ADHD Drug Eases Anxiety, Not Depression

BY KERRI WACHTER
Senior Writer

WASHINGTON — The attention-deficit hyperactivity drug atomoxetine does not appear to improve comorbid depression in adolescents, but it does appear to reduce comorbid anxiety in children and adolescents, according to data from two studies presented at the annual meeting of the Pediatric Academic Societies.

Both trials were sponsored by Eli Lilly & Co., maker of atomoxetine (Strattera).

In the first study, patients aged 8-17 years, who met the DSM-IV diagnostic criteria for both attention-deficit hyperactivity disorder (ADHD) and anxiety disorder (generalized anxiety, separation anxiety, or social phobia disorder), were randomized to receive either atomoxetine (87 patients) or placebo (89 patients) in a 12-week trial.

The mean age of the patients was roughly 12 years, and boys outnumbered girls 3-1. The target dose of atomoxetine was 1.2 mg/kg per day (split and given twice a day), said Calvin Sumner, M.D., of Eli Lilly.

ADHD symptoms were assessed using the ADHD Rating Scale (ADHDRS). The Pediatric Anxiety Rating Scale total score and the Multidimensional Anxiety Scale for Children (which allows children to rate their own anxiety) were used to assess anxiety symptoms. The last observations were carried forward.

As a way to minimize any placebo effect, those randomized to receive atomoxetine actually received placebo for the first 2 weeks of the trial. Any patients who had a 25% reduction in anxiety score during that period were allowed to finish the trial but not included in the final analysis.

For the analysis that excluded patients with less than 25% improvement in anxiety during the first 2 weeks of the trial, those on atomoxetine (55 patients) had a significant improvement in ADHD scores from baseline to the end point, compared with those on placebo (58 patients). When all patients were considered, there was a significant improvement in ADHD scores for patient on atomoxetine, compared with those on placebo.

In the second trial, placebo had a strong effect on depressive symptoms that was independent of its effect on attention-deficit hyperactive disorder.

In the smaller analysis, there also was a significant improvement in anxiety scores for those on atomoxetine, compared with those on placebo.

Among all patients, a significant improvement in anxiety scores was seen for those on atomoxetine, compared with those on placebo.

Also looking at the full group, the children who received atomoxetine had a greater perceived reduction in anxiety symptoms, compared with those who received placebo, as measured by the Multidimensional Anxiety Scale for Children.

Decreased appetite was the only adverse event that occurred more frequently in the atomoxetine group.

In the second trial, adolescents had to meet the clinical definition of both ADHD and major depressive disorder. "These were kids who really had major depression," Dr. Sumner said.

The patients, aged 12-18 years, were randomized to receive 9 weeks of treatment with atomoxetine (72 patients) or placebo (70 patients). Boys outnumbered girls 3-1.

The target atomoxetine dose was 1.2 mg/kg each day, though patients could go up to a dose of 1.8 mg/kg each day. Both placebo and atomoxetine were given once a day. The response of ADHD symptoms was measured using the 18-question ADHDRS. Depressive symptoms were measured using the Children's Depression Rating Scale. Patients were assessed using the Young Mania Rating Scale, as a way of determining whether the depression experienced by these adolescents was a heralding event for bipolar disorder or true depression.

The ADHD and depression scores at 9 weeks were analyzed as change from baseline, with last observation carried forward. Treatment emergent mania was described as a patient who started out with a score of less than 15 on the mania scale, and at the end point the mania score was 15 or greater.

"Atomoxetine really helped depression. There was a considerable reduction in the depressive rating scales. The other side of the story is, so did placebo," Dr. Sumner said.

Placebo showed a very strong effect on depressive symptoms that was independent of its effect on ADHD.

"So this was inconclusive. There was no evidence—that was separable from placebo—that atomoxetine had any benefit in reducing depressive symptoms," Dr. Sumner said.

Two patients in each group had treatment emergent mania, a result that was not interpretable.

In terms of adverse events, nausea and decreased appetite were more common in the atomoxetine group. Importantly, there were no adverse events involving suicidal ideation or suicidal behavior in either group.

The meeting also was sponsored by the American Pediatric Society, the Society for Pediatric Research, the Ambulatory Pediatric Association, and the American Academy of Pediatrics. ■

Drug Helps Manage Teens' ADHD Symptoms

BY ROBERT FINN
San Francisco Bureau

SAN FRANCISCO — Extended-release methylphenidate is effective in reducing the symptoms of attention-deficit hyperactivity disorder in adolescents, Linda Pfiffner, Ph.D., said at a meeting on clinical pediatrics sponsored by the University of California, San Francisco.

The study is significant because few placebo-controlled studies of medication for ADHD in adolescents have been conducted, said Dr. Pfiffner of the university. The randomized, double-blind, placebo-controlled study involved 177 boys and girls, aged 13-18 years, with a confirmed diagnosis of ADHD. During a 4-week, open-label period, the children were titrated to a dose of methylphenidate (Concerta) that resulted in at least a 30% improvement in ADHD symptoms, as rated by the investigators.

They were then randomized to receive placebo or their individualized methylphenidate dose for 2 weeks, after which they were eligible to participate in an 8-week open-label follow-up.

During the titration phase, 36.7% of the children reached a daily dose of 72 mg, the highest dose offered. Smaller proportions of children settled at lower doses: 27.7% at 54 mg, 28.2% at 36 mg, and 7.4% at 18 mg.

At the end of the titration phase, the mean investigator rating of ADHD symptoms fell 86% from baseline.

At the end of the double-blind phase, investigators, parents, and the children themselves independently recorded significant improvements in ADHD symptoms in favor of methylphenidate.

In fact, the patient self-assessments showed a larger difference between the placebo and active medication groups than the investigators or the parents. This suggests that the children may be more sensitive in their judgments of efficacy than the outside observers, Dr. Pfiffner said.

The study was supported by McNeil Consumer & Specialty Pharmaceuticals, which manufactures Concerta. ■

Low Serum Cholesterol in Non–African Americans Associated With Suspensions

BY MIRIAM E. TUCKER
Senior Writer

Low total serum cholesterol is associated with an increased likelihood of school suspensions and expulsions among non–African American children, said Jian Zhang, M.D., of the University of South Carolina, Columbia, and associates.

The finding corroborates and extends existing literature linking low total cholesterol and aggressive behavior in adults. Low cholesterol may be a risk factor for aggressive behavior, a risk marker for other biologic substances or genotypes that predispose to such behavior, or a biologic marker for poor prognosis. In any case, if confirmed by prospective studies, these findings may assist pediatricians in contributing to schools and to violence prevention, the investigators said (Am. J. Epidemiol. 2005;161:691-9).

The data come from 4,852 children and adolescents aged 6-16 years (mean 10) whose mothers were interviewed for the Third National Health and Nutrition Examination Survey (NHANES III), conducted during 1988-1994. None attended special schools or classes as a result of intellectual or physical health impairment. Serum cholesterol was measured, and a variety of neuropsychiatric tests administered.

The proportion who had ever been suspended from school was 15.38% among children with serum cholesterol levels less than 145 mg/dL, compared with 6.25% among those with cholesterol levels of 145 mg/dL and above. After adjustment for age and gender, the odds ratio for school suspension for low vs. high cholesterol was 1.73.

On the other hand, serum cholesterol was not predictive of ever seeing a psychologist, being shy when meeting new persons, or having difficulty getting along with others, Dr. Zhang and his associates reported.

When broken down by race, the relationship remained significant only among the 3,167 non–African American children in the sample.

For that group, a history of school suspension or expulsion was approximately threefold higher for those with total cholesterol below the 25th percentile than for children with total cholesterol at or above the 25th percentile.

The association persisted after adjustment for many other factors, including cognitive and academic performance and nutrition status, which are known to place children's emotional and behavioral development at risk, they noted.

This study is the first to demonstrate a statistically significant, ethnicity-dependent association between serum cholesterol and aggressive behaviors from a national sample of noninstitutionalized, school-aged children.

Possible biologic mechanisms to explain the association between serum lipids and violence involve the role of cholesterol and fats in brain function and behavior through modification of membranes and through effects on neurotransmitter production, reuptake, and metabolism.

The racial difference seen in this study might have to do with differences in basal prevalence. African-American children have higher rates of school suspension, so the impact of cholesterol may be lower than in non–African Americans. ■