are at increased risk of developing substance use in late adolescence, including drug use or dependence and cigarette smoking. The only significant independent risk factor for later substance use among children with ADHD was conduct disorder.

**Data Source:** Ten-year prospective, longitudinal case-control family study of ADHD youth (n = 361) and controls (n = 417) first assessed by comprehensive interview at about age 11 and, for most recent findings, at about age 20.

**Disclosures:** Dr. Wilens receives research support from numerous pharmaceutical companies that make medications used to treat ADHD. This study was funded exclusively by government grants, including from the National Institute of Mental Health.

ment, school performance, full-scale IQ or the digit span subtest, arithmetic skills, and a family history of ADHD or substance use all failed to significantly increase the risk of substance use over and above the baseline risk faced by children with ADHD.

Similarly, neither depression nor anxiety independently increased risk for substance use.

"Remember, we have a bit of a ceiling effect here,"

cautioned Dr. Wilens, who nonetheless expressed surprise at the results.

One strong trend that failed to reach significance because of a small sample size was a possible link between bipolar disorder and later substance use in children with ADHD.

Previous studies conducted by Dr. Wilens and his group also have drawn associations between substance use among older children with ADHD when they have experienced parental substance use during certain vulnerable developmental stages, he said.

Overall, however, Dr. Wilens said the study suggests that children with ADHD who do not have conduct disorder or severe mood dysregulation face a baseline elevated risk of substance abuse that is not exacerbated by other comorbidities.

He drew attention to a large body of research showing that substance use initiation is delayed if children with ADHD are well managed with medication, although the protective effects of medication are lost in adulthood.

"Aggressively treating the ADHD is really critical," he said.

He also advised careful assessment of potential conduct disorder in young children, which may present as a history of aggressiveness, bullying, a dearth of positive interactions with other children, harm to animals or younger children, a problematic response to parental discipline, and a lack of empathy.

Minor property damage such as breaking windows might be part of the picture in a 10-year-old, but conduct disorder is likely to look different in younger children, Dr. Wilens said.

"You're not going to see them stealing a car." ■

## Tailor Therapy to Minimize Psychotropic Drugs' 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 investiga-

tor] 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.

"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 ... consider referring to a pediatric endocrinologist."

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.

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.

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 accidents (Am. J. Psychiatry 2009;166:992-1001).

"The study had a bunch of flaws, pointed out in editorial 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."

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