Clinical and Neurocognitive Effects of Clozapine and Risperidone in Treatment-Refractory Schizophrenic Patients: A Prospective Study

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Background: Few controlled studies have compared the efficacy of clozapine and risperidone in treatment-refractory schizophrenic patients. The present study investigates the efficacy of both clozapine and risperidone on psychopathologic and neurocognitive measures in a prospective 12-week open-label trial in treatment-refractory schizophrenic patients from state psychiatric hospitals.

Method: Thirty-five DSM-IV schizophrenic patients with a documented history of nonresponse to typical neuroleptics were treated with either clozapine or risperidone. Response was assessed every 2 weeks by independent raters with the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impressions (CGI) scale, neurologic rating scales, and plasma drug levels. Neurocognitive tests were administered at baseline and week 12.

Results: Both clozapine and risperidone brought about significant ($p < .003$) overall improvement in psychopathology. However, clozapine was numerically superior to risperidone on PANSS total scores and PANSS positive, negative, excitement, and cognitive factors. Extrapyramidal side effects were minimal for clozapine, whereas some were present for risperidone. Patients taking risperidone improved significantly in the beginning stages of the study and remained stable thereafter. Patients taking clozapine showed a gradual improvement that occurred over the entire length of the trial. Neurocognitive measures showed minimal improvement and did not differentiate between the 2 medication groups.

Conclusion: Both clozapine and risperidone were comparably effective across a wide spectrum of psychopathologic measures. While the efficacy of clozapine was only numerically superior to that of risperidone, it was associated with fewer extrapyramidal side effects and with progressive improvement over the 12-week treatment period, suggesting that in longer trials clozapine may prove to be superior to risperidone in neuroleptic-refractory patients.

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Clozapine is the only compound available that has proven efficacy for treatment-refractory schizophrenic patients. It has shown superior efficacy in 30% of chronic schizophrenic patients who had prior poor responses to typical neuroleptics.[1] Its use, however, is limited due to the necessity for weekly blood monitoring to guard against agranulocytosis, which may occur as a side effect of clozapine treatment in about 0.8% of patients.[2]

Risperidone, another atypical antipsychotic, is increasingly being used as an alternative for patients who do not qualify for clozapine treatment or have failed treatment with traditional neuroleptics. It has shown antipsychotic efficacy for both positive and negative symptoms and a low extrapyramidal risk profile in schizophrenic patients with a history of neuroleptic response. However, few studies have examined the comparative efficacy of the 2 compounds regarding psychopathologic and neurocognitive effects in well-defined treatment-refractory schizophrenic patients. Bondolfi et al.[3] compared clozapine and risperidone during an 8-week double-blind study in 86 schizophrenic inpatients with a history of treatment failure with conventional neuroleptics. Both treatments were found to be equally effective. The mean dosage for clozapine, however, may have been too low to obtain optimal results (291.2 mg daily). Klieser et al.[4] compared the 2 medications in a 28-day randomized, double-blind, controlled trial using 2 risperidone dosages (4 mg and 8 mg daily) and a clozapine dose of 400 mg/day in a sample of 59 chronic schizophrenic patients with a history of previous response to typical neuroleptics. Tolerability was significantly better for patients taking risperidone compared with patients treated with clozapine, and risperidone was at least as effective as clozapine in improving symptoms of schizophrenia. In a more recent study, by Daniel et al.,[5] 20 treatment-refractory schizophrenic outpatients were enrolled in a randomized crossover comparison of clozapine at a mean daily dose of 375 mg and of risperidone at a mean daily dose of 6.1 mg for 6 weeks. No differences were found in clinical or neurocognitive measures for the 2 medications. The design of the study by Daniel et al. was sequential with a relatively short duration, making it difficult to evaluate the effect of passage of time.

No study has compared the neurocognitive effects of these 2 compounds in treatment-refractory patients. A small number of studies, however, describe the neurocognitive effects of clozapine on these patients. Meltzer[6] studied 25 treatment-resistant schizophrenic patients treated with clozapine and found significant improvement on different memory measures. However, minimal or no improvement was found in measures of short-term memory and executive function. Goldberg et al.,[7] in a study of 15 treatment-refractory schizophrenic patients, found no changes in cognitive functioning over an average period of 15 months of clozapine treatment. Moreover, visual memory declined with treatment. In both studies, changes in cognitive functioning were independent of changes in psychopathology. Hagger et al.[8] found significant improvement in measures of verbal fluency, attention, and memory after 6 months of clozapine treatment in 36 treatment-resistant schizophrenic patients. No changes were reported for measures of verbal learning and executive function. Buchanan et al.[9] found similar results in 19 patients treated with clozapine for 1 year. After 10 weeks, significant improvement was seen in the Category Fluency and the Weschler Adult Intelligence Scale–Revised Block Design tests. After 1 year of treatment, further improvement was found in the above-mentioned tests as well as on the Mooney Faces Closure and on the verbal fluency test. Trends of improvement were also found in the Stroop Color and Word Interference, Category Fluency, and Weschler Memory Scale–Revised Logical Memory test. Finally, Lee et al.[10] found a significant improvement in cognitive functions pertinent to verbal fluency and attention in 36 treatment-resistant schizophrenic patients after 6 months of clozapine treatment.

Additionally, few studies have examined the effects of risperidone on neurocognitive functions. In a randomized crossover study, Daniel[11] reported improvement on set-shifting and memory measures in 15 patients treated with risperidone. Stip and Lussier[12] found in a 6-month study that patients showed significant improvement in attention and alertness measures, while other areas of cognitive functions did not change. More recently, Green et al.[13] examined verbal working memory in 59 treatment-resistant schizophrenic patients as part of a double-blind comparison of risperidone and haloperidol at fixed daily dosages of 6 mg and 15 mg, respectively. Treatment with risperidone appeared to be associated with a greater positive effect on a verbal working memory measure than treatment with haloperidol. However, no study examined comparative effects of these 2 atypical antipsychotics in treatment-refractory schizophrenic patients.

Given the limited data on the comparative effects of clozapine and risperidone in well-defined treatment-refractory schizophrenic patients during an adequate length of time, we decided to study the psychopathologic efficacy and neurocognitive effects of clozapine and risperidone in treatment-refractory schizophrenic patients in a 12-week parallel, prospective, open-label trial.

METHOD

Subjects

Thirty-five patients who met DSM-IV criteria for schizophrenia were recruited from 2 state psychiatric centers after giving informed consent. Patients were selected based on the following criteria for refractoriness: (1) documented poor response to at least 2 prior neuroleptic treatments of at least 1000-mg chlorpromazine equivalents over a 6-month period each, (2) minimum baseline Brief Psychiatric Rating Scale (BPRS) score of 46, and (3) a persistent poor level of functioning over the past 2 years. Patients with a substance abuse diagnosis within the last 6 months, medical contraindications to clozapine/risperidone, or low IQ were excluded from the study. The mean age of the patients was 39.29 ± 8.78 years. The mean duration of illness since first admission was 18.20 ± 7.66 years and mean age at first hospitalization was 20.29 ± 6.07 years, indicating the chronicity and refractoriness of this sample.

Procedure

Patients' diagnoses were established based on a SCID-IV conducted by research fellows and reviewed by a senior research psychiatrist (J.-P.L.). To maintain a naturalistic and clinically meaningful design, patients who satisfied inclusion criteria were assigned to either clozapine or risperidone treatment based on their willingness to accept weekly blood drawings. We believe that this method of patient assignment to treatment groups reflected typical clinical procedures and resulted in more generalizable results. Patients' prior neuroleptic and adjunctive medications were tapered gradually over several weeks prior to study entry. Clozapine or risperidone was then initiated according to the manufacturer's recommended titration schedule and continued for 12 weeks. Dosages of clozapine and risperidone were individualized for every patient based on a "best dose" approach that aimed at maximizing response and minimizing side effects. In addition, treatment with clozapine was aimed at reaching a minimum daily dose of 400 mg and/or a minimum plasma clozapine level of 350 ng/mg at week 4; treatment with risperidone was aimed at a minimum of 3 mg b.i.d. on the third day with gradual dose escalation up to 16 mg/day if response was inadequate. No other medication was used during the trial except for anticholinergics (for extrapyramidal side effects). Patients taking clozapine received white blood cell count testing every week. Plasma levels were monitored at week 4 and week 12 for both medication groups.

Assessments included the Positive and Negative Syndrome Scale (PANSS)[14] and the Clinical Global Impressions (CGI) scale[15] and were completed at baseline and every 2 weeks, for 12 weeks, by trained raters. Interrater

Table 1. Demographics of the Cohort

	Clozapine (N = 21)		Risperidone (N = 14)		Total (N = 35)	
Variable	N	%	N	%	N	%
Male	16	76.2	10	71.4	26	74.3
Female	5	23.8	4	28.6	9	25.7
White	6	28.6	3	21.4	9	25.7
African-American	6	23.8	7	50.0	13	37.1
Hispanic	9	42.6	4	28.6	13	37.1
Schizophrenia						
Disorganized	2	9.5	0	0	2	5.7
Paranoid	6	23.8	8	57.1	14	40.0
Undifferentiated	13	61.9	6	42.9	19	54.3

Table 2. Comparison of the 2 Medication Groups*

	Clozapine (N = 21)		Risperidone (N = 14)		Total (N = 35)		
Variable	Mean	SD	Mean	SD	Mean	SD	X/F
Age, y	38.14	9.02	41.00	8.43	39.29	8.78	NS
Age at first hospitalization, y	19.90	5.07	20.86	7.49	20.29	6.07	NS
Years since first admission	17.33	7.36	19.50	8.19	18.20	7.66	NS
Current hospitalization, mo	41.76	43.01	51.64	35.42	45.71	39.89	NS
PANSS							
Baseline total	90.65	16.81	89.92	14.32	90.35	15.61	NS
Grandiosity	2.3	1.38	3.21	1.84	2.67	1.62	NS
Uncooperativeness	2.2	1.39	1.78	0.89	2.02	1.21	NS
Lack of judgment	4.95	0.99	4.21	1.52	4.64	1.27	NS
Suspiciousness/persecution	3.95	1.63	4.07	1.07	4.00	1.41	NS

*Abbreviation: PANSS = Positive and Negative Syndrome Scale.

reliability was 0.82 for the PANSS positive scale, 0.80 for the negative scale, 0.78 for the general psychopathology scale, and 0.81 for the total PANSS. In addition, neurological assessments (the Simpson-Angus Neurologic Rating Scale[16] and the Abnormal Involuntary Movement Scale [AIMS][17]) were performed at the same timepoints. Neurocognitive assessment was performed for every patient at baseline and was repeated after 12 weeks, at the end of the trial. The battery included tests assessing attention (Stroop Color and Word Test,[18] Paced Auditory Serial-Addition Test,[19] Digit-Symbol Substitution Test[20]), memory (Hopkins Verbal Learning Test,[21] Paragraph Memory Test, Pattern Memory Test[22]), and executive functions (Word List Generation,[23] Trail-Making Test[24]).

Statistical Analysis

Mean values and standard deviations of the psychopathologic measures were computed for baseline and subsequent timepoints for both treatment groups. Three methods of statistical analysis were performed on the psychopathology measures. A multivariate analysis of covariance (MANCOVA, baseline values covaried out), was performed for each variable, with the percentage of change over time as the dependent variable and medication group (clozapine vs. risperidone) as the independent variable. A repeated measures analysis of variance (ANOVA) was also performed for each variable. Medication group (clozapine vs. risperidone) was the independent variable, and time was the within-subjects variable. Finally, analysis of the effect of clozapine and risperidone on psychopathology was performed using the Hierarchical Linear Model (HLM), which has fewer restrictive assumptions than the traditional repeated measures ANOVA and handles missing cases more successfully. In this analysis, time and medication group were the independent variables, and difference scores compared with baseline were the dependent variable. A difference score (baseline minus week 12) was calculated for the neurologic measures.

Mean values and standard deviations of the neurocognitive assessment scores were computed for baseline and week 12 for both treatment groups. Analysis of the effect of clozapine and risperidone on neurocognitive performance was calculated separately for each test using repeated measures multivariate analysis of variance (MANOVA) with medication condition (clozapine vs. risperidone) as the between-subjects variable and timepoint (baseline vs. week 12) as the within-subjects variable.

RESULTS

Thirty-five patients were enrolled in this prospective open-label trial. Five patients from the clozapine group were withdrawn because of adverse events (seizure [N = 1], leukopenia [N = 2], hypertension [N = 1], tachycardia [N = 1]). Two patients were prematurely eliminated from the risperidone group because of withdrawal of consent and lack of cooperation with the research procedures. Patients with premature withdrawal were included in the analysis if they completed 6 weeks of the protocol. This excluded the 2 clozapine patients who experienced leukopenia and 1 risperidone patient who withdrew consent, leaving 19 evaluable patients for clozapine and 13 evaluable patients for risperidone (total N = 32).

Mean ± SD clozapine daily dose was 363.02 ± 90.73 mg, and mean risperidone daily dose was 8.95 ± 1.76 mg. Demographic information and clinical data for the 35 patients are shown in Tables 1 and 2. Demographic variables, including mean age, age at first admission, and duration of illness, were comparable between the 2 groups, as were gender, race, and diagnosis. Baseline psychopathology as measured by PANSS total scores and PANSS positive and negative and general psychopathology factors was not significantly different between the 2 groups. The mean PANSS positive and negative scores of this sample were in the 70th percentile rank based on Kay's[25] normative distribution of PANSS scores derived from a chronic state hos-

Table 3. Improvement in PANSS Factor Scores and CGI Scores for Clozapine and Risperidone*

	Baseline		Week 2		Week 4		Week 6		Week 8		Week 10		Week 12	
Factor	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Positive factor														
Clozapine	17.5	4.0	16.5	3.6	15.7	3.8	15.1	4.1	14.5	4.6	13.6	3.9	13.8	4.8
Risperidone	18.5	5.4	17.2	3.0	15.8	4.1	15.2	4.6	15.3	4.0	15.3	4.5	15.5	4.1
Negative factor														
Clozapine	20.6	6.8	20.3	6.2	18.3	4.7	17.5	4.2	16.8	5.3	15.3	5.3	13.8	3.6
Risperidone	20.3	6.3	17.2	4.4	18.7	5.9	18.1	5.0	18.8	6.3	15.8	5.9	16.1	6.2
Cognitive factor														
Clozapine	17.2	4.6	16.5	4.5	14.8	4.6	14.5	4.8	14.1	3.9	14.0	4.4	13.4	3.6
Risperidone	16.7	3.9	15.0	3.5	14.5	4.2	14.7	3.6	14.6	3.7	14.5	2.7	13.4	3.8
Excitement factor														
Clozapine	9.0	4.5	8.5	5.0	7.0	2.7	6.7	3.2	6.2	2.6	6.2	3.0	6.2	3.1
Risperidone	7.5	2.6	6.2	2.8	6.8	3.2	7.0	3.9	6.6	3.8	5.5	2.2	6.8	3.4
Anxiety-Depression factor														
Clozapine	8.2	3.4	7.2	3.1	6.7	2.6	7.1	2.9	6.5	2.5	7.1	2.7	6.3	1.9
Risperidone	7.4	3.0	6.8	2.8	5.3	2.2	7.3	3.5	6.4	3.1	6.0	2.6	5.5	1.9
CGI Global Severity														
Clozapine	4.8	0.7	4.6	0.7	4.4	0.9	4.2	0.7	4.2	0.9	4.1	0.8	3.9	0.7
Risperidone	4.7	0.7	4.4	0.7	4.2	0.8	4.4	0.6	4.3	0.8	3.9	0.5	3.9	0.7
CGI Global Improvement														
Clozapine	3.8	0.4	3.7	0.4	3.5	0.6	3.3	0.8	3.0	1.0	2.8	0.8	2.6	1.1
Risperidone	3.6	0.6	3.6	0.6	3.5	1.2	3.5	0.8	3.3	0.8	3.0	0.7	3.3	0.9

*Abbreviation: CGI = Clinical Global Impressions scale.

pital population, making findings from this sample very generalizable.

Psychopathology

In terms of treatment effects, both groups of patients significantly improved on PANSS positive, negative and general psychopathology scores over this 12-week trial in a comparable fashion. There was no significant difference between the 2 treatments on these outcome measures. The PANSS positive syndrome score significantly improved in both groups ($p < .003$). However, there was a numerical superiority of clozapine effect over risperidone effect. For the clozapine group, the positive syndrome scores showed a decrease in mean scores from 22.8 to 16.7, representing a 35.1% improvement, while the risperidone group showed a decrease in PANSS positive syndrome score from 24.0 to 19.8, reflecting only a 17.9% drop. The negative syndrome score improved significantly ($p < .003$) in both groups, without a significant medication group effect. Clozapine improvement was again numerically superior: the mean negative syndrome score for clozapine dropped from 25.5 to 18.6, while the risperidone group showed a decrease from 25.3 to 20.9, representing a 15.1% improvement compared with 30.5% for clozapine. The PANSS general psychopathology scores also showed a significant reduction over time ($p < .0003$), although there was no difference in effect between the 2 groups. The general psychopathology score decreased from 43.4 to 32.1 for clozapine and from 40.5 to 31.5 for risperidone, an improvement of 33.5% and 24.3%, respectively.

An alternative analysis of the PANSS has been proposed that uses 5 factors derived from confirmatory factor analysis.[26] This analysis allows an examination of treatment effects beyond the areas of positive and negative symptoms. The 5-factor model uses a positive, negative, excitement, cognitive, and anxious-depressive component and was used in a secondary analysis. Factor scores were obtained by summation of the corresponding PANSS items. Significant ($p < .003$) overall effects were observed in all 5 PANSS factors without a significant group effect. However, a general trend for numerical superiority for clozapine over risperidone was observed in all 5 PANSS factors at most timepoints during the study (Table 3). The improvement by the 2 medication conditions affected the 5 psychopathologic domains somewhat differently. While the largest improvement was seen for both clozapine and risperidone in the positive, negative, and cognitive components, clozapine affected the excitement component in this sample much more than risperidone, but the difference did not reach statistical significance. The statistical effect size, calculated as the standardized difference of total PANSS improvement (%) between the clozapine and risperidone groups, was 0.60. The calculated effect size for the PANSS negative syndrome was slightly higher at 0.69. This represents a moderate-to-large effect size.

We examined the relationship of improvement in positive symptoms with improvement in negative symptoms to shed some light on whether the observed improvement seen in negative symptoms was mainly due to improvement secondary to changes in positive symptoms. There was no relationship of positive with negative symptom improvement for risperidone ($r = .29$; NS), while clozapine showed a negative correlation ($r = –.15$; NS) pointing to the relative independence of improvement in these 2 domains.

A similar significant overall improvement was seen in the CGI score ($p < .011$), but without significant medica-

Table 4. PANSS Change Over Time

Effect on Estimates of Change	Week 2 Effect	p	Overall Effect	p
Total PANSS				
Clozapine	1.2	NS	2.0	.0001
Risperidone	10.0	.0001	0.02	NS
Positive syndrome				
Clozapine	1.0	NS	0.5	.005
Risperidone	4.3	.0001	0.01	NS
Negative syndrome				
Clozapine	–1.0	NS	0.6	.0001
Risperidone	2.5	.002	–0.005	NS
General psychopathology				
Clozapine	1.2	NS	0.8	.0005
Risperidone	3.3	.02	0.2	NS

tion group differences. However, the improvement for clozapine was again numerically superior to the risperidone group, with the score going from 3.8 at baseline to 2.6 at endpoint, while the scores for the risperidone group went from 3.6 to 3.3.

A significant difference was found in the timing of improvement between the 2 treatment groups. While the improvement for clozapine was seen as gradually occurring over the full 12 weeks of the trial, improvement for risperidone was observed to occur by the end of the second week of the trial after which there was no significant further improvement. This significant difference in timing of improvement was seen for total PANSS, positive and negative symptoms, and general psychopathology (Table 4).

Neurologic Effects

Patients taking clozapine showed a significant decrease in their extrapyramidal symptoms as measured by the Simpson-Angus Neurologic Rating Scale, while patients taking risperidone showed much less decrease in their total Simpson-Angus Neurologic Rating Scale score ($F = 6.68$; $p < .01$). The Simpson-Angus Neurologic Rating Scale score for clozapine went from 1.3 to 0.0, while the score for the risperidone group went from 0.6 to 0.2. These differences remained significant after partialling out the baseline values. Tardive dyskinetic symptoms as measured by the AIMS, on the other hand, were observed as unchanged over the duration of the trial for both groups.

Effects on Plasma Clozapine Levels

Patients taking clozapine showed a mean plasma level within the therapeutic range.[27] Levels ranged between 41 ng/mL and 588 ng/mL with a mean of 347.64 ng/mL in week 4 and between 128 ng/mL and 940 ng/mL with a mean of 457.92 ng/mL in week 12. The patient with the lowest plasma level (41 ng/mL) was a clozapine responder who was kept on a low dose schedule throughout the trial because of tachycardia that finally resulted in his early termination from the study in week 10. The patient who developed seizures had a plasma level of 487 ng/mL in week 4. At week 4, clozapine nonresponders showed a mean ± SD plasma level of 383.36 ± 141.57 ng/mL, which was comparable to the mean plasma level of responders at 328.36 ± 163.5 ng/mL. Response to clozapine was determined based on at least a 30% decrease from baseline ratings on the total PANSS score.

Neurocognitive Effects

Means and standard deviations for the neurocognitive test at both timepoints are presented in Table 5. While performance on most tests improved slightly, changes over time were rather modest for both groups. The only statistically significant change, in terms of time, was found in the Hopkins Verbal Learning Test (recall) ($p < .038$). Patients in the clozapine group showed an increase in performance, while patients in the risperidone group performed worse at week 12 compared with baseline. A trend for significance was also found in the Trail-Making Test ($p < .067$). Patients taking clozapine showed a nonsignificant decrease in performance, over time, in tests that involved executive functions (Trail-Making Test, Word List Generation) and attention (Stroop Color and Word Test, Paced Auditory Serial-Addition Test). Patients in the risperidone group showed a nonsignificant decrease in tests measuring attention (Stroop Color and Word Test, Paced Auditory Serial-Addition Test). Both groups performed at a comparable level in most of the neurocognitive tests, both at baseline and week 12.

DISCUSSION

This prospective 12-week trial comparing clozapine with risperidone in carefully defined treatment-refractory state hospital schizophrenic patients showed significant improvement on PANSS total scores and PANSS positive, negative, and general psychopathology factors for both compounds. The improvement was seen equally across the 5 schizophrenic psychopathologic domains of positive, negative, cognitive, excitement, and anxiety/depression symptoms.

Although clozapine showed superior numerical efficacy on all outcome measures, compared with risperidone, these differences did not reach statistical significance. The observation that 2 subjects in the risperidone group but none in the clozapine group prematurely withdrew from the study because of lack of response further points to the possible superiority of clozapine in this group of patients. It is possible that our results did not reach significance because of insufficient statistical power. A post hoc power analysis was performed using the standard deviations of the mean changes of the total PANSS score for the pooled clozapine/risperidone groups; results indicated that 45 patients per group were required in order to yield a power of 80% to detect significant differences between the 2 treatments. Another possibility was that the trial was not long enough

Table 5. Neurocognitive Results*

	Clozapine				Risperidone				Medication by Time	
	Baseline		Week 12		Baseline		Week 12			
Test	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	p
Trail-Making Test	300.5	223.4	373.4	262.3	262.7	208.1	226.7	163.7	3.79	.067
Stroop Test	53.5	22.8	55.2	29.6	50.5	25.3	43.9	20.4	0.46	.507
Symbol Digit Test	23.9	10.7	21.3	7.8	18.2	5.7	26.5	11.3	0.01	.941
Paced Auditory Serial-Addition Test	4.7	1.08	4.2	1.6	4.6	1.3	3.5	1.4	0.040	.537
Hopkins Verbal Learning Test										
Recall	12.6	4.5	11.0	4.5	11.1	6.5	14.9	5.3	5.00	.038[a]
Recognition	5.5	3.8	6.5	3.1	6.3	3.1	6.6	4.2	0.12	.735
Word List Generation	9.8	6.9	10.0	5.7	14.3	4.4	15.3	5.0	0.15	.707
Paragraph Memory Test										
Verbatim	4.0	2.5	5.5	2.4	7.6	4.9	8.8	4.8	0.02	.889
Paraphrase	0.5	0.5	1.1	1.0	0.3	0.3	1.2	0.9	1.42	.249
Pattern Memory Test										
Trial 1 recall	1.7	1.9	4.8	4.4	3.5	4.8	5.1	3.2	0.65	.597
Trial 2 recall	2.4	2.5	3.9	5.8	3.1	4.3	5.5	4.0	0.65	.597
Trial 3 recall	2.3	2.3	4.8	6.1	4.7	4.0	6.0	4.6	0.65	.597
Recognition	3.6	3.6	4.3	5.7	4.2	4.0	6.7	3.4	1.04	.320

*Neuropsychological test variables: Stroop Test (total number of items correctly completed); Trail-Making Test (total number of seconds B-A); Hopkins Verbal Learning Test (recognition: true positives minus related + unrelated errors, recall: total number of correct responses); Paced Auditory Serial-Addition Test (total number of incorrect responses); Symbol Digit Test (total number of correct responses); Word List Generation Test (total number of words); Paragraph Memory Test (verbatim score, paraphrase score); Pattern Memory Recognition Tests (number of correct responses minus number of incorrect responses).
[a]Statistical significance.

to show significant differences between the 2 treatments, as has been argued by Meltzer.[6] These authors have reported that the effects of clozapine can be seen up to 12 months after initiation of therapy.

Given that the assignment to the 2 medication groups was based on patients' willingness to accept weekly blood drawings, one could argue that the 2 patient groups were not comparable in severity of illness and in levels of cooperation. If this would have been the case, risperidone patients should have been sicker overall and less cooperative. We found, however, that both groups were comparable on all major demographic and clinical variables. Clozapine patients even had total PANSS and CGI scores that were slightly higher than those for risperidone patients. We further examined differences in specific PANSS items that could have been indicative of differences in cooperation in the 2 samples. Specifically, risperidone patients were not more paranoid, had no less insight into their illness, nor were they less cooperative with staff at baseline than clozapine patients.

These results are somewhat comparable to those of the Bondolfi et al.[3] study, which also found no significant difference between the 2 treatments. However, the present study was conducted over 12 weeks in contrast to their 8-week study and employed higher clozapine dosages and plasma levels. These differences may account for our finding of the trend for superiority of clozapine over risperidone. Klieser et al.[4] also found no different effects between clozapine and risperidone in a 6-week double-blind study. However, that study was conducted in acute schizophrenics with a history of prior neuroleptic response.

Similar to the Bondolfi et al.[3] study, we also found that the risperidone effect occurred early in the trial, while the clozapine effect was progressive and spread over the entire length of the trial. This seems to indicate that the effect of risperidone reaches an early plateau with little further improvement. It also supports the finding by Meltzer[6] of a slow and progressive effect for clozapine that may well extend beyond 12 weeks. It suggests that a trial with clozapine should last a minimum of 12 weeks and possibly longer, while a trial with risperidone may not need to exceed 6 to 8 weeks.

The improvement on negative symptoms showed little overlap with improvement on positive symptoms, supporting the interpretation that this improvement was predominantly seen in primary negative symptoms. Both treatments appeared to have an action on a broad spectrum of symptoms.

In terms of side effects, clozapine patients clearly were more affected than risperidone patients given the observation of 5 premature clozapine withdrawals because of medical reasons. These adverse events were not atypical for clozapine treatment and have been reported elsewhere.[28] It is possible that in a nonresearch clinical setting the symptoms for 3 of the 5 patients could have been addressed by using adjunctive medications, which were excluded in the present study.

In contrast, extrapyramidal symptoms improved markedly and significantly in the clozapine-treated group, but not in the risperidone group, confirming clozapine's protective function on neurologic side effects. It is possible that patients taking risperidone may not have responded as well

in this area because of the higher risperidone dosage used in this group, although no additional anticholinergic medication needed to be used. Neither medication ameliorated nor worsened preexisting tardive dyskinetic movements.

In terms of the relationship between plasma clozapine levels and clinical response, conclusions are limited due to the nonfixed dose design of our study and to our requirement that all clozapine patients reach a plasma level of at least 400 ng/mL. As expected, clozapine responders and nonresponders did not have different plasma levels. However, 1 responder reached a plasma level of only 41 ng/mL, pointing to the possibility that some patients may respond with levels below the range of 350 ng/mL to 450 ng/mL, which has been generally indicated as being a threshold level for clinical response.[27]

The results on the effects on neurocognitive functions were overall rather modest and comparable to previously reported findings on the effect of these atypical neuroleptics in cognition. Little improvement occurred in most cognitive measures after 12 weeks of treatment with either clozapine or risperidone despite clinical improvement. In addition, there was a nonsignificant decrement in tests measuring attention for both groups, while patients taking clozapine also showed a decrease in executive function tests. These findings are in contrast to the improvement found by Meltzer[6] in memory measures after 6 weeks of clozapine treatment and by Hagger et al.,[8] Buchanan et al.,[9] and Lee et al.,[10] who reported improvements in attention, memory, and verbal fluency, respectively, after 10 weeks and 6 months of clozapine treatment. In addition, Stip and Lussier[12] found improvements in attention after 6 months of treatment with risperidone. One explanation for the discrepancy between the findings of the above mentioned studies and our findings can be attributed to the relatively short duration of the present trial. The existing literature indicates a correlation between cognitive improvement and length of clozapine or risperidone treatment.

In conclusion, this open-label trial comparing clozapine with risperidone in well-defined treatment-refractory schizophrenic patients showed an overall significant improvement for both medication conditions, with, however, a clear numerical advantage for clozapine in all 5 domains of schizophrenia psychopathology. Although clozapine treatment was associated with more adverse events than risperidone treatment, it significantly showed an ameliorative effect on extrapyramidal symptoms. Changes in neurocognitive performance were modest overall for both medication groups and did not parallel the psychopathologic improvement. Given the possibility of only small differences between the effects of the 2 treatments, future studies need to include large samples and a longer period of observation.

Drug names: clozapine (Clozaril), haloperidol (Haldol and others), risperidone (Risperdal).

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