A Prospective, Open-Label Trial of Olanzapine in Adolescents With Schizophrenia

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ABSTRACT

Background: Olanzapine is an atypical antipsychotic that has efficacy in adults with psychotic disorders. This preliminary study examined the effectiveness of olanzapine in adolescents with schizophrenia or its related conditions. **Method:** Adolescents aged 12–17 years (inclusive) with a diagnosis of schizophrenia, schizoaffective, or schizophreniform disorder were enrolled in this 8-week, open-label, outpatient study. The Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impressions Scale (CGI), and the Children's Global Assessment Scale (CGAS) were administered as outcome measures. Extrapyramidal side effects were assessed at each visit. Olanzapine was initiated at a dose of 2.5 mg/day and could be increased to a maximum total daily dose of 20 mg. **Results:** Sixteen participants with a mean age of 13.8 (SD = 1.5) years were treated. Significant improvements were found in the PANSS, CGI severity, and CGAS scores. Reductions in both positive and negative symptoms were found. Increased appetite and sedation were the most frequently reported side effects. Two subjects required treatment for extrapyramidal side effects. **Conclusions:** Psychotic symptoms significantly improved during study. Overall, olanzapine was well tolerated. Future studies are needed to confirm these findings, to assess long-term treatment outcomes, and to compare the effectiveness of olanzapine with that of other antipsychotics. *J. Am. Acad. Child Adolesc. Psychiatry*, 2003, 42(2):170–175. **Key Words:** olanzapine, adolescent, schizophrenia, schizoaffective disorder, schizophreniform disorder.

Although schizophrenia generally begins during the third decade of life, approximately one in three adults with schizophrenia develop this condition during adolescence (Beratis et al., 1994; Häfner et al., 1993; Loranger, 1984). There is evidence to suggest that adolescent-onset schizophrenia is associated with a particularly poor clinical outcome (Cawthron et al., 1994; Gillberg et al., 1993; Krausz and Müller-Thomsen, 1993). For this reason, effective and well-tolerated treatments for adolescents with psychotic illnesses are needed.

Unfortunately, there have been very few prospective studies that have considered the pharmacological treatment of adolescent schizophrenia (Armenteros et al., 1997; Campbell et al., 1999; Kumra, 2000; Shaw et al., 2001). What data do exist suggest that typical antipsychotics, or "neuroleptics," may be useful in ameliorating symptoms of psychosis in this patient population, but a significant proportion of these youths remain symptomatic even with optimized pharmacotherapy (Pool et al., 1976; Realmuto et al., 1984). In fact, results of a retrospective study in adults with schizophrenia suggest that earlier age at onset is associated with poor response to neuroleptics (Meltzer et al., 1997). This direction of research would imply there is a need for medications that can be used early and consistently in schizophrenia. Moreover, treatment studies with the traditional "typical" antipsychotics have reported that teenagers might be at particularly high risk for developing neuroleptic-related extrapyramidal side effects (EPS) when compared with adults (Keepers et al., 1983). With the relatively recent release of the newer "atypical" antipsychotics, physicians have begun prescribing these agents to young patients with psychosis despite limited data about these drugs' safety or efficacy. This has likely occurred because of these agents' reduced propensity for EPS in adults (Schulz et al., 1998).

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Clozapine was the first of the "atypical" antipsychotic medications marketed in the United States. Results of one double-blind study (Kumra et al., 1996) and numerous open-label trials and case reports suggest that clozapine may be a useful treatment for young people with treatment-resistant psychotic disorders (Findling et al., 2000). Unfortunately, clozapine is associated with the risk of neutropenia, potentially fatal agranulocytosis, electroencephalographic changes, or even seizures. Young patients may be at particularly high risk for clozapine-related neurological side effects (Findling et al., 2000). For this reason, clinicians have turned to other atypical agents in hopes of finding effective treatments with improved side effect profiles.

One of these newer psychotropic agents is olanzapine (Zyprexa®). It is currently marketed in the United States as a treatment for schizophrenia and acute bipolar mania in adults. Olanzapine has been shown to have efficacy as a treatment for adults with either schizophrenia or schizoaffective disorder (Beasley et al., 1996a,b; Tollefson et al., 1997; Tran et al., 1997).

Initial studies that examined the effectiveness of olanzapine in youngsters focused on treatment-resistant populations. One report suggested that olanzapine was not as effective in symptom amelioration in this population as clozapine (Kumra et al., 1998). Conversely, another report suggested that olanzapine could be successfully used for treatment-resistant patients as a substitute for clozapine (Mandoki, 1997). Whether or not olanzapine is an effective therapy for treatment-resistant adolescent patients with schizophrenia has not been definitively answered.

When this study was designed, there were no prospective data available about the use of olanzapine as a treatment for adolescent patients with schizophrenia or schizoaffective disorder who were not resistant to multiple pharmacological treatments. The purpose of this study was to examine the effectiveness and safety of olanzapine in this population. It was hypothesized that treatment with olanzapine would be safe and well tolerated for these teenagers.

METHOD

This study was an 8-week, open-label, prospective outpatient trial of olanzapine in adolescents with a schizophrenia spectrum disorder in which the subjects were seen biweekly. Subjects were recruited from within the auspices of the clinical and research infrastructures within a midwestern academic division of child and adolescent psychiatry. The Institutional Review Board for Human Investigation at University Hospitals of Cleveland approved the procedures that were performed under the auspices of this study. Written informed consent was obtained from the legal guardians of all study subjects. In addition, study subjects provided written assent for study participation.

Subjects

Medically healthy patients aged 12–17 years (inclusive) who met *DSM-IV* criteria for schizophrenia, schizoaffective disorder, or schizophreniform disorder (American Psychiatric Association, 1994) who also had a symptom severity score of at least 3 (indicating at least mild symptom severity) on the Clinical Global Impressions Scale-Severity score (CGI-S) (National Institute of Mental Health, 1985a) were eligible for enrollment. During the pretreatment assessment phase of this study, each subject had a semistructured diagnostic interview administered by an experienced research assistant, as well as an additional clinical interview of approximately 90 minutes in duration by a child and adolescent psychiatrist affiliated with this study. To reach a consensus diagnosis among the study research team, all prior clinical information was considered. Both diagnostic interviews were completed before study treatments were administered.

The semistructured diagnostic interview the youths received was either the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiologic Version (K-SADS-E) or the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997). Both diagnostic instruments assess for the history of psychiatric symptoms and comorbidity based on information provided by both the subject and the subject's legal guardian. The first six subjects were interviewed with the K-SADS-E. Once the K-SADS-PL became available, it was used instead of the K-SADS-E. This was done to minimize interview burden because the K-SADS-PL has modules that can be omitted on the basis of informant response.

Exclusion criteria for this study included current alcohol or drug dependence or any evidence to indicate alcohol or drug abuse subsequent to study enrollment. In addition, subjects who were not medically healthy or had clinically significant abnormal laboratory findings were not enrolled. A diagnosis of bipolar disorder or psychosis not otherwise specified was exclusionary. Female subjects could not be pregnant or lactating. The washout period for oral antipsychotic medications was 4 days prior to study baseline.

At or before baseline, all subjects received a physical examination, an electrocardiogram, a comprehensive metabolic profile, a complete blood cell count, a urinalysis, and a urine toxicology screen. Females were given a pregnancy test. These measures were also performed at the end of the study. Subjects' height, weight, blood pressure, and pulse were monitored at each study visit.

Once study treatment was initiated, subjects were seen at least biweekly by a research assistant and a study physician to monitor for symptom severity and adverse events. If clinically indicated, subjects were seen sooner than the next scheduled study visit.

Rating Scales

The Positive and Negative Syndrome Scale (PANSS) was used to assess general psychiatric symptoms as well as the positive and negative symptoms of schizophrenia (Kay et al., 1986, 1987). Overall illness severity and clinical improvement were assessed with the CGI-S and CGI-Improvement score (CGI-I), respectively (National Institute of Mental Health, 1985a). The Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983) was use to rate subjects' overall psychosocial functioning. These instruments were administered at baseline and at each subsequent study visit.

The Neurological Rating Scale (NRS) (Simpson and Angus, 1970), the Barnes Akathisia Scale (BAS) (Barnes, 1989), and the Abnormal Involuntary Movements Scale (AIMS) (National Institute of Mental Health, 1985b) were used to assess for EPS. These instruments were also administered at baseline and the week 2, 4, 6, and 8 visits.

Study Medication

Subjects were started on a bedtime dose of 2.5 mg of olanzapine. This dose could be increased in increments of 2.5 mg every 3 days at the discretion of the study physician. All medication increases occurred during the first 4 weeks of the study. Dose decreases could occur anytime if clinically indicated. The maximum dose of olanzapine prescribed was 20 mg/day. However, subjects could receive less if the maximum dose was not necessary for the reduction of symptoms. Clinicians changed doses to maximize salutary effects while minimizing adverse events. In addition, during the first 4 weeks of the study, dosing could be changed to a twice-daily regimen to alleviate medication side effects. Medication adherence was assessed at each study visit by direct query of the subjects and their guardians.

Several concomitant medications could be prescribed. If EPS persisted despite dose reductions or if dose reductions were not deemed appropriate, benztropine could be prescribed. Lorazepam and chloral hydrate could be administered to treat sleep disturbances or symptoms of anxiety.

Side effects including neurological, gastrointestinal, and cardiovascular adverse events were monitored at each study visit by direct query of the subject and the subject's guardian.

Data Analyses

Descriptive statistics were used. Data are presented as means with their standard deviations in parentheses unless otherwise noted. Outcome data were assessed using an intent-to-treat analytic approach with last observations carried forward for those subjects with missing data. Paired-samples t tests were used to compare measurements at baseline with data at other time points during the course of the study. A Holm stepdown Bonferroni procedure (Jaccard and Guilamo-Ramos, 2002) was used to correct for the multiple analyses performed in this study, keeping the overall α for the set of all outcome measures at $p < .05$.

RESULTS

Seventeen subjects signed informed consent and were enrolled in this trial. One of these subjects withdrew consent before the baseline visit. Therefore, 16 subjects were actually administered study medication. All data reported herein are based on these 16 teenagers.

Subjects

The subjects' ages ranged from 12 to 17 years, with a mean age of 13.8 (1.5) years. This sample consisted of 12 males and 4 females. Twelve subjects had a primary diagnosis of schizophrenia, three had a primary diagnosis of schizoaffective disorder, and one had a primary diagnosis of schizophreniform disorder. Lifetime comorbid diagnoses determined by the K-SADS-PL included one subject with attention-deficit/hyperactivity disorder (ADHD) inattentive type and one adolescent with ADHD combined type. Eleven subjects had never received treatment with an antipsychotic medication prior to enrollment. Five subjects had previously received treatment with risperidone.

Thirteen of the 16 subjects completed the 8-week study. Of the three subjects who did not, one subject experienced an exacerbation of symptoms necessitating hospitalization and could not complete the trial. This patient was withdrawn during week 2. Two subjects were withdrawn because of noncompliance with study procedures that were non–treatment-related. One of these patients was withdrawn at week 2 and the other was withdrawn at week 6. Overall, the subjects participated in this study for an average of 7.1 (2.1) weeks, with a range of 2 to 8 weeks.

Psychometric Outcomes

Statistically significant reductions in total PANSS baseline and end-of-study scores were found ($t_{15} = 6.0$, $p < .0005$). Statistically significant reductions in total PANSS scores from baseline were first noted at week 2 ($t_{15} = 3.4$, $p < .005$) (Fig. 1).

A significant difference between PANSS positive symptom scores at baseline and end of study was found ($t_{15} = 6.2$, $p < .0005$) (Fig. 2). A significant difference in the PANSS positive symptom score from baseline was also found as early as the end of week 2 ($t_{15} = 6.4$, $p < .0005$). PANSS negative symptom scores and PANSS psychopathology scores indicated a significant difference between baseline and end of study ($t_{15} = 3.3$, $p < .01$ and $t_{15} = 4.4$, $p < .0005$, respectively). Furthermore, a significant change

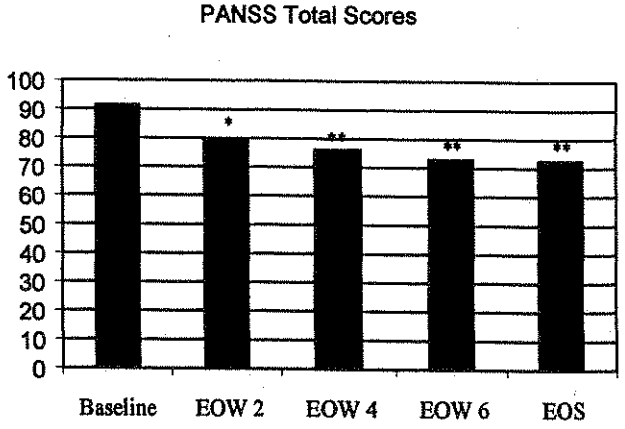

Fig. 1 Positive and Negative Syndrome Scale (PANSS) total scores over time in 16 adolescents with schizophrenia or a related disorder treated with olanzapine for up to 8 weeks. EOW = end of week; EOS = end of study. *Compared to baseline, $p < .005$; **compared to baseline, $p < .0005$.

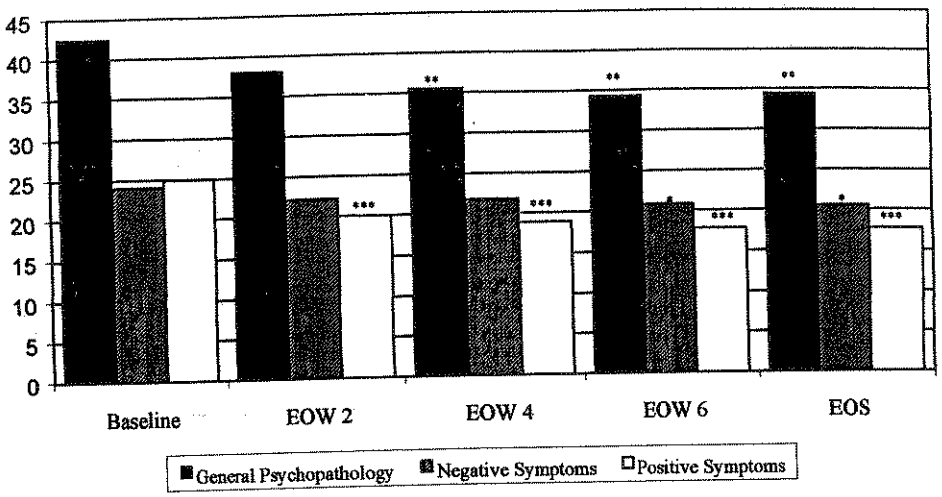

Fig. 2 Positive and Negative Syndrome Scale (PANSS) subscale scores over time in 16 adolescents with schizophrenia treated with olanzapine for up to 8 weeks. EOW = end of week; EOS = end of study. *Compared to baseline, $p < .01$; **compared to baseline, $p < .001$; ***compared to baseline, $p < .0001$.

from baseline was found in the PANSS negative symptom scores at week 6 ($t_{15} = 3.1, p < .01$) and PANSS psychopathology scores at end of week 4 ($t_{15} = 4.8, p < .0005$).

CGI-S, CGI-I, and CGAS scores are summarized in Table 1. A statistically significant difference between the mean CGI-S baseline and end-of-study scores was observed ($t_{15} = 7.3, p < .0005$), with statistically significant reductions first noted at week 2 ($t_{15} = 3.2, p < .01$). Thirteen percent ($n = 2$) received an end-of-study CGI-I score of 1 (very much improved), 56% ($n = 9$) received a score of 2 (much improved), and 31% ($n = 5$) received a score of 3 (minimally improved). The difference between the mean CGAS scores compared to baseline was found to be statistically significant for all study visits ($p < .01$).

Tolerability/Acceptability

Table 2 shows the most commonly reported side effects. EPS were assessed with the NRS, AIMS, and BAS. The mean baseline score for the NRS was 0.8 (1.3), and the mean end-of-study score was 0.8 (1.3). Participants received a mean baseline BAS score of 0.4 (1.3) and a mean score of 0.4 (1.0) at end of study. The mean baseline score for the AIMS was 0.69 (1.54), and the mean end-of-study score was 0.3 (1.0). No significant differences between the mean scores of the NRS, AIMS, and BAS for baseline and end of study were found.

Muscular stiffness was reported in two patients while they were receiving 10 mg of olanzapine per day. Benztropine successfully ameliorated this muscular stiffness when prescribed to both patients at a total daily dose of 0.5 mg. One patient began benztropine therapy after 4 weeks in the study and discontinued its use after 2 weeks. The second patient began benztropine treatment at week 2 and continued its use for the duration of the study. Of note, none of the participants developed dyskinesias while enrolled in this study. The only other concomitant medication prescribed was chloral hydrate. This was given to one patient as a bedtime dose of 500 mg from baseline to week 2.

TABLE 1

Psychometric Scores at Baseline and End of Study in 16 Adolescents With Schizophrenia or a Related Disorder Treated With Olanzapine for up to 8 Weeks

Measure	Mean (SD) Baseline Score	Mean (SD) EOW 2 Score	Mean (SD) EOW 4 Score	Mean (SD) EOW 6 Score	Mean (SD) EOS Score
CGI-S	4.5 (0.6)	4.0 (0.7)*	3.8 (0.8)*	3.5 (0.8)*	3.4 (0.9)**
CGI-I	NA	2.5 (0.6)	2.2 (0.7)	2.2 (0.7)	2.2 (0.7)
CGAS	41.9 (4.9)	48.3 (9.2)*	50.5 (8.6)**	51.1 (8.1)**	52.7 (9.0)**

Note: CGI-S = Clinical Global Impressions-Severity Scale; CGI-I = Clinical Global Impressions-Improvement Scale; CGAS = Children's Global Assessment Scale; EOW = end of week; EOS = end of study; NA = not applicable.

* Compared to baseline, $p < .01$; ** compared to baseline, $p < .0005$.

TABLE 2
Most Commonly Reported Side Effects in 16 Adolescents With Schizophrenia or a Related Disorder Treated With Olanzapine for up to 8 Weeks

Side Effect	*n*	%
Increased appetite	11	68.8
Sedation	9	56.3
Headache	4	25.0
Nausea	3	18.8
Weight gain	3	18.8
Tremulousness	2	12.5
Stiffness	2	12.5
Diarrhea	2	12.5
Stomach pain	2	12.5
Increased thirst	2	12.5

A significant difference in weight from baseline (mean = 64.9 kg, SD = 20.0 kg) and end of study (mean = 71.4 kg, SD = 20.6 kg) was observed ($t_{15} = -6.7$, $p < .0005$). Participant weight gain ranged from 1.1 kg to 13.4 kg during the course of the study. Subjects experienced a mean weight gain of 1.0 kg (SD = 0.5 kg) per week. No clinically significant changes in vital signs, laboratory tests, or electrocardiograms were seen.

Medication Dosing

The end-of-study total daily doses ranged from 3.8 to 20.0 mg/day, with a mean total daily dose of 12.4 mg/day (SD = 5.3 mg/day). Thirteen subjects received the study medication as a single dose given at bedtime, and three subjects received their total daily dose of medication twice daily (most often the result of sedation).

DISCUSSION

Overall, olanzapine was well tolerated and was associated with amelioration of both positive and negative psychotic symptoms in this outpatient population. However, patients did have residual symptoms at study's end. Strengths of this study include its diagnostic homogeneous patient population, its emphasis on a community-based cohort, its prospective design, and its 8-week duration.

Besides being complementary to the available information regarding the use of olanzapine in treatment-recalcitrant patients (Kumra et al., 1998; Mandoki, 1997), these data are substantial additions to more recently published reports that have focused on psychotic youths who are not resistant to atypical antipsychotic therapy. In a chart review study of seven youths with psychotic disorders in which treatment was given for 4–11 months, olanzapine was generally found to be beneficial. The most commonly observed side effect in that cohort was weight gain (Maagensen and Aarkrog, 1999). In another study in which 15 inpatients aged 6–13 years were treated with olanzapine for an average of 11 days, all except 2 of the children were described as receiving some benefit associated with olanzapine therapy (Sholevar et al., 2000).

Over the course of this trial, olanzapine was generally well tolerated. No patients were discontinued from treatment because of side effects, and EPS were seen in only two subjects. The most common adverse events noted in this trial were sedation and increased appetite/weight gain. As weight gain during antipsychotic pharmacotherapy can be particularly problematic for young patients treated with the atypical agents (Findling et al., 2000), whether or not this or other side effects would substantially interfere over a longer treatment course with olanzapine remains to be seen.

Limitations

This work is limited in its use of open-label methodology; however, the issue of a placebo-controlled study in this group is controversial (Armenteros and Mikhail, 2002; Weijer, 1999). In addition, as this was not a fixed-dose study and doses were increased over the first 4 weeks of therapy, it is possible that doses lower than those used during this trial may have been equally beneficial if subjects had their medication more gradually titrated over a longer period of time. Although its 8-week duration and prospective design are advances when compared to prior reports of olanzapine in community-based cohorts of adolescents with psychosis, this study's relative brevity might also be considered a limitation. Schizophrenia is a chronic condition that generally requires long-term medication management. This work does not consider long-term safety and effectiveness of olanzapine in this patient population.

Clinical Implications

Results from this study suggest that olanzapine is effective and generally well tolerated during the acute treatment of adolescents with schizophrenia and its related conditions. Future studies are needed to confirm or refute these findings. In addition, future trials should be conducted that will assess long-term treatment outcomes and that will compare the effectiveness of olanzapine with other antipsychotics, both typical and atypical.

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Self-Concept in Male and Female Adolescents With Congenital Heart Disease. Ulrike Salzer-Muhar, MD, Marion Herle, MS, Peter Floquet, MS, Michael Freilinger, MD, Susanne Greber-Platzer, MD, Alfons Haller, MD, Werner Leixnering, MD, Manfred Marx, MD, Elisabeth Wurst, PhD, Michael Schlemmer, MD

Summary: Cognitive achievement, behavioral problems, and various dimensions of personality were assessed in 48 male and female patients with congenital heart disease (CHD) aged from 12 to 16 years in comparison to a control group. The CHD group showed a lower speed of cognitive processing but seemed to have less state-anxiety and to possess a higher superego strength. Male adolescents with CHD presented with a reduced perceived capacity and self-esteem. This was not true for adolescent girls with CHD. The negative self-concept of boys with CHD may be partly explained by reduced physical ability interfering with peer relationships. Clin Pediatr 2002;41:17–24.