ORIGINAL ARTICLE

Childhood-Onset Schizophrenia

A Double-Blind, Randomized Clozapine-Olanzapine Comparison

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Background: Childhood-onset schizophrenia is a rare but severe form of the disorder that is frequently treatment resistant. The psychiatrist has a limited evidence base to guide treatment, particularly as there are no trials in children comparing atypical antipsychotics, the mainstay of current treatment.

Objective: To compare the efficacy and safety of olanzapine and clozapine, hypothesizing that clozapine would be more efficacious.

Design: Double-blind randomized 8-week controlled trial, with a 2-year open-label follow-up.

Setting: National Institute of Mental Health study, January 1998 to June 2005. Patients underwent reassessment 2 years after discharge.

Patients: Children and adolescents recruited nationally, aged 7 to 16 years, meeting unmodified *DSM-IV* criteria for schizophrenia, and resistant to treatment with at least 2 antipsychotics.

Interventions: After drug washout and a 1- to 3-week antipsychotic-free period, patients were randomized to treatment with clozapine (n=12) or olanzapine (n=13).

Main Outcome Measures: The Clinical Global Impression Severity of Symptoms Scale and Schedule for the Assessment of Negative/Positive Symptoms.

Results: Clozapine was associated with a significant reduction in all outcome measures, whereas olanzapine showed a less consistent profile of clinical improvement. While there were moderate to large differential treatment effects in favor of clozapine, these reached significance only in the alleviation of negative symptoms from an antipsychotic-free baseline ($P=.04$; effect size, 0.89). Clozapine was associated with more overall adverse events. At 2-year follow-up, 15 patients were receiving clozapine with evidence of sustained clinical improvement, but additional adverse events emerged, including lipid anomalies (n=6) and seizures (n=1).

Conclusions: While not demonstrating definitively the superiority of clozapine compared with olanzapine in treatment-refractory childhood-onset schizophrenia, the study suggests that clozapine has a more favorable profile of clinical response, which is balanced against more associated adverse events.

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CHILDHOOD-ONSET SCHIZOphrenia (COS) is a rare and severe form of the disorder, defined by an onset of psychotic symptoms before 13 years of age. Unfortunately, there is an extremely narrow evidence base to guide treatment among these patients, who exhibit severe and persisting symptoms that are resistant to first-line antipsychotic treatment.

Two randomized controlled trials established the superiority of typical antipsychotics over placebo in COS,[1,2] but only 1 double-blind study has compared the efficacy and safety of 2 antipsychotics, demonstrating superiority of clozapine over the typical antipsychotic haloperidol.[3] This finding complements reports from open trials demonstrating the efficacy of clozapine in pediatric populations[4,5] and echoes findings in adult-onset schizophrenia, with most (but not all) meta-analyses suggesting that the drug is superior to typical antipsychotics.[6,7] Unfortunately, the therapeutic benefits of clozapine are accompanied by severe adverse effects, such as agranulocytosis, seizures, and cardiac complications, that may be more severe in children.[3,5]

Olanzapine is an atypical antipsychotic that shares many of the pharmacological properties of clozapine, and meta-analyses from trials in adults with schizophrenia suggest that it may be more efficacious than typical antipsychotics[6] while lacking the potential for blood dyscrasias. Extrapolation from these adult findings, combined with open-label data suggesting that olanzapine has therapeutic benefit in children with schizophrenia,[8-13] has resulted in widespread use of olanzapine in COS. However, there are no

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controlled trials of olanzapine in pediatric populations, and there are increasing concerns about metabolic adverse effects that may be particularly severe in young people.[14-16]

In the only head-to-head comparison of atypical antipsychotics in a pediatric population, Sikich and colleagues[16] found olanzapine, risperidone, and haloperidol to be equally effective. Although informative, the study included a diagnostically heterogeneous group, a large proportion was receiving other psychotropic medications, and clozapine was not included as the comparison antipsychotic.

Thus, there are no controlled pediatric studies directly comparing the costs (adverse events) and benefits (clinical efficacy) of clozapine against olanzapine, an issue of central importance in the treatment of refractory COS. An open-label comparison of treatment with the agents in 23 patients with COS and atypical psychoses from the National Institute of Mental Health (NIMH) cohort suggested superiority for clozapine.[10] Although in that study clozapine was associated with greater improvement in negative and positive symptoms, our clinical experience strongly suggested that clozapine is particularly efficacious in ameliorating negative symptoms, a position supported by meta-analyses of adult studies.[17]

Children with schizophrenia typically require maintenance medication, and thus data on the long-term effectiveness and tolerability of antipsychotics are of importance.

We thus aimed to compare and examine the efficacy and safety of olanzapine and clozapine among children and adolescents with COS. All subjects were considered resistant to at least 2 antipsychotics and were therefore clinically eligible for treatment with clozapine. We hypothesized that clozapine would be superior in overall efficacy, particularly in the alleviation of negative symptoms.

METHODS

SUBJECTS

Children and adolescents aged 7 to 16 years were recruited nationally. Inclusion criteria were the diagnosis of schizophrenia with a definite onset of symptoms before 13 years of age. Diagnosis was determined on the basis of review of medical and school records, interview with the child and parents, and administration of the Schedule for Affective Disorders and Schizophrenia for School-Age Children.[18,19] Additional inclusion criteria were IQ greater than 70, no history of progressive neurological or medical disorders such as epilepsy, and failure to respond to 2 antipsychotic medications (typical or atypical) used at adequate doses (>100-mg chlorpromazine equivalents) and for adequate duration (≥4 weeks unless terminated owing to intolerable adverse effects). Failure was defined as insufficient response with persistence of symptoms significantly impairing the child's functioning according to child, parental, medical, and school reports or intolerable adverse effects. Exclusion criteria included nonresponse to an adequate trial of clozapine or olanzapine (an adequate trial for these medications was defined as 8 weeks of olanzapine at a dosage of 20 mg/d or of clozapine at a dosage of 200 mg/d). The protocol was approved by the institutional review board at the NIMH, and each parent and child gave informed consent or assent.

PROCEDURES

On admission, all medication dosages were tapered during a 1- to 4-week period. This was followed by a medication-free period of up to 3 weeks (mean, 2.7 weeks; SD, 1.2 weeks), as tolerated by the patient. Participants then entered the 8-week double-blind trial. On the first night, children were given 5 mg of olanzapine or 12.5 mg of clozapine. The clozapine dose was increased every other day, the first increase of 12.5 mg and thereafter in steps of 25 mg. When the clozapine dose reached 150 mg (typically on day 12), the olanzapine dose was increased to 10 mg. When the clozapine dose reached 300 mg (typically in the third week), the olanzapine dose was increased to 15 mg. Further increases were guided by clinical judgment to a maximum of 20 mg of olanzapine and 900 mg of clozapine. All medications were given in identical tablet form. The double-blind trial was conducted in an inpatient unit with a high staff-patient ratio. Children received up to 4 hours a day of specialized education and recreational and occupational therapy in addition to nursing care. After the double-blind trial, patients were offered an open trial of the second medication if nonresponse to the trial medication was evident. A 2-year, open-label, unblinded follow-up is also reported.

RANDOMIZATION

Random allocation used a random-numbers chart and was conducted in blocks of 4 (the trial was stopped at the 25th patient). Numbered containers were used to implement the random allocation sequence, which were concealed until study subject number assignment. The Pharmaceutical Development Service generated the allocation sequence, while the research team enrolled the participants and assigned participants to their groups. Participants and those administering and assessing intervention and assessing outcomes were blind to the randomization scheme. The success of the blinding was not formally assessed.

OUTCOME MEASURES

The outcome measures were scores on the Clinical Global Impression Severity of Symptoms Scale[20] (CGI-S), Scale for the Assessment of Negative Symptoms[21] (SANS), Scale for the Assessment of Positive Symptoms,[22] Brief Psychiatric Rating Scale (BPRS B1-7B, 24-item version),[23] and the Bunney-Hamburg psychosis, depression, mania, and anxiety rating scales.[24]

Measures were completed on admission, the week before randomization (when subjects were antipsychotic free), and then weekly during the double-blind trial. The same measures were also completed at 2-year follow-up. Three psychiatrists (J.W.T., A.S., and N.G.) completed most of the ratings, with interrater reliabilities estimated using the intraclass correlation coefficient between 2 different pairings (A.S. and J.W.T.; N.G. and J.W.T.) at 2 different time points. For the CGI-S, reliability values ranged from 0.89 to 0.90; for the SANS, 0.71 to 0.83; for the Scale for the Assessment of Positive Symptoms, 0.78 to 0.84; for the Bunney-Hamburg scale for psychosis, 0.81 to 0.87; for the Bunney-Hamburg scale for mania, 0.94 to 0.89; and for the Bunney-Hamburg scale for anxiety, 0.82 to 0.89. The Bunney-Hamburg scale for depression had low interrater reliability of 0.49 to 0.64.

POWER CALCULATION

Published reports on studies from the NIMH cohort before 1997 (date of the protocol) showed mean reductions in BPRS scores after 6 weeks of double-blind treatment with 31 U of cloza-

pine (SD, 13 U; n=10) and for open-label treatment with 5 U of olanzapine (SD, 18 U; n=8). This gives a differential treatment effect size of 1.7.[3,10] Further unpublished analyses comparing NIMH patients up to 1998 in open trials of clozapine (N=19) and olanzapine (N=9) found the following similarly large differential effect sizes in favor of clozapine: 1.47 for the BPRS, 1.3 for the Scale for the Assessment of Positive Symptoms, and 1.0 for the SANS (J.L.R., A.S., N.G., and D.G., unpublished data, May 2005). The present study was powered to detect differential treatment effect sizes of 1.2 with 80% power and an α of .05 (with 12 patients in each treatment wing).

SAFETY

All observed or volunteered adverse events were collected on a weekly basis by a physician blind to treatment status using the Subjective Treatment Emergent Symptoms Scale.[25] Extrapyramidal adverse effects and other abnormal movements were recorded using the Abnormal Involuntary Movements Scale[26] and the Simpson Angus Scale.[27] A complete blood cell count with differential was measured before starting the blinded medication regimen and weekly throughout the trial. Electroencephalography, electrocardiography, liver function tests, and measurement of electrolyte levels were performed before initiation of the drug regimen and repeated during the sixth week of the blinded medication administration or as clinically indicated. The body mass index was calculated immediately before study entry and at completion. Cardiac parameters included the development of hypertension (defined as 3 readings above the 95% percentile for systolic or diastolic blood pressure for the same age and height percentile group[28]) and tachycardia (mild defined as >100 and moderate as >120 beats/min on 3 readings).

At the 2-year follow-up, the clinical ratings were repeated, and further adverse events were noted.

ANALYSIS

For the double-blind study, measures of efficacy within each drug treatment were analyzed on an intention-to-treat basis, carrying forward the last observation for any patient who did not complete the 8-week double-blind phase. Paired *t* tests were applied to the baseline and end-point outcome measures within each treatment group to determine efficacy of each medication. Symptoms scores from status on admission before removal of antipsychotic drugs (admission) and after the removal of all antipsychotics (antipsychotic-free) are both used as baselines. Effect size was determined by the Cohen d statistic, which was calculated for each group by dividing the mean change score by the standard deviation of the change score.[29] Raw change scores and change scores adjusted for baseline values are given.

The comparative efficacy of clozapine and olanzapine was estimated using the following analytic approaches:

1. Analysis of covariance for determining change over time with both sets of baseline scores as the covariate.
2. Mixed-effects regression, which includes a random effect modeling within-person dependence and the fixed effects of treatment group, time (treated as a continuous variable in weeks from baseline), and the group × time interaction. In this analytic approach, initial severity is estimated at the intercept (baseline week=0), and difference in rates of symptom change is estimated by the treatment × time interaction.

To enable comparison with previous studies, a full categorical response was defined as (1) a 20% reduction in BPRS score (24-item version) and (2) a CGI-S score at the end of the trial of less than 3 or a posttreatment BPRS total score of 35 or less, similar to criteria proposed for adult studies.[10,30] Patients meeting only the first condition were labeled partial responders.

We performed Wilcoxon matched-pairs signed rank tests on the ratings at the end of the double-blind trial and at 2-year follow-up to assess significant changes in clinical status.

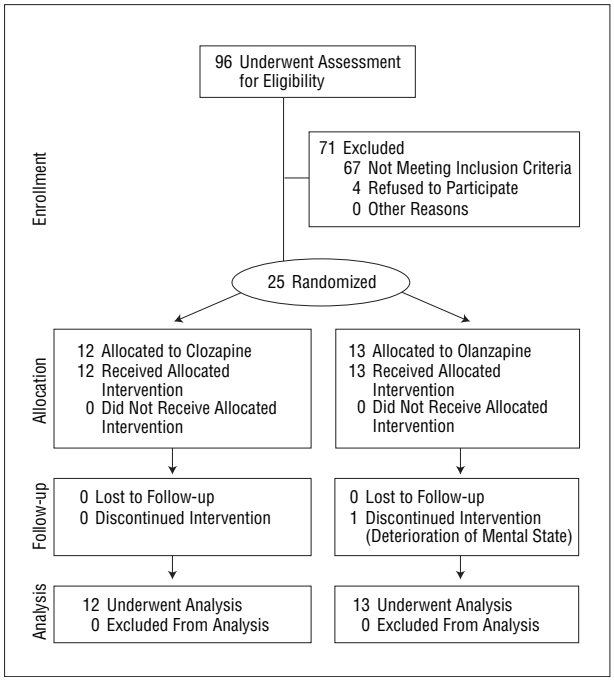

Figure 1. Patient flow diagram.

RESULTS

PATIENT CHARACTERISTICS

The patient flow diagram in **Figure 1** shows that only 1 patient, who was in the olanzapine group, failed to complete the trial, owing to a rapid deterioration in mental state.

The groups did not differ demographically or on most clinical variables, with the exception of more anxiety disorders (particularly obsessive-compulsive disorder) in patients randomized to clozapine (**Table 1**). All subjects had histories of exposure to multiple antipsychotics, congruent with the length of symptoms before admission to the NIMH study. There was sufficient clinical history to establish failure to respond to 2 antipsychotics (given at adequate doses for at least 4 weeks) in 18 patients, and to 3 or more antipsychotics in 7 patients. Prior exposure to olanzapine and clozapine was equally frequent in both groups, although the duration and/or dose of treatment with these drugs did not meet our criteria for an adequate trial of treatment.

MEDICATION DOSES DURING DOUBLE-BLIND TRIAL

The overall mean final dose of clozapine was 327 mg (SD, 113 mg; range, 150-500 mg), with a mean plasma concentration of clozapine at study completion of 715 ng/mL (SD, 405 ng/mL) and norclozapine of 350 ng/mL (SD, 185 ng/mL). One patient receiving a 5-mg dose of olanza-

Table 1. Demographic and Clinical Details of Patients*

	Clozapine Group (n = 12)	Olanzapine Group (n = 13)	Test of Significance
Sex, No. M/F	8:4	7:6	Fisher exact test, P=.69
Age at trial entry, y	11.7 (2.3)	12.8 (2.4)	t_{23} = –1.2; P=.25
SES	3.08 (1.5)	2.77 (1.1)	t_{23} = 0.6; P=.55
Ethnicity, No. of patients			
White	7	7	χ^2 = .01; P=.95
Black	3	4	
Other	2	2	
Age at onset of symptoms, y	8.6 (2.7)	9.5 (2.2)	t_{23} = 0.95; P=.35
Duration of psychosis before trial entry, y	3.1 (1.9)	3.3 (3.0)	t_{23} = 0.18; P=.86
Prior hospitalizations, mo	4.5 (7.3)	3.4 (2.6)	t_{23} = 0.49; P=.63
Past comorbidity, No. of patients			
ADHD	4	3	Fisher exact test, P=.67
ODD	2	2	Fisher exact test, P=.59
CD	1	0	Fisher exact test, P=.48
Depression	5	4	Fisher exact test, P=.68
GAD	3	0	Fisher exact test, P=.10
OCD	4	0	Fisher exact test, P=.04
Specific phobia	0	1	Fisher exact test, P>.99
Social phobia	2	0	Fisher exact test, P=.22
Agoraphobia or panic disorder	0	1	Fisher exact test, P>.99
Comorbid disorders present at time of admission, No. of patients			
ADHD/ODD/CD	4	3	P=.67
Anxiety disorders	6	1	P=.03
Depression	0	0	P>.99
No. of antipsychotics prescribed before admission			
Typical	1.25 (1.2)	1.15 (1.1)	t_{23} = 0.2
Atypical	2.75 (1.3)	2.31 (0.9)	t_{23} = 1.0
No. of antipsychotics with definite treatment failure, median (range)	2 (2-4)	2 (2-4)	Mann-Whitney test, z = 1.4; P=.17
Past medication exposure, No. (%)			
Olanzapine	9 (75)	6 (46)	Fisher exact test, P=.23
Clozapine	3 (25)	4 (31)	Fisher exact test, P>.99

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CD, conduct disorder; GAD, generalized anxiety disorder; OCD, obsessive-compulsive disorder; ODD, opposition defiant disorder; SES, socioeconomic status.
*Unless otherwise indicated, data are expressed as mean (SD).

pine withdrew from the trial at week 2. Of the remaining 12 patients in the olanzapine wing, 10 completed the trial at a dosage of 20 mg/d, and 2 at a dosage of 15 mg/d (mean dosage, 19.1 mg/d). For all 13 patients initially randomized to olanzapine, the final mean dosage was 18.1 mg/d (SD, 4.3 mg/d).

ADJUNCTIVE MEDICATIONS

Two children in the olanzapine group continued to receive valproate sodium (one for preexisting partial seizures and the other for mood stabilization) and 1 continued to receive clomipramine hydrochloride throughout the trial. One child in the clozapine group continued to receive guanfacine hydrochloride for attention-deficit/hyperactivity disorder. For acute agitation, children received doses of lorazepam (2 in the clozapine group and 3 in the olanzapine group [Fisher exact test, P>.99]) or diphenhydramine hydrochloride (4 in the clozapine group and 6 in the olanzapine group [Fisher exact test, P=.69]). On the day of the antipsychotic-free baseline assessment, 4 patients (33%) in the clozapine group and 3 (23%) in the olanzapine group received sedative medication (Fisher exact test, P=.67).

DRUG EFFICACY

Within Medication

Clozapine was associated with a significant improvement in outcome measures, regardless of the baseline used (**Table 2**). In contrast, olanzapine was associated with improvement only from the medication-free and not the admission baseline measurement (**Table 3**).

Differential Effects

The change in symptom scores was consistently greater for clozapine and associated with moderate to large differential treatment effect sizes (**Table 4**). However, the differential efficacy reached significance for the SANS score relative to the antipsychotic-free baseline (P=.04), with a trend to improvement from the admission baseline (P=.08). The evolution of this large differential treatment effect during the course of the trial is illustrated in **Figure 2**.

In exploratory correlational analyses, change in SANS scores was not correlated with change in Bunney-Hamburg ratings of overall depressive symptoms (Pearson r=0.22 [P=.29]) or extrapyramidal adverse effects scores

Table 2. Clozapine Efficacy Data

Outcome Measures	Baseline Admission Scores						Baseline Antipsychotic-Free Scores					
	Admission Score, Mean (SD)	Change Score, Mean (95% CI)	*t* Test	*P* Value	Cohen d	Adjusted Change Score, Mean (95% CI)	Antipsychotic-Free Score, Mean (SD)	Change Score, Mean (95% CI)	*t* Test	*P* Value	Cohen d	Adjusted Change Score, Mean (95% CI)
CGI-S	5.5 (0.7)	−1.1 (−1.8 to −0.2)	−3.4	.005	1.0	−0.99 (−1.59 to −0.39)	6.0 (1.2)	−1.6 (−2.3 to −0.8)	−4.7	<.001	1.4	−1.35 (−1.94 to −0.77)
SANS	48 (23)	−22 (−33 to −8)	−3.5	.005	1.0	−20 (−31 to −10)	52 (23)	−25 (−34 to −15)	−5.7	<.001	1.6	−25 (−32 to −17)
SAPS	35 (16)	−12 (−21 to −3)	−2.5	.03	0.7	−9 (−19 to 1)	45 (23)	−22 (−36 to −8)	−3.4	.006	1.0	−21 (−33 to −9)
BPRS-24	61 (12)	−9 (−15 to −3)	−3.4	.006	1.0	−9 (−15 to −2)	72 (13)	−20 (−30 to −10)	−4.4	.001	1.3	−19 (−26 to −12)
Bunney-Hamburg rating scales												
Psychotic	8.3 (2.4)	−1.7 (−2.6 to −0.7)	−3.7	.003	1.1	−1.5 (−2.9 to −0.1)	10.7 (2.4)	−4 (−5.3 to −2.7)	−6.6	<.001	1.9	−3.77 (−5.11 to −2.44)
Depression	0.5 (0.9)	0.1 (−0.5 to 0.66)	0.3	.75	0.1	0.1 (−0.9 to 1.1)	0.4 (0.7)	0.2 (−0.5 to 0.8)	0.6	.59	0.2	0.17 (−0.71 to 1.04)
Mania	0.6 (0.8)	−0.2 (−0.8 to 0.2)	−0.6	.55	0.2	−0.3 (−1.5 to 0.9)	1.2 (1.3)	−0.8 (−0.1 to 1.7)	2.1	.06	0.6	−1.08 (−2.31 to 0.15)
Anxiety	2.3 (2.6)	1.0 (3.0 to −0.9)	−1.2	.25	0.4	1.2 (−0.3 to 2.7)	2.8 (3.5)	0.6 (−2.3 to 1.1)	−0.8	.47	0.2	0.79 (−0.54 to 2.12)

Abbreviations: BPRS-24, Brief Psychiatric Rating Scale, B1-7B, 24-item version; CGI-S, Clinical Global Impression Severity of Symptoms Scale; CI, confidence interval; SANS, Schedule for the Assessment of Negative Symptoms; SAPS, Schedule for the Assessment of Positive Symptoms.

Table 3. Olanzapine Efficacy Data

Outcome Measures	Baseline Admission Scores						Baseline Antipsychotic-Free Scores					
	Admission Score, Mean (SD)	Change Score, Mean (95% CI)	*t* Test	*P* Value	Cohen d	Adjusted Change Score, Mean (95% CI)	Antipsychotic-Free Score, Mean (SD)	Change Score, Mean (95% CI)	*t* Test	*P* Value	Cohen d	Adjusted Change Score, Mean (95% CI)
CGI-S	5.2 (0.7)	−0.5 (−1.0 to 0.1)	−1.7	.11	0.5	−0.6 (−0.02 to 1.1)	5.3 (0.9)	−0.6 (−0.1 to 1.3)	−1.9	.09	0.5	−0.8 (−1.4 to −0.3)
SANS	46 (20)	−8 (−18 to 4)	−1.4	.19	0.4	−7 (−18 to 3)	52 (19)	−14 (−20 to −7)	−4.6	<.001	1.3	−15 (−22 to −8)
SAPS	29 (15)	3 (−10 to 17)	−0.5	.63	0.1	1 (−8 to 10)	45 (21)	−13 (−28 to 1)	−2.0	.07	1.0	−7 (−18 to 5)
BPRS-24	57 (8)	−1 (−8 to 6)	−0.3	.78	0.1	−1.6 (−7.8 to 4.6)	69 (12)	−13 (−22 to 6)	−3.7	.003	0.6	−13 (−21 to −6)
Bunney-Hamburg rating scales												
Psychotic	7.6 (2.2)	−0.9 (−2.7 to 0.9)	−1.1	.30	0.3	−1.0 (−2.4 to 0.3)	9.8 (4)	−3.1 (−5.0 to −1.2)	−3.5	.004	1.0	−3.3 (−4.6 to −2.0)
Depression	0.5 (1.3)	0.4 (−1.0 to 1.8)	0.6	.56	0.2	0.4 (−0.6 to 1.4)	0.5 (1.0)	0.4 (−0.6 to 1.4)	0.8	.43	0.2	0.4 (−0.5 to 0.12)
Mania	1.1 (1.5)	0.4 (−1.2 to 2.0)	0.5	.62	0.1	0.5 (−0.6 to 1.7)	1.8 (2.2)	−0.4 (−2.3 to 1.5)	−0.4	.67	0.1	−0.2 (−1.3 to 1.0)
Anxiety	0.8 (1.67)	−0.2 (−1.1 to 0.8)	−0.3	.74	0.1	−0.3 (−1.7 to 1.2)	1.2 (2.0)	−0.5 (−1.6 to 0.5)	−1.1	.29	0.3	−0.7 (−2.0 to 0.5)

Abbreviations: BPRS-24, Brief Psychiatric Rating Scale, B1-7B, 24-item version; CGI-S, Clinical Global Impression Severity of Symptoms Scale; CI, confidence interval; SANS, Schedule for the Assessment of Negative Symptoms; SAPS, Schedule for the Assessment of Positive Symptoms.

Table 4. Differential Efficacy

Outcome Measures	Difference in Change Scores Between Clozapine and Olanzapine Wings*					
	Baseline Admission Scores			Baseline Antipsychotic-Free Scores		
	$F_{1,22}$	*P* Value	Cohen d	$F_{1,22}$	*P* Value	Cohen d
CGI-S	1.18	.39	0.6	1.69	.21	0.8
SANS	3.25	.08	0.7	4.65	.04	0.8
SAPS	2.40	.14	0.4	1.84	.19	0.4
BPRS-24	2.64	.12	1.0	0.91	.35	0.4
Bunney-Hamburg rating scales						
Psychotic	0.27	.61	0.3	0.30	.59	0.3
Depression	0.24	.67	0.2	0.13	.72	0.2
Mania	1.00	.33	0.3	1.27	.27	0.2
Anxiety	2.14	.16	0.5	2.80	.11	0.5

Abbreviations: BPRS-24, Brief Psychiatric Rating Scale, B1-7B, 24-item version; CGI-S, Clinical Global Impression Severity of Symptoms Scale; SANS, Schedule for the Assessment of Negative Symptoms; SAPS, Schedule for the Assessment of Positive Symptoms.
*Calculated by means of analysis of covariance.

(for the Abnormal Involuntary Movements Scale, $r=-0.21$ [$P=.3$]; for the Simpson Angus Scale, $r=0.01$ [$P=.96$]).

In the assessment of change in CGI-S and SANS scores over time, the mixed-effects model showed a significant difference between groups in the slopes of the trajectories of symptom change, with clozapine showing a more rapid improvement (for CGI-S starting from the admission baseline, $t=2.1$ [$P=.04$], and starting from the an-

tipsychotic-free baseline, $t=2.3$ [$P=.03$]; for SANS, starting from admission baseline, $t=3.1$ [$P=.003$], and from the antipsychotic-free baseline, $t=2.7$ [$P=.006$]). There were no other significant group differences in the change over time in all other outcomes (all, $P>.1$).

Categorical response rates from the admission baseline indicated that 1 patient in the olanzapine group and none in the clozapine group showed a full response using the categorical definition criteria, and 4 in the clozapine and 2 in the olanzapine group met the criteria for partial response. The proportions of nonresponders did not differ significantly: 10 nonresponders (77%) in the olanzapine wing compared with 8 nonresponders (67%) in the clozapine wing (Fisher exact test, $P=.67$). Using the antipsychotic-free baseline, rates of categorical nonresponders were also similar in both groups, ie, 5 (42%) in the clozapine group and 4 (31%) in the olanzapine group (Fisher exact test, $P=.69$). Worsening of symptoms, reflected in deterioration in the CGI-S score, was noted in 2 patients in the olanzapine group and none in the clozapine group (Fisher exact test, $P=.48$).

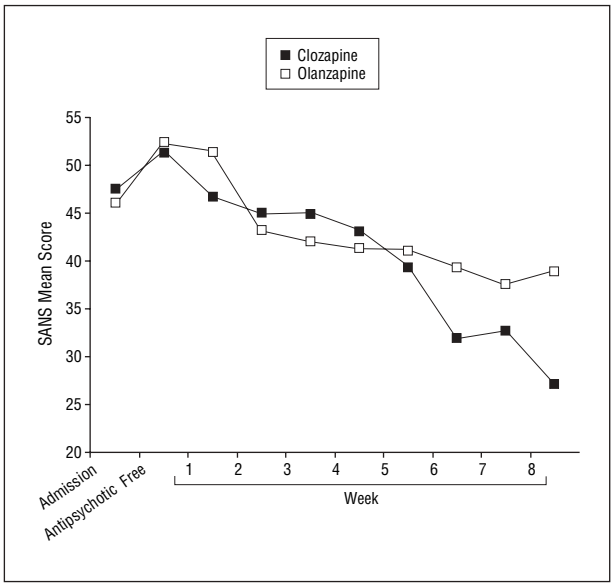

Figure 2. Weekly change in Scale for the Assessment of Negative Symptoms (SANS) score, illustrating the greater decline in the clozapine group. Antipsychotic free indicates baseline scores after withdrawal of all antipsychotic therapy.

DRUG SAFETY

Overall, there was an increased proportion of treatment-emergent adverse events and symptoms in the clozapine treatment group (clozapine-treated patients reported a total of 55 adverse effects of a maximum of 386; olanzapine-treated patients reported 28 of a maximum of 418; difference between groups, $\chi^2=12.4$ [$P<.001$]; supplementary Table 1 available at http://intramural.nimh.nih.gov/chp/cos/shaw2006supplementarytable.html shows details of individual adverse effects reported on at least 1 occasion). Adverse events present for more than 2 weeks and not present at baseline are shown in **Table 5**. Clozapine was associated with significantly more hypertension and supine tachycardia and a near-significant increase ($P=.06$) in sustained enuresis.

Electrocardiographic anomalies were noted in 2 patients in the clozapine wing (nonspecific T-wave flattening with early repolarizations in 1 patient and nonspecific ST-T–wave changes in the other). In the olanzapine

Table 5. Treatment-Emergent Adverse Effects During the Double-Blind Trial

Adverse Event	Clozapine Group	Olanzapine Group	Test of Significance
Specific events, No. of patients			
Enuresis	5/12	1/13	Fisher exact test, $P=.07$
Increased appetite	4/12	4/13	Fisher exact test, $P>.99$
Hypersalivation	8/12	4/13	Fisher exact test, $P=.11$
Constipation	2/12	2/13	Fisher exact test, $P>.99$
Difficulty concentrating	4/12	1/13	Fisher exact test, $P=.16$
Somnolence	2/12	2/13	Fisher exact test, $P>.99$
Insomnia	3/12	1/13	Fisher exact test, $P=.32$
Weight gain, kg, mean (SD)	+3.8 (6.0)	+3.6 (4.0)	$t_{22}=0.06$; $P=.96$
Change in BMI, mean (SD)	+1.6 (2.5)	+1.4 (1.6)	$t_{22}=0.30$; $P=.76$
Cardiac, No. of patients			
Hypertension	7/11	1/11	Fisher exact test, $P=.02$
Tachycardia			
>100 beats/min (supine)	7/10	2/12	Fisher exact test, $P=.03$
>120 beats/min (supine)	1/10	0/12	Fisher exact test, $P=.48$
Extrapyramidal			
AIMS, median (range)			
Antipsychotic-free baseline	10 (10-18)	10 (10-19)	Mann-Whitney test, $z=0.44$; $P=.66$
End of trial	10 (10-26)	10 (10-14)	Mann-Whitney test, $z=1.40$; $P=.14$
Simpson Angus Scale score			
Antipsychotic-free baseline	10 (10-14)	10 (10-14)	Mann-Whitney test, $z=0.29$; $P=.77$
End of trial	10 (10-13)	10 (10-12)	Mann-Whitney test, $z=0.67$; $P=.50$
Change, median (range)			
AIMS	0 (–4 to 8)	0 (–9 to 4)	Mann-Whitney test, $z=-0.56$; $P=.6$
Simpson Angus Scale score	0 (–3 to 1)	0 (–2 to 1)	Mann-Whitney test, $z=-0.45$; $P=.73$

Abbreviations: AIMS, Abnormal Involuntary Movements Scale; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters).

Table 6. Ratings at the End of the Double-Blind Trial and Change Scores at the 2-Year Follow-up*

	Clozapine Treatment Throughout				Switched to Clozapine Treatment			
Outcome Measure	End of Trial Score, Median (Min-Max)	Change Score, Median (IQR†)	Wilcoxon *z* Score	*P* Value	End of Trial Score, Median (Min-Max)	Change Score, Median (IQR†)	Wilcoxon *z* Score	*P* Value
CGI-S	4 (4-6)	0 (1)	1.1	.26	4.5 (4-7)	–0.5 (2.75)	1.4	.17
BPRS-24	47 (43-76)	–8 (18)	0.4	.67	59 (37-72)	–16 (41)	1.2	.24
SAPS	20 (9-52)	7 (27)	0.9	.34	33 (10-60)	–22 (32)	2.0	.04
SANS	30 (6-77)	8 (81)	0.5	.61	46 (12-86)	–24 (57)	1.5	.12

Abbreviations: BPRS-24, Brief Psychiatric Rating Scale, B1-7B, 24-item version; CGI-S, Clinical Global Impression Severity of Symptoms Scale; IQR, interquartile range; Min-Max, minimum-maximum values; SANS, Schedule for the Assessment of Negative Symptoms; SAPS, Schedule for the Assessment of Positive Symptoms.

*Ratings are given for patients initially randomized to clozapine who continued to receive the medication at follow-up (n = 7) and for those initially randomized to olanzapine who were switched to open-label clozapine during the follow-up period (n = 8).

†The difference between the 75th and 25th centiles.

wing, 1 patient had multiple atrial premature complexes. Cardiology consultations judged all as fit to continue. No children had seizures or developed definite epileptiform activity on electroencephalographic findings during the trial, although changes consistent with medication effects were common.

Both groups showed a similar marked increase in weight and body mass index during the double-blind trial. One patient developed hypertriglyceridemia during treatment with clozapine (fasting triglyceride level, 469 mg/dL [5.3 mmol/L]) and moderate hypercholesterolemia (fasting cholesterol level, 263 mg/dL [6.8 mmol/L]) that required treatment. One patient who was hyperprolactinemic at baseline (and had been treated with haloperidol) showed a decrease in prolactin levels during treatment with clozapine during the trial, but remained amenorrhoeic. Both groups showed few extrapyramidal symptoms, and there were no significant treatment differences in overall change.

Two patients in the clozapine group had a transient (<1 week) drop in the absolute neutrophil count below 1500 cells/μL (in both cases, the total white blood cell count remained >3500 cells/μL). One patient in the olanzapine group had a similar transient drop in the absolute neutrophil count to 1340 cells/μL. In no cases did the white blood cell count fall below 2000 cells/μL or the absolute neutrophil count below 1000 cells/μL. There were no cases of clinically significant derangement of liver function tests.

2-YEAR FOLLOW-UP

Data were available for 18 of the 20 subjects who had completed the trial at least 2 years before its termination (June 2005). Of the 10 subjects initially randomized to olanzapine on whom follow-up data were obtained, 2 continued to receive the medication at the 2-year follow-up. One of the 2 patients receiving olanzapine showed a marked improvement during the follow-up period, reflected by improvement on all outcome measures (eg, the BPRS score fell from 81 to 37). The other patient showed some sustained improvement while receiving the medication, with little change in outcome measures.

Treatment was changed to clozapine in all others owing to treatment resistance (n=8), typically immediately after the double-blind phase had ended. Although there was considerable variation in outcome, this group showed overall evidence of improvement while receiving open-label clozapine, particularly in positive symptoms (**Table 6**).

Patients initially randomized to clozapine who continued to receive the medication showed no significant change in clinical status from the end of the trial to 2-year follow-up. One patient stopped treatment with clozapine owing to extreme weight gain; treatment with aripiprazole and risperidone was accompanied by a rapid deterioration in mental state.

During the follow-up period among the patients receiving clozapine, 1 developed seizures and required treatment with anticonvulsants, and 6 developed hypercholesterolemia and/or hypertriglyceridemia.

COMMENT

We present what we believe to be the first randomized, double-blind trial among children and adolescents with COS comparing the widely used atypical agent olanzapine with clozapine, the gold standard antipsychotic in the treatment of schizophrenia. Considering first the treatment difference at the end point of the trial, clozapine was associated with greater improvement in all outcome measures and the differential effect size was large. However, given the small number of subjects in the study, this reached statistical significance only for improvement in negative symptoms and only when medication-free status was used as a baseline. When the trajectories of symptom change were compared, clozapine was associated with a more rapid improvement in CGI-S scores and negative symptoms.

Because our study was powered to detect only large effects, smaller but perhaps clinically meaningful differential treatment effects on overall clinical status were not detected. On the basis of the results for the CGI-S scores at the end of the trial, we calculated that inclusion of 19 more subjects would have been necessary to detect a significant difference (with 80% power and an α of .05). Conducting a trial of this size among this rare population is fraught with practical difficulties, and there are ethical

problems associated with continuing a trial once evidence emerges of a differential treatment effect.

Clozapine was associated with a more rapid rate of improvement in negative symptoms, resulting in a significant difference by the end point of the trial. The lack of correlation between change in extrapyramidal symptoms or mood suggests that this improvement is not a mere epiphenomenon, although caution is needed in interpretation given the small sample size.

The pharmacological basis of this differential effect we find in children and adolescents with schizophrenia is unclear but may relate to differences in the relative affinities of clozapine and olanzapine for serotonin and dopamine receptors,[31] or to differences in rates of dissociation from dopamine D_2 receptors.[32] In addition, the major metabolite of clozapine, *N*-methylclozapine, has a unique agonist action at muscarinic M1 receptors that might plausibly improve cognitive performance and thus improve negative symptoms.[33] However, although the ratio of *N*-methylclozapine to clozapine correlates with and predicts clinical improvement better than clozapine levels alone, we found among 35 patients from our COS cohort that improvement in positive rather than negative symptoms was best predicted by this ratio.[34]

DESIGN CONSIDERATIONS

There are several features of the design that warrant comment. First, we did not include a placebo wing, which makes changes within each treatment wing difficult to interpret.[35] However, given previous demonstrations of the superiority of antipsychotics over placebo in children with schizophrenia, we believed it was unethical to include a placebo wing in this severely ill and treatment-refractory pediatric population. Second, the rate of dose escalation differed between the 2 groups, with a more rapid increase in the olanzapine group, favoring this drug. Third, although the study was designed to include flexible dosages guided by clinical judgment, the initial dosing followed current prescribing guidelines for both medications and is in line with clinical practice. The final doses of clozapine attained produced mean blood levels of clozapine and norclozapine that were much greater than the suggested threshold for optimal response to clozapine[36,37] and that may have contributed to the favorable response. Similarly, the mean final dose of olanzapine of 18 mg is at the upper range of the recommended dosage. We also followed the current practice of not increasing the olanzapine dose above 20 mg; to do so increases rates of adverse events without superior clinical efficacy. The study duration of 8 weeks could be criticized because 1 study found that, although clozapine had a significant effect on negative symptoms at 8 weeks, a similar significant effect for olanzapine was not detected until 14 weeks.[38] Although efforts were made to maintain blinding, its success was not formally assessed, and differences in the rate and profile of adverse events may have partially unblinded the study and introduced bias.

We include data from 2 baseline points. At admission, patients received a variety of antipsychotics that might be considered to represent best previous treatment. Change from this baseline thus gives a real-life indication of benefit from participation in the trial over previous treatment regimens. By contrast, the antipsychotic-free baseline allows comparisons between the treatment wings in the double-blind study to be made from a uniform pharmacological starting point. Adjunctive medications were kept to a minimum and there was a very low dropout rate. The inpatient setting allowed for close monitoring of adverse events and considerable confidence in the clinical ratings. The converse of these strengths is that they may limit the generalizability of the results to other clinical settings. Thus, this demonstration of superior therapeutic efficacy of clozapine requires a similar demonstration of its therapeutic effectiveness.

SAFETY

Clozapine was associated with generally more adverse events and symptoms, with a significant increase in treatment-emergent nocturnal enuresis, tachycardia, and hypertension. The significantly greater increase in prolactin levels while receiving olanzapine compared with clozapine in this group has been reported elsewhere,[39] although in the double-blind phase no patient became symptomatic. Weight gain was marked at 4 kg during the 8 weeks in both groups.

2-YEAR FOLLOW-UP

The follow-up at 2 years benefited from its low attrition rate, with assessment of 90% of those eligible. Nearly all patients were receiving clozapine, regardless of the medication taken during the double-blind phase. Patients who were initially randomized to clozapine and continued to receive the medication varied in clinical outcome at 2 years, but the overall pattern was of sustained improvement. Patients initially randomized to olanzapine who were switched to clozapine showed a clearer pattern for improvement at the end (reflecting generally higher symptom scores in the olanzapine group at the end of the double-blind trial). Clozapine's therapeutic effectiveness is balanced against the accumulation of adverse events over time, particularly lipid anomalies (n=6) and seizures (n=1).

RELATIONSHIP TO OTHER TREATMENT STUDIES

Three head-to-head comparisons of olanzapine and clozapine in adult patients did not find any significant differences.[38,40,41] However, these trials differ from ours in several ways, not least of which is their use of patients with adult rather than childhood onset of schizophrenia. In addition, comparable doses of clozapine and olanzapine may not have been attained. In 2 of the adult studies, the modal final clozapine doses of 216 mg[40] and 303 mg[41] are substantially lower than the dose attained in our study, especially when differences in body weights are considered. The adult studies, however, reached high modal doses of olanzapine (approximately 20 mg), and it is thus possible that in these adult studies the clozapine dose was relatively low and suboptimal, which may have obscured some of its beneficial effects on negative symp-

toms. A third adult study that used slightly lower modal doses of olanzapine (11 mg) and higher modal doses of clozapine (526 mg) found that clozapine produced an earlier improvement in negative symptoms at 8 weeks, but found no significant differences between the treatments at 8 or 14 weeks.[38]

The categorical response rates in the study varied according to the baseline used but did not differ between treatment groups. Unsurprisingly, for our treatment-refractory population, the rates were lower than the categorical response rates seen in treatment-naïve psychotic children.[16]

The study can be placed in the context of other double-blind comparisons of treatments in patients with COS. Comparisons of placebo with typical antipsychotics reveal moderate to large effect sizes in the different proportions of patients showing a categorical response (placebo vs haloperidol effect size, 0.83[42]; placebo vs loxapine effect size, 0.53[1]). In turn, there is a moderate to large advantage for clozapine over typical antipsychotics in categorical response (clozapine vs haloperidol effect size, 0.45).[3] In the continuous measure of negative symptoms (SANS), clozapine is associated with greater effect sizes than the typical haloperidol (differential effect size, 0.65) and atypical olanzapine (effect size, 0.70). This pattern of differential effect sizes is an exaggerated form of the increasing treatment effects seen in meta-analyses of the adult literature, as one moves from typical to atypical antipsychotics and finally to clozapine.

CONCLUSIONS

This first, to our knowledge, double-blind comparison of 2 widely used atypical antipsychotics in children and adolescents showed clozapine to have a more even profile of clinical improvement and a unique, predicted superiority in ameliorating negative symptoms. A 2-year follow-up of patients on clozapine demonstrated sustained clinical improvement balanced by a profile of serious metabolic and neurological adverse effects. Despite its limitations, the study provides controlled data supporting clozapine's use in treatment-resistant COS.

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Correction

Error in Text. In the Arts & Images in Psychiatry cover story, *Napoleon Bonaparte Visiting the Plague-Stricken at Jaffa*, in the May issue of the ARCHIVES (2006;63:482-483), the text contained an error in a description of the painting. On page 483 in the last paragraph of the first column, the sentence should have read, "His left glove removed, Bonaparte touches an axillary bubo on a soldier who lifts his arm over his head."