Risperidone in the Treatment of Schizotypal Personality Disorder

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Objective: Schizotypal personality disorder (SPD) has many phenomenological, genetic, physiologic, and neuroanatomical commonalities with schizophrenia. Patients with the disorder often suffer from marked social and occupational impairment, yet they have been difficult to treat with medications because of their unusual sensitivity to side effects. This study was designed to determine whether low-dose risperidone treatment is acceptable to SPD patients and can reduce characteristic schizotypal symptoms. In addition, if SPD patients respond to an antipsychotic medication, this will provide support for the notion of a commonality in treatment response between SPD and schizophrenia.

Method: Twenty-five patients with DSM-IV–defined SPD were entered into a 9-week randomized, double-blind, placebo-controlled study of low-dose risperidone (starting dose of 0.25 mg/day, titrated upward to 2 mg/day) in the treatment of SPD. Patients were rated with the Positive and Negative Syndrome Scale (PANSS), the Schizotypal Personality Disorder Questionnaire, the Hamilton Rating Scale for Depression, and the Clinical Global Impressions scale. Data were collected from 1995 to 2001.

Results: The subjects had a low incidence of depression and of comorbid borderline personality disorder. Patients receiving active medication had significantly ($p < .05$) lower scores on the PANSS negative and general symptom scales by week 3 and on the PANSS positive symptom scale by week 7 compared with patients receiving placebo. Side effects were generally well tolerated, and there was no group difference in dropout rate for side effects.

Conclusion: Low-dose risperidone appears to be effective in reducing symptom severity in SPD and is generally well tolerated.

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Patients with schizotypal personality disorder (SPD) have severe impairments in their capacity to relate to others and to function in customary occupational settings. These impairments arise from the patients' difficulty in reading social cues; high levels of social anxiety; tendency to appear odd, eccentric, or peculiar; vague, overelaborate, metaphorical, or stereotyped speech; vulnerability to suspiciousness, ideas of reference, or paranoid ideation; inappropriate or constricted affect; and odd beliefs. They often have difficulty getting or keeping jobs, or at best they work at occupations considerably below a level commensurate with their levels of education. In addition to their social and occupational impairments, SPD patients often suffer symptomatic anxiety and depression. Occurring with a prevalence estimated to be 3% of the general population,[1] SPD carries with it appreciable social cost and public health impact.

There have been few studies of the pharmacologic treatment of SPD, and these studies have been subject to the confound of high borderline personality disorder comorbidity in the study populations. An open-label trial of fluoxetine in a sample of 22 patients diagnosed with borderline personality disorder, SPD, or both reported improvement in depression, anxiety, interpersonal anxiety, interpersonal sensitivity, and psychoticism,[2] but only 4 of these patients had SPD without borderline personality disorder. Five studies of treatment with low-dose typical neuroleptics have been reported,[3–7] but only 2 of these

studies were placebo controlled.[6,7] Most patients in these studies had concurrent SPD and borderline personality disorder, making it difficult to determine which disorder the medication might be treating. One study[2] did not mention whether there was comorbidity for borderline personality disorder or other personality disorders. Among the 4 remaining studies, 70% of those treated had concurrent SPD and borderline personality disorder.[8]

In general, the patients in these studies appeared to show modest improvement on treatment with low-dose neuroleptics, with the greatest effects on psychotic-like symptoms and anxiety. Dropout rates were high because of considerable sensitivity to side effects in this population. The favorable side effect profile and reported efficacy of the atypical neuroleptics for negative symptoms make these drugs particularly promising for treating SPD. To our knowledge, there is 1 published report of the use of an atypical neuroleptic in the treatment of patients with SPD.[9] That open-label study of olanzapine in the treatment of 11 borderline personality disorder patients, 7 of whom were comorbid for SPD, showed improvement in psychoticism, depression, interpersonal sensitivity, and anger. Because the majority of patients in studies of the pharmacologic treatment of SPD had comorbid diagnoses of SPD and borderline personality disorder, it remains unclear whether the reported improvements were due to the medication's effect on SPD or borderline personality disorder.

The present study is a 9-week randomized, placebo-controlled, double-blind study of the effects of low-dose risperidone in the treatment of SPD. This trial is the first to minimize the potential confound of borderline personality disorder comorbidity, as only about 20% of our SPD sample had comorbid borderline personality disorder diagnoses. Since SPD patients are often highly somatically preoccupied, we anticipated considerable side effect sensitivity in this population. We therefore designed this study to begin at a very low dose of risperidone (0.25 mg/day) with gradual stepwise increases in dosage (to 2 mg/day) over the 9-week period.

Because risperidone has been shown to treat positive and general psychopathologic symptoms, such as unusual thought content, anxiety, tension, and lack of insight in schizophrenia,[10,11] and may treat negative symptoms in schizophrenia,[12–14] we expected that SPD patients, who share many genetic and biological commonalities with schizophrenia patients,[15] would show improvement in these areas as well. Specifically, we hypothesized that SPD patients treated with risperidone would show lower levels of those SPD symptoms that appear to be linked to the positive symptoms of schizophrenia (SPD-positive symptoms, e.g., suspiciousness, odd beliefs, conceptual disorganization), those that appear to be linked to the negative symptoms of schizophrenia (SPD-negative symptoms, e.g., constricted affect, social avoidance), and general psychopathologic symptoms (e.g., somatic preoccupations, anxiety) compared with patients receiving placebo at the 3-week, 5-week, 7-week, and 9-week timepoints.

METHOD

We recruited subjects from the outpatient clinics at the Mount Sinai Medical Center (New York, N.Y.) and the Bronx Veterans Affairs Medical Center (Bronx, N.Y.) and through advertisements that described typical SPD symptoms and were placed in local newspapers. Subjects were required to meet DSM-IV criteria for SPD and not meet current or lifetime DSM-IV or Research Diagnostic Criteria[16] for schizophrenia or any schizophrenia-related psychotic disorder or for bipolar disorder. Subjects comorbid for borderline personality disorder and SPD in whom borderline personality disorder was considered primary were referred to a separate study. All subjects were medically and neurologically healthy, without abuse of illicit substances or alcohol within the past 6 months or a past history of substance dependence, and had been free of psychotropic medication for at least 2 weeks. All patients received a physical examination; electrocardiogram; complete blood count; electrolytes, liver, and renal function tests; thyroid function tests; urinalysis; and a urine toxicology screen. Subjects were male or female and between the ages of 18 and 60 years.

The Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-I/P)[17] was utilized to evaluate Axis I diagnoses. The Schedule for Interviewing DSM-IV Personality Disorders-IV (SIDP-IV)[18] was utilized to evaluate criteria for DSM-IV personality disorders on the basis of Ph.D.- or master's-level psychologists' interviews of the patient and an informant close to the patient when available. The raters had a reliability of kappa = 0.73 for SPD with a range of 0.84 to 0.68 for each SPD criterion. Kappas for the other personality disorders were 0.81 for borderline, 0.85 for schizoid, 0.69 for paranoid, 0.60 for histrionic, 0.57 for antisocial, –0.02 for narcissistic, 0.79 for avoidant, 0.85 for dependent, 0.68 for obsessive-compulsive, and 0.72 for passive-aggressive. Diagnostic decisions were made during a consensus meeting chaired by an independent senior clinician (J.S.), where all available information regarding the patient was presented; additional information was sought, when necessary, to resolve possible discrepancies. The study was approved by the institutional review boards of the Mount Sinai School of Medicine and the Bronx Veterans Affairs Medical Center, and all subjects signed a written informed consent statement after the study was explained to them. Data were collected from 1995 to 2001.

Patients were randomly assigned in a 1-to-1 ratio to receive risperidone or placebo in identical tablets. All patients received a single-blind 2-week placebo lead-in

followed by a double-blind 9-week medication trial. The dosage of risperidone was titrated upward in a stepwise design, beginning with 0.25 mg/day for the first week, 0.5 mg/day for weeks 2 and 3, 1.0 mg/day for weeks 4 and 5, 1.5 mg/day for weeks 6 and 7, and 2.0 mg/day for weeks 8 and 9. Patients were seen weekly by the research psychiatrist. Dosages could be lowered by the research psychiatrist if clinically indicated to reduce side effects.

We obtained weekly measures of symptomatology by means of the Positive and Negative Syndrome Scale (PANSS),[19] the 21-item Hamilton Rating Scale for Depression (HAM-D),[20] and the Clinical Global Impressions scale (CGI)[21] beginning before the start of the placebo lead-in and through the end of the ninth treatment week. Schizotypal symptoms were assessed with the Schizotypal Personality Questionnaire (SPQ),[22] which was administered at baseline and at weeks 2, 4, 6, and 8.

The PANSS, an instrument developed for rating positive and negative symptoms in schizophrenia, has been used extensively by our group in rating patients with SPD. It is composed of 3 subscales: a 7-item positive symptom scale, which includes measures of conceptual disorganization, suspiciousness, and delusional thinking; a 7-item negative symptom scale, which includes measures of blunted affect, social withdrawal, stereotyped or impaired abstract thinking, and impaired conversational flow; and a 16-item general psychopathology scale, which includes assessments of social anxiety, social avoidance, unusual thought content, and somatic concerns. Raters in our group demonstrated intraclass correlation coefficients of 0.80 and 0.85 for the positive symptom scale and the negative symptom scale, respectively. The PANSS was originally designed for rating symptoms of schizophrenia, and, although the PANSS has not been validated in the SPD population, its scales measure symptoms that are associated with SPD as well as with schizophrenia. A study comparing PANSS scores of schizophrenia spectrum patients (including SPD patients), schizophrenic patients, and relatives with no psychiatric disorder provides support for use of the PANSS in the schizophrenia spectrum.[23] The SPQ is a self-report instrument with 74 items based on the DSM-III-R criteria for SPD. The CGI provides an overall rating of clinical severity on a 0-to-7 scale. When administered by our raters, it has a reliability of kappa = 0.85. The occurrence of side effects was assessed weekly during an interview by one of the study psychiatrists (H.W.K., D.R., M.G., A.S.N.).

We compared the mean symptom scores for patients in each group at baseline and at 3, 5, 7, and 9 weeks of treatment using t tests. We carried out separate analyses for all subjects in the study and for those who completed the 9 weeks of treatment. Although our central research question was whether the active medication and placebo groups would differ at each timepoint, corresponding to treatment at successively increasing medication doses, we also carried out multivariate repeated-measures analyses of variance to determine whether there was an overall drug-by-time interaction. Significance was set at the .05 level, 2-tailed. Inspection of Q-Q plots was carried out to confirm that the symptom scores were approximately normally distributed.

Table 1. Sample Characteristics of Patients With Schizotypal Personality Disorder

Characteristic	Risperidone (N = 14)	Placebo (N = 9)
Age, mean (SD), y	41.5 (11.9)	39.4 (12.3)
Female, N	1	3
HAM-D score, mean (SD)	10.50 (6.00)	10.11 (4.48)
Ethnic composition, N		
White	8	6
Black	4	1
Hispanic	2	2
Comorbid personality disorder, N[a]		
Paranoid	5	5
Schizoid	3	1
Obsessive-compulsive	1	1
Histrionic	2	1
Dependent	1	1
Antisocial	0	0
Narcissistic	2	5
Avoidant	7	2
Borderline	2	3
Passive-aggressive	3	2
Personality disorder NOS	0	0

[a]A number of subjects had several personality disorders.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, NOS = not otherwise specified.

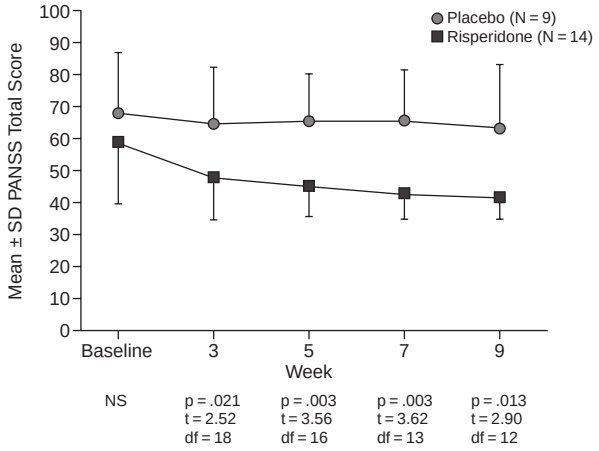
RESULTS

Of the 25 subjects entered into the study, 15 were randomly assigned to risperidone, and 10 were randomly assigned to placebo. The groups were unequal in size because of chance assignment of more subjects to the active medication group and an error in randomization of 2 subjects. One subject each in the risperidone and placebo groups dropped out within the first week, during the placebo lead-in phase, and were excluded from the analysis. The groups did not differ significantly in age, gender, or baseline HAM-D scores, and the mean depression scores were low (Table 1). As expected, most subjects met criteria for several personality disorders. Table 1 presents the ethnic composition and comorbid personality disorders in each group.

Premature Terminations

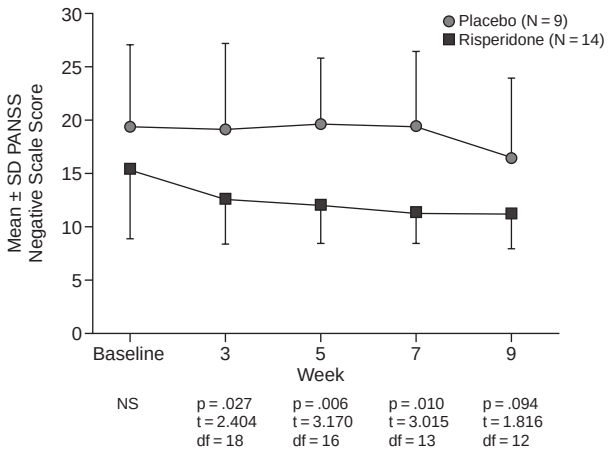
Two of 9 patients in the placebo group failed to complete the 9-week treatment trial. One patient dropped out at the 2-week point because of loss of interest in the study, and the second was withdrawn from the study by the investigators because of the subject's report that a mild tic-like movement of the neck muscles (which had been

Figure 1. PANSS Total Scores in Patients With Schizotypal Personality Disorder



Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Figure 2. PANSS Negative Scale Scores in Patients With Schizotypal Personality Disorder



Abbreviation: PANSS = Positive and Negative Syndrome Scale.

intermittently present for about 10 years prior to the study following an exposure to haloperidol) had intensified. A third subject completed the trial but did not appear for testing in the final week. Six of 14 risperidone-treated patients failed to complete the trial. Four patients dropped out: 1 at the 2-week point because of diminished sexual arousal and delayed ejaculation, 1 at the 3-week point because he tired of the study questionnaires, 1 at the 5-week point because of drowsiness, and 1 at the 6-week point for feelings of "weakness." One subject was withdrawn in the second week because of an increase in suicidal ideation, and 1 subject was withdrawn in the sixth week because of galactorrhea that did not respond to dose reduction. The groups did not differ significantly in the number of subjects who terminated prematurely (Fisher exact test p = .176, NS). A comparison between all subjects who dropped out or were terminated from the study and those who completed the study revealed no significant differences in age, gender, baseline CGI, HAM-D, SPQ scores, or baseline PANSS negative, positive, or general symptom scores.

Side Effects

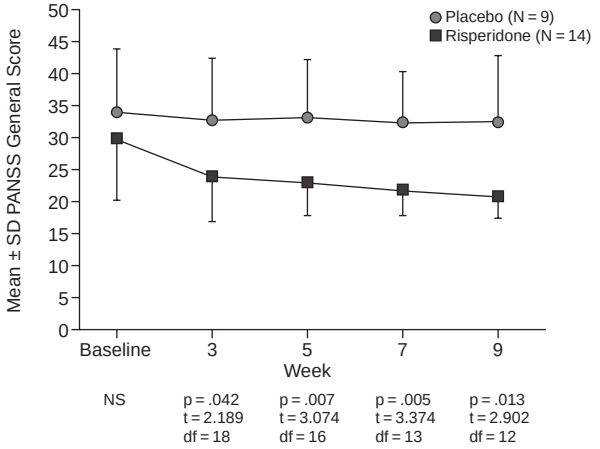
Seven risperidone subjects reported side effects. These included dry mouth, tiredness, weakness, decreased sexual arousal and delayed ejaculation, and a mild dystonic reaction that responded to 50 mg of diphenhydramine. Medication dosage was lowered because of side effects in only 1 patient. This patient developed galactorrhea at a 1-mg dose, and her medication dose was lowered to 0.5 mg/day and then 0.25 mg/day before she was terminated from the study. (Subsequent endocrinologic evaluation diagnosed a pituitary microadenoma in this subject.) Five placebo-treated subjects reported side effects. These included feeling slowed down, tiredness, dry mouth, nausea, diarrhea, and headache. Four risperidone subjects and 1 placebo subject discontinued the study because of possible side effects. The dropout rates for side effects did not differ between groups, even if we conservatively add as a fifth risperidone dropout the patient who was withdrawn from the study because of suicidal ideation (p = .340, NS, Fisher exact test).

Symptom Change

The PANSS total score declined over the 9-week trial in the active medication group, but not in the placebo group (Figure 1). Patients in the medication group had significantly lower PANSS total scores than those in the placebo group at weeks 3, 5, 7, and 9 (p = .021, p = .003, p = .003, and p = .013, respectively). The total PANSS score at baseline was slightly higher in the placebo group than in the medication group, but this difference did not reach significance. Nevertheless, to control for differences in baseline scores, we repeated the analysis using a univariate general linear model (GLM), covarying for baseline PANSS total score. The results were comparable. To insure that these differences could not be explained by early dropout of the more symptomatic patients from the risperidone group, we repeated the analysis for only those patients who completed the trial, and the differences remained significant at 3, 5, 7, and 9 weeks. A multivariate repeated-measures analysis of variance yielded a nonsignificant drug-by-time interaction, indicating no group differences in the pattern of change over time in the PANSS total score.

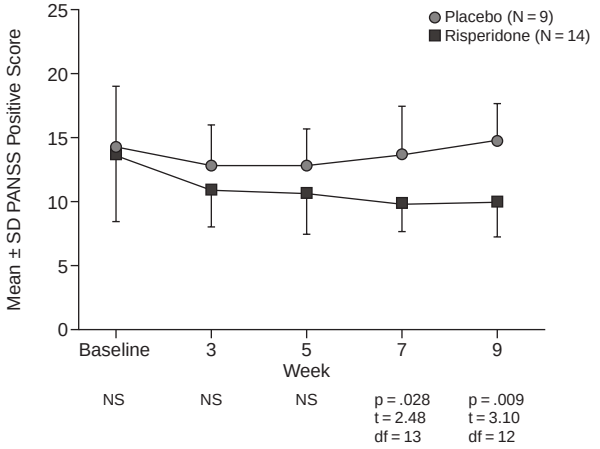
Patients in the risperidone group showed a decline in PANSS negative symptoms scores (Figure 2), with significant differences between active medication and pla-

Figure 3. PANSS General Scale Scores in Patients With Schizotypal Personality Disorder



Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Figure 4. PANSS Positive Scale Scores in Patients With Schizotypal Personality Disorder



Abbreviation: PANSS = Positive and Negative Syndrome Scale.

cebo groups at weeks 3, 5, and 7 (p = .027, p = .006, and p = .010, respectively) and a trend-level difference at week 9. In the analysis that covaried for baseline PANSS negative scores, the differences remained significant at weeks 3, 5, and 7, but there was no longer a statistical trend for a group difference at the 9-week point. In the completer analysis, subjects in the risperidone group had significantly lower PANSS negative scores than those in the placebo group at weeks 5 and 7. The multivariate repeated-measures analysis of variance yielded a nonsignificant drug-by-time interaction.

The PANSS general symptom scores did not differ significantly at baseline, but were significantly lower in the risperidone group than in the placebo group at weeks 3, 5, 7, and 9 (Figure 3). A separate analysis of completers replicated this finding. An analysis of variance that covaried for the baseline PANSS general score also found significant differences at the 5-, 7-, and 9-week points, but not at 3 weeks. The multivariate repeated-measures analysis of variance yielded a nonsignificant drug-by-time interaction.

Patients in the active medication group showed a decline in PANSS positive symptom score over the 9-week treatment period, while those in the placebo group showed a slight decline and then an increase (Figure 4). At the 7-week and 9-week points, the risperidone group had lower PANSS positive scores than the placebo group (p = .028 and p = .009, respectively). The findings were similar for the GLM univariate analysis that covaried for baseline PANSS positive scores. In the analysis for only those patients who completed the trial, placebo and active medication patients did not differ significantly in symptom level at baseline, but those receiving active medication were significantly less symptomatic at weeks 7 and 9, as in the analysis of the entire sample. A repeated-measures multivariate analysis of variance showed a significant drug-by-time interaction (F = 3.799, df = 4,9; p = .045), indicating group differences in the pattern of change over time in the PANSS positive symptoms score.

By the last week of the study, 50% (4/8) of subjects in the active medication group had improved on the PANSS positive scale, and 25% (2/8) had improved on the PANSS general, negative, and total scales, where improvement is defined as a 25% or greater reduction in score from baseline. All of those subjects who were improved at week 9 on the PANSS positive scale had improved by week 5. For the PANSS general scale, all subjects who were improved at week 9 had improved by week 7. It was not possible, however, to predict improvement at week 9 on the PANSS negative scale by improvement at an earlier timepoint. In our small sample, the pattern of improvement across symptom scales appeared to be variable, with some subjects showing improvement on all PANSS subscales and others showing improvement primarily on a single subscale.

By the ninth week, there were greater declines in SPQ score and CGI score in the risperidone group than in the placebo group (mean ± SD SPQ scores: 28.2 ± 17.4 at baseline and 19.6 ± 17.3 at week 9 for the active medication group and 33.5 ± 16.0 at baseline and 33.8 ± 19.7 at week 9 for the placebo group; CGI scores: 3.9 ± 1.2 at baseline and 3.0 ± 1.4 at week 9 for the active medication group and 4.2 ± 1.3 at baseline and 4.2 ± 1.0 at week 9 for the placebo group), but the group differences did not reach statistical significance at any of the timepoints. There was little change in HAM-D score in either group (10.50 ± 6.00 at baseline and 8.88 ± 6.79 at week 9 for the active medication group; 10.11 ± 4.48 at baseline and

12.17 ± 7.81 at week 9 for the placebo group), with none of the group differences reaching significance.

To separate out the possibility that symptomatic improvement resulted from the effect of treatment on borderline personality disorder comorbidity, we repeated the analyses, removing the 5 patients with diagnoses of borderline personality disorder from the sample. The risperidone group continued to have significantly lower PANSS total scores at weeks 5 and 7, with trend-level differences at weeks 3 and 9; to have significantly lower PANSS negative scores at weeks 5 and 7, with trend-level differences at weeks 3 and 9; to have significantly lower PANSS general scores at week 7, with trend-level differences at weeks 3, 5, and 9; and to have lower PANSS positive scores at a trend level at weeks 7 and 9 compared with the placebo group.

DISCUSSION

Patients with SPD showed significant improvement in PANSS total, negative, general, and positive symptom scores during 9-week treatment with low-dose risperidone compared with those receiving placebo. By the end of the 9-week trial, PANSS total score had been reduced by 29%; PANSS general score, by 30%; PANSS positive score, by 27%; and PANSS negative score, by 27% compared with baseline. Changes of this magnitude in the PANSS have been shown to correspond to observed clinical improvement.[24]

With the exception of 1 risperidone patient who developed galactorrhea, all patients received risperidone at the doses specified in the stepwise design. Patients receiving active medication showed significantly lower total, negative, and general symptom scores than those receiving placebo by the third treatment week, at which point patients had been receiving a dosage of 0.5 mg/day of risperidone. The group difference in positive symptom score became significant by week 7, after subjects had been receiving 1.5 mg/day of risperidone. Because of the stepwise incremental design, however, we do not know whether the improvement at the 7-week point was a result of the higher dosage or of longer duration of treatment.

By week 9, CGI score improved by 22% in the risperidone group compared with 4% in the placebo group, but the group differences did not reach significance. This may be because both groups began with relatively low CGI scores (mild-to-moderate in severity) and there was relatively little room for clinical improvement on this scale. There was also a greater change in SPQ score in the risperidone group than in the placebo group, but group differences did not reach significance, perhaps because of the small sample size or because, with its focus on a number of infrequent events, the instrument is less sensitive to acute change than the PANSS. With mean HAM-D scores of 10 (out of a possible 63), subjects in the placebo and active medication groups were not very depressed at baseline, and there was little change in depression during the study period.

Both placebo- and risperidone-treated subjects complained of a variety of mild side effects, possibly reflecting the strong tendency of SPD patients to become somatically preoccupied. There was no group difference in dropout rate for side effects. Nevertheless, among the 4 of 14 risperidone subjects who chose to discontinue because of side effects, 3 began experiencing side effects when the dosage reached 1.0 mg/day or higher. This observation coupled with the finding of improvement in our lowest dosage range warrants further study of the effectiveness of doses between 0.5 and 1.0 mg/day of risperidone in this population.

Previous studies of the treatment of SPD have been confounded by a high co-occurrence of SPD and borderline personality disorder, which has made it difficult to determine whether improvement has been due to the treatment's effect on SPD or borderline personality disorder. A strength of our study is the low incidence of borderline personality disorder in our subject population (5/23 subjects). In addition, the low level of depression in our sample makes it unlikely that symptom change is secondary to an effect of risperidone in reducing depression.

A weakness of the study is the small sample size, which limits the power and generalizability of the findings. The lower baseline rating scale scores and smaller number of comorbid personality diagnoses in the active medication group compared with the placebo group raise the possibility that those randomly assigned to the medication group were less ill than those in the placebo group and hence more apt to improve spontaneously over time. While we cannot rule out this possibility as a possible confound, a number of factors make it unlikely to account for our findings. First, the baseline differences were small and not statistically significant. Second, regression toward the mean of the higher placebo group scores would bias against finding differences in medication effect. Finally, covarying for baseline scores did not alter the efficacy finding.

While this study calls for replication, it does suggest that the symptoms of SPD respond to low doses of the atypical neuroleptic risperidone. Although SPD patients are particularly sensitive to somatic effects of medication, the 29% dropout rate due to side effects in this study is encouraging and might be further reduced if dosages are kept below the level of 1 mg/day. Thus, risperidone may be preferable to traditional neuroleptics in treating SPD because its milder side effect profile may make it more acceptable in a population with a high level of somatic preoccupation and it may be more effective in treating negative-SPD symptoms.

From the point of view of understanding the commonalities and differences in the disorders of the schizophrenia spectrum, the positive response to risperidone repre-

sents an area of commonality between SPD and schizophrenia. We had, in fact, hypothesized that risperidone would be effective in the treatment of symptoms of SPD because of the extensive similarities between SPD and schizophrenia, which are reflected in such domains as their phenomenology, cognitive functioning, genetics, psychophysiology, and neuroanatomy.[15] Deficits of cognitive function in the areas of sustained attention, working memory, and learning that are seen in SPD[25] may account for much of the functional disability in the disorder. Disordered prefrontal dopaminergic activity has been implicated in impaired working memory,[26] and the serotonin antagonism of risperidone is believed to increase dopaminergic activity in the frontal cortex.[27] This suggests that risperidone may also be useful in ameliorating cognitive deficits in SPD. A study of the effectiveness of risperidone in improving working memory, sustained attention, and learning in SPD is underway by our group.

Drug names: diphenhydramine (Benadryl), fluoxetine (Prozac and others), haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal).

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