A Double-Blind Study of Combination of Clozapine With Risperidone in Patients With Schizophrenia: Effects on Cognition

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Background: Atypical antipsychotic drugs produce improvement in some domains of cognition as well as psychopathology in patients with schizophrenia. However, the effect of combinations of atypical antipsychotic drugs on cognitive function is unknown. The aim of this study was to compare the effect of risperidone or placebo on cognitive function in patients with schizophrenia who were previously treated with clozapine monotherapy.

Method: This prospective, randomized, double-blind, placebo-controlled, 6-week study included 30 patients with DSM-IV schizophrenia. Patients whose psychopathology was no more than partially responsive to clozapine treatment were randomly assigned to receive adjunctive treatment with risperidone (N = 16) up to 6 mg/day or placebo (N = 14). Cognitive test scores for verbal learning and memory, verbal fluency, attention, executive function, verbal working memory, and motor function were the primary outcome measures. Secondary outcome measures included assessment of psychopathology, extrapyramidal side effects, and global functioning. Data were collected between November 2001 and July 2003.

Results: Significant improvement was found in both treatment groups in a variety of cognitive measures, but there was significantly greater improvement in the placebo-augmented group on measures of initial learning acquisition and attention. The improvement in cognition was not correlated with improvement in psychopathology. There were significant correlations between improvement in verbal working memory, verbal learning and memory, and attention and quality of life and global functioning in the placebo-augmented but not the risperidone-augmented group.

Conclusion: Adjunctive treatment with risperidone for 6 weeks in patients with schizophrenia who had received chronic treatment with clozapine does not significantly improve cognitive function.

(J Clin Psychiatry 2006;67:1912–1919)

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†Dr. Göğüş passed away before the writing of this paper was completed. We acknowledge his contributions to this work and to the field of psychiatry in Turkey with respect.

Supported by grants from the Stanley Medical Research Institute (Drs. Akdede and Anıl Yağcıoğlu), Janssen Pharmaceutical, the Ritter Foundation, and the William Warren Medical Research Foundation (Dr. Meltzer).

Presented at the 39th National Psychiatry Congress of Turkey, October 14–19, 2003, Antalya, Turkey.

Dr. Meltzer has received research grants or served as a consultant and lecturer for Acadia, AstraZeneca, Janssen, Novartis, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Pfizer, Sanofi, Merck, and Solvay; has received honoraria from Janssen and Pfizer; and is a stock shareholder in Acadia. The other authors report no additional financial or other relationship relevant to the subject of this article.

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Cognitive deficits of moderate-to-severe extent are present in up to 85% of patients with schizophrenia even at the earliest stages of the psychotic phase of illness.[1] Patients with schizophrenia perform 1 to 2 standard deviations below normal on a variety of cognitive measures, particularly those assessing executive function, attention, perceptual/motor processing, vigilance, verbal learning and memory, verbal and spatial working memory, and verbal fluency.[1–5] These deficits are already present in patients with first-episode schizophrenia[6,7] and may almost reach their full extent during the prodromal period.[8] Cognitive deficits have been shown to predict social and occupational functioning and capacity for independent living in a community setting.[9–12]

For these reasons, methods to improve cognition in schizophrenia, through pharmacologic intervention, cognitive remediation, or some combination thereof, are of

great interest. Typical antipsychotic drugs have not been found to improve cognition.[13] A recent meta-analysis investigating neuropsychological effects of treatment of patients with schizophrenia with clozapine, olanzapine, quetiapine, or risperidone in comparison with typical antipsychotic drugs revealed that the atypical antipsychotic drugs were superior to the typical antipsychotic drugs for improving some domains of cognition as well as overall cognitive functioning.[5] Each of the atypical antipsychotics that are dopamine D_2 receptor antagonists (or partial agonists) and serotonin 5-HT_{2A} antagonists,[14] including aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone, have been reported to improve some, but not all, domains of cognitive function, including processing speed, attention, executive function, verbal learning and memory, working memory, and motor skill.[15–21] There is some evidence that some atypical antipsychotic drugs are superior to others for improving specific domains of cognition.[5] Clozapine was found to be particularly effective in improving verbal fluency, processing speed, and motor skill.[22–27] On the other hand, the most robust cognitive improvement with risperidone has been reported for tests of verbal learning and delayed recall.[17,28–30] To date, there has been only 1 random assignment, double-blind study[26] that has included both clozapine and risperidone arms, and although no overall difference in cognitive function between the 2 treatments was identified, test specific analysis indicated that the greatest improvement with clozapine was on the digit symbol test (a measure of processing speed), whereas the strongest improvements with risperidone were on tests of learning and delayed recall.

Augmentation of atypical antipsychotic drugs with other psychotropic drugs, including a second or third atypical antipsychotic drug, a typical antipsychotic drug, mood stabilizers, antidepressants, anxiolytics, stimulants, and even nonpsychotropic drugs, e.g., cyclooxygenase 2 (COX-2) inhibitors, to improve psychopathology has been frequently attempted, with highly variable success.[31] Most adequately powered studies have failed to demonstrate reliable benefit. We have examined the effect of the addition of risperidone or placebo to clozapine in a double-blind randomized trial in partial responders to clozapine, with a primary goal of determining the effect of adjunctive risperidone on positive symptoms. As reported elsewhere, there was greater improvement in positive symptoms in the placebo-augmented patients than in those who received adjunctive risperidone.[32] Honer et al.[33] reported nonsignificantly different improvement with placebo and risperidone in a similar study, whereas Josiassen et al.[34] found some advantages with risperidone treatment. There have been efforts to augment the beneficial effects of atypical antipsychotic drugs on cognition based on hypotheses concerning the mechanism(s) by which atypicals improve cognition and the biological basis for the cognitive deficit, e.g., with 5-HT_{1A} partial agonists to enhance the efflux of cortical and hippocampal dopamine,[35] glycine site agonists to enhance *N*-methyl-D-aspartate receptor-based glutamatergic function,[36] and muscarinic agonists or cholinesterase inhibitors to utilize a cholinomimetic strategy to reverse dopaminergic or glutamatergic deficits.[37,38] Honer et al.[33] reported a small decline in verbal working memory with the addition of risperidone to clozapine in an article published after completion of the present study. There has been, to our knowledge, no study of the effect of a combination of atypical antipsychotic drugs on cognitive functioning in patients with schizophrenia. We hypothesized that the addition of risperidone to clozapine would produce a smaller positive change in cognition compared to placebo in patients with schizophrenia, based on the possibility that risperidone might interfere with the ability of clozapine to increase the efflux of cortical and hippocampal dopamine due to excessive dopamine D_2 receptor blockade.[14]

METHOD

The present study was conducted as part of a study investigating the efficacy and safety of adjunctive treatment with risperidone in schizophrenic patients partially responsive to clozapine. The trial was a prospective and randomized, double-blind, placebo-controlled study of 6 weeks' duration in 30 patients with DSM-IV schizophrenia. The study was conducted between November 2001 and July 2003 at the Departments of Psychiatry at Dokuz Eylül University School of Medicine in İzmir and Hacettepe University Faculty of Medicine in Ankara, Turkey. Approval was gained from the local ethics committees of these 2 sites. After complete description of the study, written informed consent was obtained from all patients.

Subjects

The trial included inpatients and outpatients with schizophrenia as defined in DSM-IV, 18 to 55 years of age, who were partially responsive to clozapine. All patients had to have received clozapine treatment (300–900 mg/day) for at least 6 months prior to the study. In all cases, the dose of clozapine had not been changed for at least 1 month prior to screening and was considered optimal on clinical grounds. A total Positive and Negative Syndrome Scale (PANSS) score of at least 72,[39,40] a score of at least 4 on the Clinical Global Impressions-Severity of Illness scale (CGI-S),[41] and a score of at least 3 on any 1 of the PANSS positive subscale items (0–7 scale) were required to determine partial response to clozapine. Only patients whose level of positive symptoms was stable by clinical criteria as documented in the medical chart for at least 3 months prior to study entry were included.

Patients who were receiving concomitant medications, including mood stabilizers, antidepressants, and/or antipsychotic medication other than clozapine, or who had a

Table 1. Demographic and Clinical Characteristics of Patients at Baseline

Characteristic	Risperidone (N = 16)	Placebo (N = 14)	Comparison of Groups, Wilcoxon Rank Sum Test
Age, mean ± SD, y	35.3 ± 10.8	31.2 ± 6.9	NS
Male/female, N	9/7	11/3	NS
Education, middle school/high school/university or more, N	1/11/4	2/11/1	NS
Inpatient/outpatient, N	5/11	1/13	NS
Age at onset, mean ± SD, y	20.9 ± 4.5	21.2 ± 3.7	NS
Duration of illness, mean ± SD, y	14.4 ± 9.1	9.8 ± 5.9	NS
No. of hospitalizations, mean ± SD	3.6 ± 2.5	1.5 ± 1.7	Z = –2.49, p = .01
Duration of clozapine treatment, mean ± SD, mo	26.7 ± 28.7	37.9 ± 29.7	NS
Dose of clozapine, mean ± SD, mg/d	515.6 ± 138.7	414.3 ± 96.9	Z = –2.04, p = .05

Abbreviation: NS = nonsignificant.

history of intolerance to risperidone, were excluded. Patients who had alcohol or substance dependence were also excluded. Further details of the patient population and inclusion/exclusion criteria are provided elsewhere.[32]

Demographic and clinical features of the patients at baseline are presented in Table 1. The 2 groups showed no significant differences in age, gender, education, age at onset of the disorder, duration of illness, or duration of clozapine treatment. The only significant differences between the 2 treatment groups were the clozapine dose and the number of hospitalizations. The clozapine dose was significantly higher in the risperidone-added group. The number of hospitalizations was also significantly higher in the risperidone-augmented group.

Drug Administration

Patients continued to receive the same dose of clozapine throughout the study period. Risperidone or placebo was added to clozapine after randomization. All subjects received 1 identical pill containing either risperidone (2 mg) or placebo during the first week. The dose was increased to 2 pills (risperidone 4 mg or placebo) during the second week and to 3 pills (risperidone 6 mg or placebo) during the third week. The dose could be adjusted downward after the third week based on tolerability or efficacy or both. Biperiden was added to treat extrapyramidal symptoms if needed (2–6 mg/day). Only 1 patient received biperiden. Benzodiazepines were used to treat anxiety (clonazepam, 0.5–2.0 mg/day).

Cognitive Assessment

Patients were examined with a cognitive assessment battery consisting of tests with proven reliability and validity in Turkey and administered by trained testers with established previous experience. Cognitive assessments were performed at baseline and after 6 weeks of double-blind treatment. The testers who performed the cognitive assessments were not the same as the psychopathology raters. All of the neuropsychological tests were administered by a rater who was blind to the study drug.

Efficacy variables included change from baseline in scores of cognitive tests of verbal learning and memory, verbal fluency, attention, executive function, working memory, and motor function. All of the tests in this battery have multiple dependent measures. To reduce the number of possible dependent variables and to focus the data analysis, a limited subset of the variables was selected a priori.

Rey Auditory Verbal Learning Test. Verbal memory and learning was measured using the Rey Auditory Verbal Learning Test (RAVLT).[42,43] A 15-item list of words was presented to the patient in each of 5 separate learning trials. Next, a distractor list (list B) was read to the patients, followed by short-delay free recall. A delayed free recall test was performed after a 20-minute period, followed by a choice recognition procedure. The score of each trial is the number of words correctly recalled. In this study, performance on learning trial 1, total learning over 5 trials, total score at long-delayed recall, and recognition discriminability between false and true words were selected. As alternative forms of the test are not available for the Turkish population, the same form of the test was used throughout the study.

Controlled Word Association Test. Verbal fluency was examined with the Controlled Word Association Test. The purpose of the test is to evaluate the spontaneous production of words beginning with a given letter within a limited time period. F, A, and S are the most commonly used letters for this test[42]; however, the letters K, A, and S were used in the Turkish reliability and validity study.[44] The score is the sum of all admissible words for the 3 letters.

Digit Span Test. Attention was evaluated via the Digit Span Test, as described in the Wechsler Battery.[45] This test is commonly used as a measure of immediate verbal recall.[42] The test has 2 sections, "Digits Forward" and "Digits Backward"; in the "forward" section, the patient repeats the numbers told to him or her by the rater, and in the "backward" section, the patient repeats the numbers told to him or her backwards. The score is the sum of the correctly recalled numbers in the forwards and backwards sections and the total of both sections.

Stroop Color Word Interference Test. The Stroop Test measures the ease with which a person can shift his or her perceptual set to conform to changing demands and suppress a habitual response in favor of an unusual one as a function of execution.[44,46] This test is also used as a measure of divided attention and concentration effectiveness.[42] It involves a baseline color naming condition,

reading of written names of colors, and a color/word interference condition. The time required to complete the conditions was used as the measure of performance.

Auditory Consonant Trigram Test. The purpose of this test is to assess short-term memory, divided attention, and information processing.[46] It is a measure of working memory. The study for validity and reliability of the test in Turkish was conducted simultaneously with the present study.[47] The score is the sum of the correct recalled letters throughout the test.

Finger Tapping Test. The purpose of the test is to measure motor speed of the index finger of each hand.[46] The finger tapping score is computed for each hand separately and is the mean of 3 consecutive 10-second trials within a range of 5 taps.

Clinical Assessments

The rating scales for psychosis, functioning, quality of life, and motor side effects were administered simultaneously with the neuropsychological tests. Psychopathology was assessed with the PANSS and CGI-S. Efficacy on overall functioning and quality of life were assessed with the Global Assessment of Functioning (GAF)[48] and the Quality of Life Scale (QLS).[49] Parkinsonism was evaluated with the Simpson-Angus Rating Scale (SAS)[50]; akathisia, with the Barnes Akathisia Scale (BAS)[51]; and dyskinesia, with the Abnormal Involuntary Movement Scale (AIMS).[52] These results have been reported in a previous publication.[32]

Statistical Procedures

The effects of the 2 study drugs over time on variables of a continuous nature were compared using a mixed-model analysis of variance adjusting for the baseline values.[53] When a significant time and group interaction was detected, the analysis was repeated adjusting for the change in PANSS positive scores between baseline and endpoint, as the treatment group–by-time interaction effect was significant for PANSS positive scores. The mixed model was selected due to the fact that it provides greater flexibility of selecting proper covariance structure for a longitudinal model with repeated-measures data. In addition, the mixed model is commonly used for the model involving missing data. In this study, there were only 2 subjects who did not have endpoint data. Therefore, for comparison purposes, observed case analysis was also conducted eliminating the 2 subjects from the model.

Variables with categorical responses were analyzed using nonparametric tests and an extended Cochran-Mantel-Haenszel test for raw mean scores. The Fisher exact test was used when applicable. For continuous dependent variables, the independent t test or nonparametric Wilcoxon rank sum test was used for comparisons across the study patient groups.

The Spearman correlation test was used to analyze the relationship between changes in cognitive test scores and change in psychopathology test scores and functioning.

RESULTS

Subject Characteristics

Demographics and clinical characteristics of the patients are shown in Table 1. In addition to clozapine, 14 patients (47%) received placebo and 16 patients (53%) received risperidone. The mean clozapine dose in the risperidone-augmented group (515.6 ± 138.7 mg/day) was significantly higher than in the placebo group (414.3 ± 96.9 mg/day; $p = .05$). The mean dose of risperidone was 5.2 ± 1.26 mg/day, and the mean number of placebo pills was 2.69. The 2 groups did not differ in terms of age, gender, or education, but only in number of hospitalizations and clozapine dose. The risperidone group had a higher number of hospitalizations and a higher dose of clozapine prior to the study. One patient from the risperidone group withdrew consent just prior to final visit ratings, and another patient from the risperidone group refused to take the cognitive tests at the final visit. As noted above, the mixed-model analysis described in the statistical procedures takes into account the missing values. Thus, data on patients who did not complete the study period were utilized in the mixed model; all mixed-model results are based on N = 16 for risperidone and N = 14 for placebo.

Cognitive Changes With Treatment

The mixed-model analysis showed significant treatment group–by-time interaction effects for measures of only 2 cognitive tests, the RAVLT and Stroop Test (Table 2). Because of the significant interactions, the least squares mean differences for the scores of these 2 tests were examined.

Significant time and treatment group–by-time interactions were found for the first learning trial of the RAVLT, after adjusting for baseline. The least squares mean differences for the first trial of RAVLT scores were significant at the endpoint, indicating greater improvement in the placebo-augmented group compared to the risperidone-augmented group. The effect size for the first trial of RAVLT score was 0.61. Treatment group–by-time interaction was still significant when adjusted for the change in PANSS positive scores between baseline and endpoint ($F = 5.10$, $p = .03$). Significant treatment group–by-time interaction was also found for the first trial of the Stroop Test. The least squares mean differences for this score of the Stroop Test were significant at the endpoint, with greater improvement in the placebo-augmented group compared to the risperidone-augmented group. The effect size for the first trial of the Stroop Test was 0.57. The treatment group–by-time interaction was still significant after adjusting for the change in PANSS positive

Table 2. Efficacy Measures at Baseline and Endpoint and Significance Levels of Their Change During the Study Period[a]

	Least Squares Mean (SE)		Least Squares Mean		Source					
					Treatment		Time		Treatment-by-Time	
Parameter	Risperidone	Placebo	Difference (SE)	p	F	p	F	p	F	p
RAVLT										
Learning trial 1										
Baseline	4.9 (0.32)	4.8 (0.22)	0.2 (0.44)	.73	4.3	.05	13.2	.001	4.7	.04
Endpoint	5.4 (0.32)	6.0 (0.23)	–1.37 (0.46)	.007						
Learning trials 1–5										
Baseline	36.6 (1.12)	36.1 (1.20)	–0.47 (1.64)	.77	1.3	.20	16.3	.0004	0.3	.56
Endpoint	42.5 (1.20)	40.5 (1.20)	–2.00 (1.69)	.25						
Long-delay free recall										
Baseline	6.9 (0.42)	6.8 (0.45)	–0.13 (0.62)	.83	0.09	.76	10.0	.004	0.001	.10
Endpoint	8.4 (0.45)	8.3 (0.45)	–0.12 (0.64)	.85						
Recognition discriminability										
Baseline	0.86 (0.01)	0.85 (0.02)	–0.01 (0.02)	.52	0.8	.38	0.7	.40	3.7	.06
Endpoint	0.84 (0.01)	0.89 (0.02)	0.04 (0.02)	.07						
CWAT total score										
Baseline	31.1 (1.36)	31.0 (1.45)	–0.10 (1.99)	.96	2.3	.13	4.0	.05	2.6	.11
Endpoint	31.6 (1.45)	36.1 (1.45)	4.50 (2.06)	.04						
DST										
Forwards										
Baseline	6.02 (0.30)	5.8 (0.3)	–0.16 (0.43)	.70	0.2	.62	1.8	.19	1.5	.22
Endpoint	6.04 (0.30)	6.6 (0.3)	0.52 (0.46)	.30						
Backwards										
Baseline	4.7 (0.21)	4.5 (0.23)	–0.17 (0.32)	.60	2.01	.16	3.6	.07	0.4	.50
Endpoint	5.3 (0.23)	4.8 (0.23)	–0.48 (0.33)	.16						
Total										
Baseline	10.6 (0.34)	10.7 (0.37)	0.13 (0.53)	.80	1.0	.33	4.2	.05	0.7	.40
Endpoint	11.0 (0.38)	11.7 (0.37)	0.71 (0.57)	.20						
Stroop Test										
Trial 1 (colors)										
Baseline	43.1 (2.00)	45.8 (2.07)	2.8 (2.90)	.34	1.5	.23	0.3	.58	4.1	.05
Endpoint	46.6 (2.14)	39.6 (2.07)	–6.9 (3.00)	.03						
Trial 2 (words)										
Baseline	94.9 (2.81)	94.6 (3.02)	–0.28 (4.13)	.95	1.7	.20	9.5	.005	1.4	.24
Endpoint	89.3 (3.03)	81.9 (3.02)	–7.41 (4.27)	.09						
Trial 3 (interference)										
Baseline	33.2 (0.85)	33.1 (0.88)	–0.13 (1.23)	.91	0.7	.42	1.6	.21	0.4	.53
Endpoint	35.0 (0.92)	33.7 (0.88)	–1.28 (1.27)	.32						
ACTT										
Baseline	38.0 (0.85)	37.5 (0.9)	–0.33 (1.26)	.80	0.001	.98	6.8	.01	0.1	.70
Endpoint	40.0 (0.9)	40.2 (0.9)	0.37 (1.30)	.80						
FTP										
Dominant hand										
Baseline	41.7 (1.2)	42.1 (1.3)	0.36 (1.8)	.12	3.6	.07	4.5	.04	1.6	.21
Endpoint	42.9 (1.3)	46.8 (1.3)	4.57 (1.8)	.02						
Nondominant hand										
Baseline	37.1 (1.00)	36.8 (1.06)	–0.3 (1.45)	.83	3.4	.07	13.6	.001	3.4	.07
Endpoint	39.2 (1.06)	43.1 (1.06)	3.9 (1.50)	.04						

[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 analysis of variance source table reflects the overall treatment-group effect or average treatment effect over the entire study.

Abbreviations: ACTT = Auditory Consonant Trigram Test, CWAT = Controlled Word Association Test, DST = Digit Span Test, FTP = Finger Tapping Test, RAVLT = Rey Auditory Verbal Learning Test.

subscale scores ($F = 4.06$, $p = .05$). The risperidone-augmented group showed poorer performance at the end of the 6-week trial, suggesting that risperidone augmentation diminished the overall performance of cognition in the patients who received it.

Treatment group–by-time interaction was nearly significant for discrimination score of RAVLT and Finger Tapping scores for nondominant hand. The least squares mean differences for these measures were nearly significant and significant, respectively, at the endpoint. The placebo-augmented group showed greater improvement for these 2 cognitive test measures compared to the risperidone-augmented group.

As the treatment group–by-time effect was not significant for any other cognitive measures, the overall group differences as well as overall time effects were examined. The mixed-model analysis showed significant time effects for RAVLT total and long-delay free recall scores, total scores on the Controlled Word Association Test, total scores on the Digit Span Test, scores on the

second trial of the Stroop Test, total scores on the Auditory Consonant Trigram Test, and Finger Tapping Test scores for dominant hand, indicating better performance at the endpoint than at baseline in both treatment groups. The treatment group effect was not significant for any of these cognitive measures.

The results from the observed case analysis showed essentially the same results as the results from the analysis including missing cases.

Correlation Analyses

The change scores for each of the cognitive variables were correlated with the change scores for the PANSS positive subscale, PANSS negative subscale, GAF, and Quality of Life Scale. These noncognitive outcome measures were collected at the same time as we collected the cognitive measures. All correlations were performed within each treatment group separately.

Relation of cognition to psychopathology. There were statistically significant improvements for the PANSS positive and negative scores in both treatment groups. In the placebo group, improvement in Digit Span Test total scores was related to the improvement in PANSS negative scores ($r = –0.52$, $p = .05$). None of the correlations between any cognitive measures and PANSS positive or negative scores were statistically significant for the risperidone group.

Relation of cognition to extrapyramidal side effects. There were no significant time effects for the SAS, BAS, or AIMS scores, indicating no overall change in extrapyramidal side effects in both treatment groups. Therefore, improvement in cognitive measures in both treatment groups was not likely to be related to change in motor side effects.

Relation of cognition to functioning and quality of life. Regarding overall functioning and quality of life, significant time effects were found without any significant treatment group–by-time interaction, indicating improvement in both treatment groups. In the placebo group, improvement in QLS scores was associated with the improvement in RAVLT total scores ($r = 0.66$, $p = .009$), RAVLT long-delay free recall scores ($r = 0.56$, $p = .03$), and Auditory Consonant Trigram Test scores ($r = 0.55$, $p = .04$). In addition, the change in GAF scores in the placebo-augmented group was found to be related to the improvement in Digit Span Test forwards scores ($r = 0.60$, $p = .02$). Improvement in cognitive scores was not related to improvement in QLS or GAF scores in the risperidone-augmented group.

DISCUSSION

To our knowledge, the present study is the first study to investigate the cognitive effects of augmenting clozapine with another atypical antipsychotic drug on a wide range of cognitive tests. The prediction that whatever improvement in cognition would develop during treatment with clozapine or from test-retest learning would be less in the risperidone-augmented group was partially confirmed. As hypothesized, the addition of risperidone at doses up to 6 mg/day, for 6 weeks, in clinically stable patients treated with clozapine led to lesser improvement in 2 cognitive tests compared to the addition of placebo. Of interest, one of these was a test of verbal learning and memory, the RAVLT, which had previously been reported to be one of the domains of cognition for which risperidone was particularly effective.[5] The patients who received placebo augmentation showed a greater improvement in measures of initial learning acquisition and attention. The placebo-augmented patients had a tendency to show greater improvement in 1 other measure of verbal learning and memory (discrimination score) and in motor functions for the nondominant hand, as well. There was equivalent improvement in several domains of cognition in both groups of patients that might have resulted from improved performance due to repeating the cognitive testing at a relatively short interval.

As previously reported,[32] the placebo-augmented patients showed a greater improvement on the PANSS positive subscale. However, improvement on the cognitive measures in the placebo-treated patients was not related to the improvement on the PANSS positive subscale.

Most of the other cognitive measures assessing verbal learning and memory, attention, verbal fluency, verbal working memory, and motor functions improved significantly at the 6-week testing in both patient groups. Although both treatment groups showed improvement in psychopathology, correlation analyses showed no significant associations between measures of psychopathology and cognition, with the exception in the placebo-augmented group. The improvement in the Digit Span Test scores was associated with that in the PANSS negative scores. As the extrapyramidal side effects did not change significantly in either treatment group over time, the cognitive improvement was not likely to be related to extrapyramidal side effects. Therefore, improvement on most of the measures of cognition in both treatment arms raises the possibility of practice effects due to repeating the same form of the neuropsychological tests after a relatively short interval to the same subjects. While some studies report no significant interaction between treatment and practice,[54,55] other studies suggest that improvements induced by atypical antipsychotics might result from practice-related learning in some aspects of cognition.[5,56]

As predicted, the addition of risperidone to clozapine treatment had an adverse effect on some measures of cognitive function. However, the observation that the change on several cognitive measures was less in the risperidone-augmented group than in the placebo-

augmented group requires further discussion. As mentioned earlier, improvements in verbal learning, verbal memory, and verbal working memory are some of the most consistent findings in studies of cognitive change following risperidone treatment.[17,18,26,28] The present study revealed that the improvements in verbal learning and memory (initial acquisition and recognition discriminability) following adjunctive risperidone were actually less than those observed in the placebo-augmented group. Performance in verbal working memory did not differ between groups. Honer et al.[33] examined the effect of risperidone augmentation to clozapine on verbal working memory and also found a small decline on the verbal working memory index compared to the placebo-augmented group. It seems unlikely that the improvement seen in our study in the group receiving placebo augmentation was the result of the increased duration of treatment with clozapine, since the patients had received clozapine for nearly 2 years at the onset of this short-term study. If the improvement in the placebo-augmented group was due to clozapine, one would expect a significantly greater improvement in the risperidone-augmented group, who received significantly higher doses of clozapine. Rather, it is likely that the improvement noted was due to test-retest learning. If so, this suggests that the addition of risperidone actually prevented the retention or the utilization of the knowledge gained from the first testing. We cannot distinguish between these 2 possibilities with the available data. Another possibility is that the ability of risperidone itself to improve verbal learning was inhibited by concomitant treatment with clozapine.

The absence of a positive effect of augmentation of clozapine by risperidone on any domain of cognition studied suggests that the additional effects of risperidone to block D_2, 5-HT_{2A}, 5-HT_{2C}, 5-HT_7 receptors, etc., already blocked to varying extents by clozapine provided no additional benefit. The deleterious effect on verbal learning by risperidone compared to placebo might have been due to increased blockade of D_2 receptors in both striatal and extrastriatal regions compared with the low levels of blockade due to clozapine[57] and to excessive release of dopamine in cortex and hippocampus.[58] Risperidone has the highest affinity for D_2 receptors relative to 5-HT_{2A} receptors among the atypical agents[59] and produces significant increases in dopamine release in the rat cortex and hippocampus.[58,60]

The significant correlations between improvement in verbal learning, verbal memory, attention, and verbal working memory and quality of life and GAF scores in the placebo-augmented group suggest a modest positive relationship between cognition and functioning in these patients. A significant relationship between improvement in cognition and functioning after clozapine treatment has been shown in a previous study.[11] As cognition is one of the most prominent predictors of functioning in schizophrenia,[9,12] a positive association between cognition and functioning on both treatment arms might have been expected.

Regardless of the mechanism for the observed negative influence of augmentation with risperidone, the results reported here do not provide any evidence to support the value of the clozapine and risperidone combination to improve cognition in patients with schizophrenia. It seems likely that the results reported here would also apply to the addition of other antipsychotic drugs to clozapine. This study represents additional reason to avoid treatment with 2 atypical antipsychotic drugs in patients with schizophrenia. Improvement in cognition is more likely to occur with augmentation with drugs that have a different mechanism of action than the atypical antipsychotic drugs themselves.

Drug names: aripiprazole (Abilify), biperiden (Akineton), clonazepam (Klonopin and others), clozapine (FazaClo, Clozaril, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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