

## RISPERIDONE IN CHILDREN WITH AUTISM AND SERIOUS BEHAVIORAL PROBLEMS

RESEARCH UNITS ON PEDIATRIC PSYCHOPHARMACOLOGY AUTISM NETWORK\*

### ABSTRACT

**Background** Atypical antipsychotic agents, which block postsynaptic dopamine and serotonin receptors, have advantages over traditional antipsychotic medications in the treatment of adults with schizophrenia and may be beneficial in children with autistic disorder who have serious behavioral disturbances. However, data on the safety and efficacy of atypical antipsychotic agents in children are limited.

**Methods** We conducted a multisite, randomized, double-blind trial of risperidone as compared with placebo for the treatment of autistic disorder accompanied by severe tantrums, aggression, or self-injurious behavior in children 5 to 17 years old. The primary outcome measures were the score on the Irritability subscale of the Aberrant Behavior Checklist and the rating on the Clinical Global Impressions — Improvement (CGI-I) scale at eight weeks.

**Results** A total of 101 children (82 boys and 19 girls; mean [ $\pm$ SD] age,  $8.8 \pm 2.7$  years) were randomly assigned to receive risperidone (49 children) or placebo (52). Treatment with risperidone for eight weeks (dose range, 0.5 to 3.5 mg per day) resulted in a 56.9 percent reduction in the Irritability score, as compared with a 14.1 percent decrease in the placebo group ( $P < 0.001$ ). The rate of a positive response, defined as at least a 25 percent decrease in the Irritability score and a rating of much improved or very much improved on the CGI-I scale, was 69 percent in the risperidone group (34 of 49 children had a positive response) and 12 percent in the placebo group (6 of 52,  $P < 0.001$ ). Risperidone therapy was associated with an average weight gain of  $2.7 \pm 2.9$  kg, as compared with  $0.8 \pm 2.2$  kg with placebo ( $P < 0.001$ ). Increased appetite, fatigue, drowsiness, dizziness, and drooling were more common in the risperidone group than in the placebo group ( $P < 0.05$  for each comparison). In two thirds of the children with a positive response to risperidone at eight weeks (23 of 34), the benefit was maintained at six months.

**Conclusions** Risperidone was effective and well tolerated for the treatment of tantrums, aggression, or self-injurious behavior in children with autistic disorder. The short period of this trial limits inferences about adverse effects such as tardive dyskinesia. (N Engl J Med 2002;347:314-21.)

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**A**UTISM, a chronic condition that develops in early childhood, is characterized by a marked impairment in the ability to relate to others, delayed language, and restricted patterns of behavior. The disorder affects as many as 20 children per 10,000.<sup>1</sup>

In addition to core symptoms, children with autism frequently have serious behavioral disturbances, such as self-injurious behavior, aggression, and tantrums in response to routine environmental demands.<sup>2</sup> These behavioral problems interfere with rehabilitative efforts and pose enormous challenges to parents and educators. Although behavior therapy may reduce aggression and self-injury, it tends to be highly individualized and has not been evaluated in randomized clinical trials.<sup>3</sup> Attempts to treat autism with several medications in various chemical classes have had limited success.<sup>4</sup> To date, only haloperidol, a potent postsynaptic dopamine-receptor antagonist, has been shown in more than one study to be superior to placebo for the treatment of serious behavioral problems.<sup>5,6</sup> However, many clinicians avoid using haloperidol in children because of concern about its short- and long-term side effects.<sup>7</sup>

Unlike haloperidol, atypical antipsychotic agents block postsynaptic serotonin receptors. The affinity of these agents for serotonin receptors may enhance their efficacy and provide protection against extrapyramidal symptoms.<sup>8</sup> Alternatively, atypical antipsychotic agents may be more easily displaced by endogenous dopamine, which reduces the risk of neurologic side effects.<sup>9</sup> Given the lower frequency of extrapyramidal symptoms with atypical antipsychotic agents and

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their reported efficacy for treating both positive and negative symptoms in adults with schizophrenia, there is great interest in the question of whether these agents are beneficial in children with developmental disorders.<sup>10</sup> To date, only one placebo-controlled study of risperidone in adults with autism and a handful of open-label studies in children with pervasive developmental disorders have been reported.<sup>11-13</sup> We conducted a multisite study to evaluate the efficacy and safety of risperidone in children with autism accompanied by serious behavioral disturbances.

## METHODS

### Subjects

The first phase of the study was an eight-week, double-blind, randomized, placebo-controlled trial of risperidone (Risperdal, Janssen) conducted by the Autism Network of the Research Units on Pediatric Psychopharmacology between June 1999 and April 2001. At the end of the double-blind phase, children in the placebo group who had had no improvement in their behavior were offered open-label treatment with risperidone, as were children in the risperidone group who met the predetermined criteria for a positive response. Open-label treatment was given for four months, followed by a two-month, placebo-controlled discontinuation phase, as described elsewhere.<sup>14</sup> The study sites included the University of California at Los Angeles, Ohio State University, Indiana University, Yale University, and the Kennedy Krieger Institute at Johns Hopkins University. The protocol was approved by the institutional review board at each site, and written informed consent was obtained from a parent or guardian before enrollment. Safety and adherence to the protocol were monitored through weekly conference calls, annual site visits by investigators at the coordinating center (Yale University), and quarterly reviews by the data and safety monitoring board convened by the National Institute of Mental Health.

All children met the criteria for autistic disorder described in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition,<sup>15</sup> with tantrums, aggression, self-injurious behavior, or a combination of these problems. Other enrollment criteria included an age of 5 to 17 years, a weight of at least 15 kg, and a mental age of at least 18 months. The children had to be free of serious medical disorders and of other psychiatric disorders requiring medication. We reviewed each child's past and current treatments for autism. In consultation with parents, children receiving a psychotropic drug that was deemed effective for the treatment of aggression, tantrums, or self-injurious behavior were excluded. Ineffective medications were gradually withdrawn, and a drug-free interval of 7 to 28 days, depending on the drug, was required before enrollment. Treatment with an anticonvulsant agent for seizure control was allowed if the dose had been unchanged for at least four weeks and if there had been no seizures for at least six months.

### Base-Line Assessment and Outcome Measures

The diagnosis of autistic disorder was corroborated by the Autism Diagnostic Interview — Revised. This semistructured interview was administered by a clinician with special training and systematic review to ensure reliability.<sup>16</sup> Screening also included intelligence testing; administration of the Vineland Adaptive Behavior Scales (the population mean [ $\pm$ SD] for each scale is  $100 \pm 15$ ; higher scores indicate more adaptive behavior)<sup>17</sup>; routine laboratory tests; electrocardiography; measurement of height, weight, and vital signs; medical history taking; and physical examination. The child's race was reported by the parent or primary caretaker. Clinically significant behavioral problems were defined by a rating of moderate or higher on the Clinical Global Impressions — Severity (CGI-S) scale, as determined by a clinician,<sup>18</sup> and by a score of 18 or higher on the Ir-

ritability subscale of the Aberrant Behavior Checklist, as rated by the parent (or primary caretaker) and confirmed by a clinician. The 15-item Irritability subscale includes questions about aggression, self-injury, tantrums, agitation, and unstable mood on a scale of 0 to 45, with higher scores indicating greater severity. Data from studies of developmentally disabled children indicate that a score of 18 is 1.3 to 1.5 SD above the population mean, depending on the age and sex of the child.<sup>19,20</sup> To exclude children whose symptoms might improve in response to nonspecific clinical contact, the children were reassessed at base line, 7 to 14 days after the initial assessment. Only children who met the inclusion criteria for the CGI-S scale (according to an experienced clinician) and the score on the Irritability subscale (based on the parent's or primary caretaker's rating) at base line as well as at the time of screening were eligible for randomization. The Irritability scores obtained at this second evaluation were used as base-line values.

Each child was seen weekly by two clinicians who were unaware of the treatment assignment: a primary clinician, who reviewed side effects and adjusted the dose of medication, and a clinical evaluator, who assessed the response to treatment. The primary outcome measures were the score at eight weeks on the Irritability subscale of the Aberrant Behavior Checklist, based on the parent's or primary caretaker's rating, and the rating on the Clinical Global Impressions — Improvement (CGI-I) scale, as determined by the clinical evaluator. Children who had at least a 25 percent reduction in the Irritability score and a rating of much improved or very much improved on the CGI-I scale were considered to have a positive response.

Other outcomes were scores on the other subscales of the Aberrant Behavior Checklist (Social Withdrawal, Stereotypy, Hyperactivity, and Inappropriate Speech), based on ratings by the parent or primary caretaker. At base line, the parent or primary caretaker was interviewed to identify the target symptoms and to rate compulsive behavior according to the Children's Yale-Brown Obsessive Compulsive Scale. These semistructured interviews were used in determining the score on the CGI-I scale at subsequent visits, as described in detail elsewhere.<sup>21</sup>

### Medication Schedule

For children who weighed 20 to 45 kg, risperidone was given at an initial dose of 0.5 mg at bedtime and was increased to 0.5 mg twice daily on day 4. The dose was gradually increased in 0.5-mg increments to a maximum of 2.5 mg per day (1.0 mg in the morning and 1.5 mg at bedtime) by day 29. A slightly accelerated dose schedule was used for children who weighed more than 45 kg, with a maximal dose of 1.5 mg in the morning and 2.0 mg at bedtime. For children who weighed less than 20 kg, the initial dose was 0.25 mg per day. Scheduled dose increases could be delayed because of adverse effects or because of marked improvement at a lower dose. Dose reductions to manage side effects were allowed at any time, but there were no dose increases after day 29.

### Monitoring for Safety

Laboratory tests, electrocardiographic studies, and physical examination were repeated at eight weeks; weight and vital signs were assessed weekly. At each visit, the primary clinician inquired about health problems, intercurrent illness, and concomitant medications and administered a 32-item questionnaire concerning energy level, muscle stiffness, motor restlessness, bowel and bladder habits, sleep, and appetite. Neurologic side effects were assessed weekly with the use of the Simpson-Angus scale<sup>22</sup> and the Abnormal Involuntary Movement Scale.<sup>18</sup> Adverse events noted as a result of any of these methods were documented with respect to severity, duration, management, and outcome.

### Statistical Analysis

Data were analyzed according to the intention-to-treat principle. Statistical tests were two-tailed. P values of 0.05 or less were con-

sidered to indicate statistical significance, except for the analysis of adverse events ( $P < 0.10$ ) and analyses adjusted for multiple comparisons (the Bonferroni method). The biweekly scores on the Irritability subscale were analyzed with the use of mixed-effects linear models in which the study group and site were the fixed effects and the outcome and time were the random effects.<sup>23</sup> The mixed-effects approach makes full use of available data and allowed us to combine subject-specific scores on the Irritability subscale in order to estimate the slope of the regression line for each group over time. A strong downward trend in Irritability scores in the risperidone

group, as compared with the placebo group, would indicate a statistically significant interaction between treatment and time. Interactions with the site that were not significant were removed from the final model. The parameters of the mixed-effects model were estimated with the use of SAS Proc Mixed software.<sup>24</sup>

To compare our results with those of other trials and to estimate the likelihood of a response to risperidone in other patients with similar problems, we conducted two additional analyses. First, using our previously stated definition of a treatment response, we compared the rate of positive responses in each study group with

**TABLE 1. BASE-LINE CHARACTERISTICS OF 101 CHILDREN RANDOMLY ASSIGNED TO RECEIVE RISPERIDONE OR PLACEBO.\***

CHARACTERISTIC	RISPERIDONE (N=49)	PLACEBO (N=52)	P VALUE
Male sex — no./total no. (%)	39/49 (80)	43/52 (83)	0.89
Annual household income — no./total no. (%)			
<\$20,000	5/48 (10)	8/51 (16)	0.63
\$20,001–\$40,000	12/48 (25)	16/51 (31)	0.63
\$40,001–\$60,000	10/48 (21)	7/51 (14)	0.51
>\$60,000	21/48 (44)	20/51 (39)	0.81
Education of parent or primary caregiver — no./total no. (%)			
High school or less	9/49 (18)	13/52 (25)	0.57
Trade school or college	33/49 (67)	31/52 (60)	0.55
Advanced degree	7/49 (14)	8/52 (15)	0.90
Educational placement of child — no./total no. (%)			
Regular class	5/47 (11)	3/50 (6)	0.48
Special-education program	42/47 (89)	46/50 (92)	0.91
Residential school	0/47	1/50 (2)	1.00
Mental development — no./total no. (%)			
Average or above-average IQ	3/46 (7)	2/45 (4)	0.67
Borderline IQ	8/46 (17)	4/45 (9)	0.30
Mild or moderate retardation	20/46 (43)	23/45 (51)	0.88
Severe retardation	15/46 (33)	16/45 (36)	0.84
Score on Vineland Adaptive Behavior Scales†			
Communication	45.0±16.7	42.0±14.3	0.33
Socialization	49.1±16.6	47.4±10.1	0.53
Daily living	40.8±21.0	34.0±15.6	0.07
Score on Aberrant Behavior Checklist‡			
Irritability	26.2±7.9	25.5±6.6	0.63
Social Withdrawal	16.4±8.2	16.1±8.7	0.86
Stereotypy	10.6±4.9	9.0±4.4	0.09
Hyperactivity	31.8±9.6	32.3±8.5	0.78
Inappropriate Speech	4.8±4.1	6.5±3.6	0.03
Rating on Clinical Global Impressions — Severity scale — no./total no. (%)			
Moderate	9/49 (18)	9/49 (18)	0.90
Marked	27/49 (55)	28/49 (57)	0.94
Severe	12/49 (24)	12/49 (24)	0.95
Extreme	1/49 (2)	0/49	0.49
Current anticonvulsant treatment — no./total no. (%)	2/49 (4)	2/49 (4)	1.00
Previous medication — no./total no. (%)			
None	8/41 (20)	10/35 (29)	0.90
Antipsychotic agent	4/41 (10)	1/35 (3)	0.20
Selective serotonin-reuptake inhibitor	6/41 (15)	10/35 (29)	0.49
Stimulant	14/41 (34)	7/35 (20)	0.10
α <sub>2</sub> -Adrenergic agonist	9/41 (22)	7/35 (20)	0.69

\*Plus–minus values are means ±SD.

†The population mean for each scale is 100±15; higher scores indicate more adaptive behavior.

‡Higher scores indicate more aberrant behavior. Base-line scores for Social Withdrawal and Inappropriate Speech were 1 SD above the mean score in a developmentally disabled population, and base-line scores for Irritability, Stereotypy, and Hyperactivity were 2 SD above the mean in a developmentally disabled population.<sup>20</sup>

the use of the chi-square test. Second, we calculated the size of the effect (the change from base line at eight weeks) for each scale of the Aberrant Behavior Checklist.

Differences in adverse events were tested by the chi-square test or Fisher's exact test when subgroups contained fewer than five children. Continuous variables were assessed with the use of the regression model described above.

## RESULTS

### Base-Line Characteristics

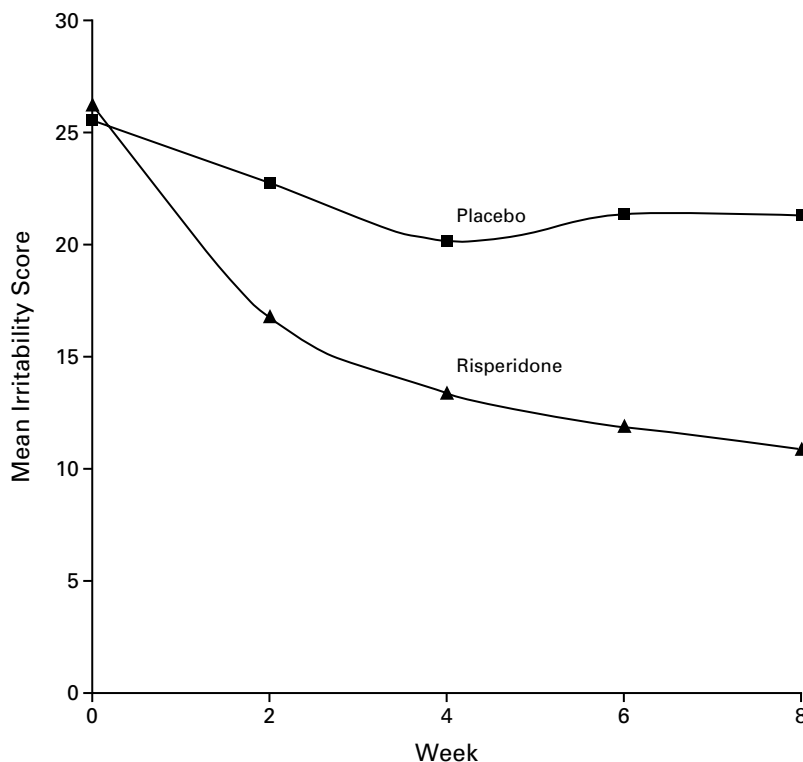
Of the 270 children who were screened for the study, 112 did not meet the criteria for enrollment, the parents or guardians of 57 children declined participation. The remaining 101 children (82 boys and 19 girls) were enrolled and randomly assigned to receive risperidone (49 children) or placebo (52). We subsequently identified four children who did not meet the entry criteria because their Irritability subscale had fallen below the threshold of 18 at base line. An analysis of the Irritability data that excluded these four children had results that were virtually identical to those with the full sample. Thus, the intention-to-treat analysis included all 101 children.

The children ranged in age from 5 to 17 years (mean

[ $\pm$ SD],  $8.8 \pm 2.7$ ); 87 percent (88 children) were prepubertal; 66 percent (67) were white, 11 percent (11) were black, 7 percent (7) were Hispanic, 8 percent (8) were Asian, and 8 percent (8) were members of other racial or ethnic groups; and 91 percent (92) lived at home with at least one parent. The two groups were similar at base line with respect to a range of demographic, developmental, and clinical characteristics, including mean scores on the Aberrant Behavior Checklist subscales, with the exception of the score on the Inappropriate-Speech subscale, which was higher in the placebo group than in the risperidone group (Table 1).

### Primary Outcome

Analysis of the scores on the Irritability subscale revealed a significant interaction between the study group and time ( $P < 0.001$ ) (Fig. 1). After eight weeks of treatment, the risperidone group had a 56.9 percent decrease in the mean Irritability score (from  $26.2 \pm 7.9$  at base line to  $11.3 \pm 7.4$  at eight weeks), as compared with a 14.1 percent decrease in the placebo group (from  $25.5 \pm 6.6$  to  $21.9 \pm 9.5$ ,  $P < 0.001$ )



**Figure 1.** Mean Scores for Irritability in the Risperidone and Placebo Groups during the Eight-Week Trial. Data are for all 101 children (49 assigned to the risperidone group and 52 assigned to the placebo group). Higher scores indicate greater irritability.

(Table 2). The rate of a positive response (at least a 25 percent improvement in the score on the Irritability subscale and a rating of much improved or very much improved on the CGI-I scale) was 69 percent in the risperidone group (34 of the 49 children had a positive response) and 12 percent in the placebo group (6 of 52,  $P<0.001$ ).

These gains in the risperidone group were maintained for six months in 23 of the 34 children (68 percent) who had had positive responses in the double-blind phase of the study. Of the other 11 children who had positive responses with risperidone, 2 did not enter the extension phase of the study because the family moved and 2 because the parents decided to evaluate the children's behavior in the absence of medication. During the extension phase, the parents of two children decided to seek other treatment in addition to risperidone; four children were withdrawn because the treatment was no longer effective, and one child was withdrawn because of an unrelated medical problem.

#### Secondary Outcomes

Table 2 shows the mean base-line and end-point scores, as well as the effect size, for all the subscales of the Aberrant Behavior Checklist in each study group. After correction for multiple comparisons, there was a significant interaction between the study group and time for scores on the Stereotypy and Hyperactivity subscales, suggesting that risperidone improved behavior in these areas as well. Scores for Social Withdrawal and Inappropriate Speech did not differ significantly between the two groups (after Bonferroni correction).

The rate of improvement over time is shown in Fig-

ure 2. The proportion of children whose behavior was rated as much improved or very much improved on the CGI-I scale differed by 44 percent between the study groups at week 4 ( $P<0.001$ ) and by 64 percent at week 8 ( $P<0.001$ ).

#### Medication Dose

The mean daily dose of risperidone during the final week of the study was  $1.8\pm 0.7$  mg (range, 0.5 to 3.5). The mean dose of placebo dispensed was equivalent to  $2.4\pm 0.6$  mg per day (range, 1.0 to 3.5;  $P<0.001$ ).

#### Adverse Events

There was a significantly greater mean increase in weight in the risperidone group ( $2.7\pm 2.9$  kg) than in the placebo group ( $0.8\pm 2.2$  kg,  $P<0.001$ ) (Table 3). The weight gain in the risperidone group was associated with a mild increase in appetite (in 49 percent of children) or a moderate increase in appetite (in 24 percent), as reported by the parent or primary caretaker ( $P=0.03$  and  $P=0.01$ , respectively, for the comparison with the placebo group).

Sixty different adverse events were recorded during the trial, 29 of which occurred in 5 percent or more of the children (Table 3). There were no serious adverse events in the risperidone group, and no children were withdrawn from the study because of an adverse event. Most adverse events were mild and self-limited. For example, 23 children (47 percent) in the risperidone group had mild fatigue, but only 6 (12 percent) had moderate fatigue. In most cases, the fatigue had subsided by week 6. Similarly, of the 24 children in the risperidone group described as drowsy by their parents

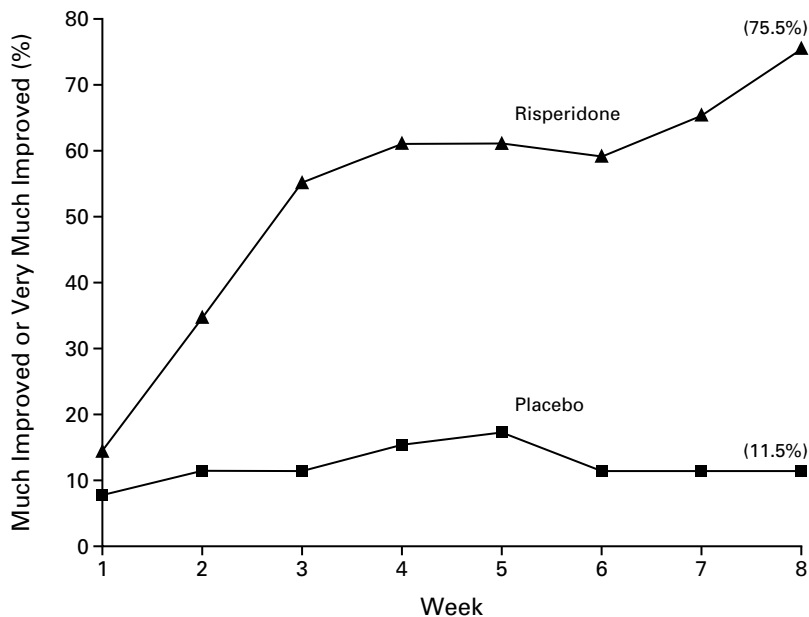
TABLE 2. SCORES ON THE ABERRANT BEHAVIOR CHECKLIST AT BASE LINE AND EIGHT WEEKS.\*

SUBSCALE	RISPERIDONE		PLACEBO		F TEST	P VALUE†	EFFECT SIZE‡
	BASE LINE	8 WK	BASE LINE	8 WK			
	mean $\pm$ SD						
Irritability	26.2 $\pm$ 7.9	11.3 $\pm$ 7.4	25.5 $\pm$ 6.6	21.9 $\pm$ 9.5	27.57	<0.001	1.2
Social Withdrawal	16.4 $\pm$ 8.2	8.9 $\pm$ 6.4	16.1 $\pm$ 8.7	12.0 $\pm$ 8.3	4.89	0.03	0.4
Stereotypy	10.6 $\pm$ 4.9	5.8 $\pm$ 4.6	9.0 $\pm$ 4.4	7.3 $\pm$ 4.8	11.32	<0.001	0.8
Hyperactivity	31.8 $\pm$ 9.6	17.0 $\pm$ 9.7	32.3 $\pm$ 8.5	27.6 $\pm$ 10.6	25.56	<0.001	1.0
Inappropriate Speech	4.8 $\pm$ 4.1	3.0 $\pm$ 3.1	6.5 $\pm$ 3.6	5.9 $\pm$ 3.8	6.68	0.03	0.3

\*Scores for the Irritability, Stereotypy, and Hyperactivity scales decreased from a base-line score that was 2 SD above the mean in a population of developmentally disabled children to a score at eight weeks that was less than 1 SD above the mean; the scores for Social Withdrawal and Inappropriate Speech decreased from 1 SD above the mean at base line to 0.5 SD above the mean at eight weeks.

†P values were derived from the F test (1,262 df) for the interaction between the study group and time in the mixed-effects linear model, with the use of data obtained at base line and at weeks 2, 4, 6, and 8 (Bonferroni correction:  $\alpha\div 5=0.01$ ).

‡The effect size was calculated by subtracting the mean score at eight weeks from the base-line score for each group. The difference in the change from base line between the two groups was then divided by the pooled standard deviation of the difference scores.



**Figure 2.** Percentage of Children with a Rating of Much Improved or Very Much Improved on the Clinical Global Impressions — Improvement Scale during the Eight-Week Trial.

Data are for all 49 children assigned to the risperidone group and for all 52 assigned to the placebo group.

or primary caretakers, 16 were considered to be mildly drowsy, and they were no longer drowsy by week 4.

Weekly assessment with the Abnormal Involuntary Movement Scale and the Simpson–Angus scale showed no extrapyramidal symptoms in either group. Parents or caretakers reported five neurologic side effects: tremor, dyskinesia, rigidity, akathisia, and difficulty swallowing. Of these, tremor was significantly more common in the risperidone group ( $P=0.06$ ). One child in each group had a value for serum glutamic-oxaloacetic transaminase that was more than twice the upper limit of the normal range at eight weeks, and one child in the placebo group had an elevated serum glutamic-pyruvic transaminase level. One child in the placebo group had a nonspecific, clinically insignificant change in cardiac conduction. The pulse, blood pressure, and results of routine laboratory tests did not differ significantly between the two groups. Eighteen children (8 in the risperidone group and 10 in the placebo group) had fever in association with a documented, time-limited illness.

#### Withdrawal from the Study

Three children in the risperidone group were withdrawn from the study because the treatment was not effective. One child in the placebo group was withdrawn because of a severe headache and a seizure attributed to the failure of a ventriculoatrial shunt. An

additional 17 children in the placebo group did not complete the study for the following reasons: withdrawal of consent (1 child), nonadherence (1), loss to follow-up (3), and lack of efficacy (12). The rate of withdrawal was 35 percent (18 of 52 children) in the placebo group, as compared with 6 percent (3 of 49) in the risperidone group ( $P=0.001$ ).

#### DISCUSSION

In this trial, risperidone was safe and effective for the short-term treatment of tantrums, aggression, and self-injurious behavior in children with autistic disorder. Improvements were also observed in stereotypic behavior and hyperactivity. Scores on the Social Withdrawal subscale, which rates social isolation and interest in communicating with others, did not differ significantly between the risperidone and placebo groups. Adverse effects such as weight gain, increased appetite, fatigue, drowsiness, dizziness, drooling, tremor, and constipation were more common in the risperidone group. Most of these adverse effects were mild and resolved within a few weeks. Thus, the risk–benefit ratio for risperidone therapy appears to be favorable.

Our findings confirm the results of small, open-label trials of risperidone in children with autism or another pervasive developmental disorder.<sup>4</sup> The benefits of risperidone in our study exceeded the improvements observed in a recent controlled study involving 38

**TABLE 3.** ADVERSE EVENTS REPORTED DURING THE EIGHT-WEEK TRIAL.\*

EVENT	RISPERIDONE (N=49)	PLACEBO (N=51)†	P VALUE‡
Increased appetite — no. (%)			
Mild	24 (49)	13 (25)	0.03
Moderate	12 (24)	2 (4)	0.01
Nasal congestion — no. (%)	25 (51)	20 (39)	0.32
Fatigue — no. (%)	29 (59)	14 (27)	0.003
Enuresis — no. (%)	15 (31)	15 (29)	0.93
Drowsiness — no. (%)	24 (49)	6 (12)	<0.001
Vomiting — no. (%)	16 (33)	12 (24)	0.43
Insomnia — no. (%)	7 (14)	15 (29)	0.11
Anxiety — no. (%)	12 (24)	10 (20)	0.73
Diarrhea — no. (%)	9 (18)	11 (22)	0.88
Constipation — no. (%)	14 (29)	6 (12)	0.06
Sleep problems — no. (%)	11 (22)	9 (18)	0.73
Skin irritation — no. (%)	11 (22)	7 (14)	0.38
Drooling — no. (%)	13 (27)	3 (6)	0.02
Headache — no. (%)	9 (18)	6 (12)§	0.52
Stomachache — no. (%)	5 (10)	9 (18)	0.43
Dry mouth — no. (%)	9 (18)	5 (10)	0.34
Increased thirst — no. (%)	6 (12)	5 (10)	0.94
Dizziness — no. (%)	8 (16)	2 (4)	0.05
Dyskinesia — no. (%)	6 (12)	3 (6)	0.45
Nausea — no. (%)	4 (8)	5 (10)	0.95
Decreased appetite — no. (%)	3 (6)	5 (10)	0.76
Tremor — no. (%)	7 (14)	1 (2)	0.06
Tachycardia — no. (%)	6 (12)	1 (2)	0.06
Upper respiratory tract infection — no. (%)	5 (10)	2 (4)	0.40
Earache — no. (%)	2 (4)	4 (8)	0.71
Muscle rigidity — no. (%)	5 (10)	1 (2)	0.11
Sore throat — no. (%)	5 (10)	1 (2)	0.11
Restlessness — no. (%)	3 (6)	3 (6)	0.71
Weight gain — kg	2.7±2.9	0.8±2.2	<0.001

\*All adverse events were in the mild-to-moderate range unless otherwise specified. Plus-minus values are means ±SD.

†One child was withdrawn from the study at base line and was therefore not included in the analysis of adverse events.

‡P values were determined by means of the chi-square test with Yates' correction; Fisher's exact test was used when subgroups consisted of fewer than five children. P values that were less than 0.10 were considered to indicate statistical significance.

§In one child, the headache was severe.

adolescents with mental retardation and explosive behavior.<sup>25</sup> In our study, there was a difference of 43 percentage points between the risperidone and placebo groups in the change from the base-line score on the Irritability subscale, whereas studies of haloperidol for the treatment of autism showed a difference of 15 to 20 percent between the placebo and active-treatment groups, depending on the measure.<sup>5</sup> Our findings with

respect to the rate and severity of adverse effects also differ from previous findings. Excessive sedation was reported in 78 percent of children who received haloperidol,<sup>6</sup> as compared with generally mild sedation in 59 percent of the children in our study who received risperidone. An acute dystonic reaction occurred in 25 percent of haloperidol-treated patients<sup>6</sup> but in none of the children in our trial who received risperidone. Although parents or primary caretakers reported tremor in a few of the children treated with risperidone, weekly neurologic assessments showed no abnormalities. The low risk of extrapyramidal symptoms in our study is consistent with the results of studies in adults.<sup>8</sup> Nonetheless, the adverse events observed in our study and the lack of a clear benefit with regard to core symptoms of autism indicate that risperidone should be reserved for treatment of moderate-to-severe behavioral problems associated with autism.

There are several limitations to this study. First, the observation period was only eight weeks long. However, a majority of the children who were classified as having a positive response during the double-blind phase of the study (23 of 34) continued to show benefit at six months. Second, the study included only children with autistic disorder. It is not clear whether our findings can be generalized to children with other forms of pervasive developmental disorder. Third, although the mean doses of risperidone used in this study were not high, the study could not identify the minimal effective dose. Finally, we focused on specific behavioral problems rather than on the core symptoms of autism. Indeed, when designing the study, we were unable to identify a validated measure for the core symptoms of autism that was suitable for repeated administration. Our focus on severe behavioral problems leaves unanswered the question of whether pharmacologic therapy and behavioral treatment could have additive effects.

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