New Findings on Antipsychotic Use in Children and Adolescents With Schizophrenia Spectrum Disorders

About one in three individuals with schizophrenia or schizoaffective disorder experiences onset of the disorder as a child or teenager (1). Those individuals with earlier onset of illness seem to have a more severe form of the disorder (2). Despite the frequency and severity of the disorder, individuals younger than 18 years old are generally excluded from treatment trials. Thus, it is exciting to see in this issue of the Journal a report of two randomized, controlled trials in this younger population. Findling and colleagues (3) compare antipsychotic treatment with placebo, while Sikich and colleagues (4) extend recent studies of antipsychotic treatment in adults to a comparison of first- and second-generation antipsychotics in children.

Findling and colleagues report on adolescents (N=302) ages 13–17 years with schizophrenia who were recruited from multiple clinical sites (N=101). The authors compared the effect of placebo with aripiprazole (twice daily doses of either 10 or 30 mg) over 6 weeks. Eighty-five percent of subjects completed the full trial. Global and positive symptom scores improved with both doses of aripiprazole relative to placebo. The effect on negative symptoms was much less pronounced, reaching significance only in those subjects receiving the 10-mg dose. Improvement was generally more rapid with the higher dose. However, by 6 weeks the benefits were approximately equivalent in both active treatment groups. Common treatment-emergent adverse events that were notably more frequent in the active treatment groups included akathisia, extrapyramidal symptoms, somnolence, and tremor. Adverse events were consistently more frequent in the higher dose group. Creatine phosphokinase levels were often elevated in the active treatment groups. Other metabolic measures, including prolactin, glucose, and lipid levels, showed no difference from placebo. There was a significant difference in weight change, primarily due to loss of weight in the placebo group rather than weight gain associated with aripiprazole. The authors concluded that aripiprazole use is associated with symptom reduction in children and adolescents with schizophrenia.

Sikich and colleagues report on children and adolescents (N=116) ages 8–19 years with either schizophrenia or schizoaffective disorder who were recruited from four clinical sites. The authors compared two second-generation antipsychotics (olanzapine and risperidone) with a first-generation antipsychotic (molindone) using a clinician-driven flexible dosing schedule. Because of difficulties in recruitment, the total number of subjects in the study was fewer than needed for the power analysis-derived plan for 168 subjects. Eighty-four percent of subjects completed the 8-week trial. Clinical response was defined as a combination of clinician-identified improvement and a decrease of 20% on a positive/negative symptom scale. Clinical response rates were low (<50%) in all three groups. However, there was significant improvement between baseline and endpoint on global scores, positive symptoms, and negative symptoms. Quantitative improvement was similar across treatment groups. There was also no difference

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in clinical response rates. A significant increase in weight and body mass index led to early discontinuation of the olanzapine treatment arm. Weight gain was less but still notable (with a mean >3 kg) in the risperidine group. Molindone was not associated with weight change. Other common adverse events included akathisia (molindone) and constipation (risperidone). Prolactin levels were increased in the risperidone group. Olanzapine was associated with elongated QTc intervals and increased levels of total cholesterol, low density lipoprotein cholesterol, alanine aminotransferase, and aspartate aminotransferase. The authors concluded that antipsychotic effectiveness in child populations is low and, consistent with what is found in adult studies, first- and second-generation antipsychotics are equally effective, but with different side effect profiles.

Practical and ethical concerns often limit randomized, controlled treatment trials of antipsychotics to 6–8 weeks’ duration. For antipsychotic use in children and adolescents, there is some suggestion that early response correlates with long-term outcome (5). Conversely, it has also been argued that there is an early nonspecific response that peaks around 6 weeks, followed by a reduction in benefit (6), and what may appear to be small nonsignificant differences between treatment arms at 6–8 weeks will gradually increase and become clinically relevant over time. Direct comparison of medications using flexible decision points and study designs of longer duration will be critical before fully informed conclusions about antipsychotic medications in this age group are available. However, within the context of these limitations, there are some conclusions that can be drawn from these two studies.

For children, there is an average delay of at least 2 years between psychosis onset and initial diagnosis and treatment (7). Sometimes this delay represents the process of symptom identification, clinical workup, and progression through the health care system to reach a qualified specialist; other times, presentation for care is associated with more acutely severe symptoms (e.g., increase in hallucinations, delusions, suicidality, or threatened violence), resource depletion (e.g., expulsion from school or parental problems, such as depression or marital discord), or increased resource utilization (e.g., hospitalization or legal or social services involvement). Findling and colleagues report that responses to both doses of aripiprazole were similar, although the higher dose was associated both with faster response and more adverse effects. For stable children and adolescent patients, the Findling et al. study supports the “start low and go slow” dosing philosophy advocated by many child- and adolescent-oriented clinicians. However, for more acutely ill or resource depleted patients, the additional risk of adverse events associated with higher dosing may be countered by the potential environmental and social advantages of more rapid response.

After 6 weeks of treatment, the Findling et al. study reported significantly more symptom benefit with both doses of aripiprazole relative to placebo. Risperidone and olanzapine have previously also been reported to be significantly more effective than placebo (8). Although molindone has never been compared to placebo in child or adolescent patients, many older studies suggest effectiveness of typical antipsychotics in this population (8). However, closer examination suggests less clinical benefit than the statistically positive results suggest. Across the two studies there were six treatment arms (placebo, molindone, olanzapine, risperidone, and two aripiprazole groups). Aripiprazole was administered at lower and higher doses. The other three active medications were administered using flexible dosing, with mean doses in the moderate range. For both studies, the target mean dose was reached within 2 weeks of study onset. All treatment arms (including placebo) demonstrated a 12%–16% decrease in symptoms over the first 2 weeks of treatment. By 6 weeks, the placebo arm had a symptom decrease of 22%, while the active treatment arms had decreases of 23%–30%. The effect size of antipsychotic medications in child and adolescent patients is thus relatively low. Furthermore, only ≤50% of subjects responded, regardless of treatment.
Although nonresponse might be expected in chronically ill patients, these relatively poor treatment responses occurred early in the course of the illness. Adolescents are more likely to be in their first episode of the illness and thus possibly more responsive to intervention. However, the younger age at onset associated with schizophrenia, as with many illnesses, often means a more severe disease course with poorer outcome and poorer response to treatment. The relative contributions of these two conflicting possibilities are difficult to disentangle. The response rate in these two studies is similar to the 50% response rate observed for olanzapine and risperidone in adult populations (9, 10). In adults, failure to respond to one antipsychotic does not necessarily predict failure to respond to a different antipsychotic (11).

Since there are few short-term differences in response to the various antipsychotic medications, side effect profiles should guide the clinician’s choice of which antipsychotic to prescribe first. In particular, olanzapine may not be an optimal first-line choice. This recommendation, however, may change as longer-term outcome studies become available. Initial doses should be low for children and adolescents with low short-term suicidal or violence risks, particularly if they are in a supportive and stable home environment. However, for children or adolescents who are more acutely at risk, either by their own behavior or because of the disease’s impact on their social support, initial higher doses are often a better choice. After 6–8 weeks, consideration of a trial with an alternative antipsychotic is appropriate. As in adults, treatment failure after two to three antipsychotic trials warrants consideration of a trial with clozapine (12). Outcomes for children and adolescents are closely tied to the stability and mental health of their parents and extended support system. Treatment should include an evaluation and intervention at the level of the support system.

In both studies, the prevalence of antipsychotic-naive patients was relatively high, in the range of 26%–33%. Few subjects had to be excluded because of a previous history of nonresponse to a study drug. Thus, the recognition and treatment of schizophrenia in childhood is still relatively incomplete. However, treatment trials increase awareness of diagnostic criteria, expectations of outcome, and the appropriate doses of medication to use in each age group. These studies may thereby increase treatment of schizophrenia in young people and paradoxically decrease the number available for future studies. Optimizing early studies, with cross-site coordination, is critical in this group.

Child- and adolescent-onset schizophrenia are continuous with the adult-onset versions of the disorder, yet there are psychological, physiological, and metabolic issues unique to this group. Early disconcerting side effects, such as akathisia or other extrapyramidal symptoms, may bias children against long-term use of effective medications. Risk of weight gain may be greater in younger populations, and early weight gain has strong lifelong negative metabolic implications (13). The effects of elevated prolactin levels in prepubertal children are unknown but worrisome, particularly in boys. Given the prevalence of symptom onset in childhood and adolescence, and the factors unique to this age group, treatment studies specifically focused on children and adolescents are critical. These two studies are an excellent addition to the literature, but additional work is required, including longer-term follow-up studies, before formalized treatment strategies or policy decisions such as hierarchical formularies should be inferred.

References


RANDAL G. ROSS, M.D.

Address correspondence and reprint requests to Dr. Ross, Department of Psychiatry, University of Colorado Denver, Bldg. 500, Mail Stop F546, 13001 East 17th Place, Aurora, CO 80045; randy.ross@ucdenver.edu (e-mail). Editorial accepted for publication August 2008 (doi: 10.1176/appi.ajp.2008.08081180).

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