Risperidone in the Treatment of Disruptive Behavioral Symptoms in Children With Autistic and Other Pervasive Developmental Disorders

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ABSTRACT. *Objective.* **To investigate the efficacy and safety of risperidone for the treatment of disruptive behavioral symptoms in children with autism and other pervasive developmental disorders (PDD).**

Methods. **In this 8-week, randomized, double-blind, placebo-controlled trial, risperidone/placebo solution (0.01–0.06 mg/kg/day) was administered to 79 children who were aged 5 to 12 years and had PDD. Behavioral symptoms were assessed using the Aberrant Behavior Checklist (ABC), Nisonger Child Behavior Rating Form, and Clinical Global Impression-Change. Safety assessments included vital signs, electrocardiogram, extrapyramidal symptoms, adverse events, and laboratory tests.**

Results. **Subjects who were taking risperidone (mean dosage: 0.04 mg/kg/day; 1.17 mg/day) experienced a significantly greater mean decrease on the irritability subscale of the ABC (primary endpoint) compared with those who were taking placebo. By study endpoint, risperidone-treated subjects exhibited a 64% improvement over baseline in the irritability score almost double that of placebo-treated subjects (31%). Risperidone-treated subjects also exhibited significantly greater decreases on the other 4 subscales of the ABC; on the conduct problem, insecure/anxious, hyperactive, and overly sensitive subscales of the Nisonger Child Behavior Rating Form (parent version); and on the Visual Analog Scale of the most troublesome symptom. More risperidone-treated subjects (87%) showed global improvement in their condition compared with the placebo group (40%). Somnolence, the most frequently reported adverse event, was noted in 72.5% versus 7.7% of subjects (risperidone vs placebo) and seemed manageable with dose/dose-schedule modification. Risperidone-treated subjects experienced statistically significantly greater increases in weight (2.7 vs 1.0 kg), pulse rate, and systolic blood pressure. Extrapyramidal symptoms scores were comparable between groups.**

Conclusions. **Risperidone was well tolerated and efficacious in treating behavioral symptoms associated with PDD in children.** *Pediatrics* **2004;114:e634–e641. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2003-0264-F;** ***autistic disorder, pervasive developmental disorders, risperidone.***

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ABBREVIATIONS. PDD, pervasive developmental disorders; EPS, extrapyramidal symptom; CARS, Childhood Autism Rating Scale; ESRS, Extrapyramidal Symptom Rating Scale; ABC, Aberrant Behavior Checklist; N-CBRF, Nisonger Child Behavior Rating Form; VAS, Visual Analog Scale; CGI-C, Clinical Global Impression-Change; ITT, intention-to-treat; RUPP, Research Units on Pediatric Psychopharmacology.

The pervasive developmental disorders (PDD) are a group of neuropsychiatric disorders that include autistic disorder, Asperger's disorder, childhood disintegrative disorder, Rett's disorder, and PDD not otherwise specified.[1] These disorders are characterized by atypical development in social, communicative, and behavior areas. Onset typically occurs within the first years of life. Prevalence rates as high as 63 per 10 000 children have recently been reported.[2] Although commonly associated with mental retardation, the developmental and behavioral features of PDD are distinct and do not simply reflect developmental level.[3,4]

PDD are characterized by severe and pervasive deficits in several areas of development.[1] These include reciprocal social interaction skills; communication skills; or the presence of stereotyped behavior, interests, and activities. Children with PDD may present with difficult behaviors including aggression, hyperactivity, inattention, impulsivity, stereotypies, screaming, and self-injurious behavior. These behaviors may be disruptive in both school and family environments; in addition, they can interfere with the progress of the child and the well-being of the child and the caregivers.

As yet, there are no pharmacologic interventions that specifically target the core deficits of the PDD profile. However, some progress has been made in ameliorating the behavioral symptoms associated with PDD. A number of studies, published since the 1960s, have shown that improved control of behavioral symptoms can be achieved through the use of conventional neuroleptics such as the dopamine receptor antagonist haloperidol.[3,5] The frequent occurrence of dyskinesias and other extrapyramidal side effects limited their use. Not surprising, as the early safety and efficacy data with the newer atypical antipsychotics became available in the late 1980s and early 1990s, interest in their use in PDD began to grow.

Risperidone is an antagonist of both dopamine (D_2) and serotonin ($5HT_{2A}$ and others) receptors.[6,7] Particularly when used at lower doses, risperidone

proved to be relatively free of the extrapyramidal symptoms (EPSs) that had limited the use of conventional agents.[8] A number of open-label trials were undertaken to investigate the use of risperidone in children with PDD.[9–18] Preliminary evidence from these studies suggested that risperidone was both safe and effective in reducing behavioral symptoms in this population. However, more rigorously designed studies were needed to confirm these findings. At the time that this study was conducted, no controlled studies had been reported. As a result, this study was undertaken to evaluate critically the efficacy and safety of risperidone for the treatment of behavioral symptoms in children with PDD.

METHODS

Study Design and Conduct

This was an 8-week, randomized, double-blind, parallel-group, Canadian, multicenter study designed to evaluate the efficacy and safety of risperidone versus placebo in the treatment of disruptive behavioral symptoms in children with PDD. Subjects attended the clinic on 7 occasions: at the baseline/screening visit and at the end of treatment weeks 1, 2, 3, 5, 7, and 8. The study was conducted in accordance with the Declaration of Helsinki as revised in 1996 and was approved by the institutional review board at each participating center. The child's parent/guardian/legal representative provided written informed consent. Supportive approaches were used to obtain the child's assent when possible. A responsible person was required to accompany the subject at clinic visits, provide reliable assessments, and administer medications.

Subjects

Physically healthy male and female outpatients who were aged 5 to 12 years inclusive were eligible to participate in this study provided that they had a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* Axis I diagnosis of PDD[1] and a total score of 30 or more on the Childhood Autism Rating Scale (CARS),[19,20] with or without mental retardation. Subjects who had schizophrenia, other psychotic disorders, clinically relevant nonneurologic disease, clinically significant laboratory abnormalities, or a seizure disorder for which they were receiving >1 anticonvulsant or if they had had a seizure in the last 3 months were excluded. In addition, subjects who had a history of hypersensitivity to neuroleptics, tardive dyskinesia, neuroleptic malignant syndrome, drug or alcohol abuse, or human immunodeficiency virus infection were excluded. Subjects were also excluded when they had used risperidone in the last 3 months, had been previously unresponsive or intolerant to risperidone, or were using a prohibited medication.

Study and Other Medications

After screening at the baseline visit, eligible subjects were randomized (1:1) to receive either risperidone or placebo in a double-blind manner. Risperidone or placebo oral solution 1.0 mg/mL was administered once daily in the morning at 0.01 mg/kg/day on treatment days 1 and 2 and increased to 0.02 mg/kg/day on day 3. Depending on the therapeutic response at day 8, the dose could be increased by a maximal increment of 0.02 mg/kg/day. Thereafter, the dose could be adjusted at the investigator's discretion at weekly intervals by increments/decrements not to exceed 0.02 mg/kg/day. The maximal allowable dosage was 0.06 mg/kg/day. In case of drowsiness, the study medication could be administered once daily in the evening, or the total daily dose could be divided and administered on a morning and evening schedule.

Medications that are used to treat EPSs were to be discontinued at the time of entry into the trial. However, during the trial, anticholinergics could be initiated to treat emergent EPSs after the Extrapyramidal Symptom Rating Scale (ESRS) had been completed. Prohibited medications included antipsychotics other than the study medication, antidepressants, lithium, α_2-antagonists, clonidine, guanfacine, cholinesterase inhibitors, psychostimulants, and naltrexone. A single anticonvulsant and/or medications for sleep or anxiety were permitted only in the case in which the subject was already taking them at a stable dose for the 30 days before enrollment. Similar restrictions were placed on the use of behavior intervention therapy. Medications for preexisting organic disorders were allowed provided that the dose and schedule of administration were kept as constant as possible.

Outcome Measures

Efficacy assessments that were scored at each clinic visit included the Aberrant Behavior Checklist (ABC),[21] the parent version of the Nisonger Child Behavior Rating Form (N-CBRF),[22] a Visual Analog Scale (VAS) for the most troublesome symptom, and the Clinical Global Impression-Change (CGI-C). The ABC consisted of 58 items subdivided among 5 scales: irritability, lethargy and social withdrawal, stereotypic behavior, hyperactivity/noncompliance, and inappropriate speech. The parent version of the N-CBRF consisted of 60 items subdivided among 6 scales: conduct problem, insecure/anxious, hyperactive, self-injury/stereotypic, self-isolated/ritualistic, and overly sensitive. The ABC and N-CBRF subscales were completed by the parent or caregiver under the guidance of the investigator; scores for both scales ranged from 0 to 3, with 0 = no problem and 3 = severe problem. At the baseline visit, the parent/guardian reported which symptom was the most troublesome. The severity of that symptom was recorded on a VAS completed by the parent/guardian with a vertical mark on a 100-mm line, with lower scores indicating a better condition. At baseline, the CGI-Severity of the subject's PDD was scored by the investigator on a 7-item scale ranging from absent to extremely severe. At subsequent visits, changes in the subject's global condition were rated by the investigator on a 7-point item scale (CGI-C) ranging from very much improved to very much worse.

Safety assessment measures, which included adverse event data, vital signs, and body weight, were collected at each visit. In addition, the presence and the severity of EPSs were assessed at each visit by the investigator using the ESRS.[23] A 12-lead electrocardiogram and routine biochemistry, hematology, and urinalysis were performed at baseline and at the end of treatment.

Statistical Analyses

The primary population for safety assessments was the intention-to-treat (ITT) population, defined as all randomized subjects who received at least 1 dose of study medication. The primary population for efficacy assessments was the ITT-efficacy population, defined as all randomized subjects who received at least 1 dose of study medication and for whom there was at least 1 postbaseline efficacy assessment. The primary efficacy parameter was the change in irritability from baseline to study endpoint (ie, the last observation) as measured on the irritability subscale of the ABC. This was a 15-item subscale that included items such as "injures self," "aggressive to other patients and staff," "temper tantrums," "irritable," "depressed mood," and "cries and screams inappropriately."[24] Secondary efficacy parameters included the changes from baseline to endpoint in the other 4 subscales of the ABC, the 6 subscales of the N-CBRF (parent version), the VAS for the most troublesome symptom, and the CGI-C. All changes from baseline in the ABC and N-CBRF subscales and in the VAS were analyzed by analysis of covariance using model terms of treatment, center, and baseline score. A "responder" analysis was also performed, whereby a "responder" was defined as having a 50% or greater decrease from baseline in at least 2 of the 5 ABC subscales with none of the other subscales presenting a 10% or larger increase. The Cochran-Mantel-Haenszel test, controlling for investigational site, was used to compare response rates between risperidone and placebo groups; it was also used to compare CGI-C scores. Adverse events were tabulated by type and incidence. Heart rate, systolic and diastolic blood pressures, and weight were analyzed using analysis of variance. Change in ESRS scores was analyzed using a Cochran-Mantel-Haenszel test with modified ridit scores (Van Elteren's test). Descriptive statistics were used to report other safety outcomes. All tests were interpreted at the 5% significance level (2-tailed) with no adjustment for multiple testing.

RESULTS

Subjects

A total of 80 subjects at 7 investigational sites met the eligibility criteria and were enrolled into this study. Of these, 41 were randomized to receive risperidone and 39 were randomized to receive placebo. One subject who was randomized to the risperidone group did not receive any study drug and had no baseline assessments. Therefore, 79 subjects (40 in the risperidone group, 39 in the placebo group) were included in the ITT population, the primary safety assessment population. In addition, because 1 subject in each group had no postbaseline efficacy data recorded, 77 subjects (39 in the risperidone group, 38 in the placebo group) were included in the ITT-efficacy population, the primary efficacy assessment population.

In the ITT population, risperidone- and placebo-treated subjects were similar in terms of their demographic and baseline data (Table 1). The mean age of participants was 7.5 years, and more than three quarters were male. Most (88.6%) lived with their parents. All subjects had a CARS score of 30 or greater, indicative of autism. More than half (55.7%) of all participants were within the "severe autism" category, as assessed by the CARS. According to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, which postdates the CARS and is a less inclusive diagnostic system, 69% of subjects had a diagnosis of autistic disorder. Twenty-three of the 40 risperidone-treated subjects and 25 of the 39 placebo-treated subjects had standard IQ testing performed; 15 (65.2%) in the former group and 12 (48.0%) in the latter group were had either mild or moderate mental retardation. Seventeen subjects (8 in the risperidone group, 9 in the placebo group), whose intellectual abilities precluded the administration of standard IQ testing, completed other cognitive testing using either the Leiter International Performance Scales or Raven's Progressive Matrices. These children would likely have fallen within the moderate to severe range of mental retardation. A total of 59 (75%) subjects presented with a currently active medical condition, most commonly ear/nose or throat, eyes, gastrointestinal, dermatologic, genitourinary, respiratory, or allergic/immunologic abnormalities.

Seventy-two (91.1%) subjects completed the 8-week study. Seven (8.9%) subjects withdrew before completion; of these, 2 had been randomized to treatment with risperidone and 5 had been randomized to placebo. Among risperidone-treated subjects, 1 withdrew because of an adverse event (the result of an accidental overdose on day 2) and 1 withdrew because of insufficient response. Among placebo-treated subjects, 1 withdrew because of an adverse event (an accidental medication overdose on day 16), 2 withdrew because of insufficient response, and 2 withdrew consent.

Study and Other Medications

Subjects received double-blind treatment with placebo for a mean of 49.6 days (range: 7–63 days) or with risperidone for a mean of 52.7 days (range: 2–62 days). The mean daily dose of risperidone administered during the treatment period, which included at

TABLE 1. Baseline Demographic and Disease Characteristics for the ITT Population

Characteristic	Risperidone (n = 40)	Placebo (n = 39)
Age, y		
Mean ± SE	7.6 ± 2.3	7.3 ± 2.3
Median (range)	7.0 (5–12)	7.0 (5–12)
Gender, *n* (%)		
Male	29 (72.5)	32 (82.1)
Female	11 (27.5)	7 (17.9)
Race, *n* (%)		
Black	6 (15.0)	6 (15.4)
White	27 (67.5)	28 (71.8)
Other	7 (17.5)	5 (12.8)
Weight, kg, mean ± SE	31.2 ± 14.5	27.6 ± 8.6
VAB score, mean ± SE	46.6 ± 13.1	52.2 ± 19.8
DSM-IV Axis I diagnosis of PDD, *n* (%)		
Autistic disorder	27 (67.5)	28 (71.8)
Asperger's disorder	5 (12.5)	7 (17.9)
Childhood disintegrative disorder	1 (2.5)	0 (0)
Rett's disorder	0 (0)	0 (0)
PDD not otherwise specified	7 (17.5)	4 (10.3)
CARS, mean ± SE	38.9 ± 5.3	39.1 ± 6.7
Nonautistic, score <30, *n* (%)	0 (0)	0 (0)
Mild/moderate, score 31–36, *n* (%)	17 (42.5)	18 (46.2)
Severe, score 37–60, *n* (%)	23 (57.5)	21 (53.8)
IQ test performed, *n* (%)	31 (77.5)	35 (89.7)
IQ of those tested		
Normal, score ≥85, *n* (%)	3 (9.7)	11 (31.4)
Borderline, score 71–84, *n* (%)	6 (19.4)	4 (11.4)
Mild, score 50–70, *n* (%)	12 (38.7)	8 (22.9)
Moderate, score 35–49, *n* (%)	10 (32.3)	12 (34.3)

VAB indicates Vineland adaptive behavior; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.

minimum a 1-week titration period, was 1.17 mg; the mean dosage was 0.04 mg/kg/day. At study endpoint, the mean daily dose of risperidone was 1.48 mg, and the mean dosage was 0.05 mg/kg/day. In the risperidone group, the majority of subjects (n = 37) started on a once-daily morning administration schedule; 8 of these subjects remained on that schedule for the duration of the trial. The dosing schedule was modified for the remaining 29 subjects (14 subjects changed to PM and 15 to twice-daily dosing) mainly because of somnolence.

A total of 62 (78.5%) subjects received at least 1 concomitant medication during the trial. More subjects in the risperidone group received concomitant medications for other medical conditions than did those in the placebo group: 36 (90%) versus 26 (66.7%), respectively. The most commonly used medications were analgesics (37.5% and 17.9%, respectively), cough and cold preparations (25% and 10.3%, respectively), antibiotics (12.5% and 12.8%, respectively), and anti-asthmatics (15% and 10%, respectively). Sedatives/hypnotics were administered to 11 (27.5%) risperidone-treated subjects and 9 (23.1%) placebo-treated subjects on an as-needed basis to relieve anxiety during laboratory testing. Anticholinergics were administered to 3 (7.5%) subjects in the risperidone group and 1 (2.6%) subject in the placebo group to treat emergent EPSs.

Efficacy Outcomes

Mean baseline scores on the irritability subscale of the ABC, the primary efficacy parameter, were comparable between the 2 groups: 18.9 and 21.2 for risperidone- and placebo-treated subjects, respectively (Table 2). At each subsequent visit, the mean scores decreased from baseline in both groups; however, the mean decrease in the risperidone group was consistently greater than that in the placebo group (Fig 1). Furthermore, the differences in these mean decreases were statistically significant at each visit from treatment week 2 ($P \leq .05$) through week 8 ($P \leq$ 0. 001). By study endpoint, the mean decrease from baseline in the irritability score experienced by risperidone-treated subjects was almost twice that of placebo-treated subjects: −12.1 compared with −6.5, respectively ($P < .001$; Table 2). At study endpoint, risperidone-treated subjects exhibited a 64% improvement over baseline irritability compared with a 30.7% improvement in placebo-treated subjects.

A similar pattern of response was observed when a subset analysis of the irritability subscale scores was performed among the 54 subjects (26 in the risperidone group, 28 in the placebo group) who had a diagnosis of autistic disorder. Mean baseline scores were 20.6 ± 8.1 and 21.6 ± 10.2 for risperidone- and placebo-treated autistic subjects, respectively. Again, differences in the mean decreases were statistically significantly in favor of risperidone from treatment week 2 on ($P \leq .05$). By study endpoint, the mean decreases from baseline in the irritability scores were −13.5 ± 5.2 and −7.5 ± 7.6 for risperidone- and placebo-treated autistic subjects, respectively ($P \leq$ .01), representing improvements over baseline of 65.5% and 34.7%, respectively.

By study endpoint, risperidone-treated subjects also experienced statistically significantly greater changes from baseline for each of the other 4 subscales of the ABC ($P \leq .05$; Table 2). The largest difference was observed for the hyperactivity/noncompliance subscale for which risperidone-treated subjects experienced a decrease of 14.9 in mean score and placebo-treated subjects experienced a decrease of 7.4 ($P < .001$). Compared with 15 (39.5%) subjects in the placebo group, 27 (69.2%) risperidone-treated subjects met the definition of a responder ($P = .01$).

Similarly, risperidone-treated subjects experienced greater improvement from baseline on the conduct problem subscale of the parent version of the N-CBRF: mean decreases at study endpoint of 10.4 versus 6.6 for placebo-treated subjects ($P \leq .01$; Table 2). Risperidone-treated subjects also showed statisti-

TABLE 2. Change From Baseline in the ABC, N-CBRF (Parent Version), and VAS at Study Endpoint

Efficacy Measure	Risperidone (n = 39)		Placebo (n = 38)	
	Baseline*	Endpoint†	Baseline*	Endpoint†
ABC subscale				
Irritability	18.9 ± 8.8	−12.1 ± 5.8‡	21.2 ± 9.7	−6.5 ± 8.4
Hyperactivity/noncompliance	27.3 ± 9.7	−14.9 ± 6.7‡	30.9 ± 8.8	−7.4 ± 9.7
Inappropriate speech	4.6 ± 3.4	−2.6 ± 2.6§	4.8 ± 3.7	−1.6 ± 3.0
Lethargy/social withdrawal	13.7 ± 7.0	−8.6 ± 5.9¶	14.3 ± 8.2	−5.7 ± 6.9
Stereotypic behavior	7.9 ± 5.0	−4.3 ± 3.8§	8.1 ± 5.6	−2.4 ± 4.0
N-CBRF (parent version) subscale				
Conduct problem	16.8 ± 9.4	−10.4 ± 7.4‡	23.3 ± 12.0	−6.6 ± 9.5
Hyperactive	17.2 ± 5.8	−8.1 ± 4.6§	18.9 ± 5.3	−5.6 ± 6.6
Self-isolated/ritualistic	7.5 ± 4.1	−4.8 ± 3.9	8.2 ± 4.5	−3.6 ± 4.6
Insecure/anxious	8.7 ± 8.1	−4.6 ± 6.5§	10.6 ± 7.6	−3.5 ± 5.5
Overly sensitive	6.9 ± 3.4	−3.8 ± 2.8§	7.4 ± 3.5	−2.7 ± 3.2
Self-injurious/stereotypic	4.2 ± 4.2	−2.6 ± 3.3	3.5 ± 4.2	−1.3 ± 2.8
VAS (most troublesome symptom)	81.0 ± 13.3	−38.4 ± 28.9§	84.8 ± 14.1	−26.2 ± 29.2

* Mean ± SD.
† Mean change from baseline ± SD.
‡ $P \leq .001$ versus placebo.
§ $P \leq .05$ versus placebo.
¶ $P \leq .01$ versus placebo.

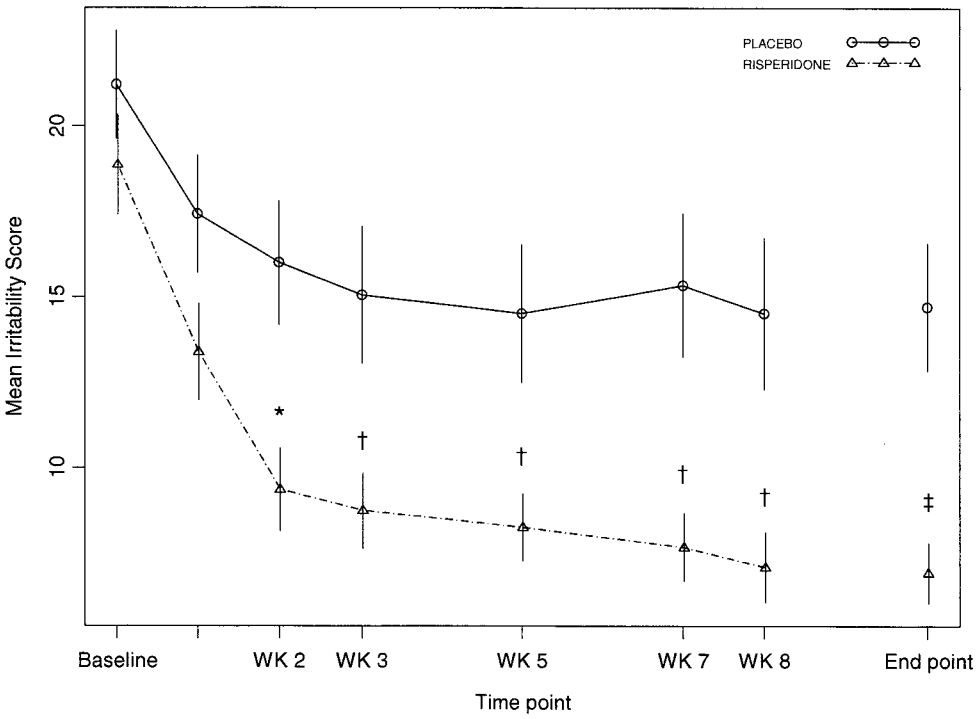

Fig 1. Irritability subscale of ABC (mean ± SE) versus time profiles by treatment group. *$P \leq .05$ for between-group comparison of change from baseline; †$P \leq .01$ for between-group comparison of change from baseline; ‡$P < .001$ for between-group comparison of change from baseline.

cally significantly greater mean decreases on the insecure/anxious ($P = .039$), hyperactive ($P = .035$), and overly sensitive ($P = .038$) subscales of the N-CBRF. Greater mean decreases were seen on the self-injury/stereotypic and the self-isolated/ritualistic subscales; however, the differences between treatments were not statistically significant.

For all subjects, the most frequently reported troublesome symptoms were aggression (23.4%), followed by tantrums/negative mood (18.2%), as rated on the VAS. At study endpoint, the mean VAS of the most troublesome symptom had decreased (improved) by a mean of 38.4 in the risperidone-treated subjects and by a mean of 26.2 in the placebo-treated subjects (Table 2). As with the 5 ABC subscales and the conduct problem, insecure/anxious, hyperactive, and overly sensitive subscales of the N-CBRF, the improvement in the mean VAS rating ($P \leq .05$) was significantly greater in the risperidone-treated subjects. More than twice the number of risperidone-treated subjects exhibited a clinical improvement in their condition at endpoint, as assessed by the CGI-C, compared with placebo-treated subjects: 34 (87.2%) versus 15 (39.5%), respectively. Three times as many risperidone-treated as placebo-treated subjects were rated as much improved or very much improved: 21 (54%) versus 7 (18%), respectively ($P < .001$). Statistically significant differences in the CGI-C between risperidone- and placebo-treated subjects were evident at each visit ($P \leq .05$).

Safety Outcomes

Risperidone, at a mean dosage of 0.04 mg/kg/day, was well tolerated by the children who participated in this 8-week study. The most common adverse events reported among risperidone-treated subjects were somnolence (72.5%), upper respiratory tract infection (37.5%), rhinitis (27.5%), and increased appetite (22.5%; Table 3). The most common events among placebo-treated subjects were aggressive reaction (20.5%), fever (17.9%), upper respiratory tract infection (15.4%), insomnia (15.4%), vomiting (15.4%), diarrhea (15.4%), and emotional lability (15.4%).

Most adverse events were mild in severity. Only 5 (12.5%) risperidone-treated subjects experienced adverse events that were categorized as severe and related to study medication: 1 case of hyperkinesia and somnolence and 1 case each of weight gain, somnolence, aggressive reaction with impaired concentration, and extrapyramidal disorder as a result of an accidental overdose. Two (5.1%) placebo-treated subjects experienced severe events that were considered related to study medication: 1 case of insomnia and sunken eyes and 1 case of accidental medication overdose. Two subjects withdrew from the study because of adverse events: the case of extrapyramidal disorder as a result of accidental overdose in the risperidone group and the case of accidental overdose in the placebo group. Both events subsequently resolved without residual effects.

Twenty-nine (72.5%) risperidone-treated subjects and 3 (7.7%) placebo-treated subjects experienced somnolence during the study with an average time to onset of first event of 8 and 15 days, respectively. Of the 29 risperidone-treated subjects, somnolence resolved in 18 of the 20 subjects who had their dosing schedule changed to either once daily in the evening or twice daily. Somnolence also resolved in the 2 subjects who had their dose reduced and in 5 of the 7 subjects for whom no dose adjustments were made.

TABLE 3. Incidence of Adverse Events Reported in ≥10% of Risperidone-Treated Subjects

Event, *n* (%)	Risperidone (*n* = 40)	Placebo (*n* = 39)
Any event	40 (100)	31 (79.5)
Somnolence	29 (72.5)	3 (7.7)
Upper respiratory tract infection	15 (37.5)	6 (15.4)
Rhinitis	11 (27.5)	4 (10.3)
Increased appetite	9 (22.5)	4 (10.3)
Abdominal pain	8 (20.0)	3 (7.7)
Fever	8 (20.0)	7 (17.9)
Insomnia	6 (15.0)	6 (15.4)
Vomiting	6 (15.0)	6 (15.4)
Coughing	6 (15.0)	4 (10.3)
Headache	5 (12.5)	2 (5.1)
Constipation	5 (12.5)	1 (2.6)
Apathy	5 (12.5)	0 (0.0)
Tachycardia	5 (12.5)	0 (0.0)
Influenza-like symptoms	4 (10.0)	2 (5.1)
Anorexia	4 (10.0)	1 (2.6)
Fatigue	4 (10.0)	1 (2.6)
Saliva increased	4 (10.0)	1 (2.6)
Weight increase	4 (10.0)	1 (2.6)
Tremor	4 (10.0)	0 (0.0)

Thus, in total, somnolence resolved in 86.2% (25 of 29) of risperidone-treated subjects who experienced this event. A subgroup analysis among risperidone-treated subjects with and without somnolence showed similar improvements on the irritability score of the ABC, suggesting that the positive effect of risperidone on the primary efficacy outcome was independent of somnolence.

By study endpoint, pulse rate had increased from baseline by a mean of 8.9 beats per minute (bpm) among risperidone-treated subjects compared with a mean decrease of 0.6 bpm among placebo-treated subjects (Table 4). Five cases of mild to moderate tachycardia in the risperidone group were reported as adverse events (Table 3); 1 of these resolved by study end.

Changes from baseline in the electrocardiogram recordings were deemed to be clinically important for 1 subject in the risperidone group; these changes included tachycardia and a possible mild conduction anomaly. In addition, by study endpoint, systolic blood pressure had increased by a mean of 4.0 mm Hg among risperidone-treated subjects compared with a mean decrease of 0.7 mm Hg among placebo-treated subjects. None of the cases of elevated systolic pressure was deemed by the investigator to be clinically significant. Over the course of the study, risperidone-treated subjects experienced a mean weight gain of 2.7 kg compared with a gain of 1.0 kg by placebo-treated subjects ($P \leq .001$).

No significant differences in the postbaseline mean total ESRS scores were evident between groups. The mean total scores on the postbaseline ESRS ranged from 0.2 to 0.9 in the risperidone group and from 0.3 to 1.1 in the placebo group. EPSs were reported as adverse events in 11 (27.5%) risperidone-treated subjects and 5 (12.8%) placebo-treated subjects. Among risperidone-treated subjects, tremor (4 cases) and extrapyramidal disorder and hypokinesia (2 cases each) were the most common EPSs. The 6 EPS events reported in the 5 placebo-treated subjects included 1 occurrence each of tardive dyskinesia, abnormal gait, ataxia, dyskinesia, hypertonia, and involuntary muscle contractions. The majority of events were mild and transient and did not require intervention. Two subjects in the risperidone group and 1 in the placebo group received anti-EPS medication; in all 3 cases, the EPS resolved by study end. Finally, most patients had hematologic, biochemical, and urinalysis parameters within normal ranges. There were no noteworthy differences in laboratory values between treatment groups.

DISCUSSION

This 8-week, randomized, multicenter, double-blind, placebo-controlled study confirmed findings reported from a number of small, open-label studies[9–18] and from a recently completed double-blind study conducted by the Research Units on Pediatric Psychopharmacology (RUPP) Autism Network.[25,26] That is, risperidone proved to be a consistently effective agent for relieving many of the behavioral symptoms associated with PDD in children. As measured by the ABC, the N-CBRF, and the VAS, risperidone was significantly more effective than placebo at alleviating irritability, hyperactivity/noncompliance, inappropriate speech, lethargy/social withdrawal, stereotypic behavior, conduct problems, hyperactive, insecure/anxious, and overly sensitive behaviors and the symptom identified as most troublesome. In addition, as measured by the CGI-C, significantly more risperidone-treated subjects exhibited clinical improvement. In addition, although mean differences in the change from baseline at study endpoint were not statistically significant, risperidone-treated subjects consistently achieved lower scores than placebo-treated subjects on each of the other subscales examined in this study. These included the N-CBRF

TABLE 4. Change From Baseline in Vital Signs and Weight at Study Endpoint

Safety Variable	Risperidone (*n* = 40)		Placebo (*n* = 38)	
	Baseline*	Endpoint†	Baseline*	Endpoint†
Pulse, bpm	90.2 ± 12.0	8.9 ± 13.9‡	95.0 ± 13.7	−0.6 ± 13.1
Diastolic BP, mm Hg	68.1 ± 9.8	0.7 ± 9.1	67.8 ± 10.3	−0.7 ± 8.8
Systolic BP, mm Hg	99.8 ± 9.6	4.0 ± 10.4‡	100.4 ± 10.5	−0.7 ± 10.7
Weight, kg	31.2 ± 14.5	2.7 ± 2.0¶	27.5 ± 8.7	1.0 ± 1.6

BP indicates blood pressure.
* Mean ± SD.
† Mean change from baseline ± SD.
‡ $P \leq .01$ versus placebo.
¶ $P \leq .001$ versus placebo.

subscales measuring self-isolated/ritualistic and self-injurious/stereotypic behaviors.

On the basis of the primary efficacy outcome (the mean change in the irritability score), risperidone was significantly more effective than placebo at each visit starting with the second postrandomization assessment at treatment week 2. By study endpoint, risperidone-treated subjects exhibited a 64% improvement over baseline in the irritability score—an improvement almost twice that exhibited by placebo-treated subjects. Similar results were observed for the subset of autistic subjects. Improvements over baseline irritability at study endpoint for children and adolescents who had autism and were randomized to risperidone treatment were 66%, whereas those who were randomized to placebo exhibited a 35% improvement. A similar difference in response was recently reported for 101 children, mean age 8.8 years, who had a diagnosis of autistic disorder accompanied by severe tantrums, aggression, or self-injurious behavior and participated in the 8-week, randomized, double-blind, placebo-controlled RUPP study.[26] In that study, risperidone-treated subjects exhibited a 57% improvement over baseline in their mean irritability score, whereas placebo-treated subjects exhibited only a 14% improvement ($P < .001$). The results of the present study are similar to those of the RUPP study and together support the effectiveness of risperidone in ameliorating some of the disruptive behavioral symptoms in children with autism and other PDD. The main limitation of this study is the relatively short duration of treatment

Treatment with risperidone was generally well tolerated: only 1 risperidone-treated subject was withdrawn from the study because of an adverse event; that event was caused by an accidental study medication overdose from which the subject recovered fully. Somnolence was reported in a majority of the risperidone-treated subjects, yet it resolved in 86% of subjects for whom it was reported. Somnolence either resolved spontaneously or was managed effectively by dose reductions or a change in dosing regimen to twice daily or evening schedules. It is interesting to note that somnolence when present did not influence the improvement seen in irritability, the primary efficacy parameter.

Over the course of 8 weeks of treatment, pulse rate increased among risperidone-treated subjects with mild to moderate tachycardia being reported as an adverse event for 5 subjects. The tachycardia resolved in 1 subject. In addition, 1 subject in the risperidone group was reported to have a possible mild conduction anomaly (on the V1 lead), which was considered clinically relevant. There was also a small but statistically significant increase in the systolic blood pressure observed in the risperidone group, although none of the cases was deemed clinically significant. These slight increases in heart rate and blood pressure in risperidone-treated over placebo-treated subjects were not seen in the recently reported controlled trial in children with autistic disorder,[26] and their possible relevance is not known.

There were no significant differences in the weekly total ESRS scores between the risperidone and placebo treatment groups either in this study or in the 8-week RUPP study that was conducted in children with autistic disorder.[26] Although more risperidone-treated subjects than placebo-treated subjects experienced at least 1 EPS, the majority of symptoms were assessed as mild and transient and did not require intervention. In subjects who did receive treatment, the events were managed effectively. No cases of tardive dyskinesia were reported for the risperidone-treated subjects. Longer-term studies to follow EPSs and other safety outcomes are warranted.

Finally, risperidone-treated subjects experienced a weight gain of 2.7 kg compared with a gain of 1.0 kg experienced by placebo-treated subjects. A similar degree of weight gain was observed in the RUPP study.[26] Longer-term studies of risperidone use in children up to 1 year in duration have demonstrated that the degree of weight gain is more pronounced during the first months of therapy.[27] Nonetheless, as a preemptive measure to prevent or diminish possible weight gain, children who have PDD and are prescribed a course of risperidone should be encouraged to institute a dietary regimen and physical activity plan.

As is the case with some other antipsychotics, hyperglycemia and exacerbation of preexisting diabetes have been reported in rare instances during risperidone use;[28] this was not observed in this study or the RUPP study.[26] Diabetic ketacidosis has also been reported.[28] Appropriate clinical monitoring is advised in diabetic patients and those with risk factors for the development of diabetes mellitus.

In conclusion, risperidone solution (mean dosage: 0.04 mg/kg/day; 1.17 mg/day) was efficacious and well tolerated in the treatment of behavioral symptoms, including aggression, in children 5 to 12 years of age with PDD, as assessed by the ABC subscales (irritability, hyperactivity/noncompliance, inappropriate speech, lethargy/social withdrawal, stereotypic behavior) and the N-CBRF subscales of conduct problem, hyperactive, insecure/anxious, and overly sensitive behaviors. Most adverse events were self-limiting or readily manageable with dosing modifications. The encouraging efficacy outcomes achieved with this agent offer new hope for the management of behavioral symptoms exhibited by children with PDD.

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