Risperidone in Children With Disruptive Behavior Disorders and Subaverage Intelligence: A 1-Year, Open-Label Study of 504 Patients

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ABSTRACT

Objective: To determine the long-term safety and effectiveness of risperidone for severe disruptive behaviors in children. **Method:** A multisite, 1-year, open-label study of patients aged 5 to 14 years with disruptive behaviors and subaverage intelligence was conducted. **Results:** Seventy-three percent of the 504 patients enrolled completed the study. The mean ± SE dose of risperidone was 1.6 ± 0.0 mg/day. The most common adverse events were somnolence (30%), rhinitis (27%), and headache (22%). The incidence of movement disorders was low, and mean Extrapyramidal Symptom Rating Scale scores decreased during risperidone treatment. No clinically significant changes in mean laboratory values were noted, except for a transient increase in serum prolactin levels. Scores on the Nisonger Child Behavior Rating Form Conduct Problem Scale improved significantly as early as week 1, and improvement was maintained throughout the trial ($p < .001$ at each time point). Significant improvements were noted on positive social behavior and other Nisonger Child Behavior Rating Form subscales, Aberrant Behavior Checklist, Clinical Global Impressions scale, and tests of patients' cognitive function (each $p < .001$). **Conclusions:** Risperidone was well tolerated and effective in the long-term treatment of disruptive behavior disorders in children with subaverage intelligence. *J. Am. Acad. Child Adolesc. Psychiatry*, 2005;44(1):64–72. Key Words: disruptive behavior disorder, risperidone, child and youth psychopharmacology.

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The prevalence of conduct disorder in children and adolescents appears to have increased over the past decades, with general population studies reporting rates ranging from less than 1% to more than 10% and a higher incidence in boys than girls (American Psychiatric Association, 2000). Although they can occur in children and adolescents with normal intelligence, disruptive behavior disorders are more commouly associated with below-average intelligence quotients (Campbell and Malone, 1991).

The consequences of disturbed behaviors for the patients and their families are profound and have serious implications for society. Hechtman and Offord (1994) have observed that conduct disorders of early childhood are predictive of "widespread social malfunction, as seen in high rates of divorce and separation, poor work history, and unsatisfactory social relationships."

Antipsychotics have been used to treat disruptive behavior disorders in children for more than 20 years (Bennett et al., 1983; Campbell et al., 1984; Greenhill et al., 1985) despite limited data on their short- and long-term efficacy and safety. A significant disadvantage of conventional antipsychotics, particularly in children, is their association with adverse events, including photosensitivity (phenothiazines), galactorrhea (thioridazine), cardiotoxicity (pimozide), sedation and drooling (molindone, haloperidol), cognitive dulling (haloperidol), and the more familiar movement disorders, such as extrapyramidal symptoms (EPS) and tardive dyskinesia (Santosh and Baird, 1999; Silva et al., 1996).

The benefits of risperidone in the short-term treatment of disruptive behavior disorders are well documented. In 1993, Vanden Borre et al. (1993) demonstrated in a double-blind, placebo-controlled trial that adjunctive risperidone was well tolerated and significantly better than placebo in treating mentally retarded adults with persistent behavioral disturbances. This report was followed by more than a dozen promising open-label studies and case reports of risperidone used alone or as an adjunctive treatment in adults, adolescents, and children with severe behavior problems. Three double-blind, placebo-controlled pilot studies involving children and adolescents with disruptive behavior disorders were also conducted and demonstrated that risperidone monotherapy was significantly more effective than placebo (Buitelaar et al., 2001; Findling et al., 2000; Van Bellinghen and De Troch, 2001). These findings have been confirmed in two large randomized, multicenter, double-blind, placebo-controlled studies of very disruptive children with subaverage intelligence (Aman et al., 2002; Snyder et al., 2002).

The goal of our 1-year, open-label, multisite trial was to investigate the long-term tolerability, safety, and effectiveness of risperidone for treating disruptive behavior disorders in a large group of children and adolescents with borderline intellectual functioning or mild to moderate mental retardation.

METHOD

This 1-year, open-label, international trial was conducted at 32 sites in 12 countries across Europe (n = 16), North America (n = 11), and South Africa (n = 5). Sites chosen were those with extensive experience in the assessment and treatment of children with conduct disorders and with a sufficient number of potential subjects. Investigators included child and adolescent psychiatrists, pediatricians, and clinical psychologists experienced in treating the types of patients enrolled in the study. A trial monitor met with each investigator and reviewed procedures to be followed in conducting the trial.

Patients

Subjects were recruited from specialized schools and residential centers and from among the patients at the investigators' sites. Patients were included in the study if they were 5 to 14 years old and had a *DSM-IV* Axis I diagnosis of conduct disorder (312.8), oppositional defiant disorder (313.81), or disruptive behavior disorder not otherwise specified (312.9); a score of ≥24 on the Conduct Problem Subscale of the Nisonger Child Behavior Rating Form (N-CBRF) (i.e., the 70th percentile for a group of children attending a center for developmental disorders) (Aman et al., 1996; Tasse et al., 1996); a *DSM-IV* Axis II diagnosis of mild mental retardation (317), moderate mental retardation (318.0), or borderline intellectual functioning (V62.89) (i.e., intelligence quotient of 36–84); and a Vineland Adaptive Behavior Scale (Sparrow and Cicchetti, 1985) score of ≤84.

Exclusion criteria included diagnoses of pervasive development disorder (299.00, 299.80, 299.10) or schizophrenia or other psychotic disorders (295.xx, 297.xx, 298.8, 293.xx), head injury as a cause of intellectual impairment, seizure disorder requiring medication, laboratory test results outside normal limits, and serious or progressive illnesses. Also excluded were children with a history of tardive dyskinesia or neuroleptic malignant syndrome, those with known hypersensitivity to antipsychotics or risperidone, and those with known human immunodeficiency virus infection.

Study Design

Each center's institutional review board approved the study design. The study was explained to each patient and his or her guardian or legal representative and the child (if capable) and the guardian or legal representative signed an informed consent form. A responsible person was required to be available to accompany the child for study visits, to provide reliable assessments, and to dispense study medication.

The screening process included a medical and psychiatric history, physical examination (including vital signs, weight, height, and Tanner staging [Tanner and Whitehouse, 1976]), psychiatric examination, electrocardiogram, clinical laboratory assessments, pharmacokinetic sampling, and completion of the N-CBRF, Aberrant Behavior Checklist (Aman et al., 1985), and Clinical Global Impressions (CGI) Scale (Guy, 1976). For each child, the most troublesome symptom was identified by the parent or caregiver and scored using a visual analog scale. The parent or caregiver also completed the Child Symptom Inventory (Gadow and Sprafkin, 1994), a standardized informant scale used to assess all major *DSM-IV* conditions in children. After the parent or caregiver completed the N-CBRF, Child Symptom Inventory, visual analog scale, and Aberrant Behavior Checklist, the clinician recorded medical and psychiatric histories, examined the child, and completed the Extrapyramidal Symptom Rating Scale (ESRS) (Chouinard et al., 1980) and CGI Scale. Based on this information, the investigator made a *DSM-IV* diagnosis. The intelligence of each child was assessed using the Stanford-Binet Intelligence Scale (Thorndike et al., 1986) or the WISC third edition (Wechsler, 1974). In addition, the inves-

tigator interviewed the parents or caregivers about the child's daily living skills using the Vineland Adaptive Behavior Scale (Sparrow et al., 1984).

After the 3-day screening period, eligible patients received single-blind treatment with placebo for 1 week and were then evaluated using the N-CBRF and Vineland Scale. Placebo responders (those with scores ≤24 on the N-CBRF Conduct Problem Subscale or ≥84 on the Vineland Scale) were excluded from the trial. The remaining patients entered the trial.

Treatment

Risperidone as an oral liquid solution was given once daily in the morning or afternoon. Doses were 0.01 mg/kg/day of risperidone on days 1 and 2 and 0.02 mg/kg/day on day 3. Thereafter, doses could be adjusted at weekly intervals as judged necessary by the clinician. Increases were not to exceed 0.02 mg/kg/day, and the maximal dose permitted was 0.06 mg/kg/day. If a patient experienced breakthrough symptoms such that disruptive behaviors occurred in the hours before the next dose, the regimen could be changed to twice-daily dosing.

Psychotropic medications other than risperidone were not permitted with the following exceptions: Psychostimulants were allowed for attention-deficit/hyperactivity disorder provided the patient had been stabilized on a constant dose for 30 days before entering the trial, sedatives or hypnotics were allowed for sleep if the patient had been receiving these medications before the screening visit, and benzodiazepines were allowed as premedication for medical procedures. No medications for sleep or anxiety were to be started during the trial. Medications used for EPS had to be discontinued at study entry. If EPS emerged during the trial, anticholinergic drug therapy could be considered if dose reduction of the study medication was unsuccessful. Behavioral therapy was permitted if it was initiated at least 30 days before the start of the study. No changes in psychostimulant use or behavioral therapy were allowed during the study.

Assessments

After screening, visits were scheduled at baseline (treatment initiation), days 7, 14, 21, and 28, and months 2 to 6, 9, and 12. Adverse events were recorded throughout the treatment period. Vital signs were assessed at each visit, and a complete physical examination, including height measurement, was performed at screening and months 1, 3, 6, and 12. We evaluated EPS severity at all time points using the ESRS. Weight measurements, clinical laboratory tests, and electrocardiography were performed at screening and months 1, 3, 6, and 12. Sexual maturation was evaluated by means of Tanner staging at baseline and months 6 and 12. Venous blood samples for pharmacokinetic analysis for risperidone and the active moiety (risperidone plus 9-hydroxyrisperidone) were taken at screening and at trough level (i.e., just before the next scheduled drug intake or 24 hours after the last drug dose) at week 4 and months 6 and 12.

We assessed cognitive function at baseline and months 6 and 12 using a modification of the children's version of the California Verbal Learning Test (MCVLT-CV) (Delis et al., 1994), which evaluates memory, and the Continuous Performance Task (Spreen and Strauss, 1998), a test of attention or vigilance. The Continuous Performance Task consists of sequential presentations of a princess and a witch on a computer screen. Patients had to alert the princess when the witch appeared by pressing the mouse control. In the "easy" version, the stimuli were presented at predictable intervals. If few errors were made on the easy version of the test (signifying a floor effect), the child was given a "hard" version in which the stimuli were presented at variable intervals and for a briefer time. Errors of omission (failures to detect the witch), errors of commission (detection of princess), and mean response time for correct detections were recorded.

Assessments of effectiveness were made at baseline, weekly for 4 weeks, and then monthly, and included N-CBRF subscales (compliant/calm, adaptive/social, insecure/anxious hyperactive, self injury/stereotyped, self-isolated ritualistic, overly sensitive), the Aberrant Behavior Checklist (each item scored from 1 [mild] to 4 [profound]), and the visual analog scale of the most troublesome symptom (ranging from 0 [not present] to 100 [extremely severe]). The CGI Scale was used to assess the overall severity of each patient's symptoms. The primary measure of effectiveness was the change from baseline to end point in scores on the 16-item Conduct Problem Subscale of the N-CBRF. Each item is scored from 0 (no occurrence of problem behavior or no problem) to 3 (many problem behaviors or a severe problem). Secondary measures of effectiveness included results from the other N-CBRF subscales, CGI Scale, visual analog scale, and Aberrant Behavior Checklist total and subscale scores.

Data Analysis

We assessed safety in all patients who entered the trial and tabulated all adverse events by type and incidence. The Wilcoxon signed rank test (two sided) was used to evaluate changes from baseline in ESRS scores (Lehmann, 1998). Changes from baseline for all other safety measures were evaluated using two-sided paired t tests. Pre- and posttreatment clinical laboratory data frequencies were calculated, including those for important abnormalities.

Effectiveness was assessed in all patients who received at least one dose of risperidone during the trial and for whom data on the Conduct Problem Subscale of the N-CBRF were available. Changes in scores from baseline to end point (the last observation for each patient) or other time points for the N-CBRF, CGI, and Aberrant Behavior Checklist were analyzed using two-sided paired t tests. Because of missing assessments at particular visits, mean scores and changes versus baseline may be based on a different number of observations. Because most of the N-CBRF and Aberrant Behavior Checklist assessments were complete, we did not impute missing items to calculate subscale scores. However, when one or more items were missing, the score of the subscale was set to missing.

Mean values and their SD are provided as descriptive statistics. In places, these data are accompanied by median values or ranges. When comparing mean values with baseline scores, the change in mean and its SEM are given using the notation mean ± SE. All statistical analyses were performed using SAS (version 6.12; SAS Institute Inc., Cary NC).

RESULTS

Baseline characteristics and patient disposition are shown in Table 1. The patients' mean age at baseline was 9.7 ± 2.5 years. Most patients had a primary diagnosis of conduct disorder (45%) or oppositional defiant disorder (36%) with or without attention deficit hyperactivity disorder. Mean IQ was 64.2 ± 13.4, and

TABLE 1
Baseline Patient Characteristics ($N = 504$)

Sex, *n* (%)	
Male	419 (83.1)
Female	85 (16.9)
Race/ethnicity, *n* (%)	
White	425 (84.3)
Black	37 (7.3)
Hispanic	6 (1.2)
Asian	2 (0.4)
Other	34 (6.7)
Age (yr)	
Mean ± SD	9.7 ± 2.5
Median (range)	10 (4–14)
<12 y, *n* (%)	375 (74.4)
Domiciliary status	
Lives with parents, *n* (%)	406 (81.4)
Other	93 (18.6)
DSM-IV Axis I diagnoses, *n* (%)	
Conduct disorder	120 (23.8)
Conduct disorder + ADHD	105 (20.8)
Oppositional defiant disorder	90 (17.9)
Oppositional defiant disorder + ADHD	95 (18.8)
Behavior disorder NOS	33 (6.5)
Behavior disorder NOS + ADHD	51 (10.1)
ADHD	10 (2.0)
DSM-IV Axis II diagnoses, *n* (%)	
Borderline intellectual functioning	189 (37.6)
Mild mental retardation	217 (43.1)
Moderate mental retardation	97 (19.3)

Note: ADHD = attention-deficit hyperactivity disorder; NOS = not otherwise specified.

mean Vineland Adaptive Behavior Scale score at baseline was 52.7 ± 13.4.

Of the 589 patients recruited, 504 entered the trial. Reasons for not receiving study medication included ineligibility (60 patients), withdrawal of consent (11 patients), lost to follow-up (eight patients), noncompliance (three patients), and other reasons (three patients). Among the 504 patients who received study medication, 367 patients (73%) completed the 1-year trial. Reasons for discontinuation were adverse events in 43 (8.5%), lost to follow-up in 26 (5.2%), withdrawal of consent in 22 (4.4%), insufficient response in 18 (3.6%), noncompliance in 17 (3.4%), and ineligibility, lack of symptoms, or other reasons in <2% of patients each.

Treatment

The mean (SE) modal dose of risperidone (i.e., most frequent) throughout the trial was 1.6 ± 0.03 mg/day. The median dose was 1.5 mg/day (range 0.1–4.3). The mean duration of treatment was 307.3 ± 5.0 days (range 1–505).

The most common additional medications used during the trial were analgesics, antibiotics, and psychostimulants. Concomitant medications taken by ≥5% of patients included paracetamol (27% of patients), amoxicillin (14%), methylphenidate or methylphenidate hydrochloride (14%), sulfamethoxazole/trimethoprim (5%), ibuprofen (5%), and aspirin (5%).

Safety

Adverse events were generally mild or moderate, the most common being somnolence (30% of patients), rhinitis (27%), and headache (22%) (Table 2). Adverse events resulting in withdrawal from the study by three or more of the 504 patients included weight gain (nine patients), increased appetite (four patients), gynecomastia (three patients), somnolence (three patients), and headache (three patients).

Severity of EPS was low at baseline (mean ESRS total score, 1.2 ± 0.1) and decreased at each assessment thereafter. The mean ESRS total score changes from baseline were −0.4 ± 0.2 at month 12 ($p < .001$) and −0.3 ± 0.1 at end point ($p = .024$, Wilcoxon signed rank test). Five patients (1%) required antiparkinsonian medications during the study, and in six patients (1%), EPS led to discontinuation. Two patients devel-

TABLE 2
Adverse Events Reported by ≥10% of Patients ($N = 504$)

	No. (%) of Patients
Any adverse event	462 (91.7)
Somnolence	149 (29.6)
Rhinitis	137 (27.2)
Headache	110 (21.8)
Weight increase	87 (17.3)
Upper respiratory tract infection	83 (16.5)
Pharyngitis	74 (14.7)
Fatigue	69 (13.7)
Coughing	67 (13.3)
Fever	62 (12.3)
Vomiting	60 (11.9)
Hyperprolactinemia	56 (11.1)
Injury	54 (10.7)
Increased appetite	53 (10.5)

oped tardive dyskinesia, which resolved a few weeks after study medication was discontinued. In one patient, symptoms may have been due to withdrawal dyskinesia because symptoms occurred 12 hours after discontinuation of risperidone.

Paired laboratory data (i.e., data at baseline and at least once during the trial) were available for 480 patients (95%). With the exception of prolactin levels, no consistent or clinically relevant changes in blood chemistry or hematology were noted during the trial. One patient had elevated levels of alanine aminotransferase at week 4 (231 U/L; upper limit of normal, 78 U/L), which returned to normal at month 3 and remained within normal limits throughout the rest of the trial.

Increases in serum prolactin levels above normal were transient. At baseline, mean serum prolactin levels were 7.7 ± 7.1 ng/mL for boys and 10.1 ± 8.1 for girls. Peak levels in boys and girls occurred at week 4 (28.2 ± 14.2 ng/mL in boys and 35.4 ± 19.1 ng/mL in girls), then decreased to 16.1 ± 11.9 and 21.6 ± 22.0 ng/mL, respectively, at end point (upper limits of normal are 18 ng/mL for boys and 25 ng/mL for girls) (Fig. 1). A total of 205 males had prolactin levels above the normal limits, as did 26 females. Adverse events that could potentially be attributed to prolactin elevation were reported in 32 patients (6.4%). Mild (15 patients) to moderate (10 patients) gynecomastia was seen in 22 boys and 3 girls. Three of these patients discontinued treatment. In eight patients, gynecomastia resolved during the study without intervention. Other adverse events possibly related to prolactin were menstrual disturbances (six patients) and galactorrhea (one patient). Except for one case of menorrhagia of moderate severity, all these adverse events were mild and spontaneously resolved during the trial.

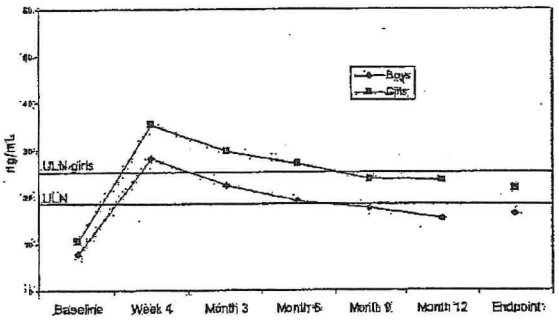

Fig. 1 Serum prolactin levels (ng/mL) from baseline to end point, with the upper limit of the normal (ULN) for girls and boys.

No changes in vital signs or electrocardiographic values were of clinical significance. Mean body weight increased from 36.4 ± 13.6 kg at baseline to 43.4 ± 15.7 kg at end point, a mean increase of 7.0 ± 2.1 kg ($p < .001$). One half of this weight gain could be attributed to developmentally expected growth (Hammill et al., 1979). Weight gain was greatest in the first 6 months of risperidone treatment and leveled off thereafter, with little change between 6 and 12 months. Mean body mass index increased from 17.9 ± 3.6 kg/m^2 at baseline to 19.8 ± 4.2 kg/m^2 at end point, a mean increase of 1.9 ± 0.6 kg/m^2 ($p < .001$).

The children's sexual maturation progressed normally during the trial. The number in Tanner stage 1 decreased from 345 at entry to 186 after 12 months and the number in higher Tanner scores increased. Mean body height increased from 139.8 ± 0.72 cm at baseline to 146.3 ± 0.8 cm at month 12, a mean increase of 6.9 ± .0.2 cm ($p < .001$).

Pharmacokinetics

Adequate drug exposure was achieved, and the overall plasma concentrations of the active moiety (i.e., risperidone plus 9-hydroxyrisperidone) remained fairly constant over the entire study period. The mean plasma levels of the active moiety were 12.1, 12.5, 12.4, and 12.6 ng/mL at week 4, month 6, month 12, and end point, respectively. Concentrations of the active moiety decreased from a mean peak level of 22.3 ± 19.8 ng/mL (101 samples) to a mean trough level of 11.8 ± 10.1 ng/mL (958 samples), which is consistent with the approximately 24-hour half-life of the active moiety.

Cognition

Patients' scores improved significantly on both tests of cognitive function. On the MCVLT-CV, mean change scores at end point were as follows: total long delay-free recall, 0.7 ± 0.1; total short delay-free recall, 2.9 ± 0.4; and total correct, 0.7 ± 0.2 (each $p < .001$ versus baseline by two-sided paired t test). On the Continuous Performance Task easy and hard tests, the number of correct responses increased and the number of errors decreased. Mean change scores at end point were as follows: total hits, 1.6 ± 0.3 and 1.6 ± 0.4, respectively; total false alarms, −2.9 ± 0.6 and −4.2 ± 0.7, respectively; and total misses, −1.5 ± 0.3 and

−1.4 ± 0.4, respectively (each $p < .001$ vs. baseline by two-sided paired t test).

Effectiveness

Significant improvement was noted at each time point after baseline on the primary measure of effectiveness, the N-CBRF conduct problem subscale (Table 3). The mean score decreased from 32.9 ± 7.5 at the open-label baseline to 17.0 ± 11.0 at end point. The mean change at end point was −15.8 ± 0.5 ($p < .001$). This represents a 48% decrease in the mean score. Considerable improvements were seen from weeks 1 to 4, and the improvements were maintained during the subsequent 11 months.

Significant improvements were also seen on the positive social behavior and problem behavior N-CBRF subscales (Fig. 2). Compliant/calm and adaptive/social both increased significantly ($p < .001$), with mean changes of 3.4 ± 0.12 and 1.9 ± 0.13, respectively. Insecure/anxious, hyperactive, self-injury/stereotypic, self-isolated/ritualistic, and overly sensitive subscale scores all decreased significantly ($p < .001$), with mean changes of −5.4 ± 0.4, −6.8 ± 0.3, −1.0 ± 0.2, −1.7 ± 0.02, and −2.1 ± 0.02, respectively.

On the CGI Severity Scale at baseline, 72% of patients had marked to extremely severe symptoms. At end point, 12% had marked to extremely severe symptoms and 66% were rated as not ill or having mild symptoms. Mean Aberrant Behavior Checklist total scores decreased from 64.3 ± 25.0 at baseline to 37.4 ± 27.0 at end point, a change of −28.3 ± 1.4 ($p < .001$). At baseline, the most troublesome symptoms were aggression in 33% of patients, oppositional defiant behavior in 30%, and hyperactivity in 16%. The visual analog scale scores of the most troublesome symptom improved significantly, from 74.3 ± 17.9 at baseline to 33.9 ± 24.0 at end point, a change of −40.3 ± 1.3 ($p < .001$); considerable improvements were seen during weeks 1 to 4 and maintained during the following 11 months.

TABLE 3
Mean Scores and Changes Versus Baseline on the Conduct Problem Subscale of the Nisonger Child Behavior Rating Form

	No. of Patients	Mean ± SD Scores	Mean ± SE Changes[a]
Baseline	487	32.9 ± 7.5	—
Week			
1	479	24.6 ± 10.4	−8.3 ± 0.4
3	463	17.8 ± 10.8	−15.2 ± 0.5
Month			
1	479	16.4 ± 10.8	−16.4 ± 0.5
3	434	16.8 ± 11.0	−16.0 ± 0.5
6	411	16.6 ± 11.2	−16.1 ± 0.6
9	390	16.0 ± 10.3	−16.6 ± 0.6
12	363	15.2 ± 10.4	−17.0 ± 0.6
End point	496	17.0 ± 11.0	−15.8 ± 0.5

[a] $p < .001$ versus baseline at each time point (two-sided paired t test).

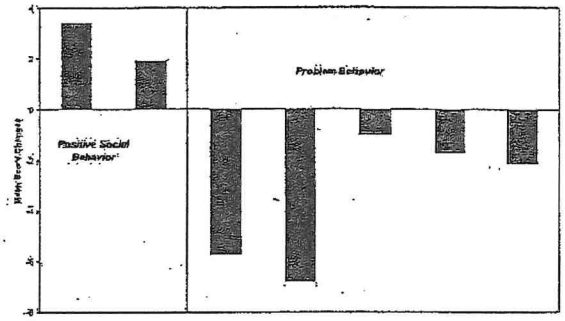

Fig. 2 Improvements from baseline to end point on the Nisonger Child Behavior Rating Form positive social behavior and problem behavior subscales. $p < .001$ versus baseline on each item.

DISCUSSION

The principal and clinically relevant finding of this study of more than 500 children and adolescents with disruptive behavior disorders is that 1 year of treatment with risperidone was generally safe and effective. Risperidone was well tolerated and substantially reduced the severity of disruptive behavior. Over the course of the 1-year study, scores on the N-CBRF, Aberrant Behavior Checklist, and visual analog scale of most troublesome symptoms were significantly reduced from baseline. One indication of the tolerability and effectiveness of treatment with risperidone in these young patients was the high overall completion rate (73%) and low rate of discontinuation for adverse events (9%) or insufficient response (4%). Risperidone also had a positive effect on the patients' social competence (as reflected in improved prosocial subscales of the N-CBRF) and cognitive function.

The only clinically relevant change in laboratory test results during the trial was an increase in serum prolactin levels. Few patients discontinued because of pro-

lactin-related adverse events, and mean prolactin levels were similar among patients who discontinued and completed the trial. The increase above the upper limit of normal was transient; peak levels were seen after 4 weeks of treatment and then decreased to within normal limits. Few adverse events possibly related to elevated prolactin levels were noted. Gynecomastia, reported in 23 boys and 2 girls, is often observed in normal pubertal boys (Glass, 1994) and girls (Findling et al., 2003), so it is not possible to assess the contribution of risperidone without a placebo control group. Both the 48-week trial of risperidone in children (Findling et al., 2004) and an analysis of combined data from long-term trials of risperidone in children and adolescents (Findling et al., 2003) reported similar transient increases in prolactin levels and few physical signs potentially associated with prolactin elevation. The long-term effects of elevated prolactin levels in the absence of clinical signs or symptoms are currently unknown. It is possible that the apparent discordance between prolactin levels and clinical symptoms in these patients may in part be explained by elevation of large prolactin forms that have no clinical activity (Fideleff et al., 2000; Larrea et al., 1985; Leslie et al., 2001).

Weight gain was the most common cause of study discontinuation (in nine patients). Mean body weight increased 7.0 ± 2.1 kg from baseline; however, one half of this weight gain could be attributed to developmentally expected growth (Hammill et al., 1979). Weight gain was greatest early on and leveled off thereafter, with little change between 6 and 12 months, suggesting that longer term treatment with risperidone would not result in a significant further weight increase. However, counseling regarding diet and exercise may be prudent when prescribing risperidone in these patients.

Growth and sexual maturation as determined by change in height and Tanner stage continued as would be expected for patients in this age group (Hammill et al., 1979). These findings are consistent with an analysis of the effects of long-term risperidone therapy on growth and sexual maturation, in which there was no evidence of delayed puberty or stunted growth in children treated with risperidone for up to 1 year (Dunbar et al., 2004).

Results of two landmark short-term (6-week), double-blind, placebo-controlled studies of risperidone in children with disruptive behavior disorders have recently been published (Aman et al., 2002; Snyder et al., 2002). The background characteristics and diagnoses of the patients in these short-term trials are similar to those of our long-term study, as are the treatment outcomes. Our findings indicate that the short-term benefits of risperidone for children with disruptive behavior disorders reported by Aman et al. and Snyder et al. can be maintained over at least 1 year. These results also confirm the long-term safety and effectiveness of risperidone reported by Turgay et al. (2002) in 77 children aged 5–12 years and by Findling et al. (2004) in 105 children aged 5–12 years with severe disruptive behavior disorders.

The effect of risperidone on problem behaviors may be due to its interaction with both serotonin and dopamine receptors. It has been suggested that impulsive behaviors including aggression may result from an imbalance between dopamine and serotonin (Swann, 2003). Thus, risperidone may have a regulatory effect on these systems that is distinct from its antipsychotic effect.

Limitations

Our study has several limitations. First, this was an open-label trial without a control group. Nonetheless, even though placebo-controlled trials are generally accepted as the gold standard, open-label studies, especially those of the size of this study, resemble more closely the conditions that may be encountered in clinical practice. A second limitation is that we included only children and adolescents with subaverage intelligence. Whether our findings can be generalized to children and adolescents with normal intelligence is not clear; however, a study by Findling et al. (2000) indicated that risperidone is effective in children with conduct disorder and normal intelligence. Finally, we focused on children with severe disruptive behaviors. Unlike disorders such as adult schizophrenia, we do not yet know whether long-term treatment of disruptive behaviors in children is useful in all patients. However, in a study of adolescents given risperidone for aggression, Buitelaar et al. (2001) observed deterioration in the 2-week washout phase that followed his 6-week, double-blind treatment period. Their data suggest that, at least in patients with the most severe problems, symptoms tend to return when treatment is stopped and therefore that some patients will benefit from long-term treatment.

Clinical Implications

Conventional antipsychotics are currently used for long-term treatment of some children with disruptive behavior disorders in the absence of evidence of long-term efficacy and safety.

The strengths of our 1-year study include the large size of the patient sample (more than 500 children and adolescents), the international character (which makes the results generalizable to three different continents), and the extensive battery of measurements. The study indicates that the results of many short-term, open-label, controlled trials in which risperidone has been shown to be well tolerated and effective in young patients with disruptive behavior disorders can now be extended to the long-term management of these patients. Our data demonstrate that long-term treatment with risperidone is generally well tolerated and that children and adolescents receiving long-term treatment with risperidone appear to have a stable response under study conditions in which there were frequent reevaluations.

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