Aripiprazole Approved for Autistic Irritability

BY ELIZABETH MECHCATIE

The atypical antipsychotic aripiprazole has been approved for treating irritability associated with autistic disorder in children and adolescents aged 6-17 years. Irritability includes symptoms of aggression toward others, deliberate self-injuriousness, temper tantrums, and quickly changing moods, the manufacturers announced.

Aripiprazole is marketed as Abilify by the manufacturers, Bristol-Myers Squibb Co. and Otsuka Pharmaceutical Co. The recommended dose for the new indication is 5 mg to 10 mg day (starting at 2 mg/day, with the maximum dose of 15 mg/day).

Since it was initially approved by the Food and Drug Administration in 2002 for schizophrenia, it has been approved for several other adult and pediatric indications, including treatment of schizophrenia in adolescents aged 13-17 years, and bipolar disorder indications down to age 10 years.

The effectiveness of aripiprazole for the autistic disorder indication was established in two 8-week multicenter studies of children and adolescents aged 6-17 years (more than 75% were younger than age 13 years), according to the revised label. They met the DSM-IV criteria for autistic disorder and exhibited behaviors that included tantrums, aggression, and/or self-injurious behavior.

In a study of 218 children and adolescents, those on aripiprazole had significantly improved scores on the irritability subscale of the Aberrant Behavior Checklist.

In one study of 98 children and adolescents, those who were on aripiprazole (starting at a dose of 2 mg/day and increasing up to 15 mg/day based on clinical response) had significantly improved scores when compared to those on placebo at 8 weeks on two scales: the irritability subscale of the Aberrant Behavior Checklist (ABC-I), a caregiver rated assessment tool, and the Clinical Global Impression-Improvement (CGI-I) scale, a tool used to monitor treatment outcomes in psychiatric disorders.

In the second study of 218 children and adolescents, those on a fixed dose of aripiprazole (5 mg, 10 mg, or 15 mg per day) had significantly improved scores on the ABC-I subscale compared with those on placebo.

In a pooled analysis of the two studies, mean weight gain among those on aripiprazole was 1.6 kg, compared with 0.4 kg among those on placebo. During the study, 26% of those on aripiprazole and 7% of those on placebo experienced clinically significant weight gain, defined as at least a 7% change from baseline, according to the company statement.

Other adverse events more common among treated patients included sedation, affecting 21% of those on aripiprazole compared with 4% of those on placebo, fatigue (17% vs. 2%), vomiting (14% vs. 7%), somnolence (10% vs. 4%), tremor (10% vs. 0%), drooling (9% vs. 0%), and extrapyramidal disorder (6% vs. 0%).

These studies were "not designed or intended to evaluate" aripiprazole for treatment of the core symptoms of autistic disorder, the company statement said. ■

Small CV Changes Seen With Concerta

BY ROBERT FINN

HONOLULU — High-dose OROS methylphenidate was associated with small but statistically significant increases in systolic blood pressure and heart rate in a 6-month, open-label study in adolescents.

The study found no significant long-term increases in diastolic blood pressure or in electrocardiographic measures, Dr. Paul Hammerness said at the annual meeting of the American Academy of Child and Adolescent Psychiatry.

The findings are consistent with studies involving younger children and lower doses, said Dr. Hammerness of Massachusetts General Hospital and Harvard Medical School, Boston.

Because of concerns about possible associations between stimulant medications for attention-deficit/hyperactivity disorder (ADHD) and cardiovascular complications—including sudden cardiac death—the Food and Drug Administration in June 2009 recommended that physicians pay special attention to a child's cardiovascular system when prescribing stimulants.

The study involved 114 adolescents with a mean age of 14 years at baseline (range 12-18 years). All were healthy, and all had a diagnosis of ADHD based on full DSM-IV criteria. The trial was intended to evaluate use of OROS methylphenidate for prevention of cigarette smoking (J. Pediatr. 2009;155:84-9).

The beginning dose of OROS methylphenidate was 0.5-0.75 mg/kg per day, and that was titrated upward to a maximum of 1.5 mg/kg per day by week 3. At week 6, the mean total daily dose was 63 mg, and 50% of the participants were taking 72 mg or more.

As expected, OROS methylphenidate was highly effective in treating the participants' ADHD. Their ADHD Rating Scale scores declined from a mean of 26.9 at baseline to 9.7 at week 6.

Of the 114 participants who entered the study, 73% were male, and their mean body mass index was 22.6 kg/m^2. At the time of data analysis, 57 participants had completed 6 months of treatment.

Mean systolic blood pressure at baseline was 113 mm Hg, and that increased to 117 mm Hg at 6 months, a significant increase. Mean diastolic blood pressure began at 63 mm Hg, increased significantly to 65 mm Hg at week 6, but then returned to 64 mm Hg at 6 months. Mean heart rate began at 82 beats per minute, increased significantly to 86 beats per minute at week 6, and remained at about that rate at 6 months.

There were no serious cardiovascular adverse events, but 10 of the 114 subjects reported one or more subjective cardiovascular complaints, such as palpitations and chest pain.

The investigators found no statistically significant or clinically meaningful changes in ECG variables, including PR, QRS, or QTC.

Reasoning that any adverse cardiovascular effects of OROS methylphenidate might be restricted to certain subsets of adolescents, the investigators separately analyzed those 16 participants who met criteria for prehypertension or hypertension at baseline, based on at least one blood pressure reading above the 90th or 95th percentile. The investigators found no impact of abnormal premedication blood pressure readings on blood pressure changes during treatment.

Participants experienced no serious adverse events or serious cardiovascular adverse events during the study. Ten of the 114 subjects reported one or more subjective cardiovascular complaints, including palpitations, chest pain, and fast or racing heartbeat. Of those, six had a lifetime diagnosis of comorbid anxiety disorder.

One participant discontinued treatment because of recurrent palpitations. She had a lifetime history of comorbid generalized anxiety disorder and migraines, but she showed no change from baseline in any cardiovascular measurement, and her primary care physician did not find her complaints to be consistent with cardiac disease. She later used a different stimulant medication with no subsequent cardiovascular symptoms.

"The FDA continues to review and still concludes that the overall risk-benefit ratio supports the use of stimulant medications for ADHD," Dr. Hammerness said. But he did recommend that clinicians carefully evaluate a child's cardiovascular symptoms and family history before prescribing stimulants.

In particular, clinicians should look for a family history of cardiovascular disease at a young age, such as QT syndrome, cardiomyopathy, or a cousin who died suddenly during exercise.

Dr. Hammerness acknowledged serving as a speaker for, receiving research funds from, or participating in CME activities or professional talks supported by Abbott, McNeil, and Shire Pharmaceuticals; and participating in research studies funded by Bristol Myers Squibb, Cephalon, Eli Lilly & Co., Johnson & Johnson, McNeil, New River, Novartis, Organon, Otsuka, Pfizer Inc., Shire, and Takeda. This study was sponsored by McNeil, which markets OROS methylphenidate under the brand name Concerta. ■

Economic Woes Taking a Toll On Addiction Services

BETHESDA, MD. — The current economic downturn has had a substantial impact on the prevalence and treatment of addiction in the United States, according to preliminary findings, Paul Roman, Ph.D., said at the annual meeting of the Association of Medical Education and Research in Substance Abuse, which was sponsored by Brown Medical School.

Dr. Roman and Amanda J. Abraham, Ph.D., both of the University of Georgia, Atlanta, collected data during interviews with treatment program administrators in the Clinical Trial Program (198), privately run programs (345), and the National Institute of Alcohol Abuse and Alcoholism (350).

The administrators reported a mean reduction of 13% in overall budget, 22% in grant funding, 17% in Medicaid income, and 12% in insurance payments. The dip in grant allocations alone correlated with an increase in uncollectible revenues, a decrease in staff and treatment slots, and the implementation of hiring freezes, he said.

Staff losses and hiring freezes cut across the management, counselor, and support staff categories: 14% of interviewees reported cuts at management level, 27% reported counselor losses, and 25% support staff losses. One-third of those interviewed said there had been hiring freezes across all three staff categories. Commensurate with these staff cuts, particularly at the counselor level, was a reduction in the number of treatment slots, which was reported by 12% of the interviewees. At the same time, there was a mean overall increase of 18% in patients.

Dr. Roman had no financial disclosures. The study was funded by National Institute of Drug Abuse and the NIAAA.

—Renée Matthews