A 3-Year Naturalistic Study of 53 Preschool Children With Pervasive Developmental Disorders Treated With Risperidone

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Background: Only sparse and short-term data are available on pharmacologic treatments in very young children with pervasive developmental disorders (PDD). The purpose of this 3-year naturalistic study (March 1999–April 2002) is to describe the clinical outcome of a consecutive sample of preschool children with PDD treated with risperidone monotherapy.

Method: The sample consisted of 45 boys and 8 girls aged 3.6 to 6.6 years (mean ± SD age = 4.6 ± 0.7 years) with a DSM-IV diagnosis of autistic disorder or PDD, not otherwise specified. Outcome measures included the Children's Psychiatric Rating Scale (CPRS), Clinical Global Impressions-Improvement scale (CGI-I), Children's Global Assessment Scale (CGAS), and a checklist for risperidone side effects.

Results: Patients received risperidone for a period ranging from 1 to 32 months (7.9 ± 6.8 months). Twenty-five patients (47.2%) continued to receive risperidone after the study was completed, while 28 (52.8%) discontinued due to side effects (22.6% [N = 12]), parents' choice (18.9% [N = 10]), lack of efficacy (5.7% [N = 3]), and decision of the treating psychiatrist (5.7% [N = 3]). The optimal dose was 0.55 ± 0.2 mg/day. Significant improvement at the last observation was found in CPRS ($p < .0001$) and CGAS ($p < .0001$) scores. On the basis of both an improvement of 25% in CPRS score and a score of 1 or 2 on the CGI-I, 46.8% (N = 22) of subjects were considered responders. Behavioral disorders and affect dysregulation were more sensitive to treatment than was interpersonal functioning. Responders received higher doses of medication for a longer period and had a greater weight gain than did nonresponders. Increased prolactin levels without clinical signs (65% [24 of 37]) and increased appetite (15% [8 of 53]) were the most frequent side effects.

Conclusion: These findings suggest that low-dose risperidone may positively affect the clinical outcome in young children with PDD not only in the short-term, but also in the long-term period.

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Various types of psychotropic drugs with effects on dopaminergic and serotonergic systems have been described as helpful in ameliorating problematic symptoms in children and adolescents with pervasive developmental disorders (PDD).[1] The dopamine receptor antagonist haloperidol is the most commonly studied medication in children with PDD, and it has been described as effective in reducing hyperactivity, aggression, and temper tantrums,[2,3] but extrapyramidal symptoms and tardive dyskinesia limit its use in pediatric PDD.[4] Newer antipsychotics, called atypical antipsychotics, with dopamine and serotonin receptor antagonism (clozapine, risperidone, olanzapine, and quetiapine) have been found to be more effective than conventional neuroleptics for both positive and negative symptoms of early-onset schizophrenia, with lower risk of acute extrapyramidal effects and tardive dyskinesia.[5,6] Some core autistic symptoms may be considered comparable to the negative symptoms of schizophrenia,[7] and they were hypothesized to be more sensitive to atypical antipsychotics.[1] Risperidone is the atypical antipsychotic most extensively used in PDD children and adolescents.[7–12] Short-term (8 weeks) efficacy and effectiveness of risperidone in children and adolescents have been recently confirmed in a multisite, randomized, double-blind trial of risperidone.[13] According to that study, 69% of the subjects in the risperidone group were responders to treatment, compared with 12% in the placebo group. In two thirds of the responders to risperidone, the positive effect was maintained after 6 months.

Although a timely, effective treatment (both psychosocial and pharmacologic) may help to improve prognosis in PDD,[14] only sparse and short-term data are available on

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pharmacologic treatments in very young children. Most of these studies suggest favorable efficacy and safety of risperidone.[8–10,15–17]

A recent study described efficacy and tolerability of risperidone treatment in 24 children aged 3.6 to 6.6 years (mean = 4.6 years) in a 16-week, open-label trial.[18] According to both a 25% improvement in Children's Psychiatric Rating Scale (CPRS) scores[19] and a score of 1 or 2 ("very much" or "much improved") on the Clinical Global Impressions-Improvement scale (CGI-I),[20] 33.3% of the subjects were responders. Risperidone was well tolerated, but another study showed a significant increase of serum prolactin levels in a strong minority of young children treated, although none of the children showed clinical signs of hyperprolactinemia.[21]

Psychopharmacology of very young patients is increasingly considered a major topic of current research even though several specific needs are largely unmet,[22] including the paucity of information about the pharmacodynamic effect of drugs on the developing brain.[23] Off-label medication use in preschool children is a widespread problem that applies not only to psychoactive drugs, but also to 80% of all medications.[24] The specificity of the medical workup, as well as the frequency of monitoring, needs further research in this age range. These considerations raise important ethical concerns both in clinical practice and in clinical trials.[25]

Although randomized, placebo-controlled clinical trials can be considered the gold standard when data about safety and efficacy are lacking and/or when there is uncertainty regarding whether a medication is a valid alternative,[25] an interesting issue is how far the results of controlled studies, on select populations intensively studied for short periods, can apply to everyday care. Systematic, naturalistic observations of long-term outcome in routine care can yield the specific, essential information needed to practice evidence-based health care.[26] Long-term, naturalistic, prospective studies might represent an important source of information regarding the effectiveness of a treatment over extended periods of time under routine clinical conditions.

We report systematic data from a 3-year naturalistic, prospective study of very young children with PDD treated with risperidone in a clinical practice setting. Data reported in this study were collected during the period March 1999 to April 2002.

METHOD

Subjects

All children, aged between 36 and 71 months, referred to our division as inpatients or outpatients during a 3-year period, were screened for psychiatric disorders using historical information, clinical interviews, and symptom ratings according to DSM-IV criteria.[27] Our clinic is a third-level research hospital with a national catchment for children and adolescents with a wide range of neuropsychiatric disorders. Inclusion criteria for the present protocol were (1) a diagnosis of autistic disorder or PDD, not otherwise specified, (PDD-NOS) according to DSM-IV criteria and a Childhood Autism Rating Scale (CARS) score above 30,[28] (2) absence of comorbid medical or neurologic conditions, (3) severe behavioral symptoms, and (4) written parental informed consent to treatment.

All diagnoses were made by investigators highly experienced in diagnosis and treatment of young children with PDD, who were properly trained in the use of diagnostic instruments and the direct observation of PDD in young children. To improve the reliability and validity of the diagnosis, clinical data were reviewed by the interviewer team (G.M., A.C., M.M.) for the purpose of consensus. When questions arose, patients were reassessed for further clarification. More details on assessment procedures are described elsewhere.[18]

Among the 120 preschool children referred for severe behavioral disorders and diagnosed with PDD, 53 were considered eligible for risperidone treatment. The remaining 67 children did not satisfy inclusion criteria in terms of severity of behavioral symptomatology (N = 37), availability of informed consent by parents (N = 25), and comorbidity with other neurologic conditions such as epilepsy (N = 5). Participants and nonparticipants did not differ according to age, gender ratio, intellectual functioning, or socioeconomic status. Participants scored higher than nonparticipants on all baseline measures (CARS, CPRS, CGI-I, and Children's Global Assessment Scale [CGAS]) ($p < .001$).

Some of these subjects had been previously treated unsuccessfully with vitamin B_6 (pyridoxine hydrochloride) and/or magnesium without significant improvement. The participants were 45 boys and 8 girls aged 3.6 to 6.6 years at the beginning of treatment (mean ± SD age = 4.6 ± 0.7 years), 37 with autistic disorder and 16 with PDD-NOS. All but 10 subjects (6 with normal intellectual level and 4 with borderline functioning) had mental retardation (10 with mild, 21 with moderate, and 12 with severe mental retardation). None of the subjects had a diagnosed genetic, metabolic, or neurologic etiology for the PDD. The children were free of other psychoactive drugs for the duration of the study. The study was approved by the Human Subjects Committee of IRCCS Stella Maris Hospital.

Physical and Laboratory Assessment

For the baseline assessment, patients' medical history was obtained, and neurologic and physical examinations, including weight, heart rate, pulse monitoring, and blood pressure, were carried out. Screening procedures included a complete blood cell count, electrolyte levels, blood urea nitrogen levels, fasting glucose levels, creatinine levels, liver function tests, an electrocardiogram (ECG), and an

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electroencephalogram during sleep.[18] Blood chemistry tests and physical examinations were repeated every 4 weeks in the first 4 months, then every 3 months thereafter. An ECG was repeated after 1 and 3 months, then every 6 months thereafter. In 37 patients, the screening procedures included obtaining serum prolactin levels using an enzyme-linked immunoadsorbent assay (normal range, 0–15 ng/mL). The progression of the patients' physical condition after hospital discharge was monitored through visits or phone contacts with parents and child psychiatrists weekly during the first 4 months, then according to clinical needs. A side effect checklist was used to assess tolerability.

Behavioral Rating Scales

Each subject was assessed for behavioral symptoms at baseline, after 8 weeks, and again at irregular intervals during the follow-up by 2 independent examiners. This monitoring did not follow a fixed interval schedule since many patients resided far from the hospital. Diagnoses of PDD achieved kappa values higher than .88 (mean $\kappa = .95$).

The diagnostic evaluation at baseline included the following scales:

1. CARS,[28] a 15-item scale with items rated from 1 to 4 measuring autistic behavior. Scores in different items can be computed to achieve a more precise clinical profile. The sum of the scores for the 15 items is used to obtain a broad measure of severity. A score of 37 or higher is considered indicative of severe autistic behavior; a score of 30 to 36.5 is considered indicative of a mild to moderate autistic disorder. The CARS is considered an objective, behaviorally based rating system with demonstrated reliability and validity.[29,30]
2. CPRS,[31] a 73-item scale scored 0 to 6. We have used a smaller subset of the scale (14 selected items), which has been proven effective for assessing and classifying behavioral symptoms in autistic children according to construct validity, sensitivity, and specificity of scores.[19] This subset of items has been shown to reliably detect changes during pharmacologic trials.[32]
3. CGI-I,[20] a single-item scale, recorded at the end of the study, that rates behavior from 1 ("very much improved") to 7 ("very much worsened"). This instrument has been extensively used in psychopharmacologic studies of PDD in children and adolescents.[8–10,12,17,18]
4. CGAS,[33] a scale that describes the severity of functional impairment on a scale from 0 (severe impairment) to 100 (superior functioning). It was designed for use with children aged 4 to 16 years; scores above 70 indicate normal functioning. The use of the CGAS as a measure of change in PDD in children and adolescents has been reported.[7,12,17,18]
5. Griffiths Developmental Scales[34] and Leiter International Performance Scale,[35] assessment of intellectual functioning at baseline.

A first evaluation of treatment outcome with the CGI-I occurred 8 weeks after the beginning of risperidone treatment. During the follow-up period, outcome measures were the CGI-I, CGAS, and CPRS. A side effects checklist was also administered.

Reliability between raters was preliminarily controlled for the outcome measures (CPRS, CARS, CGI-I, and CGAS) by independently scoring the first 15 patients with PDD. The intraclass correlation coefficient was computed at baseline and at the end of the 16-week trial, and it was considered satisfactory for all the measures (> .075). Two independent investigators assessed all the children, then the clinical data and videotapes were reviewed by the interviewer team for the purpose of consensus.

Patients were considered responders when they satisfied both of the following conditions: a CGI-I score of 1 or 2 ("very much improved" or "much improved") and at least a 25% decrease in CPRS total score.

Design and Dosing Regimen

All subjects were started on a dose of 0.25 mg at bedtime. Subsequent titration was by 0.25-mg increments at no more than weekly intervals, depending on clinical response and occurrence of side effects. The maximum dose was 1 mg daily.

Statistical Analyses

Descriptive analyses were used as appropriate. Conservative last-observation-carried-forward analyses (paired t test) were used to measure change in CPRS and CGAS scores ($p < .05$, 2-tailed). To minimize type I errors, Bonferroni correction was applied within measures, but not across measures, setting alpha at .003. Student t test ($p < .05$, 2-tailed) was used to compare groups (e.g., responders and nonresponders, subjects who discontinued the medication and subjects who did not). To analyze the relationship between baseline and after-treatment serum prolactin levels, Pearson product-moment correlation coefficient was calculated.

RESULTS

Attrition

The mean length of follow-up in the whole sample was 7.9 ± 6.8 months (range, 1–32 months). Twenty-five patients (47.2%) continued taking risperidone, whereas 28 patients (52.8%) discontinued the drug. The mean time at which treatment was interrupted was 6.1 ± 5.5 months

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Table 1. Children's Psychiatric Rating Scale Baseline and Last Observation Scores (47 patients treated with risperidone for at least 2 months)

Item	Baseline Score (mean ± SD)	Last Observation Score (mean ± SD)	t Score (df = 46)	p Value
Underproductive speech	4.39 ± 1.6	4.29 ± 1.4	0.585	.562
Fidgetiness	3.67 ± 1.1	2.56 ± 1.0	10.93	< .0001*
Hyperactivity	4.47 ± 1.1	2.93 ± 0.9	16.45	< .0001*
Hypoactivity	1.02 ± 1.3	1.07 ± 1.3	–0.53	.596
Abnormal object relationships	4.56 ± 0.9	4.16 ± 0.9	4.97	< .0001*
Withdrawal	4.44 ± 0.9	3.27 ± 0.9	11.03	< .0001*
Negative, uncooperative behavior	4.51 ± 0.8	3.29 ± 0.8	11.65	< .0001*
Angry affect	3.62 ± 1.1	2.49 ± 0.8	10.47	< .0001*
Nonspontaneous relation to examiner	4.78 ± 0.9	3.84 ± 1.0	8.7	< .0001*
Lability of affect	4.44 ± 0.8	3.07 ± 0.8	11.89	< .0001*
Low voice	0.84 ± 1.1	0.80 ± 1.0	1.43	.160
Loud voice	2.27 ± 1.1	2.11 ± 1.0	2.85	.007
Other speech deviance	3.56 ± 1.0	3.31 ± 0.9	3.77	< .0001*
Rhythmic motions (stereotypic)	4.18 ± 1.1	3.29 ± 1.0	8.35	< .0001*
Total score	51.07 ± 5.2	40.44 ± 5.9	18.5	< .0001*

*Statistically significant (Bonferroni correction, $\alpha = .003$).

(range, 1–22 months). Six subjects interrupted the treatment during the first month, and 4 patients received risperidone for more than 12 months before discontinuation. For the 25 subjects who continued taking risperidone, the length of drug treatment was 9.9 ± 7.6 months (range, 3–32 months). Age at onset of treatment, severity of baseline scores (CPRS and CARS), and drug dosage did not differentiate the subjects who continued treatment from subjects who discontinued (t test).

Twelve subjects (22.6%) discontinued because of side effects. In 10 cases (18.9%), parents proposed the discontinuation to the treating child psychiatrists after 5.8 ± 2.2 months; 8 of these subjects were minimally improved, while 2 were much improved. In 3 subjects (5.7%), drug treatment was interrupted because of lack of efficacy after 4 months, and in another 3 subjects (5.7%), the discontinuation was decided by the treating child psychiatrist after a rather long treatment period (12, 22, and 22 months) in order to evaluate the clinical course without medication.

In 9 patients, after discontinuation, a significant worsening of the clinical picture occurred, so a new trial with risperidone was begun. Five of these patients had discontinued medication for side effects (high prolactin levels), 2 were partial responders, and 2 had been treated for a substantial period.

Stability of Treatment Dosage Over Time

The optimal dose was 0.55 ± 0.2 mg/day. Although pharmacologic treatment could be changed at any time according to the clinician's judgment (symptom control, lack of efficacy, side effects), there was a relatively high degree of stability over the follow-up period. Treatment dosage at months 4 through 6 was maintained for the entire follow-up period in 22 subjects (41%). Seventeen of these subjects were considered responders, and the other 5 were partial responders, but side effects did not allow a further increase of risperidone dosage.

In the remaining subjects a further increase of dosage was decided, while none of the subjects needed a reduction of the dosage. In 17 of these subjects, the dosage was reduced after the increase because of side effects (increase of serum prolactin level in 11 subjects, increased appetite and body weight in 4 subjects, sedation and tremors in 2 subjects).

Course of the Illness During the Follow-Up

The following data describe the improvement in patients' clinical picture at the last observation. The 6 patients who discontinued risperidone during the first month were not considered, thus the treatment outcome was considered in 47 patients. The mean duration of treatment in these patients was 8.7 ± 6.7 months (range, 3–32 months).

A first evaluation of the treatment outcome occurred after 8 weeks, using the CGI-I. Twenty-seven children (57.4%) were "very much improved" or "much improved" (CGI-I score = 1 or 2). However, during the follow-up, some changes in the CGI-I score were found. While 1 subject further improved (from "much" to "very much improved"), 12 subjects had a decrease in improvement. Five subjects decreased from "very much" to "much improved"; 5, from "much" to "minimally improved"; and 2, from "minimally improved" to "unchanged." Therefore, at the last observation, none of the subjects' CGI-I scores had worsened from baseline during the study; 22 subjects (46.8%) were "very much" or "much improved" (CGI-I score = 1 or 2), 22 subjects were "minimally improved" (CGI-I score = 3), and 3 subjects were "unchanged" (CGI-I score = 4).

The mean CGAS score at baseline was 20.87 ± 4.6 and at the last observation was 29.2 ± 6.2 ($t = –15.423$, $df = 46$, $p < .0001$) (28% improvement).

Mean CPRS scores (total score and score in the 14 selected items) at baseline and at the last observation are reported in Table 1. The mean CPRS total score was

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Table 2. Comparison Between Responders and Nonresponders to Risperidone Treatment

Variable	Responders Mean ± SD (N = 22)	Nonresponders Mean ± SD (N = 25)	p Value (t test)
Age, y	4.7 ± 0.7	4.6 ± 0.8	.530
Maximum dosage, mg/d	0.70 ± 0.18	0.57 ± 0.16	.012*
Optimal dosage, mg/d	0.61 ± 0.22	0.49 ± 0.16	.036*
Duration of treatment, mo	11.3 ± 8.1	6.5 ± 4.3	.013*
CARS baseline score	40.1 ± 7.0	42.7 ± 5.2	.154
CPRS baseline score	50.5 ± 6.0	50.7 ± 5.4	.895
Weight gain, kg	3.61 ± 3.40	1.76 ± 1.98	.026*
Prolactin level at last observation, ng/mL	24.3 ± 16.3	27.5 ± 23.2	.641

*Statistically significant.
Abbreviations: CARS = Childhood Autism Rating Scale, CPRS = Children's Psychiatric Rating Scale.

51.1 ± 5.2 at baseline and 40.4 ± 5.9 at the last observation (t = 18.5, df = 46, p < .0001) (21% improvement). The areas that significantly improved (t test, p < .0001) were other speech deviance, fidgetiness, hyperactivity, abnormal object relationships, withdrawal, negative and uncooperative behaviors, angry affect, nonspontaneous relation to examiner, lability of affect, and rhythmic motions. The areas that improved more than 30% were hyperactivity (34%), fidgetiness (33%), angry affect (31%), and lability of affect (31%), while an improvement higher than 20% was found in negative and uncooperative behaviors (27.1%), withdrawal (26%), nonspontaneous relation with the examiner (20%), and rhythmic motions (21%).

The 22 subjects with a CGI-I score of 1 or 2 showed at least a 25% reduction of their CPRS total score and were considered responders.

Predictors of Response

Possible predictors of response are summarized in Table 2. Being a responder or nonresponder was not affected by age or severity scores at baseline (CARS, CPRS, CGAS). Responders had received higher doses of medication (maximum dose = 0.70 ± 0.18 mg/day vs. 0.57 ± 0.16 mg/day [t = –2.622, df = 45, p = .012]; optimal dose = 0.61 ± 0.22 mg/day vs. 0.49 ± 0.16 mg/day [t = –2.156, df = 45, p = .036]) for a longer period (11.3 ± 8.1 months vs. 6.5 ± 4.3 months [t = –2.591, df = 45, p = .013]). Furthermore, responders had a greater weight gain than did nonresponders (3.61 ± 3.40 kg [7.96 ± 7.50 lb] vs. 1.76 ± 1.98 kg [3.88 ± 4.37 lb]; t = 2.306, df = 45, p = .026). Severity of mental retardation was not related to drug response.

Safety and Side Effects

Eighteen subjects (34%) showed no side effects. Twelve subjects (22.6%) discontinued (6 during the first 2 months of treatment) because of side effects, the most frequent being a high increase of serum prolactin levels in 6 subjects. In the 6 subjects with early discontinuation, the interruption was requested by parents for the following reasons: loss of consciousness with suspected epileptic seizure, dystonic episode at the neck, tachycardia and flushes after drug intake, unspecified subjective disorders of vision, and, in 2 subjects, high levels of prolactin (54.1 and 98 ng/mL). There were no other reports of cardiac symptoms, and all ECGs were in the normal range.

Other reported side effects that did not cause drug discontinuation were increased appetite (8 subjects), agitation (4 subjects), enuresis (4 subjects), decreased appetite (2 subjects), sedation and hypoactivity (3 subjects), tremors (2 subjects), increased levels of liver enzymes (1 subject), and an increase of platelets over 500,000/mm^3 (1 subject). There were no reported withdrawal dyskinesias during treatment discontinuation.

Mean body weight at baseline was 20.6 ± 5.5 kg (45.4 ± 12.1 lb), while at the last observation, it was 23.3 ± 6.3 kg (51.4 ± 13.9 lb). Mean weight gain in the total sample was 2.4 ± 2.8 kg (5.3 ± 6.2 lb; range, 0–9.5 kg [0–20.9 lb]) and did not cause discontinuation of the medication in any of the subjects of our sample.

Serum Prolactin Levels

Serum prolactin levels were available in 37 subjects. Mean prolactin level at baseline was 13.3 ± 7.8 ng/mL, and mean prolactin level at the last observation was 28.38 ± 22.45 ng/mL (t = –3.8, df = 72, p < .0001). Thirteen subjects (35%) showed normal levels of prolactin (below 15 ng/mL). In 13 subjects (35%), prolactin levels ranged between 15 and 30 ng/mL, which can be considered a slight increase. Five subjects (14%) had prolactin levels between 30 and 50 ng/mL, and 6 subjects (16%) had prolactin levels over 50 ng/mL. Higher levels of prolactin at baseline correlated with higher levels of prolactin during treatment (r = 0.60, p = .009).

In order to explore possible predictors of greater increase of prolactin during risperidone treatment, the 13 subjects with levels of prolactin lower than 15 ng/mL were compared with the 6 subjects whose prolactin levels were higher than 50 ng/mL. The 2 groups did not differ according to age, drug dosage, severity scores at baseline (CARS, CPRS, CGAS), or weight gain.

Even though a higher dosage of risperidone did not predict a higher level of serum prolactin, a reduction of the dosage was usually associated with a decrease of serum prolactin. In several patients, when the risperidone dosage was increased, prolactin did not rise as well. For example, at a risperidone dosage of 0.50 mg/day, a patient's prolactin level rose to 59 ng/mL. When the risperidone dosage was decreased to 0.25 mg/day, the patient's prolactin level was 25.5 ng/mL and then 16.7 ng/mL. Risperidone dosage was increased to 0.40 mg/day, but the patient's prolactin level was 7.6 ng/mL. Risperidone was further increased to 1 mg/day according to clinical response, but the patient's prolactin level did not over-

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Table 3. Comparison Between Subjects With Autistic Disorder or Pervasive Developmental Disorder, Not Otherwise Specified (PDD-NOS), on Risperidone Treatment[a]

Variable	Autistic Disorder (N = 37)	PDD-NOS (N = 16)	p Value (t test or chi-square)
Age, y	4.4 ± 0.6	5.0 ± 0.8	.011*
Maximum dosage, mg/d	0.61 ± 0.19	0.67 ± 0.16	.245
Optimal dosage, mg/d	0.55 ± 0.19	0.55 ± 0.22	1.00
Weight at baseline, kg	19.1 ± 5.0	22.9 ± 4.3	.017*
Weight at last observation, kg	21.5 ± 5.9	26.1 ± 5.3	.016*
Prolactin level at last observation, ng/mL	29.0 ± 21.3	26.1 ± 26.0	.696
Duration of treatment, mo	11.30 ± 8.11	6.48 ± 4.29	.013*
CGAS score at baseline	19.6 ± 4.0	23.9 ± 4.6	.002*
CGAS score at last observation	27.1 ± 5.9	33.4 ± 4.7	< .0001*
CARS score at baseline	43.9 ± 5.3	35.9 ± 4.0	< .0001*
CPRS score at baseline	51.0 ± 5.9	41.8 ± 4.6	< .0001*
CPRS score at last observation	42.5 ± 5.4	34.6 ± 3.2	< .0001*
Responders/ nonresponders, N	12/21	10/4	.06

[a]All values shown are mean ± SD unless otherwise specified.
*Statistically significant.
Abbreviations: CARS = Childhood Autism Rating Scale, CGAS = Children's Global Assessment Scale, CPRS = Children's Psychiatric Rating Scale.

come 23 ng/mL. Another patient's prolactin level was 40 ng/mL at a 0.50-mg/day risperidone dosage. After 1 month, it was 14 ng/mL at a 0.25-mg/day dosage, and after 6 months, it was 16.9 ng/mL at a 0.75-mg/day dosage. A third patient's prolactin level was 27.9 ng/mL at a 0.50-mg/day risperidone dosage. After 1 month, it was 9.70 ng/mL at a 0.30-mg/day dosage, and after 6 months, it was 12.7 ng/mL at 0.60 mg/day.

Differences Between Autistic Disorder and PDD-NOS

Subjects with autistic disorder and PDD-NOS were compared according to several parameters (Table 3). Children with autistic disorder were significantly younger (4.4 ± 0.6 years vs. 5.0 ± 0.8 years), had less body weight at baseline and at the last observation, and were more severely impaired at baseline (CARS, CPRS, CGAS). CGAS and CPRS scores at the last observation showed a significantly greater impairment in autistic disorder children. Drug dosages, as well as the duration of treatment and the percentage of patients who discontinued the medication, were similar in the 2 groups. In the PDD-NOS group, 10 (71.4%) of 14 were considered responders, while in the autistic disorder group, 12 (36.4%) of 33 were considered responders, with a trend toward significance ($\chi^2 = 3.55$, df = 1, p = .06).

DISCUSSION

Our data, derived from a 3-year prospective observation of very young children with PDD treated with risperidone, demonstrated the presence of a significant number of responders under conditions of routine clinical practice. The mean duration of treatment was 7.9 ± 6.8 months (range, 1–32 months). The improvement of the CPRS total score was 21%, which is similar to previous findings of our 16-week treatment study.[18] The areas that significantly improved the most were those related to behavior control (fidgetiness, hyperactivity) and affect (angry affect, lability of affect), while items related to abnormal relationships with others (abnormal object relationships, withdrawal, negative and uncooperative behaviors, nonspontaneous relation to examiner), although significantly improved, were less sensitive to treatment. This finding is consistent with previous data from a 16-week open-label study,[18] as well as a recent placebo-controlled study,[13] in which irritability, hyperactivity, and stereotypy, but not social withdrawal and inappropriate speech, significantly improved.

Twenty-two subjects (46.8%) were considered clinical responders. This finding is consistent with findings from the placebo-controlled study,[13] in which 69% were responders at 8 weeks, but 46.9% were responders at 6 months. A similar, slight decrease of the clinical response over time is confirmed in our study, when the early response (8 weeks) and the last observation are compared. Only 5 children who were initially responders became nonresponders during the follow-up, because they passed from "much improved" to "minimally improved." However, when baseline assessments and last observations were compared, none of the subjects worsened. It cannot be excluded that the variability of improvement over the course of follow-up may be attributed to the use of global measures to assess effectiveness (CGI-I) as compared with more symptom-oriented measures, such as the CPRS.

Responders had received higher doses of medication and for a longer period. It may be hypothesized that higher doses have been more effective in reducing psychiatric symptoms in our patients. Furthermore, the weight gain was higher in the responder group. This may be one of the reasons why none of the participants discontinued the medication for weight increase. A positive correlation between weight gain and clinical response has also been reported in adult schizophrenic patients treated with the atypical antipsychotics.[36] The nature of this association is far from clear, although several mechanisms have been hypothesized, including the blockade of serotonergic receptors, which may mediate both weight gain and antipsychotic response.[36]

A trend toward a smaller treatment effect in autistic disorder patients compared with PDD-NOS patients was found. Autistic patients were more severely impaired at baseline but received medication at the same dosages and for the same period as patients with PDD-NOS. Autistic children may thus represent a more treatment-refractory

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population, or they may need higher doses of the medication in order to show similar response rates. However, autistic disorder patients were also younger than patients with PDD-NOS, which may have affected the treatment outcome. It can be hypothesized that higher doses of risperidone may have resulted in a greater clinical improvement. A more prudent approach in our sample was induced by the consideration that autistic disorder children were younger and that they weighed less.

Twenty-eight patients (52.9%) discontinued the drug during the 3-year period. In 9 patients, after the discontinuation, there was a significant worsening of the clinical picture, thus a new trial with risperidone was started. Twelve of the patients (22.6%) discontinued the medication because of side effects, 6 of them during the first month of treatment. In 2 of these subjects, a significant increase in prolactin level (54.1 and 98 ng/mL, respectively) induced parents to ask for the discontinuation. In the other 4 children, tachycardia and flushes after drug ingestion, a syncope-like attack, acute dystonic movements, and unspecified "vision disorders" were reported by local pediatricians and induced them and the parents to discontinue treatment. Other reported side effects that did not cause drug discontinuation were mild and transient. An important clinical question is, how long does one maintain a child on treatment before changing to another treatment? According to our clinical experience, a significant response can be determined after 8 weeks of treatment. If improvement has not been detected by this point, a subsequent improvement can be considered unlikely.

Cardiac symptoms in young children during risperidone treatment should be considered. A transient increase in heart rate and a QTc prolongation on the ECG have been reported in previous studies[15–17] addressing risperidone treatment in very young children. A transient increase in heart rate was reported in 2 of the 6 preschool autistic patients in treatment with risperidone described by Casaer et al.,[15] who considered these episodes as transitory and benign. Posey et al. reported tachycardia and QTc interval prolongation on ECG, which resolved when risperidone was discontinued.[16] In our study, effects on ECG during risperidone treatment were not reported. Tachycardia has been reported in 12% of the children in the placebo-controlled study.[13] An ECG at baseline and as part of routine monitoring is recommended.[16]

The negative effect of risperidone on liver function, previously reported,[37] was not confirmed in our study, even though 1 patient showed a slight and transient increase of liver enzymes. Extrapyramidal symptoms related to rapid dosage escalation of risperidone have been reported.[38] One child from our sample showed dystonic movements during the first month, requiring discontinuation of medication, while another had only mild and transient tremors. Withdrawal dyskinesias have been reported in 33.9% of 118 PDD children during haloperidol discontinuation.[4] This side effect, specifically monitored, did not occur in any of our patients during the slow discontinuation of risperidone.

Increased appetite and weight gain have been frequently reported during risperidone treatment in children and adolescents.[5] Mean weight gain in our total sample was 2.4 ± 2.8 kg (5.3 ± 6.2 lb), which is similar to previous studies in older children[9–13] and may be partly accounted for by normal developmental gain. Only 1 patient had a massive weight increase (15 kg [33 lb]), but, given the patient's impressive clinical improvement, it did not cause discontinuation.

The major reason for discontinuation was an increase in serum prolactin levels.[21] In 35% (N = 13) of the participants who were specifically monitored, prolactin levels did not show an increase above the normal upper level of 15 ng/mL, and another 35% (N = 13) had a moderate increase (below 30 ng/mL). The remaining 30% (N = 11) had a significant increase, with prolactin levels up to 98 ng/mL. However, these high levels of prolactin were not associated with clinical signs in any of the children. Possible predictors of greater increase in prolactin levels during risperidone treatment were not detected, even if higher baseline prolactin levels positively correlated with higher levels during treatment. In all children with higher levels of prolactin, a reduction in risperidone dose led to a decrease of serum prolactin levels. In some of these patients, a further increase of risperidone did not change prolactin levels, suggesting possible mechanisms of adaptation.

There is no consensus regarding at what level and after what time period an increase in prolactin levels becomes dangerous or unacceptable. This is particularly puzzling in those severely impaired children who are successfully treated with risperidone dosages leading to hyperprolactinemia. None of the children in our study showed side effects that may be caused by hyperprolactinemia, independently from the level of prolactin. No data are available for the effect of stable antipsychotic-induced hyperprolactinemia in young children. Data from children with prolactinomas suggest that growth arrest, osteopenia, and delayed pubertal development may be caused by enduring high levels of prolactin.[39,40] These data should be considered cautiously, because prolactin levels in these patients are much higher than those normally found in children treated with antipsychotics (688 ± 907 ng/mL in the 26 young patients described by Colao et al.[39]); furthermore, symptoms may be affected by the effect of a prolactinoma on pituitary function. In these patients, a late occurrence of symptoms is generally reported, even in the presence of hyperprolactinemia for many years, and diagnosis is difficult if symptoms of tumor expansions do not occur. Due to a lack of clear guidelines, a careful consideration of the risk-benefit ratio, including a clear discussion with the parents, should be the leading concept in clinical

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management of these patients. However, monitoring serum prolactin levels during treatment with risperidone may be warranted.

The first and most important limitation of our study is the lack of a controlled placebo group. However, the recent placebo-controlled study confirmed efficacy and safety of risperidone treatment in older children and adolescents with similar response rates after 6 months.[13] Second, we used a rather low dosage of risperidone compared with other studies in older children. Greater improvement and/or more side effects may have resulted if higher dosages had been used. However, given the paucity of available information on chronic treatment with risperidone in very young autistic children, a conservative approach was followed to minimize dose-dependent side effects (prolactin increase, weight gain, tremors). Third, reliance on few ratings from baseline to last observation may preclude strong conclusions.

Although these considerations may limit our findings in terms of efficacy, this study offers some contributions relative to the existing literature. Sparse data are available about long-term pharmacologic treatments in preschool children with PDD treated in routine clinical care settings. Our results are encouraging in this regard. It may be hypothesized that an early treatment can allow for a greater improvement of social function in children with PDD and may positively affect the natural history. This may in turn enhance the effects of educational and psychosocial interventions in these severely disturbed children.

Drug names: clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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