Atomoxetine Feasible in Young Children with Attention-Deficit/Hyperactivity Disorder

Speaker: Christopher J. Kratochvil, MD, Associate Professor, Department of Psychiatry, University of Nebraska; Member, Graduate Faculty of Psychiatry, University of Nebraska Medical Center; and Assistant Director, Psychopharmacology Research Consortium, University of Nebraska, Omaha, Nebraska

Atomoxetine (Strattera, Eli Lilly), a novel agent that strengthens the chemical signals between brain cells and increases neurotransmitters to improve concentration, was effective and well tolerated for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children five to six years of age. The findings supported the feasibility of a multicenter, double-blind, placebo-controlled study of atomoxetine in this age group.

Twenty-two young children with ADHD were enrolled in an eight-week, open-label pilot study in which they received atomoxetine daily. The pharmacotherapist presented psychoeducational modules for behavioral management with each pharmacotherapy visit.

Overall, the children demonstrated a significant mean decrease in ADHD-IV Rating Scale total scores of 20.68; on the Inattentive subscale, 10.18 (out of a total of 24); and on the Hyperactivity/Impulsive subscale, 10.50 (out of a total of 27) \((P < .001)\). The most frequently reported adverse event was decreased appetite, in 11 participants, with a mean decrease of 1.04 kg \((P < .001)\). None of the children discontinued therapy because of adverse events or a lack of efficacy, but two children dropped out because of their inability to swallow capsules.

OROS Methylphenidate for Attention-Deficit/Hyperactivity Disorder plus Epilepsy

Speaker: Joseph Gonzalez-Heydrich, MD, Chief of Psychopharmacology, Department of Psychiatry, Children’s Hospital; and Assistant Professor of Psychiatry, Harvard Medical School, Boston, Massachusetts

Osmotic Release Oral System methylphenidate (OROS MPH) (Concerta, McNeil-PPC, Inc.) was observed to be safe and well tolerated for the treatment of ADHD in patients with epilepsy. The stimulant produced no serious adverse events or increases in seizures. Compared with placebo, this agent resulted in a significant reduction in ADHD Rating Scale scores.

Although package inserts for all MPH products contain warnings not to use MPH preparations in patients with epilepsy, few studies have evaluated the risks and benefits of MPH in children with ADHD and comorbid epilepsy, and none have evaluated OROS MPH in this population. A study was therefore performed to assess the safety and efficacy of OROS MPH in patients with ADHD and epilepsy.

Twenty-seven children, 10.7 years ± 3.1 years of age (or 7.6 to 13.8 years of age), were randomly assigned to receive OROS MPH at target doses of 18, 36, or 54 mg/day or placebo. The children were then crossed over to the other group in a double-blind design. They underwent an initial one-day trial of intermediate-release (IR) MPH 5 mg twice daily, followed by weekly increases up to the maximum dose for each OROS MPH dose group.

Each patient continued with the maximum dose of OROS
Divalproex Extended Release for Pediatric Bipolar Disorder

Speaker: Russell E. Scheffer, MD, Associate Professor, and Division Director, Child and Adolescent Psychiatry, Department of Psychiatry and Behavioral Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin

The conversion algorithm that accounts for the lower bioavailability of divalproex sodium extended-release tablets (DVP-ER) (Depakote-ER, Abbott) resulted in a safe transition from divalproex sodium delayed-release tablet (DVP-DR) to DVP-ER. The switch produced consistent improvement of symptoms, fewer side effects, greater patient satisfaction, relatively stable valproic acid trough levels, and better adherence to treatment as a result of once-a-day dosing in children and adolescents with bipolar disorder.

To determine whether product insert guidelines were acceptable for transitioning patients from DVP-DR to DVP-ER and whether side effects decreased as a result of fewer peaks, investigators conducted an eight-week study. Eighteen female and male patients, from 7 to 17 years of age, with a diagnosis of bipolar I or II disorder with or without ADHD, were enrolled. All of the patients were clinically stable on DVP-DR; however, they were converted to DVP-ER either because of persistent side effects or because of convenience of use.

The researchers switched the patients from their stable ongoing dose of DVP-DR by dividing the dose by 0.8 to 0.9. If this resulted in a DVP-ER dose that was a multiple of 500 mg after 10% to 20% was added, conversion ensued. If not, the patients were not enrolled in the study.

Several scales were used to perform analyses that measured the difference between values at baseline and at eight weeks. These included:

- the Young Mania Rating Scale (YMRS)
- the Children’s Depression Rating Scale (CDRS-R)
- the CGI–S Scale, items 1, 2, and 3
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- The CGI–I Scale, items 1, 2, and 3
- total scores on the Side Effects for Children and Adolescents (SEFCA) Scale
- serum levels of valproic acid

Twelve patients, 11 of whom were females, were evaluable. Hair loss and gastrointestinal (GI) distress were most commonly cited as the reasons for conversion.

Patients who were switched to DVP-ER from DVP-DR demonstrated improvement in clinical symptoms. These youngsters tended to have improved YMRS scores, CDRS, scores, and CGI–S scores on items 1 and 3, but the results were not significant. Patients did, however, show significantly improved CGI–S scores for item 2 and better CGI–I scores for items 1, 2, and 3.

Patients who were switched showed improvements in side effects, lending support to the idea that lower peaks lead to fewer adverse effects with the same daily equivalent dose. Hair loss and GI distress significantly improved with conversion to DVP-ER in all patients who reported these effects at the baseline examination.

Finally, valproic acid blood levels increased slightly but not significantly.

**Olanzapine Useful in Adolescent Mania**

**Speaker:** Carol Robertson-Plouch, DVM, Clinical Research Advisor, Lilly Research Laboratory, Indianapolis, Indiana

Olanzapine (Zyprexa, Eli Lilly) effectively reduced the symptoms of mania in adolescents with bipolar disorder. Although this treatment provided therapeutic benefits for these young patients, the risk–benefit ratio in this population should be carefully evaluated, because the severity and magnitude of some adverse events appear to be greater than those seen in adults.

A three-week, randomized, double-blind clinical trial of 161 patients, 13 to 17 years of age, who had a manic or mixed episode of bipolar disorder, was conducted. The patients were randomly assigned, in a ratio of 2:1, to receive either olanzapine (n = 107) or placebo (n = 54).

Olanzapine therapy was begun at 2.5 or 5 mg/day. The dose was increased daily, by 2.5 or 5 mg, to achieve a level of 10 mg/day or more by the fourth visit, up to a maximum tolerable dose of 20 mg or more daily. The mean daily dose was 8.86 mg/day. The primary efficacy analysis was a mean change from baseline to endpoint in Young’s Mania Rating Scale (YMRS) total scores.

Significantly greater reductions in YMRS total scores were noted for olanzapine (~17.7) than for placebo (~10) (P < .001).

Treatment was also associated with higher response rates (44.8%, 18.5% for placebo; P = .002), remission (35.2% vs. 11.1% for placebo; P = .001) and response (44.8% vs. 18.5% with placebo, P = .002).

The treated patients also experienced shorter times to reach those criteria. Their time needed to achieve a response was 15 days, compared with 26 days for those receiving placebo, at the 25th quantile; (P = .003), and their time needed to achieve remission of mania was 18 days, compared with 26 days for the placebo patients, at the 25th quantile (P = .002).

Somnolence, sedation, increased appetite, and weight gain occurred at significantly greater rates with olanzapine than with placebo.

The olanzapine patients experienced greater mean changes in fasting glucose and total cholesterol levels compared with changes observed in the placebo group. More olanzapine-treated patients gained 7% or more of their baseline body weight compared with patients receiving placebo. Compared with the placebo-treated patients, the olanzapine patients also showed a higher incidence of elevated prolactin levels.

**Intramuscular Ziprasidone Controls Acute Agitation**

**Speaker:** Drew H. Barzman, MD, Assistant Professor, Division of Child and Adolescent Psychiatry, University of Cincinnati College of Medicine and Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio

A retrospective chart review demonstrated that intramuscular (IM) ziprasidone (Geodon, Pfizer), a dopamine/serotonin antagonist used in the treatment of schizophrenia, was well tolerated and effective for the management of acute agitation in children and adolescents.

These findings were concluded from a retrospective chart review of children and adolescents admitted to psychiatric units at the Cincinnati Children’s Hospital Medical Center between January 1, 2002, and July 11, 2005. During that period, 59 children and adolescents received 77 injections of IM ziprasidone for acute agitation. Medical records were reviewed to determine demographic and clinical information as well as the agent’s tolerability and effectiveness.

The Behavioral Activity Rating Scale (BARS) was used retrospectively to assess clinical response. The primary objective of the study was to evaluate effectiveness and tolerability of IM ziprasidone for impulsivity and reactive aggression in these hospitalized young patients. The secondary response was to examine demographic and clinical factors associated with treatment response.

Overall, the mean ± standard deviation (SD) BARS score decreased from 6.5 ± 0.7 to 3.1 ± 1.3. On this scale, 1 represents good behavior, and 7 represents most violent behavior (with restraints required).

Regression analyses showed no significant effects of such demographic factors as age, sex, ethnicity, or primary psychiatric diagnosis on treatment response. Adverse events were rare, with sleepiness or falling asleep recorded in 23 patients. The remainder of adverse events included an increase in seizure frequency, dizziness, nosebleeds, sore muscles, general aches, and confusion. Each event was reported in only one patient.

**Aripiprazole Valuable in Pediatric Tic Disorder or Tourette Syndrome**

**Speaker:** Dong-Ho Song, MD, PhD, Professor, Department of Psychiatry and The Institute of Behavioral Science, Yonsei University College of Medicine, and the Yongdong Severance Hospital, Seoul, Korea

Aripiprazole (Abilify, Bristol-Myers Squibb), a stabilizer of the dopamine-responsive/detected circuits related to the
pathophysiology of tics, was effective in managing tic symptoms and was well tolerated in children and adolescents with tic disorder or Tourette syndrome.

In a study that examined the short-term tic-suppressing effect of the antipsychotic agent aripiprazole, 21 children and adolescents with these disorders were enrolled in an eight-week, open-label study. Sixteen patients with Tourette syndrome and five patients with chronic motor tic disorder received aripiprazole, given at an initial daily dose of 5 mg. This amount was increased every two weeks in 5- to 10-mg increments to an effective and tolerable dose.

Outcome measures included The Yale Global Tic Severity Scale, the Tic CGI–S Scale of 1 (normal) to 7 (extremely ill), and CGI–I Scale of 1 (very much improved) to 4 (no change). Side effects also were assessed after aripiprazole administration.

Overall, the aripiprazole dose during eight weeks was 17.5 ± 7.3 mg/day. Significant reductions in the Yale Tic scores and CGI–S scores were noted between pretreatment and at post-treatment at the eighth week. Changes in CGI–I scores at the eighth week after treatment included “very much improved” in two patients (10%), “much improved” in nine patients (43%), minimally improved in six patients (28%), and “no change” in four patients (19%). Possible drug-related adverse events included sleep problems (insomnia in one patient and hypersomnia in five patients), dizziness in two patients, and headache in one patient. No extrapyramidal symptoms, agitation, sedation, or weight gain was observed.

Topiramate Helpful for Patients with Binge-Eating Disorder

Speaker: Ema Saito, MD, Psychiatrist and Research Scientist, Zucker Hillside Hospital, Glen Oaks, New York

Results from a 16-week pilot study indicated that topiramate (Topamax, Ortho-McNeil), a well-known anticonvulsant that has shown efficacy in reducing the frequency of binge-eating in short-term studies, proved effective in decreasing the frequency of episodes in adolescents and young adults with binge-eating disorders.

A 16-week, open-label study enrolled 12 individuals (mean age, 17.75 years), seven with bulimia nervosa and five with binge-eating disorder. The subjects received a flexible dose of topiramate, ranging from 25 to 400 mg. The dose was titrated by 25 mg to 50 mg weekly according to the clinical response, as assessed by binge-eating diaries and patients’ tolerability. If binge-eating behavior decreased by 50%, compared with the previous week, the dose of topiramate was to remain the same.

Follow-up was performed weekly for 10 weeks. If patients were stable after week 10, they were seen every two weeks. The patients were allowed to continue co-medication and psychotherapy throughout the study period. Six patients received additional medication for comorbidities or both.

The researchers conducted an assessment of adverse effects at the baseline evaluation, at the 10th week, and at the study’s endpoint. Laboratory evaluations were also performed at these three time points. The following instruments were used:

- the Hillside Adverse Events Form
- the Binge-Eating Scale (BES)
- cognitive function tests: Boston Naming Tests (BNT), Trail-Making Tests A & B (TMT-A&B), and the Barrett Impulsive Scale, version II (BIS-II)

Seven patients completed the 16-week study, and two others completed at least 10 weeks of study participation. Three patients dropped out.

The time (P < .007) and topiramate dose (mean dose, 112.5 mg/day) (P < .02) were significant factors in bringing about a decrease in the frequency of binge-eating, from 5.3 episodes per week to one episode per week.

Barrett Scale-II and Trail-Making Test-B scores did not show any significant differences between the two time points. The change in weight was not significant between the two time points: 154.1 pounds at beginning of the study to 152.5 pounds at the endpoint. Improvements in the Boston Naming Test between the two time points, however, were significant (P < .0014)—from a score of 52.9 to 56. The normal score was 56.1.

Trail-Making Test-A scores also improved.

Paroxetine May Increase Risk of Suicidal Behavior in Young Adults

Speaker: David J. Carpenter, MS, PharmD, Senior Director of Psychiatry, Neurosciences Medicine Development Center, GlaxoSmithKline, King of Prussia, Pennsylvania

Data from all GlaxoSmithKline placebo-controlled, paroxetine (Paxil) clinical trials enrolling young adults with major depressive disorders (MDD), along with other psychiatric disorders, suggest that this population might be at a significantly increased risk of suicidal behavior or ideation, compared with subjects receiving placebo.

The data were pooled from 62 studies of four to 12 weeks in duration. All of these studies involved 30 or more 18- to 24-year-old patients; 876 received paroxetine, and 542 received placebo.

The investigators compared the incidence of definitive suicidal behavior or ideation (DSBI) and definitive suicidal behavior (DSB) in subjects receiving paroxetine or placebo. Suicidal behavior encompassed a completed suicide, a suicide attempt, or a preparatory act relating to suicide.

Overall, a higher incidence of suicidal behavior, with or without ideation, was observed in those young adults receiving paroxetine than in those receiving placebo. In the DSBI group of patients, the incidence of suicidal behavior was 2.6% with paroxetine and 1.3% with placebo; in the DSB young adults, it was 2.2% with paroxetine and 0.9% with placebo.

Similar patterns were observed in both depressive and nondepressive disorders. This possible increase in the risk of suicidal behavior in the paroxetine-treated patients was noted despite the efficacy of active drug therapy.