Efficacy of Atypical Antipsychotics in Early-Onset Schizophrenia and Other Psychotic Disorders

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Early-onset psychotic illnesses in children and adolescents are not as rare as is commonly believed. These disorders, which include schizophrenia, schizoaffective disorder, bipolar disorder with psychotic features, and major depression with psychotic features, often have a chronic and severe course and poor long-term outcome. Many patients with early-onset schizophrenia have greater functional impairments than most patients with adult-onset schizophrenia. Magnetic resonance imaging studies show that patients with early-onset schizophrenia experience substantial gray matter loss during adolescence, which is not observed in studies of patients with adult-onset schizophrenia. The chronic course, severe functional impairments, and poor prognosis of early-onset psychosis create a great need to identify effective and safe treatments for youth with psychosis. Although atypical antipsychotics have been considered superior to traditional antipsychotics, there has been little controlled information to inform clinical decisions until recently. Over the past 5 years, several studies have been initiated to address these questions. The results of the studies completed to date are reviewed.

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The prevalence and course of early-onset psychosis are not well characterized; however, a child or adolescent with psychotic symptoms usually has a chronic and severe mental illness, regardless of diagnosis. Treatment with antipsychotics may improve functioning and outcome, but few studies exist that conclusively show the benefits and disadvantages of specific medications. Limited research has demonstrated the efficacy of a few typical antipsychotics in young patients with schizophrenia but has also highlighted potentially serious side effects, such as sedation, acute dystonia, and tardive dyskinesia. When initially introduced, atypical antipsychotics were considered more efficacious and safer than typical agents in children and adolescents based upon initial results in adults. Ongoing research has clearly established the efficacy of these agents but also highlighted their potential side effects.

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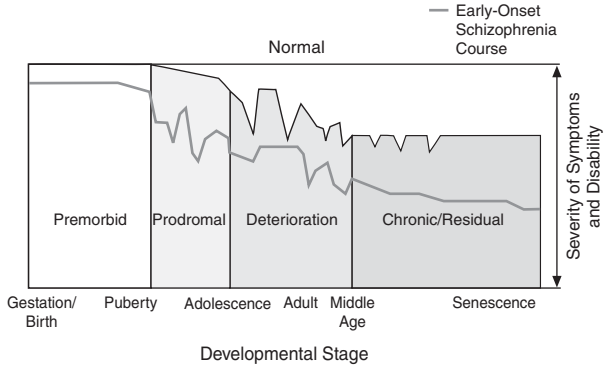
COURSE OF ILLNESS

In adult-onset schizophrenia, subtle prodromal symptoms frequently present in individuals 5 years prior to onset of psychosis, which most often occurs between 15 and 25 years of age. During the first 10 to 15 years of the illness, patients often experience a series of abrupt psychotic episodes interspersed with periods of considerably better functioning. Subsequently, most affected individuals will enter a state of stability with less severe psychotic breaks, but also decreased overall functioning compared with premorbid functioning (Figure 1).[1] The pattern in individuals with early-onset schizophrenia spectrum disorders is shifted earlier in development and is somewhat different. Subtle symptoms often present from early childhood. Psychotic episodes are less clearly delineated and more chronic, with few periods of recovery. As the illness progresses into adulthood, these individuals generally experience worse functioning than individuals with adult-onset schizophrenia.

GRAY MATTER LOSS

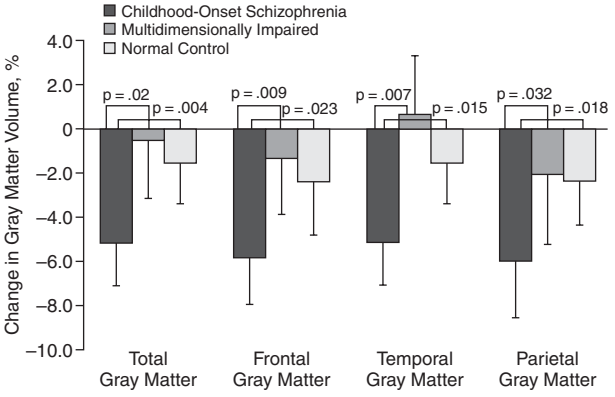
Magnetic resonance imaging (MRI) studies by investigators working with the National Institute of Mental Health (NIMH) intramural group[2] show that youth with early-onset schizophrenia experience more progressive gray matter loss compared with typically developing peers. Over a 5-year period,[3] young adolescents (mean age 13 years at initial scan) with early-onset schizophrenia had pronounced gray matter loss compared with age- and gender-matched peers without schizophrenia. Healthy

Figure 1. Comparison of Stages of Illness in Early-Onset and Adult-Onset Schizophrenia[a]



[a]Adapted with permission from Lieberman et al.[1]

Figure 2. Comparison of Percent Changes in Total and Regional Gray Matter Volumes[a]



[a]Reprinted with permission from Gogtay et al.[5] Volumes measured in 23 patients with childhood-onset schizophrenia, 19 patients who were multidimensionally impaired, and 38 healthy controls over 2.5 years. The p values were obtained with 1-way analysis of variance with Tukey Honestly Significantly Different post hoc testing. Error bars indicate SD. The multidimensionally impaired and healthy controls groups do not differ significantly for any measure ($p > .6$).

controls also lost gray matter, but the difference in loss was significant ($p < .00002$). Initial gray matter loss was particularly prominent in the parietal cortex, which supports associative and visuospatial thinking. Later, gray matter loss was more prominent in the dorsolateral prefrontal cortex and in the superior temporal gyrus.[4]

Pronounced gray matter loss appears to be much more extreme in patients with early-onset schizophrenia than in patients with psychotic symptoms occurring with nonschizophrenic illnesses. Youth with psychotic symptoms who did not meet criteria for schizophrenia but were classified as multidimensionally impaired (comparable to psychosis not otherwise specified) did not show differences in gray matter volume relative to healthy controls. Both the healthy controls and multidimensionally impaired youth showed less gray matter loss than youth with schizophrenia ($p = .004$ and $p = .02$, respectively) (Figure 2).[5]

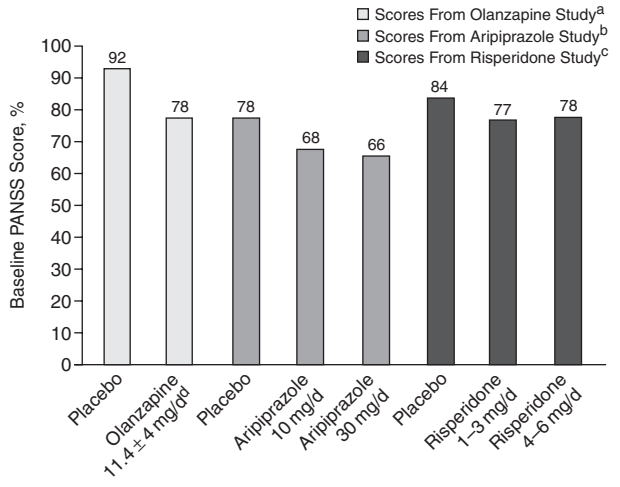
The rate of gray matter loss in specific regions was correlated with psychotic symptom severity and the extent of gray matter loss was correlated with cognitive functioning of the patients during the follow-up period.[4] Other studies[6–8] of older adolescents and young adults with schizophrenia have found similar correlations between rate of brain changes and functional outcomes. However, in these studies, reductions in white matter volume have been related to negative symptoms as well. This early gray matter loss may help to explain why the illness course for children and adolescents with early-onset schizophrenia differs from the illness course for patients with adult-onset schizophrenia.

Newer antipsychotics have shown promise in the prevention of some of this gray matter loss. A pivotal MRI study[8] randomly assigned 263 patients (16 to 40 years) with first-episode schizophrenia to treatment with either haloperidol or olanzapine. Patients treated with the typical agent haloperidol exhibited reduced gray matter volume over time compared with healthy controls, but patients treated with the atypical antipsychotic olanzapine did not differ from healthy controls. Research in animals and cell culture systems suggests that atypical antipsychotics may have neuroprotective effects,[10] but more human research is needed to support this finding.

TYPICAL ANTIPSYCHOTIC TREATMENT

Only a few studies[11–13] have investigated the use of typical antipsychotics for pediatric psychosis, which provided the basis for antipsychotic use in children with psychotic symptoms until the mid-1990s. Pool et al.[11] compared 75 teenagers with psychosis treated with loxapine, haloperidol, or placebo. Both loxapine and haloperidol were better than placebo in reducing positive symptoms, and the drugs were not significantly different from one another. Data about side effects in this study were not presented in a way that can be compared with data from more modern studies. Subsequently, Realmuto et al.[12] examined 21 teenagers with psychosis and compared treatment outcomes with thiothixene, a mid-potency typical agent, and thioridazine, a low-potency typical agent. About half of the teenagers in each group had significantly decreased positive symptoms ($p < .05$). However, many responded poorly to treatment or experienced sedation, leading the authors to suggest the use of a high-potency neuroleptic instead. Finally, Spencer et al.[13] examined 12 children treated with haloperidol or placebo and found that haloperidol reduced positive symptoms but that there were a number of side effects, particularly extrapyramidal side effects.

Figure 3. Change in PANSS Scores Observed in Atypical Antipsychotic Trials



[a]Data from Kryzhanovskaya et al.[21]
[b]Data from Robb.[22]
[c]Data from Haas et al.[23]
[d]Mean ± SD.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

ATYPICAL ANTIPSYCHOTIC TREATMENT

Initially, atypical antipsychotics were believed to be safer to use with children and adolescents than typical antipsychotics, and there was widespread belief that atypical antipsychotics were potentially more effective than typical antipsychotics. Consequently, atypical antipsychotic treatment for children and adolescents increased dramatically.[14] However, as these agents have been used more extensively, a different adverse effect profile has been identified with a generally higher risk for weight gain and metabolic side effects.

Despite the escalating use of atypical antipsychotics in children and adolescents with psychosis, several critical questions remain. Although the atypical antipsychotics appear to have significant benefits, what are the specific effects of antipsychotics on positive symptoms, negative symptoms, neurocognitive changes, and the return to normal development? How safe are they when used long-term? How do different atypical antipsychotics compare to each other in efficacy and safety? The U.S. Food and Drug Administration (FDA) recognized a pressing public health need to answer these questions and issued requests for pediatric trials of all atypical antipsychotics (except clozapine) for early-onset schizophrenia spectrum disorders and bipolar disorder. The NIMH has recognized the importance of these questions for several years. Five studies[15–19] comparing antipsychotics in children and adolescents have been funded by the NIMH over the past 2 decades.

In addition, considerable research is being done to examine the efficacy of cognitive-behavioral treatment and cognitive remediation in young adults with schizophrenia. If the results are promising, these psychological treatments might be generalized to children and adolescents in the future.

Ziprasidone

A multisite open study[20] of ziprasidone in early-onset schizophrenia spectrum disorders examined 40 children with schizophrenia or schizoaffective disorder treated with ziprasidone for up to a year. Although the majority of the children were outpatients, the participants were severely ill when they began treatment, with a mean Positive and Negative Syndrome Scale (PANSS) score of 95.9. The dosage was flexible and determined by the patient's response and the presence of side effects, with a mean final dose of 118 mg/day. Preliminary results suggest that ziprasidone was effective after 8 weeks of treatment in slightly more than half of the 40 youth treated. The PANSS score dropped by about a third in those that responded. Side effects included mania, sedation, anxiety, and insomnia.

Olanzapine

A double-blind, placebo-controlled study[21] examined olanzapine versus placebo in 107 adolescents with schizophrenia for 6 weeks (Figure 3). Of 72 patients treated with olanzapine, 68% completed the study, whereas only 43% of placebo-treated patients completed. Compared with placebo, patients treated with olanzapine experienced significantly greater improvement in Brief Psychiatric Rating Scale for Children (BPRS-C) scores ($p = .003$) and Clinical Global Impression-Severity of Illness scale (CGI-S) scores ($p = .004$). Response was defined as ≥ 30% reduction in BPRS-C scores and CGI-S score ≤ 3, but the difference between response rates with olanzapine (37.5%) and placebo (25.7%) was not significant. Patients given olanzapine experienced significantly more weight gain than those given placebo ($p = .001$) and also had increased fasting triglycerides ($p = .029$).

Aripiprazole

A multisite, 6-week study[22] compared 2 fixed doses of aripiprazole (10 and 30 mg/day) with placebo in adolescents with schizophrenia (Figure 3). Of the 201 patients treated with aripiprazole, 83% completed the trial, whereas 90% of the 101 patients treated with placebo did so. The mean baseline PANSS total score was 94.5. After 6 weeks, patients showed a reduction in PANSS scores of –26.7 for the 10-mg dose and –28.6 for the 30-mg dose, both of which were statistically significantly greater than the reduction of –21.2 with placebo. Only 5% of the patients randomly assigned to receive aripiprazole discontinued the study due to side effects.

Risperidone

In a multicenter study,[23] 160 adolescents experiencing acute exacerbation were randomly assigned to treatment with risperidone or placebo. Adolescents received 1 to 3 mg/day of risperidone, 4 to 6 mg/day of risperidone, or placebo for 6 weeks (Figure 3). Of the 106 patients treated with risperidone, 83% completed the trial; 87% of those treated with placebo completed. A significantly higher percentage of patients responded to risperidone than placebo ($p < .001$), and risperidone was associated with rapid improvement in symptoms, illness ratings, and functioning. Some side effects were associated with risperidone use. Patients given 1 to 3 mg/day experienced somnolence, agitation, and headache, while patients given 4 to 6 mg/day experienced extrapyramidal symptoms, dizziness, and hypertonia. The best benefit-to-risk ratio was found with 3 mg/day of risperidone.

Medications for Treatment-Refractory Early-Onset Schizophrenia

Two randomized controlled trials[15,16] comparing clozapine to another antipsychotic in youth with childhood-onset schizophrenia have been conducted by the NIMH intramural group, and 1 study of more heterogenous treatment-resistant youth has been conducted in a community setting.[17] The first study[15] compared clozapine with haloperidol for 6 weeks in 21 patients who had not responded to treatment with typical antipsychotics. Clozapine was shown to be superior to haloperidol in treating both positive and negative symptoms of schizophrenia. However, clozapine was more likely to be associated with medically serious side effects, such as seizures and neutropenia, than haloperidol. A subsequent study[16] done at NIMH compared clozapine with olanzapine in 25 patients with childhood-onset schizophrenia who had not responded to at least 2 prior antipsychotics in a double-blind, randomized, 8-week controlled trial. Patients treated with clozapine showed significantly greater improvements in negative symptoms from baseline ($p = .04$) compared to those treated with olanzapine. There was also a numeric trend for greater improvements with clozapine than olanzapine on other measures, although these were not statistically different. More adverse events were associated with clozapine than olanzapine. At a 2-year follow-up, 6 of the 12 patients from the clozapine group had lipid anomalies and 1 had seizures.

The community study led by Kumra et al.[17] examined 40 children and adolescents with variable age at onset of schizophrenia who had required long-term psychiatric hospitalization (mean = 12.6 mo) and who had been resistant to or intolerant of at least 2 antipsychotic agents. Youth were randomized to treatment with clozapine or high-dose olanzapine (up to 30 mg/day). Response criteria were met by 66% of patients taking clozapine but only 33% of patients taking olanzapine. Weight gain and metabolic abnormalities were associated with both treatments.

Comparison of First-Line Agents

Few studies compare the efficacy and safety of antipsychotics in youth with early-onset schizophrenia spectrum disorders. However, 1 pilot study[19] compared risperidone, olanzapine, and haloperidol for acute treatment of psychosis occurring in the context of a schizophrenia spectrum illness or affective illness in 50 children and adolescents. All 3 medications significantly reduced symptoms relative to baseline total BPRS-C scores ($p = .0018$ for risperidone and olanzapine; $p = .012$ for haloperidol). Further, a substantial percentage of patients met response criteria with olanzapine (88%), risperidone (74%), and haloperidol (53%). However, all patients experienced some side effects, including mild to moderate sedation, extrapyramidal symptoms, and weight gain (olanzapine and risperidone caused the most weight gain). Recruitment has been completed but analyses are ongoing in the NIMH-funded multisite Treatment of Early-Onset Schizophrenia Spectrum Disorders (TEOSS) study[18] of risperidone, olanzapine, and molindone (a mid-potency typical agent) in children and adolescents with early-onset schizophrenia spectrum disorders.

CONCLUSION

All of the antipsychotics evaluated have shown efficacy for treating children and adolescents with early-onset schizophrenia spectrum disorders by reducing psychotic symptoms to a greater extent than placebo. Trials comparing clozapine with other antipsychotics have consistently demonstrated its superiority for symptom amelioration but have highlighted a significant potential for adverse effects. Trials comparing multiple first-line antipsychotics for youth with psychosis have demonstrated little difference in efficacy between treatments but highlighted differences for side effects, including weight gain. Results from such studies will be important for guiding treatment choices.

While atypical antipsychotics show promise in treating children and adolescents, associated side effects that appear more frequently and severely in youth than adults have medically significant and long-term consequences. Therefore, young patients treated with these medications should be closely observed and interventions should be used to address side effects when necessary. Further comparative research and longer term safety data are essential to inform subsequent treatment decisions.

Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), loxapine (Loxitane and others), molindone (Moban), olanzapine (Zyprexa), risperidone (Risperdal), thiothixene (Navane and others), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of her knowledge, none of the drugs described in this article are approved by the U.S. Food and Drug Administration for the treatment of early-onset schizophrenia and other psychotic disorders except

haloperidol (approved for psychosis, agitation, and behavioral disorders in children aged 3 to 12 years) and aripiprazole and risperidone (approved for bipolar disorder in children aged 10 years and older and for schizophrenia in youths aged 13 years and older).

REFERENCES

1. Lieberman J, Perkins D, Belger A, et al. The early stages of schizophrenia: speculations on pathogenesis, pathophysiology, and therapeutic approaches. Biol Psychiatry 2001;50:884–897
2. Rapoport JL, Giedd JN, Blumenthal J, et al. Progressive cortical change during adolescence in childhood-onset schizophrenia: a longitudinal magnetic resonance imaging study. Arch Gen Psychiatry 1999;56:649–654
3. Giedd JN, Jeffries NO, Blumenthal J, et al. Childhood-onset schizophrenia: progressive brain changes during adolescence. Biol Psychiatry 1999; 46:892–898
4. Thompson PM, Vidal C, Gochman P, et al. Mapping adolescent brain change reveals dynamic wave of accelerated gray matter loss in very early-onset schizophrenia. Proc Natl Acad Sci USA 2001;98: 11650–11655
5. Gogtay N, Sporn A, Clasen LS, et al. Comparison of progressive cortical gray matter loss in childhood-onset schizophrenia with that in childhood-onset atypical psychoses. Arch Gen Psychiatry 2004;61:17–22
6. Paillère-Martinot M, Caclin A, Artiges E, et al. Cerebral gray and white matter reductions and clinical correlates in patients with early onset schizophrenia. Schizophr Res 2001;50:19–26
7. Cahn W, Hulshoff Pol HE, Lems EB, et al. Brain volume changes in first-episode schizophrenia: a 1-year follow-up study. Arch Gen Psychiatry 2002;59:1002–1010
8. Ho BC, Andreasen NC, Nopoulos P, et al. Progressive structural brain abnormalities and their relationship to clinical outcome: a longitudinal magnetic resonance imaging study early in schizophrenia. Arch Gen Psychiatry 2003;60:585–594
9. Lieberman JA, Tollefson GD, Charles C, et al. Antipsychotic drug effects on brain morphology in first-episode psychosis. Arch Gen Psychiatry 2005;62:361–370
10. Li XM, Xu H. Evidence for neuroprotective effects of antipsychotic drugs: implications for the pathophysiology and treatment of schizophrenia. Int Rev Neurobiol 2007;77:107–142
11. Pool D, Bloom W, Mielke DH, et al. A controlled evaluation of loxitane in seventy-five adolescent schizophrenic patients. Curr Ther Res Clin Exp 1976;19:99–104
12. Realmuto GM, Erickson WD, Yellin AM, et al. Clinical comparison of thiothixene and thioridazine in schizophrenic adolescents. Am J Psychiatry 1984;141:440–442
13. Spencer EK, Kafantaris V, Padron-Gayol MV, et al. Haloperidol in schizophrenic children: early findings from a study in progress. Psychopharmacol Bull 1992;28:183–186
14. Olfson M, Blanco C, Liu L, et al. National trends in the outpatient treatment of children and adolescents with antipsychotic drugs. Arch Gen Psychiatry 2006;63:679–685
15. Kumra S, Frazier JA, Jacobsen LK, et al. Childhood-onset schizophrenia: a double-blind clozapine-haloperidol comparison. Arch Gen Psychiatry 1996;53:1090–1097
16. Shaw P, Sporn A, Gogtay N, et al. Childhood-onset schizophrenia: a double-blind, randomized clozapine-olanzapine comparison. Arch Gen Psychiatry 2006;63:721–730
17. Kumra S, Kranzler H, Gerbino-Rosen G, et al. Clozapine and "high dose" olanzapine in refractory early-onset schizophrenia: a 12-week randomized and double-blind comparison. Biol Psychiatry 2008;63:524–529
18. McClellan J, Sikich L, Findling RL, et al. Treatment of early-onset schizophrenia spectrum disorders (TEOSS): rationale, design, and methods. J Am Acad Child Adolesc Psychiatry 2007;46:969–978
19. Sikich L, Hamer RM, Bashford RA, et al. A pilot study of risperidone, olanzapine, and haloperidol in psychotic youth: a double-blind, randomized, 8-week trial. Neuropsychopharmacology 2004;29:133–145
20. Sikich L, Findling R, McClellan J, et al. Initial findings from the early-onset schizophrenia spectrum disorder research group. Presented at the 53rd annual meeting of the American Academy of Child and Adolescent Psychiatry; Oct 25, 2006; San Diego, Calif
21. Kryzhanovskaya LA, Schulz S, McDougle C, et al. A double-blind, placebo-controlled study of olanzapine in adolescents with schizophrenia. In: New Research Abstracts of the 159th Annual Meeting of the American Psychiatric Association; May 20–25, 2006; Toronto, Ontario, Canada. Abstract NR387:161
22. Robb AS. Efficacy of aripiprazole in the treatment of adolescents with schizophrenia. In: New Research Abstracts of the 160th Annual Meeting of the American Psychiatric Association; May 19–24, 2007; San Diego, Calif. Abstract NR742:319
23. Haas M, Unis AS, Copenhaver M, et al. Efficacy and safety of risperidone in adolescents with schizophrenia. In: New Research Abstracts of the 160th Annual Meeting of the American Psychiatric Association; May 19–24, 2007; San Diego, Calif. Abstract NR516:221–222