Efficacy of Risperidone in Reducing Positive and Negative Symptoms in Medication-Refractory Schizophrenia: An Open Prospective Study

Robert C. Smith, M.D., Ph.D., Jayson W. Chua, M.D., Boris Lipetsker, M.D., and Anjan Bhattacharyya, M.S.

Background: Although risperidone has been shown to be an effective antipsychotic medication in schizophrenia, the clinical studies performed for the Food and Drug Administration's approval process focused on only a mixed group of schizophrenic patients. Most of these studies did not directly address the efficacy of risperidone in chronic nonresponding schizophrenics. To better evaluate whether risperidone has a substantial degree of efficacy in schizophrenic nonresponders, we conducted an open prospective study of risperidone in a sample of chronically hospitalized schizophrenic patients.

Method: Twenty-five patients who met DSM-III-R criteria for schizophrenia or schizoaffective psychosis, who were chronically hospitalized at a tertiary care state facility, and who had not responded to conventional neuroleptics were evaluated before and during treatment with risperidone by using several standard rating scales and adjunctive assessments.

Results: Endpoint analysis showed that 36% (N = 9) of the patients were classified as responders on the basis of at least a 20% decrease in total Brief Psychiatric Rating Scale score at final evaluation. A higher percentage of patients were classified as responders when other rating scale criteria were used. Reductions in psychopathology scores were seen in scales reflecting positive symptoms but not in scores of negative symptoms. High baseline negative symptom scores were correlated with poorer response to risperidone as indicated by the decrease in positive symptom scores.

Conclusion: This study offers evidence that risperidone may reduce positive symptoms of schizophrenia for a subgroup of chronically hospitalized schizophrenic patients who have not responded to conventional neuroleptics. The comparative evaluation of the efficacy of risperidone versus that of clozapine in these types of patients requires further study.

(J Clin Psychiatry 1996;57:460–466)

Received Sept. 11, 1995; accepted June 6, 1996. From the Department of Psychiatry, New York University School of Medicine (Dr. Smith) and Manhattan Psychiatric Center (all authors), New York, N.Y.

Publication and presentation costs supported in part by a grant from Janssen Pharmaceuticals.

Reprint requests to: Robert C. Smith, M.D., Ph.D., Department of Psychiatry, NYU, c/o P.O. Box 316, Hewlett, NY 11557-0316.

Risperidone has been shown to have efficacy in reducing psychotic symptoms in schizophrenia,[1,2] but the extent of its efficacy in reducing positive and negative symptoms in schizophrenic patients who are chronically hospitalized and have not responded to conventional neuroleptics has not been extensively studied. The U.S. collaborative risperidone study[1] may have included two or three sites with a larger percentage of chronically hospitalized nonresponders, although only one site (Camarillo State Hospital, Camarillo, Calif.) had a mean length of current hospitalization (5 years) that was similar to the mean length (4.15 years) reported in the original collaborative clozapine study[3] in schizophrenic nonresponders. However, the response to risperidone of patients who could be classified as chronically hospitalized, medication-refractory schizophrenics was not separately shown. Clozapine has been specifically studied in samples of schizophrenic nonresponders and reported to produce significant improvement in about 30% of patients.[3] Other studies have suggested that some chronic schizophrenic patients respond after longer periods of treatment with clozapine (e.g., up to 6–12 months), with an overall response rate approaching 40% to 50% in some small series.[4,5] Risperidone requires less monitoring during drug administration because it does not have the side effect risk of agranulocytosis; this side effect sometimes makes clinicians hesitant to use clozapine in situations in which they cannot assure constant proper monitoring of weekly white blood cell counts. Pharmacologically, risperidone is an atypical neuroleptic, which influences the brain dopaminergic and serotonergic systems. However, it has not been established whether these atypical properties will give risperidone an advantage for efficacy in samples

Table 1. Characteristics of 25 Patients Who Participated in Risperidone Study*

Characteristic	Measure
Age (mean ± SD y)	41.0 ± 8.6
Sex	
Men	15
Women	10
Race	
White	7
Black	11
Hispanic	7
Highest education (mean ± SD y)	11.2 ± 2.4
Diagnosis	
Schizophrenia	21
Schizoaffective psychosis	4
No. of years ill (mean ± SD)	21.8 ± 9.2
No. of years of current hospitalization (mean ± SD)	8.7 ± 6.6
No. of patients hospitalized > 4 y	18
Dose of neuroleptics prior to risperidone (chlorpromazine equivalents, mean ± SD mg/d)	1265.3 ± 797.6
Poor response to prior trial of clozapine (N)	6
Baseline psychopathology score (mean ± SD)	
BPRS total	44.6 ± 8.3
BPRS psychosis factor	20.1 ± 5.3
SAPS total	32.6 ± 14.7
SANS total	38.0 ± 27.7
Baseline side effect score (mean ± SD)	
SAMD total	1.5 ± 2.3
SAMD akinesia	0.1 ± 0.3

*Abbreviations: BPRS = Brief Psychiatric Rating Scale, SAMD = Schedule for the Assessment of Movement Disorders, SANS = Scale for the Assessment of Negative Symptoms, SAPS = Scale for the Assessment of Positive Symptoms.

of chronically hospitalized, medication-refractory schizophrenics. We present results from an open prospective study in which risperidone was administered to chronically hospitalized patients who had failed to respond sufficiently to traditional neuroleptics. The object of the study was to evaluate whether risperidone produced an improved clinical response in these patients, as evaluated by rating scale scores of positive and negative symptoms and clinicians' evaluations.

METHOD

Patients

Subjects for the study were 25 patients who met DSM-III-R criteria for schizophrenia or schizoaffective psychosis, who had multiple prior hospitalizations, who had been hospitalized for at least 1 year during their current hospitalization, and who had prominent positive and/or severe negative symptoms of schizophrenia in spite of more than 1 year of treatment with neuroleptics. Most of the patients had been treated with multiple neuroleptics. Six patients had failed to respond sufficiently to a prior trial of treatment with clozapine. Patient characteristics are presented in Table 1.

Table 2. Number of Patients Taking Various Doses of Risperidone

Risperidone Dose (mg/d)	At Highest Dose	When BPRS Total Score Was Lowest
6	4	6
8–10	1	4
11–12	10	10
13–16	10	5

Study Design and Risperidone Dosing

The design was an open prospective study in which multiple evaluations were conducted before and during risperidone treatment. There was no washout period. Patients resided on different wards where their dose of risperidone was adjusted by their treating psychiatrist with the advice and consultation of the principal investigator. Patients began with a dose of 1 mg of risperidone b.i.d., and the dose was raised to 3 mg b.i.d. over 1 week. Other neuroleptics were discontinued during the first 1 to 3 weeks of risperidone treatment. In some patients, additional nonneuroleptic medications (lithium, valproic acid) were continued or restarted during risperidone treatment, and in a few cases, mood stabilizers or antidepressants were added during risperidone treatment. Patients did not receive other neuroleptics, except occasional intramuscular p.r.n. doses of neuroleptics or benzodiazepines as necessary to control temporary agitation. If patients were judged as not responding well enough to the 6-mg/day dose of risperidone, the dose was raised, usually over 2 to 6 months; the maximum allowable dose was 16 mg/day. Doses of risperidone and ancillary medication are summarized in Tables 2 and 3. Five of 25 patients were terminated from risperidone treatment before 4 months' time because of deterioration of their clinical condition or other administrative reasons. The remainder of the patients were followed for a mean of 7.6 months (range, 5–14 months).

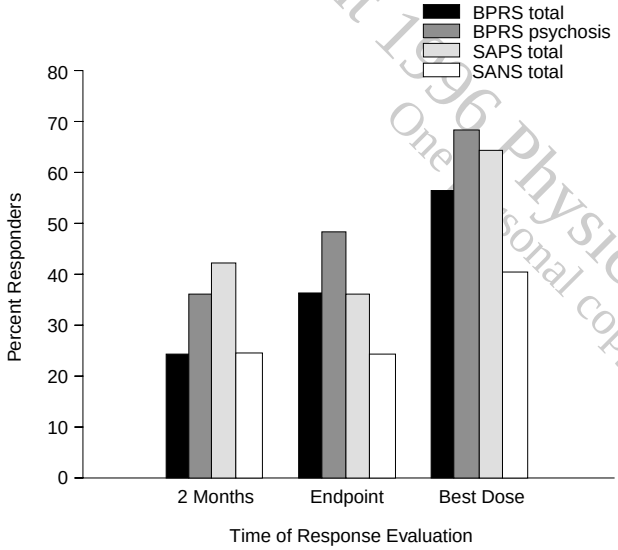
Psychopathology and Related Evaluations

Psychopathology ratings were performed by using the Brief Psychiatric Rating Scale (BPRS),[6] Scale for the Assessment of Positive Symptoms (SAPS),[7] and Scale for the Assessment of Negative Symptoms (SANS),[8] before risperidone treatment was begun (baseline) and during treatment with risperidone. Extrapyramidal and related symptoms were rated by using a new scale, the Schedule for Assessment of Movement Disorders (SAMD) (Alpert M, Pouget E. Available from the authors upon request). Evaluations were done approximately once a month for the first 3 to 4 months and subsequently once every 1.5 to 3 months. All rating scale evaluations were performed by a single rater. Because of patient uncooperativeness or unavailability, occasional scheduled ratings could not be completed. Administration of p.r.n. medications was assessed from the patients' medication records in their

Table 3. Number of Patients Taking Concomitant Psychotropic Medication Prior to and During Risperidone Treatment

Medication	Previous to Risperidone	After Start of Risperidone: Continued From Before Risperidone	After Start of Risperidone: Added or Restarted After Starting Risperidone
Valproic acid	4	2	4
Carbamazepine	3	1	0
Lithium	5	3	0
Antiparkinsonian agent	12	2	6
Antidepressant	0	0	2

Figure 1. Percentage of Responders to Risperidone When Different Rating Scale Criteria Are Used at 2 Months, Endpoint, and Best Dose*



*Responders are defined as patients who achieved a ≥ 20% reduction in the indicated psychopathology score compared with baseline (pre-risperidone). Percentages are based on N = 25, except for endpoint SANS (N = 24).

charts. At a time close to the final evaluation, each patient's treating psychiatrist was interviewed to obtain evaluation data on the Clinical Global Impressions (CGI) scale.

Statistical Analysis and Responder Definitions

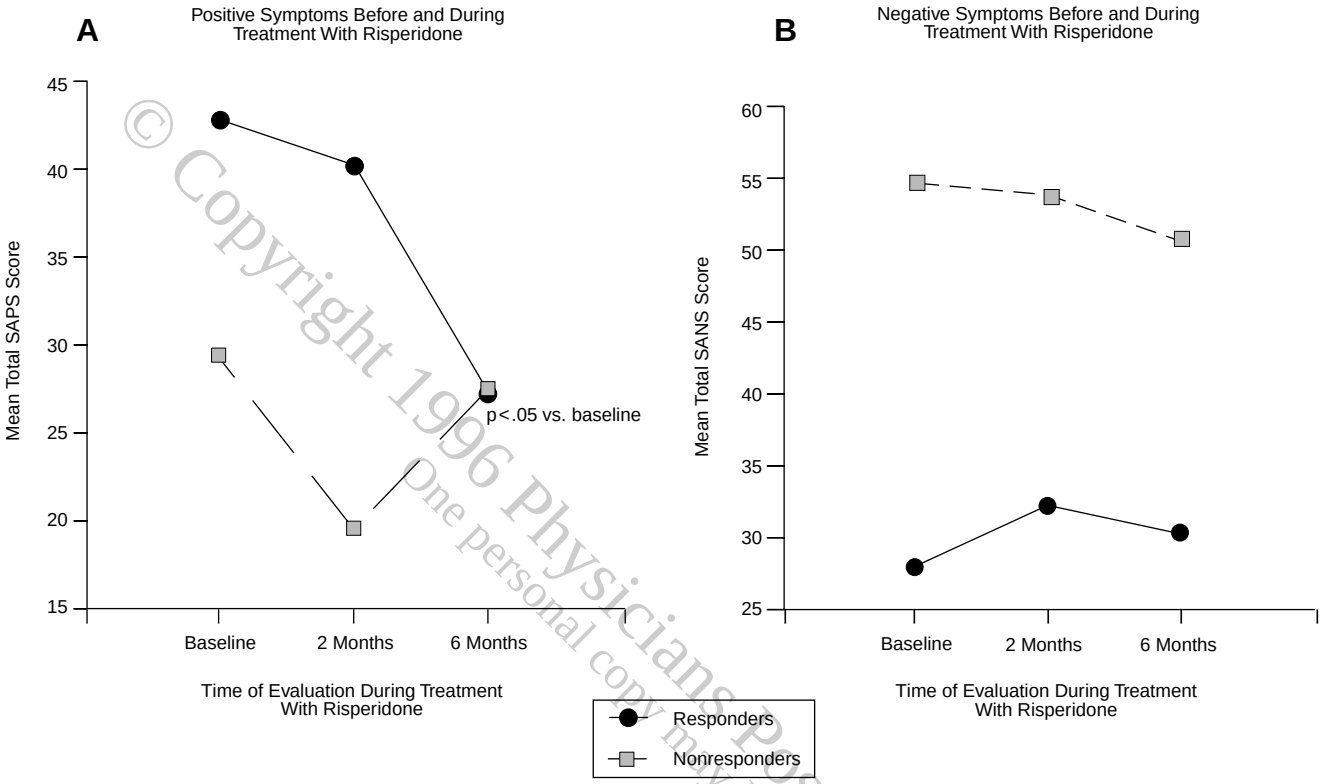
We hypothesized that risperidone would decrease the patients' psychopathology scores and decrease both positive and negative symptom scale scores. Analysis of improvement was based on several criteria. The main criterion was rating scale scores both at the final evaluation (endpoint) and at the dose and time showing the lowest rating scale score (best dose). Additional analysis compared responses at approximately 2 months after start of treatment. Analysis of time course was done by comparing responses at approximately 2 months and 6 months. Responders to risperidone were designated as patients who showed a 20% or greater decrease in a specific psychopathology score. A 20% decrease on the BPRS total score was used as the main criterion for differentiating responders versus nonresponders. This is similar to that used in several other recent studies.[1,3] Calculations of percentage improvement scores on the BPRS scale (total and factor scores) were done with a conversion to remove the limit imposed by a score of 1 representing "no symptoms" on each item, as suggested by a recent review.[9] Another criterion for definition of responder was a 20% decrease in BPRS Total *and* a CGI rating of "much improved."

Statistical analysis utilized descriptive statistics, paired t tests, and the Wilcoxon matched-pairs signed-rank test. Repeated measures analyses of variance were also performed for scores at baseline, 2 months, and 6 months for the following variables: BPRS total score, BPRS psychosis factor, SAPS total score, and SANS total score. For each subject, the evaluation time point closest to 2 months after the start of risperidone treatment was taken as the 2-month time point, and the evaluation time point between 5 and 7 months, which was closest to 6 months after the start of risperidone treatment, was taken as the 6-month time point. The relationships between variables were assessed with Pearson correlation coefficients and regression analysis.

RESULTS

In our entire sample of 25 chronic schizophrenic nonresponders, comparison of difference scores at endpoint versus baseline scores showed a significant decrease in two scale scores: BPRS Total (mean ± SD decrease = 4.0 ± 9.5; $t = 2.090$, $df = 24$, $p < .05$) and BPRS psychosis factor (mean ± SD decrease = 2.9 ± 6.0; $t = 2.317$, $df = 24$, $p < .05$). Results were similar at the 6-month evaluation point. When the significance levels were corrected for multiple t tests performed by using the Bonferonni method, none of the differences were significant at the conventional level ($p < .05$). However, a proportion of patients showed a moderate to marked decrease in their psychopathology scores (Figure 1), and some were rated as substantially improved by their treating clinician. By the endpoint evaluation, 9 patients (36%) showed a 20% or greater decrease in BPRS total score, and 4 patients (16%) had both a 20% decrease in BPRS score and were rated as "much improved" on the CGI scale by their primary treating psychiatrist. Definition of responder using other rating scale criteria yielded response rates ranging from 24% to 48% at endpoint evalu-

Figure 2. Changes in SAPS and SANS Scores During 6 Months of Treatment With Risperidone*



*N = 18 subjects who had values at baseline, 2 months, and 6 months. Responders are defined as subjects with a ≥ 20% decrease in BPRS total score at endpoint evaluation. Repeated measures analysis of variance of SAPS scores showed no statistically significant effect of time but a significant interaction effect of responder status by time ($F = 3.31$, $df = 2$, $p = .049$). Responders showed significant improvement in SAPS scores at 6 months compared with baseline ($p < .05$).

ation (Figure 1). Eight patients (32%) had a BPRS total score ≤ 35 at endpoint. Four patients (14%) showed a moderate worsening of their symptoms during risperidone treatment. After approximately 2 months of risperidone treatment, a similar percentage of patients showed improvement on positive symptoms, but a smaller number showed improvement on BPRS total score (Figure 1).

A higher percentage of patients showed at least a 20% decrease in rating scale score at some time in their treatment (Best Dose, Figure 1), but some failed to maintain this responder status later in treatment. The mean best dose for improvement was 10.7 mg/day on the BPRS total score and 10.0 on the SAPS total score. The patient with the most complete clinical response responded at the 6-mg/day dose, but was later raised to 8 mg/day during extended outpatient treatment. The mean time to greatest decrease in the BPRS total score was 3.7 months, and 40% (N = 10) of patients achieved their best response by 2 months of treatment and 84% (N = 21) achieved their lowest score by 6.5 months.

For 18 of the 25 patients for whom we have rating scale evaluations at both 2 and 6 months, there was a trend for continued improvement between these time points. Results of repeated measures analyses of variance showed a trend for continued improvement on BPRS total, BPRS psychosis, and SAPS total scores from baseline to 6 months, but this trend was not statistically significant at conventional levels. However, there was a significant responder versus nonresponder by time interaction effect. Responders showed a statistically significant effect for continued improvement in these scores (see example in Figure 2A). For the 18 patients for whom we have data at all three time points, Newman-Keuls test comparisons also showed that the 6-month scores for the BPRS total and BPRS psychosis factor scores were significantly ($p < .05$) improved from baseline scores.

Risperidone appeared to decrease agitation or excitement in a proportion of the patients. Thirteen (52%) of 25 patients had at least a 20% decrease in the BPRS excitement-hostility subscale score (tension, excitement, hostility items). There was also a trend for a decrease in the use of p.r.n. doses of neuroleptics and benzodiazepines after the start of risperidone, although this difference was not statistically significant.

In this patient sample, risperidone had a greater effect on improving positive symptoms of schizophrenia than negative symptoms. In the full sample, mean SANS scores showed a small increase by endpoint whereas

Table 4. Relationship Between Decrease of Positive Symptoms During Risperidone Treatment and Baseline Positive and Negative Symptom Scores*

Treatment Response Score	SANS Total Score	BPRS Anergia Factor	SAPS Total Score
Decrease in BPRS psychosis factor score at endpoint	–.52[a]	–.49[b]	+.45[b]
Decrease in SAPS total score at endpoint	–.48[b]	–.43[b]	+.59[a]
Decrease in SAPS total score at best dose	–.43[b]	–.46[b]	+.37

*Each number represents Pearson correlation coefficient based on N of 25. [a]p < .01; [b]p < .05.

mean SAPS scores showed a 5 point decrease. Furthermore, patients classified as responders, on the basis of a 20% or greater decrease in BPRS total scores at endpoint, did not show a mean decrease in SANS total score at endpoint, whereas they showed a significant decrease in SAPS total scores (see Figure 2 for time course). There were similar results with another negative symptom measure, the BPRS anergia factor score. The mean risperidone dose at the greatest percentage decrease in SANS scores was 10.0 mg/day. At the 2-month time point, when most patients were receiving doses of 6 to 8 mg/day, there was also no decrease in mean SANS or BPRS anergia scores.

Extrapyramidal symptoms assessed at baseline before risperidone were relatively low in our sample (Table 1). There were also no significant changes in extrapyramidal symptoms as assessed by change in SAMD total or subscale scores during risperidone treatment as compared with baseline, although fewer patients received antiparkinsonian medication during risperidone. Low-dose antiparkinsonian medication, when prescribed, was usually reinstituted after risperidone doses were above 10 or 12 mg/day.

High scores on measures of negative symptoms at baseline were a predictor of poor response to risperidone. There were statistically significant negative correlations between SANS baseline scores and decrease in BPRS total, BPRS psychosis, and SAPS total scores (Table 4). Higher baseline positive symptom scores were correlated with a greater decrease in positive symptoms during treatment with risperidone. There were no significant correlations between baseline side effect scores and a decrease in positive symptoms (r = .14 to .20). Patients' age, number of years since onset of illness, number of years of current hospitalization, and ratio of positive to negative symptoms at baseline did not consistently correlate with these rating scale measures of clinical response.

None of the 6 patients who had a previous unsuccessful prior trial of treatment with clozapine was a responder to risperidone at endpoint evaluation, although one of these patients had shown a substantial decrease in positive symptoms earlier in the course of treatment with risperidone. If we remove these 6 patients who were previous nonresponders to clozapine, then at endpoint evaluation, 47% (N = 9) of the remaining 19 patients would be considered responders to risperidone on the basis of ≥ 20% decrease in BPRS total score or SAPS total score.

Two patients, who had been hospitalized 2 years or more, were discharged on risperidone therapy and have continued to function well in outpatient treatment. Another patient who had a worsening of symptoms while she was on risperidone treatment (and continued to have persistent auditory hallucinations both on risperidone and haloperidol therapy) was discharged to a half-way house about 3 months after she was switched back to the previous neuroleptic (haloperidol). One or two additional risperidone responders were almost ready for discharge, but administrative or social problems impeded their discharge at the end of the study.

DISCUSSION

Our study had a design that approximates the clinical practice a psychiatrist might follow in treating patients with risperidone to evaluate whether this atypical neuroleptic will benefit a chronically hospitalized patient with medication-refractory schizophrenia. In this sample, our results showed the efficacy of risperidone in reducing both total psychopathology scores and more specifically positive symptoms; the apparent percentage of responders to risperidone was similar to that in other reports of treatment of chronic nonresponding schizophrenics with the atypical neuroleptic clozapine.[3,5]

Several important weaknesses in our study design, however, may limit the generalizability of our findings or the confidence we can place in the numerical estimates of risperidone's degree of efficacy. Our study was an open study with a well-characterized, but relatively small, sample of chronically hospitalized nonresponding schizophrenics, and there was no parallel control group of patients who received a traditional neuroleptic such as haloperidol or chlorpromazine. Furthermore, we did not strictly control the dose of risperidone or the additional adjunctive medication the patients were receiving. We have previously reported that psychopathology scores in adequately medicated hospitalized chronic schizophrenics can fluctuate from month to month.[10] Although all the patients in this sample had a documented history of poor response to traditional neuroleptics and were severely symptomatic on these medications prior to the start of the risperidone trial, we do not have a quantitative history of the degree of fluctuation in their symptoms scores in the prior year. It is possible that some of the improvement seen in these patients on risperidone treatment could reflect the fluctuation in their psychopathology over time,

rather than the specific effects of risperidone. The greater percentage of risperidone responders at best dose compared to endpoint evaluation could potentially be due to this month-to-month fluctuation in symptoms. In a small sample, without a control group, small differences in these types of factors could substantially affect the percentage of patients classified as responders to risperidone. To more accurately assess the true proportion of risperidone responders or the extent of the efficacy of risperidone in medication-refractory schizophrenia, it would be necessary to examine a larger series of these patients in a controlled study with either parallel group or crossover design.

It is interesting to note that two other recent studies, both with relatively small samples, which directly compared the effects of clozapine versus risperidone in schizophrenic patients and used either crossover or parallel-group designs,[11,12] reported a similar clinical efficacy of risperidone and clozapine, as reflected in BPRS, Positive and Negative Syndrome Scale, or CGI scores. However, these samples did not consist of schizophrenic patients hospitalized for the long term who had shown years of very poor response to conventional neuroleptics.

Our failure to find any therapeutic effect of risperidone on negative symptoms of schizophrenia contrasts with the results of some earlier reports.[1,13] The U.S. collaborative study of risperidone reported significant decreases in both positive and negative symptoms in their entire sample of patients as well as in a subset of their patients who had predominantly negative symptoms as the clinical presentation of their illness.[1,14] However, other groups[15,16] have not reported a therapeutic effect of risperidone on negative symptoms, and one review suggests that risperidone may have an effect only on secondary negative symptoms at fairly low doses of 4 to 8 mg/day.[17] Our failure to find a reduction in negative symptoms cannot be attributed to the higher doses prescribed to some of our patients by the time of endpoint evaluation on risperidone; even after the first 2 months, when risperidone doses were fairly low (6–8 mg/day) for most patients, there was no decrease in negative symptoms in this sample. It may be that if risperidone has therapeutic efficacy against negative symptoms of schizophrenia, this will only be evident in mixed samples of relapsing schizophrenics and not characterize its effect on symptoms in chronically hospitalized nonresponders.

Reinforcing our findings that risperidone did not improve negative symptoms is our result that an important predictor of the therapeutic effect of risperidone on positive symptoms was a lower negative symptom score at baseline. Although we did not classify our patients on the deficit/nondeficit distinction proposed by Carpenter and associates,[18] a number of our patients had chronic amotivational behavior patterns. It is possible that those patients with high negative symptoms might fit the deficit syndrome criteria. Secondary negative symptoms are sometimes correlated with extrapyramidal side effects. Treatment with low doses of risperidone, which has little tendency to induce extrapyramidal side effects, might, therefore, be expected to reduce secondary negative symptoms. However, our sample had very low baseline motor side effect scores, these scores did not significantly decrease on risperidone treatment, and baseline side effect scores were not correlated with clinical improvement. These results are consistent with an interpretation that patients in our sample that had high negative symptoms scores had a primary deficit symptom picture, and these symptoms may not respond to risperidone. However, to evaluate whether this interpretation is valid would require studies of a larger sample in which primary and secondary negative symptoms, or deficit versus nondeficit schizophrenia, were accurately classified. This would help clarify whether high scores on measures of negative symptoms or only high deficit symptoms would predict poor response to risperidone in medication-refractory schizophrenia.

Drug names: carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clozapine (Clozaril), haloperidol (Haldol and others), risperidone (Risperdal), valproic acid (Depakene and others).

REFERENCES

1. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. Am J Psychiatry 1994;115:825–835
2. Chouinard G, Jones B, Remington G, et al. A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. J Clin Psychopharmacology 1993;13:25–40
3. Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry 1988;45:789–796
4. Meltzer HY. Dimensions of clozapine response. Br J Psychiatry 1992;160 (suppl 17):46–53
5. Meltzer HY, Bastani B, Kwon KY, et al. A prospective study of clozapine in treatment-resistant schizophrenic patients, I: preliminary findings. Psychopharmacology (Berl) 1989;99(suppl):S68–S72
6. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. Psychol Rep 1962;10:799–812
7. Andreasen NC. The Scale for the Assessment of Positive Symptoms in Schizophrenia (SAPS). Iowa City, Iowa: University of Iowa; 1984
8. Andreasen NC. The Scale for the Assessment of Negative Symptoms in Schizophrenia (SANS). Iowa City, Iowa: University of Iowa; 1983
9. Thompson PA, Buckley PF, Meltzer HY. The Brief Psychiatric Rating Scale: effect of scaling system on clinical response assessment. J Clin Psychopharmacol 1994;14:344–346
10. Smith RC. Lower dose therapy with traditional neuroleptics in chronically hospitalized schizophrenic patients [letter]. Arch Gen Psychiatry 1994;31: 427–429
11. Klieser E, Lehmann E, Kinzler E, et al. Randomized, double-blind controlled trial of risperidone versus clozapine in patients with chronic schizophrenia. J Clin Psychopharmacol 1995;15(suppl 1):45S–51S
12. Daniel D, Goldberg T, Weinberger D, et al. Cross-over comparison of risperidone and clozapine on clinical, cognitive and side effect measures in treatment-resistant psychosis. Presented at the 34th New Clinical Drug Evaluation Unit meeting; June 1994; Marco Island, Fla
13. Claus A, Bollen J, De-Cuyper H, et al. Risperidone versus haloperidol in the treatment of chronic schizophrenic inpatients: a multicenter double-blind comparative study. Acta Psychiatr Scand 1992;85:295–305

14. Schooler NR. Negative symptoms in schizophrenia: assessment of the effect of risperidone. J Clin Psychiatry 1994;55(5, suppl):22–28
15. Wilms G, Van Onbgeval C, Baert AL, et al. Ventricular enlargement, clinical correlations and treatment outcomes in chronic schizophrenic inpatients. Acta Psychiatr Scand 1992;85:306–312
16. Muller-Span F, the International Risperidone Research Group. Risperidone in the treatment of chronic schizophrenic patients: an international double-blind parallel-group study versus haloperidol. Clin Neuropharmacol 1992;15(suppl 1):90A–91A
17. Carpenter WT. Serotonin-dopamine antagonists and treatment of negative symptoms. J Clin Psychopharmacol 1995;15(suppl 1):30S–35S
18. Carpenter WT, Heinrichs DW, Wagman AMI. Deficit and nondeficit forms of schizophrenia: the concept. Am J Psychiatry 1988;145: 578–583