A Randomized, Double-Blind Comparison of Clozapine and High-Dose Olanzapine in Treatment-Resistant Patients With Schizophrenia

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Background: Clozapine, despite its side-effect burden, has been considered to be the drug of choice for patients with schizophrenia whose psychotic symptoms fail to respond adequately to other antipsychotic drugs. There are conflicting data concerning the potential utility of olanzapine in treatment-resistant schizophrenia at doses beyond the 10- to 20-mg/day range that has proven to be effective for most nonrefractory patients with schizophrenia.

Objective: The main objective of this study was to compare the efficacy and tolerability of high-dose olanzapine (target dose, 25–45 mg/day) and clozapine (300–900 mg/day) in patients with schizophrenia or schizoaffective disorder who had failed to respond adequately to prior treatment with other antipsychotic drugs.

Study Design/Method: This 6-month, randomized, double-blind, parallel-group study compared the efficacy and tolerability of olanzapine (mean dose, 34 mg/day; N = 19) or clozapine (mean dose, 564 mg/day; N = 21) in patients with treatment-resistant schizophrenia or schizoaffective disorder, diagnosed according to DSM-IV criteria. Outcome measures included psychopathology, cognitive performance (as assessed with a comprehensive neuropsychological test battery), and tolerability. The study was conducted between May 2000 and December 2003.

Results: Robust and significant (mostly $p < .001$) improvement in multiple measures of psychopathology, mainly between 6 weeks and 6 months of treatment, was found in both treatment groups, with no significant difference between the 2 treatments except for the Global Assessment of Functioning score, which favored clozapine ($p = .01$). Improvement in some domains of cognition was significant—and equivalent for both drugs, as well. Nonsignificantly different improvement in Verbal List Learning-Immediate Recall ($p < .05$), Controlled Word Association Test ($p < .05$), and Digit Symbol Substitution Test ($p < .001$) was found. There were no significant differences in extrapyramidal symptoms. Weight gain was significantly ($p = .01$) greater with olanzapine.

Conclusions: Olanzapine, at higher than customary doses, demonstrated similar efficacy to clozapine in treatment-resistant schizophrenia and schizoaffective disorder in this study. However, the small sample size precludes definitively concluding that the 2 treatments are equivalent, at these doses, in treatment-resistant schizophrenia. The metabolic side effects of olanzapine are a limitation in its use.

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See also Commentary on page 176.

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The main basis for the approval of clozapine for use in schizophrenia, despite its serious adverse-effect burden, is its ability to improve psychotic symptoms in treatment-resistant schizophrenic patients.[1–9] It has been estimated that about 30% of patients with schizophrenia are treatment-resistant according to the criteria of Kane et al.,[1] which emphasize the persistence of psychotic symptoms and poor function, despite usually adequate treatment with antipsychotic drugs.[10–12] Consistent with this estimate, the recent double-blind, randomized, 18-month Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study comparing perphenazine, a typical neuroleptic, with the atypical antipsychotic drugs quetiapine, risperidone, and ziprasidone in patients with schizophrenia (excluding those treated with olanzapine, for reasons that will be discussed), found that 292 (29.2%) of 1002 patients discontinued treatment with these drugs because of lack of efficacy.[13]

Clozapine, which shares the pharmacologic profile of other atypical antipsychotic drugs,[14] has been demonstrated to have superior efficacy to reduce psychotic symptoms for most, but not all, patients with treatment-

resistant schizophrenia.[1,3,8] Specific advantages for clozapine over typical neuroleptic drugs have been demonstrated for positive and negative symptoms, cognition, and long-term relapse prevention, although the extent of the differences varies, being greatest for positive symptoms and least for negative symptoms.[5,6,15,16] Clozapine has been found to be superior to olanzapine in reducing the risk for suicide.[17] However, its adverse-effect burden, especially agranulocytosis (necessitating close medical monitoring), cardiovascular risk, seizures, metabolic side effect, and, perhaps, its costliness, have limited its use to about 5% of patients with schizophrenia or schizoaffective disorder.[6,9,11]

Given clozapine's limitations, there has been considerable interest in studying other atypical antipsychotic drugs in patients with treatment-resistant schizophrenia, but the results are conflicting.[6,18–21] Olanzapine has been the most widely studied atypical antipsychotic drug other than clozapine in treatment-resistant schizophrenia. A number of case reports and retrospective studies suggest that doses of olanzapine higher than conventional doses (10–20 mg/day) may be effective in some treatment-resistant patients with schizophrenia,[22–31] but because of the uncontrolled and retrospective nature of these studies, they are of limited value in resolving the controversy about the efficacy of olanzapine in treatment-resistant patients. Clinical trials of olanzapine in treatment-resistant schizophrenia include comparisons with typical neuroleptics,[32] clozapine,[33,34] and/or other atypical antipsychotics[35,36] using conventional (5–20 mg/day)[32–34,36] or high (> 20 mg/day up to 50 mg/day) doses of olanzapine.[35,37,38] While some of these studies report that high-dose olanzapine is effective and tolerable in treatment-resistant schizophrenic patients,[34–36] others (all from the same center) do not.[32,37,38] These results are difficult to interpret because these studies utilized variable definitions of treatment resistance, often included neuroleptic-intolerant patients, and used questionably adequate doses of comparator agents, including lower doses of clozapine than might be optimal for treatment-resistant patients.[33,35] Nevertheless, Chakos et al.[5] concluded from a review of the early, least-controlled data that treatment-resistant schizophrenic patients treated with olanzapine had more favorable outcomes with regard to categorical response and compliance rates than those treated with typical neuroleptic drugs. A recent Cochrane review of olanzapine-treated patients concluded that there were no clear differences between olanzapine and clozapine in patients with treatment-resistant schizophrenia, based on 4 randomized controlled trials (N = 457) that included dosages of olanzapine 5–50 mg/day and clozapine 100–700 mg/day and included many non–treatment-resistant patients.[39] In phase 2 of the CATIE study, in which clozapine was compared to olanzapine, clozapine was more effective on some measures but not on time to discontinuation for lack of efficacy.[15] However, as will be discussed, the dosage of olanzapine was permitted to reach 30 mg/day, which overlaps with the doses studied here. In addition, clozapine was administered in a nonblinded manner, whereas olanzapine, quetiapine, and risperidone were blinded; thus, patients' and clinicians' evaluations of these treatments, as well as efficacy ratings, may have been compromised. Other than CATIE, none of these studies addressed effects on cognitive dysfunction, a cardinal feature of schizophrenia that has become a major focus of schizophrenia research due to its relationship to better functional outcome.[40]

The rationale for studying olanzapine in treatment-resistant patients at doses higher than those used in non–treatment-resistant patients is based, in part, on comparison of the dose of clozapine that is effective in treatment-resistant schizophrenic patients (average mean dose, 450 mg/day)[1,3] with that used in non–treatment-resistant schizophrenia (100–300 mg/day).[3,41] Similarly, melperone, an atypical antipsychotic drug approved for use in Europe,[42] was reported to require approximately twice the dose for treatment-resistant compared to non–treatment-resistant patients.[43,44] These considerations, together with the evidence reviewed above, that doses of olanzapine in the 10- to 25-mg/day range were less effective than clozapine in treatment-resistant patients, suggested that the dose of olanzapine that might be effective in treatment-resistant patients with schizophrenia might be in the 30- to 50-mg/day range. A recent study comparing doses of olanzapine in non–treatment-resistant schizophrenia showed that a 10-mg/day dose was as effective as a 20- or 40-mg/day dose.[45] Therefore, the current study evaluated the comparative efficacy for psychopathology, cognition, and tolerability of high-dose olanzapine and clozapine in a cohort of patients with treatment-resistant schizophrenia or schizoaffective disorder in a double-blind, randomized clinical trial. However, the study was designed to test the hypothesis that clozapine would be superior to olanzapine in treatment-resistant schizophrenia despite the higher dose of olanzapine, as previously reported by Conley et al.,[32] since an equivalency study would have required a much larger sample than was feasible given available resources.

METHOD

Forty physically healthy men and women (aged 18–58 years) who met DSM-IV diagnostic criteria for schizophrenia or schizoaffective disorder were recruited from 3 U.S. outpatient community mental health treatment facilities (22 patients from the Centerstone Mental Health Center in Nashville, Tenn., and 9 patients from each of 2 other mental health centers). All study participants were required to have a documented history of treatment-resistant schizophrenia based on the criteria of Kane

et al.[1] Specifically, patients were eligible for the study if their medical records and clinical evaluation at the time of study entry indicated moderate to severe levels (a score ≥ 4) for at least 2 of the following 4 types of positive symptoms—delusions, hallucinations, conceptual disorganization, and unusual thought content—despite 2 or more trials of typical or atypical antipsychotic drugs from different chemical classes, with usually adequate doses for at least 6 weeks. Patients were excluded from the study if they had a history of nonresponsiveness to adequate trials of conventional doses of either clozapine or olanzapine or if they had a history of substantial neurologic disorder, cardiac disease, or active substance abuse.

Study Design and Clinical Procedures

This study was a 6-month, prospective, double-blind, flexible-dose, randomized, parallel-group trial of efficacy for psychopathology, cognition, and tolerability of olanzapine 25–45 mg/day versus clozapine 300–900 mg/day. All patients provided written informed consent after receiving explanation of the nature of the study, the potential risks and benefits, and alternatives to participation. The study received institutional review board approval in May 2000, and the last subject completed in December 2003.

After diagnostic screening, patients who met inclusion criteria and provided informed consent were tapered off their current medication. For individuals who were receiving oral antipsychotic medications, the dosage was reduced to a 10-mg/day haloperidol equivalent over 7–14 days and then discontinued. None of the patients were receiving long-acting medications. All but 2 of the patients were receiving an atypical antipsychotic drug with a mean dose equivalent to risperidone 6.2 mg/day. Four patients received a typical antipsychotic drug in addition. Two patients received only typical antipsychotic drugs with a mean dose in chlorpromazine equivalents of 640 mg/day. Sixteen patients, equally divided between the olanzapine- and risperidone-treated patients, received a mood stabilizer, antidepressants, or both. The mood stabilizers were also withdrawn in those who did not have schizoaffective disorder.

Medication tapering was followed by a postdiscontinuation 2- to 7-day washout period, after which patients were randomly assigned to treatment with either olanzapine or clozapine using a previously generated randomization list for each site. There was no exacerbation of symptomatology in any patients in the study during the medication tapering and brief washout period. Haloperidol was given to 1 patient during the tapering period. Study medications were packaged by an off-site pharmacy according to batch numbers that corresponded to patient identification codes.

In order to maintain the blind, all patients had their white blood count monitored weekly for the 6-month duration of the study. Furthermore, packaging for the titration phase was separate from that for the maintenance phase. A double-dummy method was used for both titration and maintenance treatment.

Clozapine was initiated at a dose of 25 mg/day for 2 days, increased by 25- to 50-mg/day increments on days 3 and 4, and then increased further by 25-mg/day increments daily until a target dose of 400 mg/day was reached on days 17 and 18. Thereafter, the dose could be increased up to a maximum of 900 mg/day, based upon clinical response and tolerability. Olanzapine was initiated at a dose of 10 mg/day for 7 days, after which the dose was increased to 15 mg/day on days 8–14, and 20 mg/day on days 15–18. Thereafter, the dose could be raised up to a maximum of 45 mg/day. Haloperidol was permitted as a rescue medication during the titration phase but could not be used during maintenance treatment. During the maintenance phase, all patients continued to receive 9 capsules, each of which contained clozapine 100 mg, olanzapine 5 mg, or placebo. The latter was necessary to equalize the number of pills taken in order to maintain the blind. Clinicians could raise or lower the dose by ordering 1 or more capsules containing active drug at weekly intervals. They were instructed to adjust the number of capsules per day to optimize response and tolerability and minimize dropouts. During maintenance treatment, flexible dosing of both agents was allowed, up to 900 mg/day for clozapine and 45 mg/day for olanzapine. No other antipsychotic drug or mood stabilizer was permitted during the maintenance phase. The use of lorazepam, benztropine, and fluoxetine was permitted on an as-needed basis during the maintenance phase.

Efficacy and Safety Assessments

Ratings were performed by bachelor's or master's level raters whose interrater reliability was confirmed on a quarterly basis as approximately 95%. Raters who provided baseline assessment for patients performed all subsequent ratings on those same cases throughout the study. The Positive and Negative Syndrome Scale (PANSS)[46] for schizophrenia was assessed at baseline, 6 weeks, and 6 months. The maximum PANSS score is 180 (0–6 ratings). The baseline ratings were obtained just prior to beginning active medication. Other outcome measures included the Schedule for the Assessment of Negative Symptoms (SANS),[47] the Schedule for the Assessment of Positive Symptoms (SAPS),[48] the Global Assessment of Functioning (GAF)[49] scale, the Clinical Global Impressions (CGI)[50] scale, and the Clinical Global Impressions-Severity of Illness (CGI-S)[50] scale as measures of general level of psychosocial functioning. Categorical criteria for treatment response were determined a priori as ≥ 20% decrease from baseline in PANSS total score at 6 months for completers, or at 6 weeks for those who dropped out after week 6 for reasons other than lack of efficacy.

Table 1. Subject Demographics and Discontinuations

Variable	Clozapine Group (N = 21)	Olanzapine Group (N = 19)
Gender, N (%)		
Male	15 (71.4)	12 (63.2)
Female	6 (28.6)	7 (36.8)
Ethnic background, N (%)		
White	12 (57.1)	14 (73.7)
African American	8 (38.1)	3 (15.8)
Asian	0 (0.0)	2 (10.5)
Other (not specified)	1 (4.8)	0 (0.0)
Diagnosis, N (%)		
Schizophrenia	17 (80.9)	16 (83.2)
Schizoaffective disorder	4 (19.1)	3 (16.8)
Age, mean (SD), y	37.2 (9.2)	36.4 (11.1)
Age at onset, mean (SD), y	22.5 (7.3)	19.4 (10.5)
Duration of illness, mean (SD), y	14.7 (7.8)	16.6 (12.7)
No. previous hospitalizations, mean (SD)	5.9 (4.0)	6.8 (7.8)
Dropouts prior to 6 wk, N (%)[a]	6 (28.6)	2 (10.5)
Completers at 6 mo, N (%)[b]	10 (47.6)	14 (73.7)

[a] $\chi^2 = 2.03$, $p = .15$.
[b] $\chi^2 = 2.82$, $p = .09$.

Neurocognitive performance was assessed at baseline, 6 weeks, and 6 months for the following domains using the following tests: (1) verbal memory: Verbal List Learning-Immediate Recall (VLL-IR)[51] and Verbal List Learning-Delayed Recall (VLL-DR),[51] (2) working memory: Peterson Consonant Trigram Test,[52] (3) sustained attention: Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol Substitution Test (DSST),[53] (4) verbal fluency: Controlled Word Association Test (CWAT),[54] and (5) executive functioning/reasoning: Wisconsin Card Sorting Test-Category and Perseveration[55] and Wechsler Intelligence Scale for Children-Revised (WISC-R) Mazes.[56] The development of this battery has been described in detail previously.[57]

To assess safety and tolerability, the following measures were performed at baseline, 6 weeks, and 6 months: the Barnes Akathisia Scale,[58] the modified Simpson-Angus Scale,[59] and the Abnormal Involuntary Movement Scale (AIMS)[60] (to assess tardive dyskinesia), and weight and body mass index (BMI, defined as kg/m^2) were obtained.

Statistical Analysis

Sample size determination was based upon prior studies that indicated a baseline Brief Psychiatric Rating Scale total mean ± SD score of 55 ± 10 and that clozapine treatment would decrease this score by 15 points over a 6-month period.[1–3] We estimated that olanzapine at a high dose would produce a 5-point decrease in score based on data from Conley et al.[32] We calculated that a sample size of 17 per treatment group would be sufficient to provide 80% power, with a type I error rate of .05, to show that clozapine was superior to olanzapine. Treatment effects were analyzed by repeated-measures analysis of variance (ANOVA), with time (outcome-measure scores at baseline vs. 6 weeks and at baseline vs. 6 months) as the within-subjects factor and treatment group as the between-subjects factor, using a mixed model.[61] The primary outcome measure specified in the protocol analysis plan was the total PANSS score. The mixed model provided estimates of missing data by using available data from all subjects to estimate the missing data. Baseline values for dependent variables were adjusted in order to neutralize baseline differences between groups for a truer comparison of agents at 6 weeks and 6 months. The relationship between categorical variables was analyzed using χ^2 analysis. Effect sizes were determined with the use of the Cohen d statistic, which provides a measure of the differences in the mean values of changes in symptom severity between groups in relation to the pooled standard deviation.[62] All main effects were tested at a 2-tailed alpha level of .05. All analyses were performed using SAS statistical software (SAS Institute Inc., Cary, N.C.).

Table 2. Dosage of Clozapine and Olanzapine at 6 Weeks and 6 Months

Variable	Mean ± SD, mg/d	Range, mg/d	Median, mg/d	Percent of Subjects at ≥ 500 mg/d for Clozapine or ≥ 35 mg/d for Olanzapine
Clozapine dose at 6 wk	400 ± 158	75–700	400	23
Clozapine dose at 6 mo	564 ± 243	275–900	700	56
Olanzapine dose at 6 wk	32.7 ± 5.94	20–40	30	47
Olanzapine dose at 6 mo	33.6 ± 11.2	30–45	40	71

RESULTS

A total of 40 patients (27 male, 13 female) completed all baseline assessments and were randomly assigned to the 2 treatment arms: clozapine (N = 21) and olanzapine (N = 19). The demographics of the 2 groups of patients and dropouts during the study are summarized in Table 1. There were no significant differences between treatment groups with respect to demographic characteristics. The reasons for the 8 early dropouts (20%) were patient refusal to continue to participate in the study for personal reasons rather than lack of efficacy or tolerability. The reasons for the dropouts after 6 weeks in the clozapine group were administrative reasons (N = 2) and inadequate response (N = 3). The reason for the 3 later dropouts in the olanzapine group was lack of response. There was a trend for a higher completer rate favoring olanzapine (p = .09).

Drug Treatment and Concomitant Medications

Dosages of clozapine and olanzapine are given in Table 2. By the end of the study, 56% of individuals assigned to the clozapine arm were taking ≥ 500 mg/day of clozapine,

Table 3. Psychopathology Measures at Baseline, 6 Weeks, and 6 Months[a]

Assessment	Timepoint	Least-Squares Mean (SE)		Least-Squares Mean Difference		ANOVA Source		
		Clozapine	Olanzapine	Difference, Mean (SE)	p Value	Treatment Group, F Statistic	Time, F Statistic	Treatment Group by Time, F Statistic
PANSS total	Baseline	91.9 (2.3)	92.2 (2.4)	–0.35 (3.3)	.92	0.06	31.31***	0.10
	6 Weeks	84.0 (2.8)	85.9 (2.5)	–1.90 (3.8)	.61		ES = 1.60	
	6 Months	72.1 (3.4)	71.7 (2.8)	0.41 (4.3)	.92			
PANSS positive	Baseline	23.1 (0.8)	23.0 (0.8)	0.07 (1.1)	.95	3.10	30.94***	1.58
	6 Weeks	19.3 (0.9)	21.2 (0.9)	–1.89 (1.3)	.14		ES = 1.56	
	6 Months	15.1 (1.1)	17.8 (0.9)	–2.67 (1.4)	.07			
PANSS negative	Baseline	22.1 (0.8)	23.0 (0.9)	–0.97 (1.2)	.43	0.07	3.86*	1.03
	6 Weeks	22.1 (1.0)	22.1 (0.9)	–0.03 (1.4)	.98		ES = 0.55	
	6 Months	20.9 (1.2)	19.1 (1.0)	1.72 (1.6)	.28			
PANSS general	Baseline	46.3 (1.4)	46.7 (1.4)	–0.41 (2.0)	.84	0.02	26.03***	0.12
	6 Weeks	42.1 (1.7)	42.9 (1.5)	–0.86 (2.3)	.70		ES = 1.43	
	6 Months	35.9 (1.9)	35.2 (1.7)	0.67 (2.6)	.79			
PANSS cognition	Baseline	12.1 (0.5)	12.2 (0.5)	–0.09 (0.7)	.89	0.29	13.91***	1.24
	6 Weeks	11.0 (0.6)	11.3 (0.5)	–0.38 (0.7)	.61		ES = 1.04	
	6 Months	10.1 (0.7)	8.8 (0.6)	1.23 (0.9)	.15			
SANS global	Baseline	13.5 (0.7)	13.6 (0.7)	–0.15 (1.0)	.88	2.87	7.99**	0.88
	6 Weeks	11.5 (0.8)	12.8 (0.7)	–1.31 (1.1)	.23		ES = 0.80	
	6 Months	9.6 (0.9)	11.6 (0.8)	–2.04 (1.2)	.10			
SANS affect-flat	Baseline	2.7 (0.2)	2.8 (0.2)	–0.11 (0.3)	.71	3.78	3.54*	0.74
	6 Weeks	2.0 (0.2)	2.5 (0.2)	–0.53 (0.3)	.11		ES = 0.53	
	6 Months	2.0 (0.3)	2.5 (0.2)	–0.56 (0.4)	.13			
SANS alogia	Baseline	2.3 (0.2)	2.4 (0.2)	–0.12 (0.3)	.71	0.00	6.33**	0.11
	6 Weeks	1.9 (0.3)	1.8 (0.2)	0.09 (0.4)	.80		ES = 0.71	
	6 Months	1.5 (0.3)	1.5 (0.2)	–0.01 (0.4)	.99			
SANS anhedonia	Baseline	3.0 (0.2)	3.0 (0.2)	0.03 (0.3)	.92	1.97	1.99	1.15
	6 Weeks	2.7 (0.2)	2.9 (0.2)	–0.16 (0.3)	.59			
	6 Months	2.3 (0.3)	2.9 (0.2)	–0.62 (0.3)	.08			
SANS avolition	Baseline	2.6 (0.2)	2.7 (0.2)	–0.10 (0.3)	.71	1.99	3.32*	0.35
	6 Weeks	2.5 (0.2)	2.7 (0.2)	–0.22 (0.3)	.46		ES = 0.52	
	6 Months	1.9 (0.3)	2.4 (0.2)	–0.44 (0.3)	.19			
SANS attention	Baseline	2.8 (0.2)	2.8 (0.2)	0.004 (0.3)	.99	3.52	6.37**	1.50
	6 Weeks	2.3 (0.2)	3.0 (0.2)	–0.67 (0.3)	.04		ES = 0.72	
	6 Months	1.9 (0.3)	2.3 (0.2)	–0.44 (0.4)	.22			
SANS negative	Baseline	10.6 (0.6)	10.8 (0.6)	–0.19 (0.8)	.82	1.95	6.05**	0.59
	6 Weeks	9.2 (0.7)	9.9 (0.7)	–0.72 (1.0)	.45		ES = 0.70	
	6 Months	7.7 (0.8)	9.3 (0.7)	–1.60 (1.1)	.14			
SAPS global	Baseline	9.8 (0.5)	9.9 (0.5)	–0.07 (0.7)	.92	0.32	28.49***	0.34
	6 Weeks	7.7 (0.6)	8.5 (0.6)	–0.83 (0.8)	.32		ES = 1.51	
	6 Months	5.6 (0.7)	5.6 (0.6)	–0.02 (0.9)	.98			
SAPS hallucinations-global	Baseline	3.2 (0.2)	3.2 (0.3)	–0.04 (0.3)	.91	0.06	11.03***	0.01
	6 Weeks	3.1 (0.3)	3.2 (0.3)	–0.06 (0.4)	.89		ES = 0.95	
	6 Months	2.0 (0.3)	2.1 (0.3)	–0.10 (0.4)	.82			
SAPS delusions	Baseline	3.3 (0.2)	3.4 (0.2)	–0.02 (0.3)	.95	0.88	12.66***	0.63
	6 Weeks	2.4 (0.3)	2.8 (0.2)	–0.48 (0.3)	.17		ES = 1.00	
	6 Months	2.2 (0.3)	2.3 (0.3)	–0.13 (0.4)	.74			
SAPS bizarre	Baseline	1.4 (0.2)	1.3 (0.2)	0.02 (0.2)	.93	0.21	12.12***	0.13
	6 Weeks	0.8 (0.2)	1.0 (0.2)	–0.15 (0.3)	.55		ES = 0.99	
	6 Months	0.5 (0.2)	0.5 (0.2)	–0.07 (0.3)	.80			
SAPS positive thought contents	Baseline	1.9 (0.2)	2.0 (0.2)	–0.03 (0.2)	.90	0.17	21.57***	0.44
	6 Weeks	1.3 (0.2)	1.3 (0.2)	–0.04 (0.3)	.89		ES = 1.31	
	6 Months	0.9 (0.2)	0.6 (0.2)	0.28 (0.3)	.36			
PANSS negative adjusted for SAS	Baseline	22.0 (0.8)	23.3 (0.9)	–1.27 (1.2)	.30	0.16	4.06*	1.06
	6 Weeks	21.7 (1.0)	22.8 (0.9)	–1.08 (1.4)	.45		ES = 0.58	
	6 Months	20.7 (1.2)	19.5 (1.0)	1.23 (1.6)	.43			
GAF	Baseline	45.2 (1.5)	45.1 (1.6)	0.02 (2.2)	.99	2.03	34.31***	3.55*
	6 Weeks	50.0 (1.9)	50.7 (1.7)	–0.70 (2.5)	.78		ES = 1.67	ES = 0.54
	6 Months	62.4 (2.1)	54.8 (1.8)	7.61 (2.8)	.01			

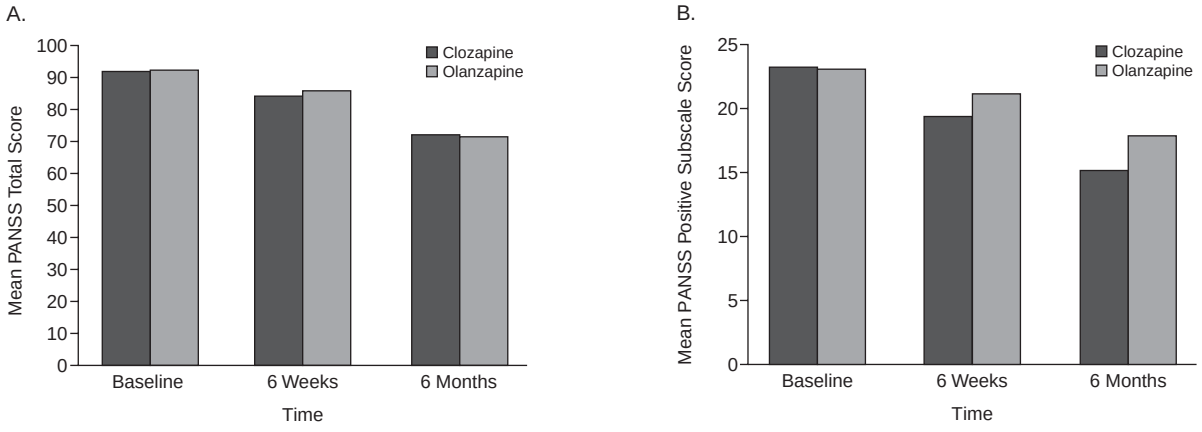
(continued)

Table 3 (continued). Psychopathology Measures at Baseline, 6 Weeks, and 6 Months[a]

Assessment	Timepoint	Least-Squares Mean (SE) Clozapine	Least-Squares Mean (SE) Olanzapine	Least-Squares Mean Difference Difference, Mean (SE)	Least-Squares Mean Difference p Value	ANOVA Source Treatment Group, F Statistic	ANOVA Source Time, F Statistic	ANOVA Source Treatment Group by Time, F Statistic
CGI	Baseline	1.6 (0.5)	2.4 (0.5)	–0.79 (0.7)	.29	0.33	3.61*	0.35
	6 Weeks	3.4 (0.5)	3.7 (0.6)	–0.26 (0.8)	.75		ES = 0.76	
	6 Months	2.6 (0.8)	2.3 (0.6)	0.32 (1.0)	.76			
CGI-S	Baseline	4.7 (0.2)	4.7 (0.2)	–0.05 (0.2)	.83	0.00	24.05***	0.30
	6 Weeks	4.2 (0.2)	4.1 (0.2)	0.15 (0.3)	.55		ES = 0.58	
	6 Months	3.6 (0.2)	3.6 (0.2)	–0.08 (0.3)	.78			

[a]The intrasubject covariance matrix used is compound symmetry. When there is a significant treatment-group-by-visit interaction, the p value for least-squares mean difference reflects the treatment group effect at each visit, while the p value for the ANOVA source table reflects the overall treatment group effect or average treatment group effect over the entire study.
*p < .05, **p < .01, ***p < .001.
Abbreviations: ANOVA = analysis of variance, CGI = Clinical Global Impressions scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, ES = effect size, GAF = Global Assessment of Functioning scale, PANSS = Positive and Negative Syndrome Scale, SANS = Schedule for the Assessment of Negative Symptoms, SAPS = Schedule for the Assessment of Positive Symptoms, SAS = Simpson-Angus Scale.

Figure 1. Positive and Negative Syndrome Scale (PANSS) Total Score (A) and PANSS Positive Subscale Score (B) for Clozapine and Olanzapine Treatment Over Time



while 71% of patients assigned to the olanzapine arm were taking ≥ 35 mg/day of olanzapine. Three of the olanzapine-treated and 4 of the clozapine-treated patients received antidepressants at some point in the study. The schizoaffective disorder patients who were receiving mood stabilizers at study entry continued to receive them during the course of the study. Adjunctive treatment with either benztropine or lorazepam was rarely needed and was comparable across treatment groups.

Efficacy Measures

There were no significant differences between treatment groups with respect to baseline clinical ratings (Table 3). There was significant improvement in psychopathology ratings over time for both treatment groups (Table 3). Specifically, a significant time effect was found for the PANSS total score ($F = 31.31$, $p < .001$), as well as the PANSS positive ($F = 30.94$, $p < .001$), negative ($F = 3.86$, $p < .05$), general ($F = 26.03$, $p < .001$), and cognitive ($F = 13.91$, $p < .001$) subscales. The time effect for PANSS negative subscale scores was significant after adjusting for Simpson-Angus Scale scores ($F = 4.06$, $p < .05$). The change scores for the PANSS total and the PANSS positive subscale are given in Figure 1. Effect sizes for the PANSS total and PANSS positive and negative subscales were 1.60, 1.56, and 0.55, respectively. There was a trend towards greater improvement in the PANSS positive subscale favoring clozapine at 6 months ($p = .07$). At 6 weeks, 18% of olanzapine-treated patients and 7% of clozapine-treated patients were treatment responders based on the a priori criterion of a 20% or greater decrease in PANSS total score. At 6 months, 50% of the olanzapine group and 60% of the clozapine group met criteria for treatment response.

There was also a significant time effect for SANS global score ($F = 7.99$, $p < .01$), for all SANS subscale scores except anhedonia, and for SAPS global score ($F = 28.49$, $p < .001$) (Table 3). There were trends toward greater im-

Table 4. Cognitive Measures at Baseline, 6 Weeks, and 6 Months[a]

Assessment	Timepoint	Least-Squares Mean (SE) Clozapine	Least-Squares Mean (SE) Olanzapine	Least-Squares Mean Difference Difference, Mean (SE)	Least-Squares Mean Difference p Value	ANOVA Source Treatment Group, F Statistic	ANOVA Source Time, F Statistic	ANOVA Source Treatment Group by Time, F Statistic
Peterson Consonant Trigram Test	Baseline	34.6 (1.5)	34.3 (1.6)	0.30 (2.2)	.89	0.28	0.64	0.55
	6 Weeks	34.2 (1.8)	37.1 (1.8)	–2.88 (2.6)	.27			
	6 Months	33.6 (2.2)	33.7 (2.1)	–0.10 (3.0)	.97			
WISC-R Mazes	Baseline	15.9 (0.5)	16.0 (0.5)	–0.07 (0.7)	.92	9.95**	2.04	3.71*
	6 Weeks	15.1 (0.6)	16.5 (0.5)	–1.46 (0.8)	.07			ES = 0.56
	6 Months	15.4 (0.7)	18.5 (0.6)	–3.14 (0.9)	.002			
Verbal List Learning-Immediate Recall	Baseline	29.9 (1.4)	29.2 (1.6)	0.69 (2.2)	.75	0.23	4.47*	2.00
	6 Weeks	35.3 (2.2)	29.9 (2.0)	5.34 (3.0)	.08		ES = 0.79	
	6 Months	33.5 (2.8)	37.2 (2.0)	–3.64 (3.4)	.30			
Verbal List Learning-Delayed Recall	Baseline	5.8 (0.5)	5.5 (0.5)	0.31 (0.7)	.67	0.00	0.18	4.26*
	6 Weeks	6.5 (0.7)	4.4 (0.7)	2.14 (1.0)	.04			ES = 0.64
	6 Months	4.7 (0.9)	7.2 (0.7)	–2.47 (1.1)	.04			
WAIS-R Digit Symbol Substitution Test	Baseline	34.5 (1.2)	34.6 (1.4)	–0.10 (1.9)	.96	0.54	9.09***	2.20
	6 Weeks	36.7 (1.5)	37.9 (1.5)	–1.17 (2.1)	.58		ES = 0.89	
	6 Months	42.4 (1.7)	38.0 (1.5)	4.43 (2.3)	.06			
WCST-Categories Formed	Baseline	3.0 (0.2)	3.0 (0.2)	0.02 (0.3)	.96	1.19	0.43	1.34
	6 Weeks	2.5 (0.3)	3.3 (0.3)	–0.75 (0.4)	.07			
	6 Months	3.1 (0.4)	3.2 (0.3)	–0.14 (0.5)	.76			
WCST-Percent Perseveration	Baseline	23.4 (2.5)	23.6 (2.5)	–0.13 (3.5)	.97	0.04	1.18	0.01
	6 Weeks	26.9 (3.1)	27.9 (2.7)	–1.01 (4.2)	.81			
	6 Months	24.4 (3.7)	24.8 (3.1)	–0.50 (4.9)	.92			
Controlled Word Association Test	Baseline	25.3 (1.1)	25.3 (1.2)	–0.03 (1.6)	.98	0.00	4.37*	0.06
	6 Weeks	28.7 (1.4)	29.2 (1.2)	–0.56 (1.9)	.77		ES = 0.59	
	6 Months	27.3 (1.6)	26.9 (1.4)	0.41 (2.1)	.85			

[a]The intrasubject covariance matrix used is compound symmetry. When there is a significant treatment-group-by-visit interaction, the p value for least-squares mean difference reflects the treatment group effect at each visit, while the p value for the ANOVA source table reflects the overall treatment group effect or average treatment group effect over the entire study.
*p < .05, **p < .01, ***p < .001.
Abbreviations: ANOVA = analysis of variance, ES = effect size, WAIS-R = Wechsler Adult Intelligence Scale-Revised, WCST = Wisconsin Card Sorting Test, WISC-R = Wechsler Intelligence Scale for Children-Revised.

provement in the SANS global (p = .10) and anhedonia (p = .08) subscale scores at 6 months favoring clozapine. There was comparatively greater improvement with clozapine on the SANS attention subscale (p = .04) at 6 weeks but not at 6 months. A significant time effect for the CGI (F = 3.61, p < .05) and CGI-S (F = 24.05, p < .001) scales was found, and significant time (F = 34.31, p < .001) and treatment-group-by-time interaction effects (F = 3.55, p < .05) on GAF scores favoring clozapine were found (Table 3). The difference was nonsignificant at 6 weeks but was significant (p = .01) at 6 months. There were no other significant treatment-group-by-time interactions or treatment group effects.

Cognitive Performance

Significant time effects were observed for VLL-IR (F = 4.47, p < .05), CWAT (F = 4.37, p < .05), and WAIS-R DSST (F = 9.09, p < .001), indicating no significant differences in improvement in both groups over time (Table 4). Treatment-group-by-time interaction effects favoring olanzapine treatment were observed for the WISC-R Mazes (F = 3.71, p < .05) and VLL-DR (F = 4.26, p < .05) (Table 4). Further examination of results for WISC-R Mazes showed significant (p = .002) differences in least-squares means between clozapine and olanzapine at 6 months, but the difference was not significant at 6 weeks. For VLL-DR, the differences at 6 weeks and 6 months were significant (p = .04). No other significant time effects or treatment-group-by-time interaction effects were identified for other measures of neurocognitive performance.

Tolerability

Patients in both groups had relatively low motor symptoms on each of the 3 rating scales at study entry. There was a trend toward lower AIMS scores for the olanzapine-treated group (p = .07) at 6 weeks, but at 6 months, AIMS total score had increased compared to baseline. None of the changes reached statistical significance (Table 5). Akathisia was minimal in both treatment groups at any point in the study.

Both patient groups were obese, on average, at the time of study entry. There were significant time effects for weight (F = 7.32, p < .01) and BMI (F = 4.85, p < .05) (Table 5). A treatment-group-by-time interaction effect favoring clozapine approached statistical significance for both weight (p = .06) and BMI (p = .06), with a mean weight gain for clozapine of 3.5 lb, and for olanzapine,

Table 5. Measures of Extrapyramidal Symptoms, Weight, and BMI at Baseline, 6 Weeks, and 6 Months[a]

		Least-Squares Mean (SE)		Least-Squares Mean Difference		ANOVA Source		
Assessment	Timepoint	Clozapine	Olanzapine	Difference, Mean (SE)	p Value	Treatment Group, F Statistic	Time, F Statistic	Treatment Group by Time, F Statistic
AIMS total	Baseline	1.1 (0.5)	1.1 (0.5)	0.01 (0.7)	.99	0.14	1.00	2.46
	6 Weeks	2.0 (0.6)	0.5 (0.5)	1.44 (0.8)	.07			
	6 Months	1.4 (0.7)	2.3 (0.6)	–0.89 (0.9)	.30			
SAS total	Baseline	2.5 (0.4)	2.6 (0.4)	–0.13 (0.6)	.84	3.10	1.45	1.51
	6 Weeks	2.5 (0.5)	1.0 (0.5)	1.50 (0.7)	.04			
	6 Months	2.3 (0.6)	1.6 (0.5)	0.66 (0.8)	.40			
Weight (lb)	Baseline	201.1 (2.3)	201.1 (2.5)	–0.03 (3.4)	.99	3.35	7.32**	3.05^{+}
	6 Weeks	203.6 (3.0)	206.0 (2.7)	–2.41 (4.1)	.56		ES = 0.79	ES = 0.53
	6 Months	204.6 (3.3)	217.0 (2.9)	–12.29 (4.4)	.01			
BMI	Baseline	30.3 (0.4)	30.4 (0.4)	–0.06 (0.5)	.89	4.26*	4.85*	3.01^{+}
	6 Weeks	30.6 (0.5)	31.0 (0.4)	–0.48 (0.6)	.62		ES = 0.64	ES = 0.51
	6 Months	30.6 (0.5)	32.6 (0.4)	–2.00 (0.7)	.006			

[a]The intrasubject covariance matrix used is compound symmetry. When there is a significant treatment-group-by-visit interaction, the p value for least-squares mean difference reflects the treatment group effect at each visit, while the p value for the ANOVA source table reflects the overall treatment group effect or average treatment group effect over the entire study.

$^{+}p < .10$, *$p < .05$, **$p < .01$.

Abbreviations: AIMS = Abnormal Involuntary Movement Scale, ANOVA = analysis of variance, BMI = body mass index, ES = effect size, SAS = Simpson-Angus Scale.

15.9 lb. At 6 months, the olanzapine group also evidenced greater mean increases in BMI (clozapine, 0.3 vs. olanzapine, 2.2). For weight, the difference at 6 months was significant (p = .01). For BMI, the difference between the least-square means was significant at 6 months (p = .006) but not at 6 weeks. There was no significant relationship between olanzapine dose and change in weight at either 6 weeks or 6 months.

DISCUSSION

The major finding in this study was that the improvement for both treatment groups in PANSS total, positive, negative, general, and cognitive scores, all SAPS and SANS scores (except for SANS anhedonia), and CGI and CGI-S scores was not significantly different. The magnitude of the improvement for both treatments in PANSS total and subscale scores was large, as indicated by an effect size of 1.60 for the PANSS total. In this study, 18% of patients in the olanzapine-treated group and 7% of patients in the clozapine-treated group were treatment responders at 6 weeks by the a priori criterion of ≥ 20% decrease in baseline PANSS total score. At 6 months, these figures rose to 50% and 60%, respectively. The findings in this study are consistent with the majority of previous studies of the efficacy of high-dose olanzapine in treatment-resistant schizophrenia[22–31,34–36] and the conclusions of a Cochrane meta-analysis.[39] The magnitude of the improvement in PANSS total scores at 6 weeks in this study for both drugs was virtually identical with those reported by Volavka et al.[35] The greater improvement in our study after 26 weeks is consistent with a previous report that approximately 30% of treatment-resistant patients require up to 6 months' treatment with clozapine to show improvement in psychopathology[2] as well as some domains of cognition.[63] This delayed response to both drugs is evident from the data in Table 3, which demonstrate the much greater decrease in ratings between 6 weeks and 6 months than between baseline and 6 weeks.

The recent CATIE study[13,15] data support these findings as well. The olanzapine dose in CATIE phase 1 ranged from 7.5–30.0 mg/day, with a mean modal dose of 20.1 mg/day and with 40% of the patients receiving 30 mg/day. Olanzapine was superior to perphenazine, quetiapine, and risperidone with regard to time to discontinuation for lack of efficacy. The 25- to 30-mg/day doses of olanzapine used in those patients were significantly higher relative to the standard dose of olanzapine than were the doses of perphenazine, quetiapine, or risperidone. In the CATIE phase 2 study[15] of patients who had discontinued for lack of efficacy, olanzapine (N = 19), quetiapine (N = 15), and risperidone (N = 17) were compared with clozapine (N = 49). Note that the sample size in the olanzapine group was comparable to our study. The mean ± SD modal dose of olanzapine in CATIE phase 2 was 23.4 ± 7.9 mg/day, with 59% receiving 30 mg/day. Clozapine did not differentiate from olanzapine in this group for all-cause discontinuation, although it was superior to quetiapine and risperidone. However, clozapine was superior to olanzapine in terms of treatment discontinuation due to lack of efficacy. Higher doses of olanzapine may have shown even better response in the treatment-resistant patients.[15] However, noting the trend in the current study toward greater improvement in the PANSS positive, SAPS global, and SANS anhedonia scales, as well as the significantly greater improvement in GAF score favoring clozapine, it is possible that a larger study might find superiority of clozapine over olanzapine

in treatment-resistant schizophrenia in at least some outcome measures.

The fairly high (28.6%) dropout rate at the beginning of our study in the clozapine-treated group compared to the olanzapine group (10.5%) may have been due to the slower rate at which the dose of clozapine was titrated compared to olanzapine. We did use a slower titration rate for olanzapine than would have been required to minimize this difference. The dropout rate for clozapine was less than that reported in the phase 2 CATIE study[15] for clozapine (56%), although the dropouts occurred over multiple months. It can be estimated from Figure 2 of the CATIE study that the rate was 20% at 6 weeks,[15] which is not significantly different from that reported here.

The comparison of clozapine and olanzapine in our study was based on the assumption that 100 mg of clozapine is the equivalent of 5 mg of olanzapine in non–treatment-resistant schizophrenia. In our study of treatment-resistant schizophrenic patients, the median number of clozapine capsules at week 6 was 4, while for olanzapine it was 6. At 6 months, these numbers were 7 and 8, respectively. The results would suggest that olanzapine 5 mg was slightly less effective than clozapine 100 mg in treatment-resistant patients with schizophrenia. Nevertheless, the olanzapine-treated patients were not undertreated because they received more capsules with drug than did the clozapine-treated patients, and only a few patients in each group received 9 capsules of active drug. Thus, the design of the study did not bias toward olanzapine or clozapine. The results suggest that 6 mg of olanzapine may provide equivalent therapeutic benefit to 100 mg of clozapine in treatment-resistant schizophrenia. This possibility will need to be studied in a larger, fixed-dose trial.

Ours is the first study to compare cognitive performance during treatment with high-dose olanzapine or clozapine in treatment-resistant schizophrenic patients. Olanzapine produced statistically significant but modest improvement in executive function (WISC-R Mazes) ($p = .002$) and delayed recall memory (VLL-DR) ($p = .04$). Bilder et al.[64] also reported beneficial neurocognitive performance effects for olanzapine (mean dose, 20.2 mg/day) relative to haloperidol and clozapine in a cohort of patients who met stringent criteria for treatment-resistant schizophrenia in a 14-week double-blind study.[64] It would appear from our data that there is no marked advantage to either drug with regard to cognition, but the small sample size makes further study essential. The major metabolite of clozapine, *N*-desmethylclozapine, may have specific advantages for cognition, which could be evident in a larger study.[65]

The present study also afforded the opportunity to examine the adverse-effect burden associated with use of greater than usual doses of olanzapine and standard doses of clozapine. The lack of dropouts on high-dose olanzapine due to tolerability is consistent with 2 previous studies.[25,38] This result may reflect a relationship between weight gain and greater improvement in psychopathology, which has been reported frequently with clozapine and to some extent olanzapine.[66] There were only small changes in extrapyramidal symptoms with either treatment (Table 5). Perhaps because of the small sample size, none of the fluctuations reached statistical significance. We noted a trend toward fewer tardive dyskinesia and parkinsonian symptoms in the olanzapine-treated compared with clozapine-treated patients at 6 weeks. There were no significant differences between the groups with respect to extrapyramidal adverse effects at the end of 6 months. The results reported here are consistent with those of Kelly et al.[38]

Increases in weight and BMI were documented for both treatment groups in the present study; however, both were significantly ($p \leq .01$) higher in the olanzapine group at the 6-month assessment relative to the clozapine group. The nearly 16-lb weight gain experienced by olanzapine patients in our study over 6 months, although significantly greater than the 3.5-lb weight gain in the clozapine-treated patients, was not outside the range of mean increases of 10–25 lb reported by others during long-term standard-dose olanzapine treatment. Both olanzapine and clozapine are known to cause the greatest weight gain among the atypical antipsychotic drugs. This effect, along with the increase in lipids and other measures of insulin resistance, is very likely to be associated with increased risk of cardiovascular disease and stroke.[67,68]

Our study, unlike many others with a similar purpose, did not include patients who were neuroleptic-intolerant or non–treatment-resistant, and it is the longest blinded trial of olanzapine versus clozapine in treatment-resistant schizophrenia, to our knowledge, and the first to assess the relative effects of high-dose olanzapine on neurocognitive performance. This study, as well as that of Volavka et al.,[35] indicates that the advantages of high-dose olanzapine as well as clozapine are more evident with longer treatment periods, and this finding is an important advantage of this study. Upon inspection of the time-dependent outcome measures in the phase 1 CATIE study, the advantage of olanzapine, even at higher doses, was not evident until after 3 months.

The small sample size in this study is a limitation that restricts the confidence in the conclusions one can draw from it about the comparable efficacy of clozapine and olanzapine in patients with treatment-resistant schizophrenia. However, the sample size was determined by our power analysis. The results reported in this study are consistent with prior research summarized above, which also reported the effectiveness of high doses of olanzapine in treatment-resistant schizophrenia. Additional limitations of this study include lack of a placebo arm and the absence of a neuroleptic-treated group. A neuroleptic-

treated group would have controlled for possible rater bias but would have exposed patients to drugs to which they had previously shown only minimal response and would have increased the risk for tardive dyskinesia. Because of the absence of either a placebo- or neuroleptic-treated group, it is theoretically possible that the improvement noted here was not related to either olanzapine or clozapine and was a study effect, e.g., the result of rater bias or increased contact with medical staff. However, this possibility seems unlikely because these patients had received comparable levels of contact prior to study entry and because of the persistent psychotic symptoms evidenced prior to study entry. The flexible-dose schedule used here has advantages and disadvantages. Not all patients randomly assigned to either drug may have achieved sufficiently high plasma levels to produce optimal response. Future studies to replicate and extend these results should include fixed doses between 25 and 50 mg/day of olanzapine, or perhaps even higher doses. It remains to be determined whether patients who fail to respond to clozapine will respond to olanzapine, or vice versa.

The biological basis for the apparently greater response to higher doses of clozapine, melperone, or olanzapine in patients with treatment-resistant schizophrenia is unclear. First-episode patients with schizophrenia often respond to lower doses of antipsychotic drugs than patients who remain responsive to these drugs but have had multiple episodes of psychosis,[69,70] suggesting that patients with schizophrenia develop tolerance to the action of antipsychotic drugs due to disease progression or, possibly, adverse effects of the drugs themselves at the cellular level. The fact that the majority of the patients who responded to either clozapine or olanzapine did so after 6 weeks and before 6 months may provide some clue as to mechanism. It may be that some slower biological process involving restoring synaptic integrity, e.g., neuroplastic changes in dendritic density, may be required before beneficial effects of these drugs on neurotransmission are possible. It has previously been suggested that the delayed therapeutic action of antipsychotic drugs may be related to their promotion of neuroplasticity leading to modification of synaptic connections.[71] There is evidence that olanzapine has a neuroprotective effect.[72] This action may apply to clozapine as well.

In conclusion, the results of this study suggest that olanzapine and clozapine, at equivalent doses, may have similar efficacy for positive and negative symptoms, as well as cognition, in treatment-resistant patients with schizophrenia or schizoaffective disorder. Both drugs resulted in considerable weight gain; however, olanzapine treatment was associated with markedly greater weight gain. The results of this study clearly demonstrate the need for careful monitoring of metabolic adverse effects. Furthermore, it is necessary to test whether higher doses of other atypical antipsychotic drugs with similar pharmacology to clozapine and olanzapine, e.g., melperone, quetiapine, risperidone, sertindole, and ziprasidone, may also prove comparable to clozapine (and high-dose olanzapine) in treating this difficult group of patients. If clozapine is not acceptable to patients because of the risk of agranulocytosis (and the required white blood cell monitoring) or other adverse effects, a trial of high-dose olanzapine in treatment-resistant patients should be considered.

Drug names: benztropine (Cogentin and others), clozapine (Clozaril, FazaClo, and others), fluoxetine (Prozac and others), haloperidol (Haldol and others), lorazepam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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