Mania Tx Data Lacking; New Results Expected

BY JEFF EVANS
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NEW YORK — Sparse evidence from double-blind, placebo-controlled trials backs the effectiveness of treatments for acute mania in children and adolescents with bipolar I disorder, but results from ongoing trials should be available soon, Dr. Gabrielle A. Carlson said at a psychopharmacology update sponsored by the American Academy of Child and Adolescent Psychiatry.

Double-blind, placebo-controlled trials have been conducted with olanzapine (Zyprexa), topiramate (Topamax), and oxcarbazepine (Trileptal) for the treatment of acute mania in children and adolescents, but other drug trials are yet to be completed, said Dr. Carlson, director of child and adolescent psychiatry at the State University of New York at Stony Brook.

Trials of that nature are underway for divalproex (Depakote) and the atypical antipsychotics risperidone (Risperdal), quetiapine (Seroquel), ziprasidone (Geodon), and aripiprazole (Abilify).

No trials have been planned for lithium or clozapine (Clozaril).

Based on the primary end point of the amount of change in the Young Mania Rating Scale (YMRS) from baseline, only olanzapine has shown statistically significant efficacy, in comparison with placebo. Topiramate and oxcarbazepine have not reached statistical significance on this end point in a double-blind, placebo-controlled trial, she said.

In the olanzapine trial of patients aged 13-17 years, 49% of the 107 adolescents who received active treatment had greater than 50% improvement in their YMRS score, compared with 22% of the 54 patients who received placebo.

The rate of remission at the end of 3 weeks of treatment also was significantly higher for olanzapine (35%) than for placebo patients (11%).

The oxcarbazepine trial of 116 children and adolescents appeared to show some efficacy of the anticonvulsant in patients aged 7-12 years, because YMRS scores improved by greater than 50% in significantly more patients in that age group who received oxcarbazepine (41%) than in those who received placebo (17%).

Adolescents aged 13-18 years did not differ significantly in their response to carbamazepine (43%) or placebo (40%).

In the topiramate trial, mean YMRS scores improved from 31.7 to 22 for the 29 patients who received the anticonvulsant and from 29.9 to 25.2 for the 27 patients who received placebo.

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The topiramate study was stopped early because the separate adult trials that involved topiramate failed to show efficacy for acute mania (J. Am. Acad. Child Adolesc. Psychiatry 2005;44:539-47).

In the topiramate and olanzapine trials, the clinician-rated scale of Clinical Global Impressions showed a statistically significant difference in the percentage of patients who were improved or very much improved.

In a head-to-head, double-blind, randomized trial of 50 patients, divalproex and quetiapine appeared to have similar efficacy in treating acute mania in hospitalized adolescents.

YMRS scores at baseline improved from an average of about 35 in each group to 17 in divalproex patients and to 13 in quetiapine patients.

"There wasn't a [significant] difference, because both of them work," Dr. Carlson said.

No double-blind, placebo-controlled trials of lithium in children and adolescents for acute mania have been conducted, even though the drug has been used openly in adults and kids since the 1950s.

Most of the open-label, discontinuation, and/or add-on trials of lithium, divalproex, and carbamazepine have shown positive results for the treatment of acute mania in children and adolescents.

Similar results have been reported with risperidone, olanzapine, and quetiapine.

Polypharmacy studies in which a drug is added to augment the effects of another medication appear to be beneficial in patients who are able to tolerate the combination, Dr. Carlson said.

In one randomized, double-blind study of 30 patients, a combination of divalproex and quetiapine resulted in a significantly higher response rate (87%) than did divalproex plus placebo (53%), she noted.

Patients who took the combination also had significantly greater improvement on mean YMRS scores from baseline to 42 days (from 34 to 10 vs. from 31 to 17) (J. Am. Acad. Child Adolesc. Psychiatry 2002;41:1216-23).

The combination of divalproex and lithium also appears effective when tolerated.

An open-label study of this combination showed that 42 of 90 children and adolescents with mostly bipolar I disorder met stringent criteria for remission after an average of 13 weeks of treatment.

The 90 patients had an average YMRS score of 22 at baseline; this score improved to a mean of less than 1 in the patients who remitted (J. Am. Acad. Child Adolesc. Psychiatry 2003;42:895-901). ■

CLINICAL CAPSULES

Escitalopram: Age Appears Relevant

Escitalopram failed to significantly improve the symptoms of depression in children aged 6-11 years, but it did appear to improve symptoms in children aged 12-17 years, wrote Dr. Karen Dineen Wagner of the University of Texas, Galveston, and her colleagues.

The study included 264 children and adolescents aged 6-17 years who had been diagnosed with major depressive disorder. The Children's Depression Rating Scale–Revised (CDRS-R) served as the primary outcome measure (J. Am. Acad. Child Adolesc. Psychiatry 2006;45:280-8).

The patients received either a placebo or 10 mg/day of escitalopram (Lexapro) for the first 4 weeks, with the option to increase the dosage up to 20 mg/day for the next 4 weeks, depending on the patient's response to the medication and tolerance.

Overall, the average changes in scores on the CDRS-R from baseline were not significantly different among the 102 escitalopram patients and 115 placebo patients who completed the study (–21.9 vs. –20.2).

However, a later analysis that adjusted for age group revealed significant improvements in CDRS-R scores from baseline among the 77 children aged 12-17 years who took escitalopram, compared with the 80 children aged 12-17 years who took a placebo, based on observed cases (–22.3 vs. –17.8).

In addition, adolescents in the escitalopram group showed significant improvements in symptoms based on several secondary outcome measures, including the Clinical Global Impressions-Severity scale.

Headaches and abdominal pain were the only reported adverse events that occurred in more than 10% of patients in either group, and the discontinuation rate in both groups was 1.5%.

The study was supported by Forest Laboratories, one of many companies from which Dr. Wagner has received research support.

Quetiapine May Ease Mania in Teens

Quetiapine was at least as effective as divalproex in alleviating manic symptoms in adolescents in a randomized, double-blind pilot study, wrote Dr. Melissa P. DelBello and her colleagues at the University of Cincinnati, Ohio.

The 28-day pilot study of 50 adolescents aged 12-18 years was the first known to directly compare an atypical antipsychotic with an antiepileptic in adolescents with mania, the researchers noted (J. Am. Acad. Child Adolesc. Psychiatry 2006;45:305-13).

The study was supported by a grant from AstraZeneca Pharmaceuticals, which markets quetiapine (Seroquel), and is one of the many companies from which Dr. DelBello has received research funding.

The adolescents who received quetiapine started with a 100-mg dose on the first day, which was increased to 400 mg by days 4-7, up to a maximum of 600 mg/day. Those who received divalproex started with a 20-mg/kg dose on the first day, which was increased to achieve serum valproic acid levels of 80-120 µg/mL. At the end of the study, the mean doses were 412 mg/day to 422 mg/day in the quetiapine group, and a valproic acid level of 101 µg/mL in the divalproex group.

Overall, patients in both groups showed statistically significant improvements in their scores on the Young Mania Rating Scale at the end of the study, compared with their baseline scores. However, the response was quicker among the quetiapine patients, compared with divalproex patients, and the overall response rate on the Clinical Global Impressions-Bipolar Version-Improvement scale was significantly greater in the quetiapine group, compared with the divalproex group (72% vs. 40%).

Both medications were well tolerated, and no patient in either group withdrew because of adverse effects. There were no significant differences between the treatment groups in terms of age, gender, race, or age of onset of bipolar disorder.

Depression and Violence

Girls who display depressive symptoms during adolescence are at increased risk for physical violence at the hands of their intimate partners, reported Jocelyn A. Lehrer, Sc.D., of the University of California, San Francisco and her colleagues.

The investigators analyzed interview data from 1,659 girls in grades 7-12 at 80 high schools and 52 middle schools in the United States.

The data were part of the National Longitudinal Study of Adolescent Health, and the girls participated in three waves of at-home interviews; the second wave was 1 year after the first, and the third was 5-6 years after the second (Arch. Pediatr. Adolesc. Med. 2006;160:270-6).

Overall, 28% of girls who reported high levels of depression at baseline also reported some type of intimate partner violence within the past year at the third wave follow-up interview, compared with 17.5% of girls with lower levels of depressive symptoms. High levels of depression were defined as scores of 23 or higher on the Center for Epidemiologic Studies Depression Scale, and the incidence of violence was assessed using self-administered questionnaires.

Each increase of a single standard deviation in baseline depressive symptomatology was associated with a 3% increase in the odds of exposure to either mild, moderate, or severe degrees of partner violence.

Depressive symptoms have been associated with a range of risky behaviors in adolescence, and depressed teens may be more likely than their nondepressed peers to associate with risky peer groups, and to select intimate partners from these groups, the researchers noted. However, the question of whether depressive symptoms independently predict intimate partner violence or simply predict risk for partner violence remains uncertain.

—Heidi Splete