A Double-Blind Controlled Study of Adjunctive Treatment With Risperidone in Schizophrenic Patients Partially Responsive to Clozapine: Efficacy and Safety

A. Elif Anıl Yağcıoğlu, M.D.; Berna B. Kıvırcık Akdede, M.D.; Tolga İ. Turgut, M.D.; Mevhibe Tümüklü, M.D.; M. Kâzım Yazıcı, M.D.; Köksal Alptekin, M.D.; Aygün Ertuğrul, M.D.; Karu Jayathilake, M.S.; Ahmet Göğüş, M.D.; Zeliha Tunca, M.D.; and Herbert Y. Meltzer, M.D.

Background: Several open trials and case studies have reported beneficial effects following the addition of risperidone for partial responders to clozapine. The purpose of this study was to carry out a placebo-controlled, randomized, double-blind trial of the efficacy, safety, and tolerability of adjunctive treatment with risperidone in patients with schizophrenia partially responsive to clozapine.

Method: In this 6-week double-blind study, 30 patients with DSM-IV schizophrenia who had partial response to clozapine despite being treated for a mean of 32 months were randomly assigned to risperidone (N = 16) up to 6 mg/day or placebo (N = 14). Efficacy assessments included the Positive and Negative Syndrome Scale (PANSS), the Calgary Depression Scale, the Clinical Global Impressions-Severity of Illness scale, the Global Assessment of Functioning scale, and the Quality of Life Scale. A variety of safety and tolerability measures were also obtained. Data were collected between November 2001 and July 2003.

Results: Significant improvement was noted in both groups on a variety of measures of psychopathology, but there was significantly greater improvement in the placebo-treated patients on the primary outcome measure, the PANSS positive symptom subscale. There were no significant differences between the treatment groups regarding extrapyramidal symptoms, weight gain, vital signs, serum clozapine levels, and QTc interval. The only side effect significantly more severe in risperidone-treated compared to placebo-treated patients was sedation. The patients treated with risperidone developed significant increases in plasma prolactin levels.

Conclusion: Adjunctive risperidone treatment in schizophrenia patients partially responsive to clozapine does not significantly improve psychopathology or quality of life compared to placebo in a 6-week period.

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Corresponding author and reprints: A. Elif Anıl Yağcıoğlu, M.D., Hacettepe University Faculty of Medicine, Department of Psychiatry, Sıhhiye, Ankara 06100, Turkey (e-mail: eanil@hacettepe.edu.tr).

Treatment of patients with schizophrenia with multiple antipsychotic drugs, a common form of polypharmacy, is sometimes resorted to when 1 drug alone fails to produce the desired response or as a means to reduce or prevent the emergence of dose-dependent side effects. Data from 3 prescription surveys (excluding patients being tapered and/or cross-tapered with one of the agents) indicates that up to one fourth of patients in several U.S. outpatient clinics are taking 2 or more antipsychotics at the same time.[1] There are, however, few controlled studies that indicate enhanced efficacy, with or without significant change in tolerability, as the result of adjunctive treatments.[2,3] Increasing dopamine D_2 receptor blockade by adding a neuroleptic to clozapine or other atypical antipsychotic drugs has been offered as the main pharmacologic rationale for this strategy.[2–4] Shiloh and colleagues[5] have reported the first controlled trial and encouraging findings supporting this rationale. In their double-blind, placebo-controlled study of adjunctive treatment with sulpiride, a selective D_2 blocker, 28 people with schizophrenia, previously unresponsive to typical

antipsychotics and only partially responsive to current treatment with clozapine, received 600 mg/day of sulpiride or placebo. The patients' clinical status was evaluated before, during, and at the end of 10 weeks of sulpiride addition. Significant improvement in negative symptoms and a trend for significant improvement in positive psychotic symptoms and overall symptomatology was observed.

The use of a second antipsychotic as adjunctive treatment with clozapine has been frequently studied, in part, because clozapine is usually reserved for the least responsive patients and because the improvement it produces is often less than optimal.[2,4] Although it is recommended that initial treatment with clozapine should be as monotherapy,[4] various pharmacologic strategies have been employed to enhance the response to clozapine when response is limited, including the addition of other antipsychotic drugs. There are few reliable data on the extent of clozapine augmentation in representative clinical settings. A cross-sectional survey of patients with schizophrenia treated with clozapine in 5 mental health centers in the United States in 1999 found that only 4 (4%) of 99 patients receiving clozapine were also receiving another antipsychotic drug, compared to 37 (37%) who were receiving an antidepressant or mood stabilizer (H.Y.M. and G. McCleery, Ph.D., unpublished data, Nov. 2000). In a recent chart review of patients with schizophrenia in a psychiatric clinic in Turkey, Anil and colleagues[6] found that 7% of 86 patients receiving clozapine were also receiving another atypical antipsychotic drug, compared to 22% who were receiving other psychotropic drugs or electroconvulsive therapy.

Risperidone has been the most widely reported antipsychotic drug augmentation strategy for clozapine partial responders.[7–12] In a series of case reports involving 11 patients, improvement in psychotic symptoms with no increase in side effects was seen in all but 1 patient.[9] For example, Morera and colleagues[10] reported on 2 patients who failed to respond to adequate trials of risperidone alone or clozapine alone but did respond well to the combination. Pharmacokinetic interactions did not explain the improvement in one study of 2 patients,[7] whereas another study[8] reported that serum clozapine levels increased from 344 ng/mL to 598 ng/mL after addition of risperidone.

Three studies have reported the effect of adjunctive risperidone treatment involving patients with schizophrenia partially responsive to clozapine (Table 1). Henderson and Goff[13] conducted a 4-week open trial of augmentation of clozapine with risperidone in treatment-resistant schizophrenia (N = 10) and schizoaffective disorder (N = 2) patients who had been taking clozapine for at least a year but had persistent psychotic symptoms. They noted improvement in 10 of 12 patients (83%), as indicated by a 20% reduction in the Brief Psychiatric Rating Scale (BPRS)[14] total score, with no evidence of a pharmacokinetic interaction between the 2 drugs.

In a second open study,[15] 1 schizoaffective disorder and 12 schizophrenia patients (of whom 9 had previously been treated with risperidone monotherapy) who had partially responded to clozapine treatment (mean duration = 22 weeks; range, 4–45 weeks) received open adjunctive treatment with risperidone for a mean of 12 weeks.[15] A 20% or greater reduction in total Positive and Negative Syndrome Scale (PANSS)[16] score was found in 7 of the 13 subjects.

In both of those studies,[13,15] the dose of risperidone was 2 to 6 mg/day. However, a third study found no benefit from the combination of clozapine and risperidone compared to clozapine alone.[17] A maximum of 6 mg/day of risperidone was added to ongoing (for at least 6 months) clozapine treatment. At the end of 4 weeks, no significant improvement was seen in 11 schizophrenia patients who continued the study; no significant changes in serum clozapine levels were observed.

The conflicting results in these case reports and open trials suggest the need for controlled studies. The aim of the present study was to conduct the first placebo-controlled, double-blind, randomized study of the addition of risperidone to clozapine in partially responsive patients, with a primary focus on psychopathology. Global functioning and quality of life, safety and tolerability, and the pharmacokinetic interaction between the 2 antipsychotics were also assessed. The primary hypothesis to be tested in this study was that the addition of risperidone to clozapine would produce a greater reduction in PANSS positive subscale (POS) scores than would the addition of placebo. Secondary hypotheses were that risperidone would produce greater improvement in the PANSS total score, a worsening in extrapyramidal symptoms (EPS), and an increase in serum prolactin levels.

METHOD

The study was conducted in accordance with Good Clinical Practice procedures and the Declaration of Helsinki. The study was completed between November 2001 and July 2003 at the Departments of Psychiatry at Hacettepe University Faculty of Medicine in Ankara, and Dokuz Eylül University School of Medicine in İzmir, Turkey. Approval was gained from the local ethics committees at the 2 sites. All patients gave informed and written consent.

Inclusion and Exclusion Criteria

Patients aged 18 to 55 years who were diagnosed with schizophrenia or schizoaffective disorder by DSM-IV criteria and all available clinical data and who had been receiving clozapine treatment (300–900 mg/day) for at least 6 months prior to the study were included. All patients in

Table 1. Open Trials of Risperidone as an Adjunct to Clozapine Treatment in Schizophrenia Patients

Study	N	Baseline Severity, mean (± SD) score	Trial Duration, wk	Clozapine Dose and/or Serum Level, mean (± SD)	Risperidone Dose, mean ± SD, mg	Response,[a] N (%)
Henderson and Goff 1996[13]	12	BPRS total = 42.2 (± 5.0)	4	479.2 (± 121.5) mg/ 483.3 (± 195.6) ng/mL	3.8 ± 1.4	10 (83)
Taylor et al 2001[15]	13	PANSS total > 95	12	317 mg	3.0 ± 1.2	7 (54)
de Groot et al 2001[17]	12	PANSS total = 81.6 (± 12.9)	4	355.1 (± 97.0) µg/L	5.3 ± 1.4	0

[a]≥ 20% decrease in baseline total severity.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, PANSS = Positive and Negative Syndrome Scale.

the study, including those patients diagnosed as having residual schizophrenia in whom negative symptoms were more prominent than positive symptoms, had previously failed to respond adequately, i.e., had persistent positive symptoms, to at least 2 trials of adequate duration and dose of antipsychotic drugs other than clozapine. Overall, the mean (SD) duration of clozapine use was 31.9 (29.2) months. The patients' dose of clozapine had been unchanged for at least 1 month prior to screening.

Only patients whose level of positive symptoms was stable by clinical criteria and reported in written notes for at least 3 months prior to study entry were included. All patients were known to have had a significantly greater level of positive symptoms prior to starting treatment with clozapine but still had persistent psychotic symptoms at the time of screening. A total PANSS score of at least 72, a score of at least 4 on the Clinical Global Impressions-Severity of Illness scale (CGI-S),[18] and a score of at least 3 on any 1 of the PANSS POS items (0–7 scale) were required for entry. The inclusion criteria of a PANSS total score of at least 72 was chosen as a cutoff that reflects a moderate level of total psychopathology.

Twenty patients who were concomitantly receiving mood stabilizers, including lithium carbonate, antidepressants, and/or antipsychotic medication other than clozapine, were excluded. Five patients who had a history of intolerance to risperidone for reasons other than EPS, e.g., sedation, headache, or who had EPS that were not adequately responsive to the addition of anticholinergic medication when receiving risperidone equal to or less than 6 mg/day were also excluded. Two patients who had alcohol or substance dependence within 3 months of protocol entry were not included.

Study Design

The study design was prospective and randomized, double-blind, placebo-controlled, 6 weeks in duration, and included 30 outpatients or inpatients. A power analysis conducted prior to the study on the basis of an estimate of a 10% improvement in PANSS total score in the risperidone-treated group compared to the placebo-treated group indicated the need for 40 patients. However, enrollment was curtailed after 30 patients because of an inability to find other patients who met study criteria who were willing to participate.

At screening (1–7 days), a physical exam, weight and height measurements, biochemistry (electrolyte, blood urea nitrogen, and creatinine levels; a panel of liver enzyme levels; and creatine kinase, total bilirubin, direct and indirect bilirubin, fasting glucose, total cholesterol, total triglyceride, and amylase levels), 12-lead electrocardiogram, and complete blood cell count were obtained. A urine pregnancy test was done for female patients.

PANSS and CGI-S ratings were collected by the blinded investigators in the study (A.E.A.Y., B.B.K.A., T.İ.T., M.T.) who have extensive experience with both instruments. All efficacy ratings throughout the study for a given patient were performed by the same blinded rater. Patients completing the screening period were evaluated for eligibility for inclusion in the treatment phase. Patients meeting all of the inclusion and none of the exclusion criteria during screening (N = 30) were randomly assigned to risperidone (N = 16) or placebo (N = 14) after the baseline measures were obtained.

Randomization was planned by one of the unblinded investigators prior to the initiation of the study in a 1:1 ratio, and a pre-assigned random sequence was determined for each site. The patients arriving at each site were assigned the study medication according to this sequence in order with their enrollment. Each site had equal numbers of patients taking both study medications.

Patients continued to receive the same dose of clozapine throughout the study period, with the same daily administration schedule (b.i.d. or q.h.s.) as prior to the study. All subjects initially received 1 identical pill, containing either risperidone (2 mg) or placebo, administered after the evening meal. This was increased to 2 pills (risperidone 4 mg or placebo) after the first week and to 3 pills (risperidone 6 mg or placebo: 1 pill after breakfast, 2 after evening meal) after the second week. The dose could be adjusted downward after the third week based on tolerability or signs of diminished efficacy compared to earlier weeks. Biperiden (2–6 mg/day) was added to treat EPS if needed.

Efficacy Assessments

Psychopathology was assessed with the PANSS, the CGI-S, and the Calgary Depression Scale (CDS).[19] Efficacy on overall functioning and quality of life was assessed using the Global Assessment of Functioning

scale (GAF)[20] and the Quality of Life Scale (QLS).[21] The PANSS POS assessment was the primary efficacy measure in the study. The PANSS total score; negative (PANSS NEG) and general psychopathology (PANSS GP) subscores; CDS, CGI-S, and GAF scores; and QLS total and subscores were the secondary efficacy measures assessed.

The PANSS and the CGI-S were completed at baseline, at the end of each week of treatment (days 7, 14, 21, 28, 35, 42, and 49 and, on a few occasions, ± 2 days from these study visits), and at the end of the study period. The GAF and QLS were administered at baseline and at the end of the study. The PANSS was used to assess positive and negative symptoms and general psychopathology through a semistructured interview. The PANSS evaluation included the total score (30 items), the POS subscore (7 items), the NEG subscore (7 items), and the GP subscore (16 items). Each PANSS item was rated on a 7-point scale. The CGI-S assessed severity of illness on a 1 to 7 scale. The QLS total score and the 4 subscale scores—interpersonal relations, instrumental role, intrapsychic foundations, and common objects and activities—were assessed. Each of the 21 QLS items was assessed on a 0 to 6 scale.

Safety and Pharmacokinetic Interaction Assessments

Serum clozapine levels, clinical laboratory measures (not repeated if normal at screening), white blood cell count, serum prolactin levels, weight, and vital signs (systolic and diastolic blood pressure and pulse) were evaluated at baseline and endpoint. Weight and vital signs were recorded at each study visit.

Side effects were evaluated using the Udvalg for Kliniske Undersogelser-The Committee on Clinical Investigations (UKU) Side Effect Rating Scale.[22] The UKU was administered at baseline, at the end of each week of treatment, and at the end of the study to measure the presence and severity of an adverse event on a 0 to 3 scale.

Parkinsonism was evaluated using the Simpson-Angus Rating Scale for Extrapyramidal Side Effects (SAS),[23] akathisia with the Barnes Akathisia Scale (BAS),[24] and dyskinesia with the Abnormal Involuntary Movements Scale (AIMS).[25] All 3 scales were administered at baseline, at the end of each week of treatment, and at endpoint.

Concomitant Medication

All psychotropic medication included in the exclusion criteria was prohibited during the study. Benzodiazepines (clonazepam, 0.5–2.0 mg/day) were used to treat anxiety, and biperiden (2–6 mg/day) was used to treat EPS, if necessary.

Statistical Procedures

The effects of the 2 study drugs over time on continuous variables were examined using a mixed model with adjustment for baseline values as specified a priori. The mixed model provides greater flexibility of selecting a proper covariance structure for a longitudinal model than the last observation carried forward; the drug effect was the between-subject factor, and the time effect was the within-subject factor.

Independent t tests on nonparametric Wilcoxon rank sum test were used for comparisons. For continuous variables, the analysis for the variables with categorical responses was done using the extended Cochran-Mantel-Haenszel test for raw mean scores and the nonparametric Fischer Exact test. All analyses were conducted with Statistical Analysis System software.[26]

RESULTS

Patient Demographics and Clinical Characteristics

A total of 30 patients (20 male, 10 female), all meeting DSM-IV criteria for schizophrenia, were randomly assigned to 2 treatment groups, risperidone (N = 16) or placebo (N = 14), for 6 weeks. There were 6 inpatients and 24 outpatients. The subtypes included paranoid (N = 16, 53%), disorganized (N = 1, 3%), residual (N = 8, 27%), and undifferentiated (N = 5, 17%). Patients with few positive symptoms (but not none) were diagnosed as residual and classified as such in their charts. The total PANSS POS score range in the residual patients was 13 to 16 (mean ± SD = 14.0 ± 1.2), which was lower than that in the paranoid (19.3 ± 3.4), disorganized (19.0 ± 0.0), and undifferentiated (19.2 ± 1.1) subtypes. Safety evaluations and pharmacokinetic interaction measurements were completed for all patients. One patient from the risperidone group withdrew consent just prior to final visit ratings. 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 are utilized in the mixed model; all mixed model results (see Tables 3 and 4) are based on N = 16 for risperidone and N = 14 for placebo.

Baseline demographic variables and clinical characteristics were not significantly different between treatment groups, except that the mean number of hospitalizations and mean clozapine dose were higher in those randomly assigned to risperidone (Table 2). There were also no significant differences between the 2 treatment groups regarding family psychiatric history (schizophrenia or other), diagnosis subtypes, marital status, education, work status, hand dominance, number of previous suicide attempts, and previous risperidone usage. The risperidone-treated group had a significantly higher number of smokers compared to the placebo group ($\chi^2 = 4.7$, df = 1, p = .03).

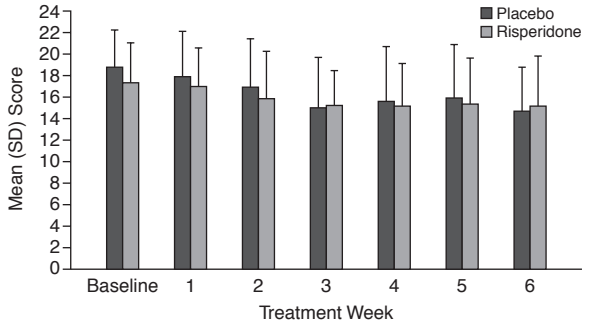
Prior treatment with risperidone occurred in 12 patients, 9 of whom discontinued due to lack of efficacy and 3 for reasons unrelated to EPS or other side effects, e.g.,

Table 2. Baseline Demographic and Clinical Characteristics of Patients Partially Responsive to Clozapine Randomly Assigned to Adjunctive Treatment With Risperidone or Placebo

Characteristic	Risperidone	Placebo	Statistical Analysis[a]
Male/Female, N	9/7	11/3	NS
Inpatient/Outpatient, N	5/11	1/13	NS
Diagnosis, N			
Disorganized	1	0	NS
Paranoid	10	6	NS
Catatonic	0	0	NS
Undifferentiated	1	4	NS
Residual	4	4	NS
Age, mean ± SD, y	35.3 ± 10.8	31.2 ± 6.9	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
Total no. of hospitalizations, mean ± SD	3.6 ± 2.5	1.5 ± 1.7	z = –2.49, p = .01
Duration of clozapine, mean ± SD, mo	26.7 ± 28.7	37.9 ± 29.7	NS
Dose of clozapine, mean ± SD, mg/day	515.6 ± 138.7	414.3 ± 96.9	z = –2.04, p = .05

[a]Wilcoxon rank sum test.
Abbreviation: NS = nonsignificant.

Figure 1. Mean Scores on the Positive Subscale of the Positive and Negative Syndrome Scale for Patients Partially Responsive to Clozapine Randomly Assigned to Adjunctive Treatment With Risperidone or Placebo



desire to try another medication. Treatment resistance to multiple courses of treatment with typical or atypical neuroleptic drugs was the reason for initiation of clozapine for all patients.

The mean (SD) dose and serum level of risperidone in this study at the end of the 6 weeks were 5.1 (1.3) mg/day and 8.9 (7.6) μg/L (therapeutic range, 1–10 μg/L), respectively. The mean (SD) number of capsules received was 2.5 (0.6) in the risperidone group and 2.8 (0.4) in the placebo group. Nine of the 15 patients in the risperidone group who completed the study remained on 6 mg of risperidone from the end of week 2 to the end of week 6. The dose was decreased by 2 mg in 6 patients at the end of week 3 and remained constant for the following 3 weeks.

Efficacy Data

Primary efficacy measures. After adjusting for baseline, significant time ($p < .0001$) and treatment-group by time ($p = .03$) interaction effects were found for the PANSS POS subscale scores. There were no significant treatment-group effects. Because of the significant interactions, the least square mean differences for PANSS POS scores were examined. The least square mean differences for the PANSS POS scores ($p = .02$) were significant at the endpoint, indicating greater improvement in the placebo-treated compared to the risperidone-treated group. The weekly change in the PANSS POS raw mean scores for both treatment groups can be observed in Figure 1. The effect size for the PANSS POS scores (0.81) was large.

The delusion item was the only individual item from the PANSS POS subscale that showed a significant treatment-group by time interaction. The improvement in this item in the group who received adjunctive placebo was significantly greater than in the group receiving adjunctive risperidone. Among the patients who completed the study period, 4 (27%) of 15 from the risperidone group and 7 (50%) of 14 from the placebo group had a ≥ 20% improvement in the PANSS POS score ($\chi^2 = 1.68$, $df = 1$, $p = .2$).

A stepwise regression method was used to predict the PANSS POS endpoint scores from the PANSS POS baseline scores, treatment group, sex, age, illness duration, duration of clozapine treatment, clozapine dose, and total number of hospitalizations. PANSS POS baseline score was a strong predictor of the final score. Apart from that, only treatment-group effect ($\beta = 2.38$, $p = .04$) was a significant predictor. This finding indicated that none of the other variables listed in the model contributed to improvement in the final PANSS POS score.

Secondary efficacy measures. The treatment-group by time interaction effect was not significant for any of the secondary efficacy measures assessing psychopathology (PANSS total, PANSS NEG, PANSS GP, CDS, CGI-S). Examination of the time and treatment-group effects for these measures using the mixed model analysis found improvement in both treatment groups for PANSS total,

Table 3. Efficacy Measures at Baseline and Endpoint and Significance of Change During the Study Period for Patients Partially Responsive to Clozapine Randomly Assigned to Adjunctive Treatment With Risperidone or Placebo[a]

		Least Square Mean (SE)		Least Square Mean		Effect		
Assessment	Timepoint	Risperidone	Placebo	Difference (SE)	p Value	Treatment Group F Value (df = 1,27)	Time F Value (df = 1,28)	Treatment Group by Time F Value (df = 1,28)
PANSS score								
Total	Baseline	77.4 (1.65)	77.4 (1.78)	0.04 (2.43)	.98	0	37.8‡	2.9
	Endpoint	69.7 (1.65)	64.0 (1.78)	–5.7 (2.43)	.02			
Positive	Baseline	17.9 (0.53)	17.9 (0.56)	0.1 (0.77)	.93	0.2	27.3‡	5.5*
	Endpoint	16.2 (0.53)	13.8 (0.56)	–2.4 (0.77)	.002			
Negative	Baseline	23.3 (0.52)	23.4 (0.56)	0.05 (0.76)	.95	0.5	12.9**	0.4
	Endpoint	21.7 (0.52)	21.1 (0.56)	–0.6 (0.76)	.42			
General	Baseline	36.1 (0.86)	36.2 (0.92)	0.1 (1.26)	.94	1.2	37.3‡	1.9
	Endpoint	31.7 (0.86)	29.2 (0.92)	–2.5 (1.26)	.05			
Delusion	Baseline	4.0 (0.16)	4.0 (0.17)	0.01 (0.23)	.96	2.2	13.2**	5.1*
	Endpoint	3.7 (0.16)	3.0 (0.17)	–0.7 (0.23)	.002			
CGI-S score	Baseline	4.5 (0.12)	4.5 (0.13)	0.01 (0.18)	.96	0.2	5.5*	0.9
	Endpoint	4.3 (1.12)	4.0 (0.13)	–0.2 (0.18)	.20			
CDS score	Baseline	2.9 (0.50)	2.4 (0.51)	–0.5 (0.73)	.51	4.7*	3.8	0.1
	Endpoint	1.6 (0.50)	1.4 (0.51)	–0.2 (0.73)	.81			
GAF score	Baseline	48.5 (1.3)	48.4 (1.4)	–0.1 (1.93)	.96	0.9	9.2**	2.2
	Endpoint	50.3 (1.4)	54.8 (1.4)	4.5 (1.96)	.02			
QLS score								
Total	Baseline	46.4 (2.14)	45.9 (2.29)	–0.5 (3.14)	.88	6.0*	17.7†	0
	Endpoint	55.8 (2.21)	55.0 (2.29)	–0.8 (3.19)	.80			
Interpersonal relations	Baseline	16.0 (0.88)	15.6 (0.94)	–0.3 (1.29)	.79	12.7**	19.2†	0.1
	Endpoint	19.7 (0.91)	19.5 (0.94)	–0.2 (1.32)	.89			
Instrumental role	Baseline	7.4 (0.74)	7.5 (0.79)	0.1 (1.08)	.93	1.7	1.8	0
	Endpoint	8.9 (0.76)	8.6 (0.79)	–0.3 (1.10)	.78			
Intrapsychic foundations	Baseline	17.4 (0.98)	17.0 (1.05)	–0.4 (1.44)	.77	4.3*	9.9**	0.2
	Endpoint	20.5 (1.02)	20.8 (1.05)	0.4 (1.47)	.80			
Common objects	Baseline	5.85 (0.23)	5.7 (0.25)	–0.1 (0.35)	.67	8.5**	0.2	0.4
	Endpoint	5.57 (0.24)	6.0 (0.25)	0.4 (0.36)	.25			

[a]The intrasubject covariance matrix used is compound symmetry. When there is a significant treatment-group by visit interaction, the p value for least square 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-group effect over the entire study.

*p < .05; **p < .01; †p < .001; ‡p < .0001.

Abbreviations: CDS = Calgary Depression Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, GAF = Global Assessment of Functioning Scale, PANSS = Positive and Negative Syndrome Scale, QLS = Quality of Life Scale.

NEG, and GP scores and CGI-S scores. The treatment-group effect during the course of the study was significant due to higher scores in the risperidone-treated patients for the CDS (Table 3). Overall, 2 patients (13%) from the risperidone group and 4 (29%) from the placebo group had a ≥ 20% improvement in the PANSS total score (Fisher exact test p = .39). Among the patients who completed the study period, 1 (7%) of 15 from the risperidone and 4 (29%) of 14 from the placebo group had a ≥ 20% improvement in the PANSS NEG score (Fisher exact test p = .17). Four patients (27%) from the risperidone group and 6 patients (43%) from the placebo group, had a ≥ 20% improvement in the PANSS GP score ($\chi^2 = 0.84$, df = 1, p = .36).

Regarding overall functioning and quality of life, no significant treatment-group by time interaction effects were found. However, significant time effects were found for the QLS total scores, QLS subscores for interpersonal relations and intrapsychic foundations, and GAF scores, indicating improvement. The treatment-group effect for GAF scores was not significant, but treatment-group effects for QLS total scores and all QLS subscores except for instrumental role were significant (Table 3).

Safety Data

No serious adverse events were observed during the study, and, in general, risperidone augmentation was well tolerated. Side effects reported in more than 20% of the patients in the risperidone and placebo groups were sleepiness/sedation (5/16, 31% of risperidone group) and impaired memory (3/14, 21% of placebo group), respectively. Only the sleepiness/sedation side effect was more severe in the risperidone group (F = 7.64, df = 1,28; p = .01) (Table 4). Using the mixed model, the data for SAS, BAS, and AIMS were also analyzed. None of the treatment-group by time interaction effects were significant for these 3 scales. The treatment-group effects were significant for SAS and AIMS; however, the time effects were nonsignificant (Table 4). Only 1 patient (from the risperidone group) required the addition of biperiden to treat EPS. The mean ± SD increase in weight was 0.5 ± 2.4 kg

Table 4. Safety Measures at Baseline and Endpoint and Significance of Change During the Study Period for Patients Partially Responsive to Clozapine Randomly Assigned to Adjunctive Treatment With Risperidone or Placebo[a]

		Least Square Mean (SE)		Least Square Mean		Effect		
Assessment	Timepoint	Risperidone	Placebo	Difference (SE)	p Value	Treatment Group F Value (df = 1,27)	Time F Value (df = 1,28)	Treatment Group by Time F Value (df = 1,28)
UKU sleepiness and sedation score	Baseline	0.4 (0.09)	0.4 (0.10)	0.02 (0.13)	.87	2.6	0	7.6*
	Endpoint	0.7 (0.09)	0.2 (0.10)	–0.51 (0.13)	.0003			
SAS score	Baseline	12.4 (0.37)	12.2 (0.40)	–0.2 (0.55)	.77	11.0**	1.4	2.0
	Endpoint	12.3 (0.37)	13.2 (0.40)	0.9 (0.55)	.11			
BAS score	Baseline	0.37 (0.15)	0.36 (0.16)	–0.01 (0.22)	.98	3.3	0.2	2.4
	Endpoint	0.18 (0.15)	0.72 (0.16)	0.5 (0.22)	.02			
AIMS score	Baseline	1.4 (0.21)	1.5 (0.23)	0.1 (0.31)	.69	21.6†	1.3	1.3
	Endpoint	1.3 (0.22)	1.0 (0.23)	–0.4 (0.32)	.23			
Weight, kg	Baseline	67.8 (0.42)	67.8 (0.44)	–0.03 (0.61)	.96	32.5†	2.4	0.1
	Endpoint	68.6 (0.42)	68.3 (0.44)	–0.3 (0.61)	.66			
Prolactin level, ng/mL	Baseline	15.4 (4.80)	16.3 (5.13)	0.9 (7.04)	.90	43.7†	46.4†	37.6†
	Endpoint	78.3 (5.0)	18.2 (4.80)	–60.2 (7.17)	< .0001			
QTc interval, ms	Baseline	440.9 (7.8)	436.8 (8.34)	–4.1 (11.44)	.72	0	0	1.8
	Endpoint	430.3 (7.8)	450.0 (8.34)	19.8 (11.44)	.09			
Serum clozapine level, μmol/L	Baseline	2.3 (0.30)	2.4 (0.31)	0.1 (0.43)	.88	0	0	0.8
	Endpoint	2.5 (0.30)	2.0 (0.31)	–0.5 (0.43)	.26			

[a]The intrasubject covariance matrix used is compound symmetry. When there is a significant treatment-group by visit interaction, the p value for least square 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-group effect over the entire study.
*p < .05; **p < .01; †p < .0001.
Abbreviations: AIMS = Abnormal Involuntary Movements Scale, BAS = Barnes Akathisia Scale, SAS = Simpson-Angus Rating Scale for Extrapyramidal Side Effects, UKU = Udvalg for Kliniske Undersogelser (The Committee on Clinical Investigations Side Effect Rating Scale).

in the placebo group and 0.9 ± 2.2 kg in the risperidone group. Using the mixed model, only the treatment-group effect was significant for weight (Table 4), reflecting more the small variance in weight gain than a large effect of risperidone. Clinically significant weight gain (≥ 7% increase from baseline) was present in only 1 patient in each treatment group. There were no clinical differences in the vital signs measured in any of the treatment groups.

The QTc interval was calculated using Bazett's formula ($QTcB = QT/RR^{0.5}$). Using the mixed model, the treatment-group, time, and treatment-group by time interaction effects were all nonsignificant for the QTc interval (Table 4). A clinically significant increase was operationally defined as a QTc of 450 ms or more and a 10% increase over baseline. None of the patients in the risperidone group had an increase in QTc interval that met this criterion, whereas 3 patients in the placebo group experienced a potentially clinically significant increase in QTc interval.

The mean ± SD serum prolactin change was 1.8 ± 5.7 ng/mL in the placebo and 59.3 ± 40.1 ng/mL in the risperidone group. The treatment-group by time interaction effect was significant ($F = 37.59$, $df = 1,28$; $p \leq .0001$) as were the time and treatment-group effects (Table 4). There was also a significant sex effect, with females showing a greater increase in prolactin level ($p < .0001$); in the analysis adjusted for sex, the time, treatment-group, and treatment-group by time interaction effects all remained significant ($p < .0001$).

Pharmacokinetic Interaction Data

Using the mixed model, the treatment-group, time, and treatment-group by time interaction effects were all nonsignificant for serum clozapine levels (therapeutic level: 0.1–2.1μmol/L) (Table 4).

CONCLUSION

The main finding in this study is that the addition of risperidone at doses up to 6 mg/day for 6 weeks in clinically stable patients with partial response to clozapine did not lead to improvement in any of the domains of psychopathology, overall functioning, and quality of life compared to placebo. The lack of improvement with the addition of risperidone compared to the addition of placebo is the first evidence from a controlled study showing lack of efficacy with the combination of clozapine and another atypical antipsychotic drug.

The significant time effect found in PANSS, CGI-S, GAF, and QLS ratings indicates a significant study effect. This may have been due to increased contact with clinical staff, patient expectation that improvement would occur from treatment, and possible rater expectations. It is not possible to distinguish among these. There were no side effects that made it possible to determine which group patients were assigned to, with the possible exception of the 1 patient who required the addition of biperiden to treat EPS. Sedation was more common in the patients who received risperidone, but this side effect was not attributed to risperidone during the course of the study. Rater bias,

had it occurred, would have been expected to favor risperidone, but there was no evidence to suggest this occurred.

The small size of the sample is an important limitation of this study. It is, however, the largest study to date and is larger than the 3 previous open studies discussed earlier. The sample was large enough to detect significant improvement in a variety of measures, but this improvement was not related to treatment with risperidone. We, therefore, think this study provides valuable information because of its superior design and the wide array of safety parameters assessed.

The 2 groups of patients differed with regard to gender and inpatient/outpatient status with slightly more male than female patients receiving risperidone, while nearly all the patients receiving placebo were male. We examined the difference in response to risperidone between male and female patients and found no evidence that male patients were more responsive than female patients. We also found no difference in baseline characteristics of the 6 inpatients who participated in the study, nor was there any evidence for a differential response to the addition of risperidone between the inpatients and outpatients.

These results are consistent with the previous studies that found some evidence of improvement during the course of risperidone treatment.[13,15] However, our results indicate that this improvement was no greater and, in the case of positive symptoms, the primary outcome measure, was significantly less than that due to the addition of placebo, indicating some negative effect of risperidone compared to placebo on this measure.

The subjects in this study were similar to the subjects in the 3 open studies with regard to important clinical patient characteristics such as age, treatment-resistance status, duration of prior clozapine exposure, and mean clozapine dose.[13,15,17] There was some evidence that the group that received risperidone in this study might have had a greater severity of illness compared to the placebo group, as indicated by a greater number of hospitalizations and the higher dose of clozapine prescribed prior to study entry. However, the improvement in all clinical parameters was adjusted for baseline severity of the measured parameter.

A possibly important factor is that the mean dose of risperidone added to clozapine was higher in this study and the other negative report[17] (5.1 and 5.3 mg) compared to the 2 open studies,[13,15] which reported improvement following the addition of risperidone (3.8 and 3.0 mg). The absence of any adverse side effects due to D_2 receptor blockade in this patient group is some evidence that the dose of risperidone was not excessive. Moreover, almost all case reports indicating improvement with the combination of clozapine and risperidone have used risperidone titrated up to 6 mg/day.[7,10–12] It is not possible to rule out that a lower dose of risperidone might have been more effective than the dose used in this study, even though this seems unlikely for the reasons given above.

Several hypotheses have been proposed regarding the rationale for adding an atypical antipsychotic to improve efficacy in partial responders to clozapine or other atypical antipsychotics.[27] The first hypothesis involves achieving optimal dopamine D_2 receptor occupancy by adding agents that are more potent D_2 antagonists, such as haloperidol or risperidone.[2,3,28] The second hypothesis involves achieving a broader spectrum of pharmacologic receptor activity to affect nondopaminergic (such as adrenergic, glutamatergic, and serotonergic) systems. However, clozapine, along with ziprasidone, is the most broad-spectrum of all antipsychotic drugs, making it unlikely that the addition of risperidone would be beneficial in this regard.[29] Meltzer and colleagues[30] proposed that the weak D_2 receptor blockade and more potent serotonin 5-HT_{2A} receptor blockade of clozapine contribute to its atypical profile and suggested that the additional D_2 receptor blockade produced by risperidone might interfere with the efficacy of clozapine. The finding that the placebo-treated group improved more than the risperidone-treated group on the delusion item of positive symptoms, as assessed by the PANSS, indicates a negative effect of risperidone on the improvement related to clozapine treatment or study participation. Overall, our findings suggest that additional dopamine receptor blockade resulting from the addition of risperidone, which is supported by the increase in serum prolactin levels, does not lead to additional improvement. Furthermore, this additional dopamine receptor blockade might have interfered with the neurochemical basis for the improvement in psychosis produced by clozapine, in conjunction with the positive effect of study participation.

It is unlikely that an additional 6 weeks of treatment with clozapine alone would have produced the extent of improvement noted in the patients who were augmented with placebo. It is more likely that study participation, which included significant interaction with staff and the hope that the addition of a second medication would produce positive results, led to the improvement in PANSS scores.

The significant improvement in the negative symptoms (Scale for the Assessment of Negative Symptoms) and the trend for significant improvement in the positive psychotic symptoms (Scale for the Assessment of Positive Symptoms) and overall symptomatology (BPRS) observed in the Shiloh and colleagues study[5] seem to contradict the described view that additional dopamine receptor blockade does not provide benefit for a better outcome. Although equivalent dosing does not necessarily indicate similar D_2 receptor occupancy, the 600 mg/day of sulpiride used in that study is nearly equivalent to the 5.1 (1.3) mg/day mean dose of risperidone utilized in the present study. The improvement reported in the previous double-blind study[5] could be related to the longer duration (10 weeks)

of treatment. A more likely explanation for the inconsistency of the results could be the less stringent inclusion criteria employed regarding unsatisfactory responsiveness to prior clozapine treatment in the adjunctive sulpiride study[5] and thus inclusion of relatively less severely ill patients. In that study, patients with prior duration of clozapine treatment of at least 12 weeks and a baseline BPRS (18 items, 0–6 severity) score of at least 25 (23% of the highest total possible score) were included, whereas the present study required at least 6 months of prior clozapine treatment and a score of at least 72 on baseline PANSS (34% of the highest total possible score).

Following the completion of this study, lamotrigine, an anticonvulsant drug whose mechanism of action has been suggested to be due to its ability to block voltage-gated Na^+ channels at presynaptic sites, leading to an increase in the release of γ-aminobutyric acid (GABA) and a decrease in the release of glutamate,[31] was reported to be effective in improving positive and general but not negative symptoms.[32] This 14-week, randomized, double-blind, placebo-controlled crossover trial included 34 hospitalized, treatment-resistant patients with chronic schizophrenia who had had variable responses to clozapine during prior treatment. These results are consistent with a previous report of an open trial of the addition of lamotrigine to clozapine partial responders.[33] Again, the patients in the crossover trial were slightly less ill as indicated by the mean baseline PANSS total score (69 vs. 77). There was no mention of the duration of treatment with clozapine prior to the entry of the trial. The longer duration of the trial with lamotrigine compared to this trial may have been a factor contributing to the positive result achieved with lamotrigine.

Considering the beneficial effects observed in the 2 above-mentioned double-blind, placebo-controlled studies,[5,32] it is possible to conclude that 6 weeks of treatment with risperidone was not long enough to obtain significant improvement in psychopathology and overall functioning or quality of life, which might both be delayed. However, also considering the lack of any sign of greater improvement in psychopathology in the risperidone group by 6 weeks, an acceptable period to observe antipsychotic efficacy, this conclusion is unlikely. The possibility remains that adjunctive treatment is beneficial in less severely ill patients with partial response to clozapine treatment.

Regarding the safety of adjunctive treatment with risperidone, the combination was generally well tolerated. There was no discontinuation from the study due to an adverse event. The adverse events reported previously in clozapine-risperidone combinations included exacerbation of hoarding behavior,[9] mild akathisia, and increase in hypersalivation,[13] orthostatic hypotension,[17] oculogyric crisis,[34] agranulocytosis,[35] atrial ectopics,[36] and neuroleptic malignant syndrome.[37] In our study, sedation was the only side effect that was significantly more severe in the risperidone group compared to placebo. Sedation is a frequent side effect of clozapine but is reported less with risperidone. Combination of the 2 agents might have caused a pharmacodynamic interaction that resulted in a possible increase in the antihistaminergic effect and, thus, more sedation.

Although EPS are side effects that are frequently reported with risperidone, especially at high doses (> 6 mg/day), no statistically significant difference between the placebo and risperidone groups on any of the EPS measures was observed in this study. Since risperidone was given at a mean dose of 5.1 ± 1.3 mg/day, more EPS could have been expected. Clozapine may have blocked EPS from emerging. Clozapine's ability to block 5-HT_{2A} receptors and stimulate 5-HT_{1A} receptors as well as its potent M_2 muscarinic anticholinergic effects may, together, diminish the risk of EPS caused by increased dopamine D_2 receptor blockade following the addition of risperidone.

A previous study has shown that the serum prolactin elevation due to the addition of risperidone can be quite marked and is comparable to that reported in patients not receiving clozapine.[38] In addition, mild EPS have earlier been reported in spite of the high D_2 receptor occupancy following addition of haloperidol to clozapine.[39] Similarly, our results show low propensity for EPS in spite of significant increase in serum prolactin levels with the risperidone-clozapine combination.

Weight gain is an important side effect of almost all typical and atypical antipsychotics. It increases the risk of type 2 diabetes mellitus and/or cardiovascular disease and can decrease treatment compliance. Among the atypical antipsychotics, clozapine and olanzapine cause weight gain in a higher proportion of patients than do quetiapine, risperidone, and ziprasidone.[40] No clinically significant weight gain has been reported in previous case reports and open trials of risperidone and clozapine combination. Similarly, weight gain did not differ between the placebo- and risperidone-treated groups in this study.

Controversial reports exist regarding a pharmacokinetic interaction between clozapine and risperidone. Two studies have reported increases in plasma clozapine levels after risperidone addition,[8,33] whereas 1 did not.[13] Risperidone is metabolized by cytochrome P450 (CYP) 2D6 to 9-hydroxy risperidone, and neither compound has been shown to inhibit any cytochrome enzymes. Clozapine is primarily metabolized by CYP1A2 and CYP3A4, while the role of CYP2D6 is equivocal.[41–43] An adverse pharmacokinetic interaction between clozapine and risperidone would thus not be expected. Consistent with this, serum clozapine levels were not affected significantly by addition of risperidone. This finding also suggests that smoking in a higher number of patients in the risperidone group did not affect the metabolism of clozapine.

In conclusion, the results reported here indicate no significant benefit with regard to psychopathology and function during a 6-week trial of the addition of risperidone to clozapine-treated patients with schizophrenia. It is likely that these results apply to all antipsychotic drugs, not just risperidone. Although it is possible that relatively less ill treatment-resistant patients respond better to adjunctive treatment, the more severely ill group of patients remain with the need for promising treatment options. Treatment with other antipsychotics adjunctive to clozapine merits further investigation in controlled studies with comparable methodologies and/or meta-analyses of the original data from various trials to detect treatment differences in a reliable manner.

Drug names: biperiden (Akineton), clonazepam (Klonopin and others), clozapine (Fazaclo, Clozaril, and others), haloperidol (Haldol and others), lamotrigine (Lamictal), lithium (Lithobid, Eskalith, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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