Open-Label Risperidone for Asperger's Disorder: Negative Symptom Spectrum Response

Jeffrey L. Rausch, M.D.; Elizabeth L. Sirota, M.D.; Donna L. Londino, M.D.; Maria E. Johnson, M.D.; Benjamin M. Carr, M.D.; Renu Bhatia, M.D.; and Stephen Miller, Ph.D.

Objective: Asperger's disorder consists of negative symptoms similar to those seen in schizophrenia, autism, schizoid personality disorder, and schizotypal personality disorder. We investigated whether risperidone, which is effective in treating the negative symptoms of schizophrenia, would improve such symptoms observed in Asperger's disorder in a prospective, open-label trial.

Method: Thirteen male patients aged 6 to 18 years who were diagnosed with Asperger's disorder by DSM-IV criteria were enrolled in a 12-week, prospective, open-label pilot study from March 13, 2002 to August 11, 2003. All subjects were started on risperidone 0.25 mg twice per day. Doses were increased based on clinical indication and tolerability. The primary efficacy variable was the Scale for the Assessment of Negative Symptoms (SANS). Each subject's baseline score served as his control. Secondary efficacy measures included the Positive and Negative Syndrome Scale, Brief Psychiatric Rating Scale, Montgomery-Asberg Depression Rating Scale, Global Assessment Scale, and a modified Asperger Syndrome Diagnostic Scale.

Results: We found a statistically significant improvement from baseline for last-observation-carried-forward (LOCF) analyses as well as for analyses of 12-week completers (N = 9) in our primary outcome measure, SANS scores ($F = 13.41$, $p < .0001$ for 12-week completers; $F = 9.64$, $p < .0001$ for LOCF). We also found statistically significant improvement in all secondary efficacy measurements (F values range, 8.41 to 15.73, p values range, < .0001 to < .005 for 12-week completers; F values range, 6.53 to 7.75, all $p < .0001$ for LOCF).

Conclusions: Subjects' symptoms significantly improved after risperidone. The open-label nature of this small pilot study suggests caution in interpreting these data, but the results suggest that placebo-controlled trials should follow.

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Corresponding author and reprints: Jeffrey L. Rausch, M.D., Dept. of Psychiatry and Health Behavior, Medical College of Georgia, 1515 Pope Ave., Augusta, GA 30912 (e-mail: jeffreyr@mail.mcg.edu).

Asperger's disorder is a pervasive developmental disorder characterized by severe and sustained impairments in social interaction and the development of restricted, repetitive patterns of behavior, interests, and activities.[1] The prevalence of the disorder is a matter of some uncertainty but has been estimated by some work to have a minimum prevalence of 0.4%.[2] Although it is possible for individuals with Asperger's disorder to attain social and financial independence, the majority face often severe isolation, anxiety, and depression.[3–5] Historically, treatment has focused on maximizing the patients' quality of life through motor skills training, remedial education, and vocational skills training.[5–8] Pharmacotherapy has been used to treat the complications of the disorder, such as anxiety and depression,[9] but no drug has effectively targeted the underlying condition.[10]

The DSM-IV criteria for the diagnosis and description of Asperger's disorder contain prominent similarities to the cluster of negative symptoms that characterize other diagnoses. We recently reviewed the similarity of the negative symptoms of schizophrenia to those of Asperger's disorder, schizoid personality disorder, and schizotypal personality disorder (J.L.R., E.L.S., D.L.L., et al., manuscript submitted). The results indicated that these disorders present with receptive and expressive deficits of emotion in social context as well as cognitive and behavioral stereotypies. The negative symptoms associated with these conditions, with schizophrenia being

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the most prominent example, are often largely refractory to pharmacotherapy with conventional antipsychotic agents. Newer atypical antipsychotic drugs have held more promise for treating negative symptoms of schizophrenia.[11–14]

Consequently, we questioned whether atypical antipsychotic drugs such as risperidone might have a beneficial effect in treating the negative symptoms of a disorder like Asperger's. Previous reports had suggested that conventional antipsychotics held little anecdotal benefit for the core symptoms of Asperger's disorder,[15–17] although more recent controlled studies have indicated that the atypical antipsychotics, such as risperidone, may improve the disruptive and hyperactive behavior and affective dysregulation in some children and adolescents with other pervasive developmental disorders.[3–5] Moreover, one small study to date has also shown supportive evidence for the efficacy of risperidone in Asperger's disorder.[18] To test the hypothesis, specifically that the negative symptoms of Asperger's syndrome would improve after atypical antipsychotic treatment, we piloted the effects of prospective, open-label risperidone in 13 patients with Asperger's disorder.

METHOD

Thirteen patients aged 6 to 18 years who were diagnosed with Asperger's disorder by DSM-IV criteria were enrolled in a 12-week, prospective, open-label pilot study from March 13, 2002, to August 11, 2003. Informed consent was obtained from either the subjects or their legal guardians after the study was reviewed and approved by the Medical College of Georgia's institutional review board. Female subjects of childbearing age were required to have a negative urine pregnancy test at screening and at baseline and had to be effectively practicing an acceptable method of birth control (oral or parenteral hormonal contraceptives, intrauterine device, or barrier and spermicide). All subjects included were free of serious, unstable medical conditions as determined by physical examination, medical history, electrocardiogram (ECG), blood chemistry and hematology, and a urinalysis. A negative urine drug screen was also required.

Subjects were excluded if they met DSM-IV criteria for any psychotic disorder including schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder due to a general medical condition, substance-induced psychotic disorder, psychotic disorder not otherwise specified, major depressive disorder with psychotic features, or bipolar disorder. Other exclusionary diagnoses included paranoid personality disorders, autistic disorder, or pervasive developmental disorder not otherwise specified. Subjects who met the criteria for substance abuse or dependence within the 3 previous months (nicotine and caffeine being exceptions) were excluded. Subjects who were believed by the investigator to be at significant risk for suicide or violent behavior, were pregnant or nursing females, or had known or suspected seizure disorder were excluded. For subject consistency related to drug exposure, those who received neuroleptics within 3 months of baseline evaluation, antidepressants or lithium within 4 weeks of evaluation, fluoxetine within 6 weeks of evaluation, or any psychotropic medication within 1 week of the trial were excluded.

The 13 patients who met the initial criteria for the study underwent a 3-day screening period for safety assessments, including the aforementioned history and physical examination, laboratory tests, vital signs, and ECG. This time allowed for definitive diagnosis of Asperger's disorder and ruled out potential comorbidities. After this period, the subjects began receiving a risperidone dose of 0.25 mg twice per day. All participants in the study were instructed not to take any over-the-counter or prescription medications.

The subjects' response to the drug was evaluated by the Scale for the Assessment of Negative Symptoms (SANS)[19] (our primary outcome measure) at 3, 6, 9, and 12 weeks, and compared to an initial baseline score. Secondary efficacy measurements included a modified Asperger Syndrome Diagnostic Scale (ASDS),[20] the Positive and Negative Syndrome Scale (PANSS),[21] the Montgomery-Asberg Depression Rating Scale (MADRS),[22] the Brief Psychiatric Rating Scale (BPRS),[23] and the Global Assessment Scale (GAS).[24] The potential for movement disorders was monitored by the Abnormal Involuntary Movement Scale (AIMS).[25]

The study design anticipated dose adjustments to occur after week 6, but allowed adjustments earlier based on clinical presentation, according to response and tolerability in the judgment of the clinical investigator. Doses from 1 to 2 mg per day at 6 weeks and 1 to 4 mg per day at 9 weeks were allowed by the study design.

Response was assessed by repeated-measures comparison of negative symptoms from baseline to the end of the study, as assessed by SANS score. The primary and secondary efficacy measures were statistically analyzed by repeated-measures analysis of covariance (ANCOVA) using a significance criterion of $p < .05$. Dose was used as a covariate for the repeated-measures design. By this design, each patient served as his own control and the statistical significance of response to treatment was calculated in comparison to baseline.

RESULTS

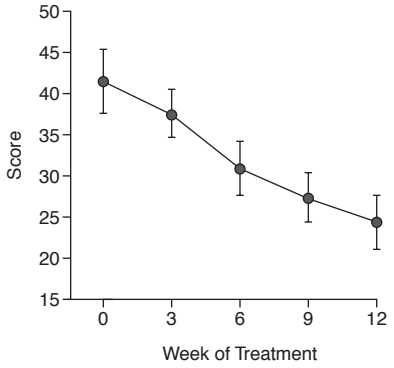
All of the subjects eligible for the study were male. The actual risperidone doses received by the subjects were much lower than the maximum allowed by the study design. All subjects started on a baseline dose of 0.5 mg per day. Doses ranged from 0.5 mg to 1.0 mg at 3 weeks,

Table 1. Repeated-Measures ANCOVA Statistics for Significance of Improvement Over Baseline in Patients With Asperger's Disorder Treated With Risperidone

	12-Week Completers Analysis (N = 9)		12-Week LOCF Analysis (N = 13)	
Efficacy Measurements	F	p	F	p
SANS	13.41	< .0001	9.64	< .0001
PANSS	10.63	< .0001	7.32	< .0001
BPRS	8.90	< .0001	7.75	< .0001
MADRS	15.73	< .005	7.51	< .0001
GAS	10.06	< .0001	6.53	< .0001
ASDS total	8.41	< .0001	7.45	< .0001
Language dysfunction	5.66	.001	5.30	< .001
Social behavior	8.82	< .0001	8.43	< .0001
Maladaptive behavior	4.95	< .005	4.25	.005
Cognitive dysfunction	3.82	< .02	3.12	< .05
Sensorimotor dysfunction	5.85	.001	6.64	< .0001
General dysfunction	4.68	< .005	5.29	.001

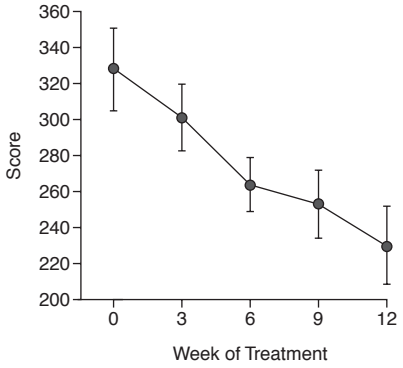
Abbreviations: ANCOVA = analysis of covariance, ASDS = Asperger Syndrome Diagnostic Scale, BPRS = Brief Psychiatric Rating Scale, GAS = Global Assessment Scale, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale, SANS = Scale for the Assessment of Negative Symptoms.

Figure 1. Risperidone Effect on SANS Scores in Asperger's Disorder: LOCF Analysis (N = 13)[a]



[a]p < .0001.
Abbreviations: LOCF = last observation carried forward, SANS = Scale for the Assessment of Negative Symptoms.

Figure 2. Risperidone Effect on ASDS Scores in Asperger's Disorder: LOCF Analysis (N = 13)[a]



[a]p < .0001.
Abbreviations: ASDS = Asperger Syndrome Diagnostic Scale, LOCF = last observation carried forward.

0.5 mg to 0.75 mg at 6 weeks, 0.5 mg to 1.5 mg at 9 weeks, and 0.5 to 1.5 mg at the end of the 12-week trial. The repeated-measures data were analyzed in 2 ways: one for the 9 subjects who completed the trial (completers analysis) and the other for all subjects, using the last-observation-carried-forward (LOCF) method.

Efficacy

A statistically significant improvement from baseline in SANS score was found for the 12-week completers ($F = 13.41$, $p < .0001$) and 12-week LOCF ($F = 9.64$, $p < .0001$). Results were also significant for PANSS scores ($F = 10.63$, $p < .0001$ for 12-week completers; $F = 7.32$, $p < .0001$ for 12-week LOCF), BPRS scores ($F = 8.90$, $p < .0001$ for 12-week completers; $F = 7.75$, $p < .0001$ for 12-week LOCF), MADRS scores ($F = 15.73$, $p < .005$ for 12-week completers; $F = 7.51$, $p < .0001$ for 12-week LOCF), and GAS scores ($F = 10.06$, $p < .0001$ for 12-week completers; $F = 6.53$, $p < .0001$ for 12-week LOCF).

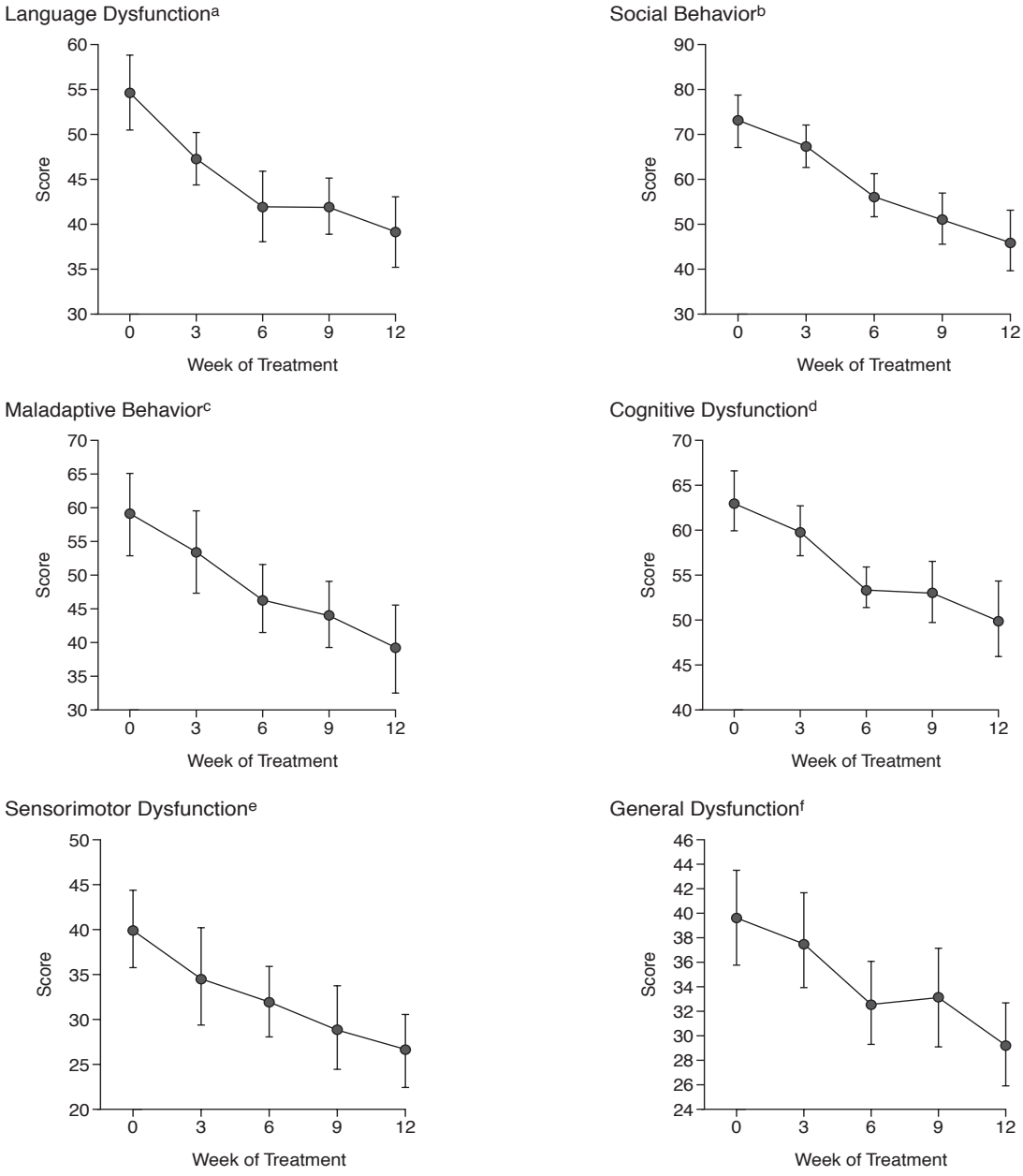
Statistically significant improvement was also observed in the total ASDS score ($F = 8.41$, $p < .0001$ for 12-week completers; $F = 7.45$, $p < .0001$ for 12-week LOCF) and in each separate component score. The ANCOVA results for improvements on the component scores of the ASDS are summarized in Table 1.

The SANS scores, our primary efficacy measure, decreased from a mean of 41.5 to a mean of 24.3 by the end of the trial (Figure 1). The ASDS total score decreased from a mean of 327 at baseline to 264 at week 6 and to 230 at week 12 (Figure 2). The results of the ASDS component scores previously mentioned are displayed in Figure 3.

Our analyses suggested that negative symptom improvement was not due to any carryover effect of positive symptom improvement; that is, the change in positive symptoms did not have a significant effect on the improvement in SANS score ($t = 0.779$). After covariance for changes in positive symptoms was factored out, the improvement in SANS was still significant ($F = 4.9$, $p = .002$).

In similar fashion, improvement in social behavior was not simply a derivative of the improvement in maladaptive behavior with risperidone. Maladaptive behavior was a significant covariate on the improvement of social behavior ($t = 3.68$, $p < .005$), but improvement of social behavior (on ASDS) was still significant ($F = 3.14$, $p < .023$) after accounting for maladaptive behavior improvement. The severity of depression (measured by MADRS) decreased from a mean of 9.9 at baseline to a mean of 6.0 at week 6 and a mean of 5.0 at week 12 (LOCF: $F = 7.51$, $p < .0001$). These results are presented in Table 1 and Figure 4.

Figure 3. Risperidone Effect on ASDS Component Scores in Asperger's Disorder: LOCF Analysis (N = 13)



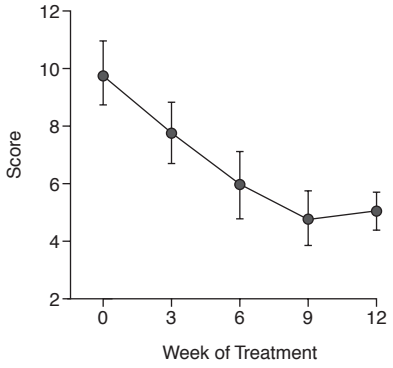
[a]p < .001; [b]p < .0001; [c]p < .005; [d]p < .05; [e]p < .0001; [f]p < .001.
Abbreviations: ASDS = Asperger Syndrome Diagnostic Scale, LOCF = last observation carried forward.

Safety

The most commonly reported adverse effect of risperidone administration was a mild increase in appetite. Six of the 13 subjects showed increase in appetite at week 3, which remitted in all but 2 by week 6. Of those 2, 1 of the subjects' increased appetite remitted by week 9. The other subject had increased appetite through the duration of the study. Appetite increase was consistent with an increase in the mean body weight of the total sample. Six of the 13 subjects showed a weight increase of greater than 1%, 2 had a 5% increase in weight, and 3 had weight increases ranging from 7% to 12% of their body weight. This represented a 3.5% mean increase in weight, from a mean weight of 36.2 kg at entry into the study to a mean weight of 37.7 kg by study termination. Mean weight gain for the whole population was 1.4 kg, ranging from a loss of 0.1 kg to a gain of 5.1 kg.

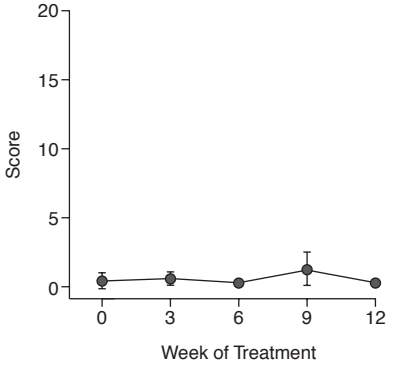
Other side effects included moderate sedation (5 subjects) and extrapyramidal side effects (EPS). Sedation appeared at 3 weeks in 2 of the 13 subjects and had resolved

Figure 4. Risperidone Effect on MADRS Scores in Asperger's Disorder: LOCF Analysis (N = 13)[a]



[a]p < .0001.
Abbreviations: LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale.

Figure 5. Risperidone Effect on AIMS Scores in Asperger's Disorder: LOCF Analysis (N = 13)[a]



[a]p = nonsignificant.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, LOCF = last observation carried forward.

in each of those subjects at weeks 6 through 12. A third subject had sedation appear at week 9 and resolve at week 12. Two other subjects experienced sedation for the first time at week 12.

Extrapyramidal side effects were evident in 3 of the 13 subjects at week 3. One of those subjects experienced an increase in EPS through weeks 6 and 9, but EPS dramatically decreased by week 12. A fourth subject had slight EPS appear at week 6 and remain the same through week 12. By week 12, only 2 of the subjects had EPS, with very low AIMS scores, each scoring a 1 on the AIMS, although 1 subject was withdrawn at week 6 from the study secondary to akathisia. AIMS scores varied from 0 to 6 at baseline, 0 to 5 at week 3, 0 to 2 at week 6, 0 to 16 at week 9 (1 subject had an AIMS score of 1, and 1 subject had an AIMS score of 16), and 0 to 1 at week 12. There was no statistically significant change in AIMS scores on repeated-measures analysis. An initial increase in AIMS scores during the first 9 weeks of the study from a baseline mean of 0.5 to a mean of 1.3 was followed by a decrease to a mean of 0.2 by the end of the study (Figure 5).

DISCUSSION

Some previous work is consistent with the findings in our study. We could find 2 previous such studies, 1 in which 3 patients with Asperger's disorder were treated with risperidone,[26] and 1 in which 6 patients who had been diagnosed with Asperger's as their sole diagnosis were treated with risperidone.[19] Both studies reported beneficial effects of risperidone on social functioning, the latter study specifically for negative symptoms on PANSS. Although this work, as evidenced by sparse publications in the literature, is in its early stages, the preliminary data to date have been consistent in demonstrating positive outcomes in prospective, open-label trials of treating Asperger's disorder. Future work may extend to placebo-controlled studies in Asperger's disorder as well as potential extensions of similar work in other negative symptom spectrum disorders.

Some caution is indicated in interpreting these data. A major caveat is the open-label nature of the trial. Placebo-controlled studies are necessary to validate the finding. In the present study, each subject served as his own control by comparing efficacy measures after treatment to his baseline. This comparison allowed for improvement to be observed and statistics analyzed in comparison to baseline, but not in comparison to placebo. These pilot data now provide strong support for a placebo-controlled study.

The second caveat is that we do not know whether this information would apply to female subjects. Despite the study's being designed for male and female subjects, all of the subjects who met the inclusion criteria were male. This outcome appears to be consistent with the observation that Asperger's disorder is more common in males.[2]

Another caveat is that, although the majority of subjects responded well to this treatment, some of the subjects had limited responses. Nine of the 13 subjects originally enrolled completed the 12-week trial. One subject was withdrawn for akathisia and maintenance of aggressive behaviors, 1 was withdrawn for maintenance of baseline difficulty with schoolwork, and 2 subjects were withdrawn for lack of compliance. Although our statistical analysis accounted for these subjects by carrying the last observation forward, supporting the statistical significance of the effect for the whole sample, the finding that subjects improved on risperidone treatment compared to baseline on average may not apply to every patient.

Another consideration is the small sample size of this trial (N = 13) and large age range (6 to 18 years). Despite

the small sample size, strong statistical significance on all measures was found. Also, this study more than doubles the sample size of the world's available literature on the subject of atypical antipsychotics in Asperger's disorder. However, a larger study is necessary to elucidate the risks and benefits of use of these drugs compared to placebo in this pediatric population. With a larger sample, better analysis could be done on the effect of age and response or side effects of risperidone.

A final caveat relates to the innovative use of the PANSS and ASDS in this study. The PANSS was developed to measure severity of symptoms in schizophrenia but has not been validated for measurement of symptom severity for patients with Asperger's disorder. Additionally, the ASDS used in this study was developed for the diagnosis of Asperger's disorder. The ASDS was utilized in this study for the purpose of measurement of symptom severity. Therefore, caution should be used in the interpretation of these results. The same is true for the other scales used in this study, as sensitive scales developed for the longitudinal measurement of symptom severity in Asperger's disorder were not available to us prior to the initiation of this trial.

Our data reiterate an important caution in the use of atypical antipsychotics—weight and appetite monitoring. The mean weight gain for subjects participating in the study, many of whom were growing children, was approximately 3 lb. Although the majority of subjects experienced either no or slight weight gain, some subjects did show a significant weight gain during the trial (1 subject's weight increased by 12% of his original body weight). Consequently, these data underscore the importance of monitoring weight with the use of neuroleptics.

Asperger's disorder, autism, schizoid personality disorder, and schizotypal personality disorder share symptom complexes closely resembling the negative symptoms of schizophrenia (J.L.R., E.L.S., D.L.L., et al., manuscript submitted). On the basis of these similarities, we have proposed that these disorders encompass a spectrum of negative symptom disorders. If these disorders do in fact share the commonality of similar negative symptoms, it follows that effective treatment for negative symptoms in one disorder may likely be effective in the others. The efficacy of risperidone in treating the negative symptoms of schizophrenia[11,13] parallels that of these findings, suggesting similar improvement of negative symptoms in Asperger's disorder.

The implications of this work may potentially extend beyond Asperger's disorder. It is possible that a number of negative symptom spectrum disorders may respond to such treatment. It is also possible that some neurochemical processes linked to negative symptoms in schizophrenia could be present in Asperger's disorder, insofar as there may be some commonalities of neuropharmacologic response.

Drug names: fluoxetine (Prozac and others), lithium (Lithobid, Eskalith, and others), risperidone (Risperdal).

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