Olanzapine and Pediatric Bipolar Disorder: Evidence for Efficacy and Safety Concerns

Pediatric bipolar disorder remains the focus of considerable debate. At the crux of the issue is how to define the illness in youth, and whether the same medications approved for treating bipolar disorder in adults should be used in children and adolescents. The paucity of randomized treatment trials in this population adds fuel to the controversy.

In this issue of the *Journal*, Tohen et al. report the first adequately powered controlled trial of a second-generation antipsychotic agent for the treatment of bipolar disorder in adolescents. This industry-sponsored study utilized a 3-week, multisite, parallel double-blind, randomized placebo-controlled design to examine the efficacy and safety of olanzapine (2.5–20 mg/day) for acute mania or mixed episodes in adolescents (ages 13–17 years). Twenty-six sites across the United States and Puerto Rico participated. The primary outcome measure was the mean change from baseline to endpoint on the Young Mania Rating Scale.

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The study enrolled 161 subjects; 107 were randomly assigned to olanzapine and 54 to placebo. The mean modal dose of olanzapine was 10.7 mg/day. Olanzapine was associated with a significantly greater reduction in Young Mania Rating Scale scores, a higher response rate (48% versus 22%), and a higher rate of symptom remission (35% versus 11%).

Significant safety concerns were also noted, particularly with regard to weight gain and metabolic parameters. Youth who were randomly assigned to olanzapine gained an average of 3.7 kg. Clinically significant weight gain (≥7% increase from baseline) occurred in 42% of subjects receiving active medication versus only 2% of those receiving a placebo. Olanzapine also was associated with significant elevations of fasting glucose and lipids. Fortunately, most of these increases did not reach clinically significant levels, although 23% of adolescents receiving olanzapine had borderline to high levels of triglycerides at some point during the 3-week trial. Finally, olanzapine was also associated with significant increases in hepatic enzymes, prolactin, and uric acid. Clinically abnormal elevations of aspartate transaminase and alanine transaminase occurred in a substantial portion of olanzapine-treated subjects (22% and 33%, respectively) compared with only 2% of those receiving placebo.

The findings of Tohen et al. support the short-term efficacy of olanzapine for pediatric mania. However, the safety data are concerning and raise questions as to whether olanzapine should be used as a first-line agent in juveniles. In the adult literature, randomized controlled trials of second-generation antipsychotics for acute mania support the efficacy of olanzapine but also note significant weight gain (1, 2). Among the second-generation antipsychotics, olanzapine and clozapine are associated with the greatest degree of weight gain and metabolic complications, including diabetes mellitus and dyslipidemias, in adults (3). Unfortunately, youth receiving second-generation antipsychotics appear to be at greater risk for treatment-emergent metabolic sequelae, with olanzapine and clozapine proffering the greatest risk (4). In a recently completed publicly funded multisite trial of different antipsychotic agents for early onset schizophrenia spectrum disorders, the olanzapine arm was discontinued by the data safety monitoring board because of weight gain (5).

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The slope of the weight gain curve in the Tohen et al. study is particularly worrisome. In adult trials, olanzapine is associated with a mean weight gain of approximately 4 kg over 10 weeks of treatment (6) and mean gains of 6–12 kg in trials lasting up to 1 year (3). In comparison, the adolescents randomly assigned to olanzapine in this study gained an average of 3.7 kg in only 3 weeks. In their risk-benefit analysis, Tohen et al. note that while the probability of responding to olanzapine is good, the probability of gaining weight is greater. The authors defer to the need for longer-term studies to determine the ultimate risk-benefit ratio for ongoing therapy. Unfortunately, the impact on metabolic parameters is not likely to subside with continued treatment. The data as presented arguably suggest that the metabolic adverse events outweigh the benefits. Longer exposure to olanzapine, at least for those subjects demonstrating substantial weight gain or significant elevations in glucose or lipids, appears contraindicated. This study had a 6-month open-label extension phase, and therefore more data regarding the long-term safety of olanzapine in this sample should be forthcoming.

Thus, as it stands, olanzapine is the only agent (second-generation antipsychotic or otherwise) for which there is a well-powered randomized controlled trial supporting its efficacy for acute mania in youth. Yet, the study by Tohen et al. also adds to the growing literature documenting serious metabolic consequences of the agent. The long-term consequences of obesity, dyslipidemia, and insulin resistance—and the risk of diabetes and cardiovascular disease—raise serious questions over the risk-benefit ratio of olanzapine as a first-line treatment in juveniles.

What are the implications for clinical care? This study is an important step toward developing an evidence-based treatment approach for pediatric bipolar disorder. Essentially, all current practice for this condition is off label and/or justified based solely on the adult literature. There is a modicum of empirical support for lithium, valproate, and quetiapine (7). The only other published, adequately powered (N=116), randomized controlled medication trial for juvenile mania found that oxcarbazepine was not more efficacious than placebo (8). The widespread use of second-generation antipsychotics in youth necessitates a thorough vetting of their effectiveness and tolerability in well-designed clinical trials. Tohen et al. provide essential information that as a first step potentially supports the efficacy of second-generation antipsychotics as a class, while also confirming the need to closely monitor metabolic parameters in youth being treated with these agents. The substantial weight gain associated with olanzapine perhaps suggests a preference to treat first with a more weight-neutral agent. Of course, given the overall lack of data supporting any available option, the main implication is that further studies are needed.

A final caveat is the recognition that pediatric bipolar disorder is characterized by enormous clinical and etiologic heterogeneity. Group differences in rates of response or side effects have limited utility in clinical practice, especially when addressing complex variable syndromes often associated with diagnostic comorbidity and complicated psychosocial factors. The results of Tohen et al. highlight the need for markers to better predict which individuals will respond and/or which are more vulnerable to untoward consequences, including weight gain. Over the next generation, intervention research must focus on the identification of neurobiological or pharmacogenomic mechanisms underlying psychopathology, treatment response, and/or propensity toward adverse events.

References

1. Scherk H, Pajonk FG, Leucht S: Second-generation antipsychotic agents in the treatment of acute mania: a systematic review and meta-analysis of randomized controlled trials. Arch Gen Psychiatry 2007; 64:442–455
2. Smith LA, Cornelius V, Warnock A, Tacchi MJ, Taylor D: Acute bipolar mania: a systematic review and meta-analysis of co-therapy vs. monotherapy. Acta Psychiatr Scand 2007; 115:12–20
3. Newcomer JW: Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. CNS Drugs 2005; 19(suppl 1):1–93
4. Correll CU, Carlson HE: Endocrine and metabolic adverse effects of psychotropic medications in children and adolescents. J Am Acad Child Adolesc Psychiatry 2006; 45:771–791

5. McClellan JM, Sikich L, Findling R, Frazier J, Vitiello B, Hlastala S, Williams E, Ambler D, Hunt-Harrison T, Maloney A, Ritz L, Anderson R, Hamer R, Lieberman L: The Treatment of Early Onset Schizophrenia Spectrum Disorders (TEOSS): rationale, design and methods. J Am Acad Child Adolesc Psychiatry 2007; 46:969–978
6. Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, Weiden PJ: Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999; 156:1686–1696
7. McClellan J, Kowatch R, Findling RL, Work Group on Quality Issues: Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 2007; 46:107–125
8. Wagner KD, Kowatch RA, Emslie GJ, Findling RL, Wilens TE, McCague K, D'Souza J, Wamil A, Lehman RB, Berv D, Linden D: A double-blind, randomized, placebo-controlled trial of oxcarbazepine in the treatment of bipolar disorder in children and adolescents. Am J Psychiatry 2006; 163:1179–1186

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