Data Should Alleviate Concerns

Stimulants *from page 1*

years of follow-up. This finding is at odds with the previously reported 4-year follow-up in this same patient population, which showed that stimulant therapy had a protective effect against substance use disorders.

The reason for the divergent findings regarding development of substance use disorders at 4 and 10 years' follow-up is unclear. One possibility is that during the first 4 years, patients were still young enough to be under tight parental control. Another possible explanation is that stimulants delay but do not stop subsequent substance use disorders.

Regardless, the key take-away point is that these 10-year longitudinal data help alleviate widespread physician and parental concerns that prescribing stimulants to children with ADHD may predispose them to future substance use disorders. It's worth emphasizing that in this study, neither the age at which stimulant therapy began nor its duration was associated with subsequent substance use disorders, added Dr. Biederman, who is chief of the clinical and research program in pediatric psychopharmacology and adult ADHD at Massachusetts General Hospital.

The study involved 140 consecutive white boys with and 120 without ADHD who were a mean of 12 years old at study entry. Ten years later, 112 children with ADHD and 105 controls were available for reassessment. Eighty-two ADHD patients had been treated with stimulants for a mean of 6 years starting when they were on average 8.8 years old, and 30 were not treated with stimulants.

The study was undertaken because although stimulants are the mainstay of ADHD treatment and have convincingly been shown to improve the disorder's core symptoms, little was known about stimulant therapy's impact, if any, on the risk of developing the psychiatric comorbidities for which patients with ADHD are at high risk.

Stimulant therapy turned out to have a profound protective effect. At 10 years' follow-up, it was associated with a highly significant 78% reduction in the relative risk of developing major depression, compared with ADHD patients who did not take stimulants, a 79% decrease in conduct disorder, an 85% reduction in the risk of having two or more anxiety disorders, and a 79% reduction in oppositional defiant disorder, all diagnosed based on DSM-IV criteria. Stimulant-treated patients were also 75% less likely to have repeated a grade.

Moreover, stimulant-treated patients were 53% less likely to be diagnosed with bipolar disorder during 10 years of follow-up, a trend which approached but did not achieve statistical significance.

"This issue is of high clinical importance considering the large and bidirectional comorbidity between ADHD and bipolar disorder and the concern that treatment with stimulants may activate children with bipolar disorder," Dr. Biederman observed.

One audience member asked how stimulant therapy could be effective both for control of ADHD symptoms and for preventing subsequent major depression, given that the neurobiology of the two disorders is quite different.

"I was very surprised by my own findings," he acknowledged. "The short answer is I don't know. The longer answer …is that I suspect that the continued use of stimulant therapy allows the child to be more successful, minimizes friction at home, minimizes psychosocial vulnerabilities, and that in turn may reduce the risk of developing psychiatric comorbidities like depression.

He noted that this study carries a key message regarding the importance of medication adherence in ADHD.

"The adherence we have with stimulants, at least in the U.S., is among the worst in the entire field of medicine. One year out, 80% of children are no longer taking their medication. Given these data showing that treatment is so important to avert bad outcomes, adherence is extremely important," Dr. Biederman said.

Another audience member commented that the study results cannot be considered definitive because participants were not randomized to stimulant therapy or a control group. Dr. Biederman replied that the days are long gone when a randomized placebo-controlled study of stimulants in ADHD would be possible. "These data are the best we're going to have," he said.

ADHD affects up to 10% of children and 5% of adults the world over. Ten-year follow-up data from the investigators' parallel study of girls with ADHD are now being analyzed.

The ongoing longitudinal study is supported by the National Institutes of Health. Dr. Biederman disclosed receiving research support from and serving as a consultant and/or advisory board member to numerous pharmaceutical companies. ■

Psychiatric Illness Associated With Nonadherence to Antiepileptics

BY SUSAN LONDON

SEATTLE — Epileptic children are less likely to take antiepileptic drugs as prescribed if they also have psychiatric illnesses, according to a review of an administrative claims database.

"It's well established that nonadherence to prescribed antiepileptic drugs has serious potential consequences, including exacerbation of seizures, morbidity, and, now we are learning, even potentially mortality," said Dr. Alan B. Ettinger, a neurologist at the Comprehensive Epilepsy Center at North Shore Long Island Jewish Medical Center, New Hyde Park, N.Y. "Establishing a possible relationship between these issues—psychiatric comorbidity and adherence—really has practical utility because if this is the case, then clinicians need to use some special interventions to try to promote better adherence."

The most common psychiatric illnesses among the 5,343 children whose claims were reviewed were ADHD and attention deficit disorder.

Using a PharMetrics administrative claims database, Dr. Ettinger and his colleagues reviewed claims for January 2000 through December 2006 for more than 50 million individuals covered by U.S. managed care plans.

The researchers found 5,343 children aged 4-18 years who had a diagnosis of epilepsy, received at least one prescription for an antiepileptic drug (AED), and were enrolled in their health plan for at least 1 year before and 1 year after starting the medication. There were slightly more boys than girls (55%), and about half of the children were 11 years old or younger.

Fully 65% of the children were nonadherent to their AED therapy. The children's mean medication possession ratio, a measure of adherence, was 0.54. Children with a ratio of less than 0.8 were considered nonadherent. The ratio was calculated by dividing the total number of days for which AEDs were supplied during the 1-year follow-up period by 365 days, Dr. Ettinger said at the annual meeting of the American Epilepsy Society.

Nearly half of the children had a psychiatric illness, as diagnosed by any physician, said Dr. Ettinger.

The most common were attention-deficit/hyperactivity disorder (17%) and attention deficit disorder (10%). But sizable proportions of children had more serious psychiatric illnesses, such as bipolar disorder (8%), developmental disorders (5%), schizophrenia (1%), or other psychoses (7%).

In multivariate analyses that took into account age, sex, geographic region, overall comorbidity burden, type of AED (newer vs. older), starting regimen (monotherapy vs. combination therapy), and initial AED dosing (one or fewer pills daily vs. more), children were significantly more likely to be nonadherent if they had a diagnosis of attention-deficit/hyperactivity disorder or bipolar disorder before starting AED therapy (odds ratios, 1.17 and 1.22, respectively) and if they received a diagnosis of bipolar disorder after starting AED therapy (odds ratio, 1.37).

Schizophrenia alone was not associated with elevated odds of nonadherence. But relative to their counterparts who did not have any of the more serious psychiatric illnesses, children who had at least one of them (regardless of type) were significantly more likely to be nonadherent (odds ratio, 1.15).

"Recognizing psychiatric comorbidity in pediatric patients with epilepsy is very important, and we hope that this study lends another compelling reason why clinicians need to be screening for psychiatric comorbidity," concluded Dr. Ettinger, who reported that he is a project consultant for GlaxoSmithKline. ■

Guanfacine Gets the Nod as Once-Daily Therapy for ADHD

BY ALICIA AULT

The Food and Drug Administration approved guanfacine (Intuniv) for treatment of attention-deficit/hyperactivity disorder for children and adolescents aged 6-17 years.

The extended-release form of the drug is a selective alpha-2A adrenergic receptor agonist and was first approved for the treatment of hypertension in 2002, and for ADHD in 2007. But its use was limited by its short half-life. The once-daily version will be available in four dosages: 1 mg, 2 mg, 3 mg, and 4 mg.

Unlike many other drugs for ADHD, Intuniv is not a controlled substance. According to manufacturer Shire Pharmaceuticals, Intuniv "has no known potential for abuse or dependence." The company said that it expected the drug to be available in November.

The FDA sent Shire an "approvable" letter in January 2008, but in early August, the company was told by the agency that it still was not in agreement on the final labeling for the extended-release form of guanfacine.

With approval, Shire said that Intuniv's labeling will contraindicate use in patients with a history of hypersensitivity to guanfacine or any of its active ingredients. Because hypotension, bradycardia, and syncope were all observed in clinical trials, the drug should be used with caution in patients who have experienced any of those conditions previously, or who may be predisposed to syncope, or who are taking antihypertensives.

Labeling will also note that sedation and somnolence were observed in trials.

The mechanism of action is unknown, but, according to statement from Shire, the drug seems to stimulate the postsynaptic alpha-2A receptors, which are "thought to strengthen working memory, reduce susceptibility to distraction, improve attention regulation, improve behavioral inhibition, and enhance impulse control." ■