ORIGINAL ARTICLE

A Double-blind, Placebo-Controlled Study of Risperidone in Adults With Autistic Disorder and Other Pervasive Developmental Disorders

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Background: Neurobiological research has implicated the dopamine and serotonin systems in the pathogenesis of autism. Open-label reports suggest that the serotonin$_{2A}$–dopamine D_2 antagonist risperidone may be safe and effective in reducing the interfering symptoms of patients with autism.

Methods: Thirty-one adults (age [mean + SD], 28.1 ± 7.3 years) with autistic disorder (n = 17) or pervasive developmental disorder not otherwise specified (n = 14) participated in a 12-week double-blind, placebo-controlled trial of risperidone. Patients treated with placebo subsequently received a 12-week open-label trial of risperidone.

Results: For persons completing the study, 8 (57%) of 14 patients treated with risperidone were categorized as responders (daily dose [mean ± SD], 2.9 ± 1.4 mg) compared with none of 16 in the placebo group ($P<.002$). Risperidone was superior to placebo in reducing repetitive behavior ($P<.001$), aggression ($P<.001$), anxiety or nervousness ($P<.02$), depression ($P<.03$), irritability ($P<.01$), and the overall behavioral symptoms of autism ($P<.02$). Objective, measurable change in social behavior and language did not occur. Nine (60%) of 15 patients who received treatment with open-label risperidone following the double-blind placebo phase responded. Other than mild, transient sedation, risperidone was well tolerated, with no evidence of extrapyramidal effects, cardiac events, or seizures.

Conclusion: Risperidone is more effective than placebo in the short-term treatment of symptoms of autism in adults.

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THE MOST consistently effective drug treatments for patients with autistic disorder (autism) and related pervasive developmental disorders (PDDs) have been those that have targeted central dopamine and serotonin (5-hydroxytryptamine) systems; these neurotransmitters have been shown to be dysregulated in some patients with autism.[1-4]

The dopamine antagonist haloperidol has been one of the most extensively studied drugs for treating children with autism. Controlled trials have shown haloperidol to be superior to placebo for reducing withdrawal, stereotypy, hyperactivity, abnormal-object relationships, fidgetiness, negativism, angry affect, and lability of affect.[5] A prospective, longitudinal study, however, found that in 40 (33.9%) of 118 autistic children, drug-related dyskinesias developed during longer-term haloperidol administration.[6]

More recently, controlled investigations have demonstrated that for reducing interfering repetitive behavior and aggression and enhancing some elements of social behavior in autistic patients, the potent serotonin reuptake inhibitor clomipramine hydrochloride (for children)[7,8] is more effective than the potent norepinephrine reuptake inhibitor desipramine hydrochloride and placebo, and the selective serotonin reuptake inhibitor fluvoxamine maleate (for adults)[9] is more effective than placebo.

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Risperidone, an atypical neuroleptic agent, is a highly potent serotonin$_{2A}$–dopamine D_2 antagonist[10] that has been shown in controlled studies to be better tolerated and more effective than haloperidol and placebo for reducing the positive and

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PATIENTS AND METHODS

PATIENTS

Thirty-one adults diagnosed as having autism or PDD NOS and their parent(s) or legal guardian(s) provided voluntary, written informed consent (or assent for patients with cognitive limitations) for participation in this study, which had been approved by the Human Investigation Committee of Yale University School of Medicine, New Haven, Conn. Seventeen of the patients met diagnostic criteria for autistic disorder, and 14 met criteria for PDD NOS; none of the patients met criteria for a diagnosis of Rett disorder, childhood disintegrative disorder, or Asperger disorder. Diagnoses were based on *DSM-IV*[27] criteria for PDD. Criteria of the Autism Diagnostic Interview[28] and the Autism Diagnostic Observation Schedule[29] were used to aid in the diagnosis. Incorporating this information, the final diagnosis of autism or PDD NOS was determined by consensus agreement of 2 board-certified psychiatrists (C.J.M. and L.H.P.). The patients did not meet criteria for any other formal *DSM-IV* Axis I or Axis II disorder other than mental retardation (as described later), although many of the patients (n = 16) were difficult to assess fully because they were nonverbal or minimally verbally responsive. The sample consisted of 9 women and 22 men, including 6 African Americans, 24 whites, and 1 Hispanic, aged 18 to 43 years (age [mean ± SD], 28.1 ± 7.3 years), who were referred by schools, the State of Connecticut Departments of Mental Health and Addiction Services and Mental Retardation, group homes for adults with developmental disabilities, community-based psychiatrists, and family members. All subjects were evaluated and treated within the outpatient (n = 24) and inpatient (n = 7) divisions of the Clinical Neuroscience Research Unit at the Connecticut Mental Health Center, New Haven. The study was conducted between June 27, 1994, and February 28, 1997.

Each patient's symptoms were at least "moderate" in severity, as defined by global severity of illness rating on the Clinical Global Impression (CGI) Scale.[30] In addition, each patient met the following entry criteria for symptom severity for the study: a Yale-Brown Obsessive Compulsive Scale (Y-BOCS) compulsion (repetitive behavior) subscale score of greater than 10, a Self-injurious Behavior Questionnaire (SIB-Q) score of 25 or greater, or a Ritvo-Freeman Real-life Rating Scale overall score of 0.20 or greater. Each of these behavioral rating scales is referenced and described in detail in the "Rating Scales" section below. Full-scale IQ was measured with the Wechsler Adult Intelligence Scale–Revised[31] in the 15 verbal patients, and the Leiter International Performance Scale[32] was used to assess IQ in the 16 nonverbal patients. The IQ (mean ± SD) for the entire group of 31 patients was 54.6 ± 23.9. The degree of mental retardation for each patient is presented in the **Table**.

Additional screening procedures included a medical history, physical and neurologic examinations, a complete blood cell count with differential, electrolytes, fasting glucose level, serum urea nitrogen concentration, creatinine level, liver and thyroid function tests, fragile X testing (negative in all subjects), urinalysis, and electrocardiogram. All women had negative serum pregnancy tests. Subjects were excluded if they met *DSM-IV* criteria for schizophrenia or had psychotic symptoms or if a significant acute medical condition was identified. One man had neurofibromatosis; none of the other patients had a diagnosed genetic, metabolic, or neurologic cause for their syndrome. Twenty-four (77%) of the patients had received previous treatment with psychotropic drugs. Clinical characteristics, prior drug treatment data, and family history are presented in the Table.

STUDY DRUG ASSIGNMENT AND TREATMENT

Subjects had not taken any psychotropic drugs for at least 4 weeks before the start of the trial. After 2 visits during which baseline behavioral ratings were obtained, patients were randomly allocated according to a computer-generated list to 12 weeks of double-blind treatment with risperidone or placebo (lactose) in identical-appearing capsules. To ensure compliance, medication was administered by parents or other primary caregivers. The risperidone or placebo regimen was started at 1 mg every night. Based on telephone contact with either or both the research nurse clinician (J.P.H.) and the prescribing psychiatrist (C.J.M.), the dosage could then be increased by 1 mg daily every 3 to 4 days to a maximum dosage of 10 mg/d, in a morning and bedtime dosing regimen, as tolerated, if a maximal clinical response was not obtained. Thus, the maximal dosage of risperidone was attained within 5 weeks, and patients received this dose for at least 7 weeks. The prescribing psychiatrist, the research nurse clinician who performed the behavioral ratings, the patients, and all family and other members of the patients' treatment teams were unaware of the drug assignment (blind). Other than chloral hydrate up to 2 g/d, as needed to help with symptoms of agitation, no other drugs were administered during the study.

Fifteen patients were randomly assigned to receive risperidone and 16 to receive placebo. Fourteen of the 16 placebo-treated patients were subsequently given open-label risperidone for 12 weeks (1 additional patient completed 4 weeks) following completion of the double-blind placebo phase. For those patients, risperidone was prescribed in a manner identical to that described above.

RATING SCALES

Each patient, along with the members of the treatment team (eg, parents, teachers, case workers, group home staff, workshop staff), participated in 2 detailed assessments of behavioral symptoms at baseline and again at the end of weeks 4, 8, and 12 of the controlled trial. Repetitive behavior was rated with a modified version of the Y-BOCS.[33,34] Each of the 10 items on the Y-BOCS is scored on a 5-point scale from 0, indicating "least symptomatic," to 4, indicating "most symptomatic," so that the total Y-BOCS score ranges from 0 to 40. The first 5 items of the Y-BOCS are designed to assess the severity of repetitive thoughts, whereas the last 5 items determine the severity of repetitive behavior. Because 16 (52%) of the patients were nonverbal and thus unable to provide information about repetitive thoughts, we chose to assess only repetitive behavior for each patient; thus, the maximum Y-BOCS score for each patient was 20. Based on previous findings,[35] the ego-dystonicity diagnostic criterion for obsessive-compulsive disorder was eliminated in rating the repetitive behavior of the patients with PDD. Aggression was rated with the SIB-Q, a 25-item clinician-rated instrument that assesses self-injurious behavior, physical aggression toward others,

destruction to property, and other maladaptive behavior (T. Gualtieri, MD, unpublished data). Patients could receive a score from 0, indicating "not a problem," to 4, indicating "severe problem," on each of the 25 items (range for total score, 0-100). The Ritvo-Freeman Real-life Rating Scale[36] served as an observational measure (30 minutes during each behavioral rating session) of a variety of symptoms of autism, including subscales for assessing sensory motor behaviors (eg, hand-flapping, rocking, pacing) (subscale I), social relationship to people (eg, appropriate responses to interaction attempts, initiating appropriate physical interactions) (subscale II), affectual reactions (eg, abrupt changes in affect, crying, temper outbursts) (subscale III), sensory responses (eg, agitated by noises, rubbing surfaces, sniffing self or objects) (subscale IV), and language (eg, communicative use of language, initiating appropriate verbal communication) (subscale V). Each of the 5 subscales contains a number of individual items that are scored on a 4-point scale: 0 indicates "never"; 1, "rarely"; 2, "frequently"; and 3, "almost always." The average score from the mean value of each of the 5 subscale scores was determined to yield an overall score on the Ritvo-Freeman scale (range for overall score, – 0.42 to 2.58). The Ritvo-Freeman scale score increases as the number and frequency of symptoms of autism increase. A mathematical sign correction to subtract normal behavior is necessary on subscales II, IV, and V; this results in some scores with a negative value. Different mood states were assessed on 10 clinician-rated visual analog scales,[37] scored on a 100-mm line where 0 indicates "not at all," and 100 indicates "most ever." The 10 items included "anxious or nervous," "calm," "depressed," "eye contact," "happy," "irritable," "restless," "social interaction," "talkative," and "tired." Finally, the CGI global improvement item—7 indicates "very much worse"; 4, "no change"; and 1, "very much improved"[30]—was recorded at the end of weeks 4, 8, and 12 of treatment (compared with the predrug baseline). Global improvement ratings were based on an aggregate assessment of the patient's social behavior and the level of the patient's interfering repetitive and aggressive behavior. For the 15 patients who received treatment for 12 weeks with open-label risperidone following the double-blind placebo phase, the rating scales were administered in a manner identical to that described above.

PHYSIOLOGICAL MEASURES AND ADVERSE EFFECTS ASSESSMENT

Sitting and standing blood pressures and pulse rate, temperature, respiratory rate, and weight were recorded at baseline and at the end of 4, 8, and 12 weeks of the risperidone trial. Each patient was systematically examined for extrapyramidal (abnormal gait, ataxia, dystonia, hyperkinesia, hypertonia, hypokinesia, hyporeflexia, involuntary muscle contractions, oculogyric crisis, and tremor) and other adverse effects (agitation, constipation, coughing, diarrhea, dizziness, dry mouth, dyspepsia, enuresis, gynecomastia, headache, insomnia, menstrual pattern changes [women], nausea, restlessness, rhinitis, sedation, sialorrhea, and vomiting) at baseline and after 4, 8, and 12 weeks of treatment with risperidone or placebo.

STATISTICAL ANALYSIS

Of the 31 patients who entered the controlled phase of the investigation, 24 completed the entire 12-week study. Of the 7 patients who did not complete the entire trial, 1 patient with autism had to be withdrawn from the study after 1 week because of the emergence of notable agitation (active drug), 4 patients (2 with autism, and 2 with PDD NOS) were removed because of interfering agitation after 4 weeks (placebo), 1 patient with PDD NOS had an abnormal gait develop after 4 weeks (active drug), and the remaining patient (with autism) dropped out after 4 weeks because of a lack of significant improvement in symptoms (active drug). Data from the 30 patients who completed at least 4 weeks of the trial were included in the efficacy analysis. For the 6 patients who completed only 4 weeks of double-blind treatment, the last-observation-carried-forward, intention-to-treat method was used in the data analysis.

Baseline ratings were obtained from the mean scores of the 2 initial behavioral assessment sessions. Student *t* tests were calculated to determine if significant differences existed on baseline rating scale measures between the risperidone and placebo groups; there were no statistically significant baseline differences. Student *t* tests were used to determine if significant differences existed between groups in age, full-scale IQ, or dose of risperidone vs placebo. The χ^2 test with the Yates correction was used to determine if significant differences existed between groups for sex distribution, diagnostic subtype distribution, or treatment setting.

A 2-way analysis of variance (ANOVA) with repeated measures was calculated for the 12 weeks of risperidone or placebo treatment to assess the significance of main effects of drug, time, and drug × time interactions (only drug × time interactions are reported below). An analysis of covariance (ANCOVA), using the baseline score as a covariate, was used to determine when significant risperidone-placebo differences took place. A 1-way ANOVA with repeated measures was calculated to determine the main effect of time for the 15 patients who received open-label risperidone following the initial placebo randomization phase. The reported *P* values for all ANOVAs and ANCOVAs used the Huynh-Feldt correction factor. This correction factor decreases the degrees of freedom used in the ANOVA or ANCOVA to reflect a lack of homogeneity in the variance of measures across time points; for clarity, uncorrected degrees of freedom are given. Results from the ANOVAs for both the intent-to-treat sample (n = 30) and the completer sample (n = 24) are presented below.

The χ^2 test with Yates correction was used to compare the 2 groups for the rate of responders vs nonresponders and to determine if response was related to sex, diagnostic subtype, or treatment setting. Point by serial correlation was used to determine if a categorical response was correlated with age, full-scale IQ, or baseline measures of repetitive behavior (Y-BOCS compulsion subscale score), aggression (total SIB-Q score), level of autistic behavior (Ritvo-Freeman scale overall score), or dose of risperidone. Response was determined by scores obtained at the end of the last week of treatment on the CGI global improvement item compared with baseline. Patients with CGI scores of "much improved" or "very much improved" were categorized as responders; all others were considered nonresponders. Data are given as mean ± SD, unless otherwise indicated, and results are reported as significant when $P<.05$ (2 tailed).

Clinical Characteristics of Adults With Autism and Pervasive Developmental Disorder (PDD) Not Otherwise Specified (NOS) Treated With

Patient No.	*DSM-IV* Diagnosis	Age, y/Sex/ Race	Full-Scale IQ	Treatment Setting	Prior Drug Treatment	Daily Dose of Agent, mg
						Risperidone
1	Autistic disorder	18/M/W	40	Outpt	Thioridazine hydrochloride	5
2	Autistic disorder	38/M/W	96	Outpt	Fluvoxamine maleate, haloperidol, clonazepam, pimozide, sertraline hydrochloride	2
3	Autistic disorder	27/M/AA	45	Outpt	Thioridazine	4
4	Autistic disorder	20/M/W	28	Outpt	Phenytoin sodium, phenobarbital	1
5	Autistic disorder	31/M/AA	34	Outpt	Phenytoin	2
6	Autistic disorder	25/F/W	43	Outpt	Phenytoin, perphenazine, valproic acid	3
7	Autistic disorder	21/M/W	50	Inpt	Lorazepam, chlorpromazine hydrochloride	3
8	Autistic disorder	36/M/W	113	Inpt	Clomipramine hydrochloride, lorazepam, buspirone hydrochloride, valproic acid, fluvoxamine, haloperidol, clonazepam, imipramine hydrochloride, perphenazine	4
9	Autistic disorder	22/M/W	58	Inpt	Clonazepam	1
10	PDD NOS	34/M/W	22	Outpt	Haloperidol	6
11	PDD NOS	20/M/AA	74	Outpt	Perphenazine	3
12	PDD NOS	34/F/W	57	Outpt	None	2
13	PDD NOS	23/M/W	85	Outpt	None	4
14	PDD NOS	21/M/W	64	Outpt	Methylphenidate hydrochloride	3
15	PDD NOS	21/M/W	24	Outpt	Methylphenidate	1
Mean (±SD)	. . .	26.0 (±6.7)	55.5 (±26.8)	. . .	. . .	2.9 (±1.4)
						Placebo
16	Autistic disorder	26/M/W	41	Inpt	Hydroxyzine hydrochloride, haloperidol, imipramine, thioridazine, methylphenidate	6
17	Autistic disorder	25/M/W	61	Outpt	Haloperidol, pimozide	6
18	Autistic disorder	24/M/W	42	Outpt	None	4
19	Autistic disorder	31/M/AA	38	Outpt	Trifluoperazine hydrochloride	6
20	Autistic disorder	25/M/AA	25	Outpt	None	4
21	Autistic disorder	35/M/W	68	Outpt	None	2
22	Autistic disorder	25/F/H	22	Outpt	Thioridazine, carbamazepine	2
23	Autistic disorder	20/M/W	84	Outpt	Thioridazine	2
24	PDD NOS	38/M/W	92	Inpt	Clomipramine, lorazepam, buspirone, fluoxetine hydrochloride, haloperidol, clonazepam, thioridazine, nortriptyline hydrochloride, imipramine, perphenazine	3
25	PDD NOS	18/F/W	38	Outpt	None	4
26	PDD NOS	29/F/AA	61	Outpt	Lorazepam, clonazepam, sertraline	6
27	PDD NOS	42/F/W	61	Outpt	Hydroxyzine, thioridazine, phenobarbital, methylphenidate, diazepam	4
28	PDD NOS	34/M/W	70	Outpt	Lorazepam, fluvoxamine, methylphenidate, diazepam	4
29	PDD NOS	39/F/W	50	Outpt	None	4
30	PDD NOS	43/F/W	81	Inpt	Clonazepam, chlorpromazine, chlordiazepoxide hydrochloride, thioridazine, fluphenazine hydrochloride	2
31	PDD NOS	27/F/W	28	Outpt	Nortriptyline, methylphenidate, sertraline	1
Mean (±SD)	. . .	29.7 (±7.8)	52.9 (±22.1)	. . .	. . .	3.9 (±1.5)
Mean (±SD)	. . .	28.1 (±7.3)	54.6 (±23.9)	. . .	. . .	3.3 (±1.6)

**AA indicates African American; H, Hispanic; Outpt, outpatient; Inpt, inpatient; and OCD, obsessive-compulsive disorder.*

Risperidone or Placebo*

Weeks Completed	Treatment Response	Adverse Effects	Family History
Group			
12	Very much improved	None	Paternal first cousin with Down syndrome; paternal second cousin with Down syndrome
12	Much improved	Sedation, dry mouth	Brother: Asperger disorder; 3 paternal first cousins: mental retardation and seizure disorders
12	Much improved	Agitation	Mother: paranoid schizophrenia; maternal aunt: Down syndrome; brother: mental retardation
12	Much improved	Weight gain, sedation, enuresis	Maternal uncle: Down syndrome
12	Much improved	Sedation	Father: alcohol abuse; brother: mental retardation
12	Minimally improved	Enuresis, sedation	None
12	Minimally worse	Sedation	Paternal uncle: paranoid disorder; maternal uncle: mental retardation
4	Minimally worse	None	Maternal grandmother: chronic vocal tic disorder; maternal first cousin: trichotillomania; maternal first cousin: autistic disorder; maternal first cousin: seizure disorder
1	Much worse	Agitation	Mother: generalized anxiety disorder; maternal great uncle: mental retardation; maternal third cousin: mental retardation
12	Very much improved	Sedation, weight gain	2 Paternal first cousins: mental retardation
12	Much improved	Sedation	Family history of psychosis and learning disabilities
12	Much improved	Dyspepsia, diarrhea, constipation	None
12	Minimally improved	Sedation	None
12	Minimally improved	Sedation	None
4	Minimally improved	Abnormal gait, sialorrhea	None
. . .	. . .	. . .	. . .
Group			
12	Minimally improved	None	Mother: suicide; maternal grandmother: schizophrenia; paternal side: history of cerebral palsy and mental retardation
12	No change	None	Paternal second cousin: chronic motor tic disorder
12	No change	None	None
12	No change	None	None
12	No change	None	None
12	No change	None	Mother: generalized anxiety disorder, schizoid personality disorder; father: schizoid personality disorder
4	No change	Agitation	None
4	Minimally worse	Agitation	Father: Asperger disorder
12	Minimally improved	None	Father: social phobia and dysthymia; mother: major depression; paternal grandfather: alcohol abuse
12	Minimally improved	None	Mother: dysthymia; maternal family history of OCD; sister: alcohol abuse, major depression, and anorexia nervosa; father: alcohol abuse and suicide
12	No change	None	Paternal first cousin: mental retardation
12	No change	None	None
12	No change	Agitation	Father: alcohol abuse
12	No change	None	None
4	Much worse	Agitation	Paternal grandfather: major depression; nephew: autistic disorder
4	Much worse	Agitation	Brother: spina bifida and major depression; paternal niece: learning disability; father: Asperger disorder
. . .	. . .	. . .	. . .

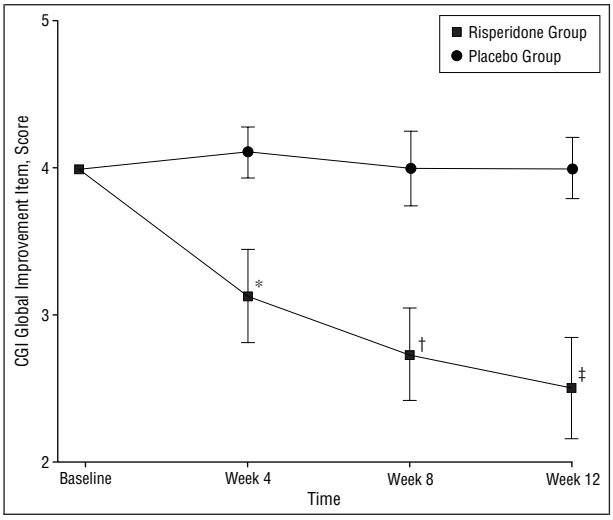

Figure 1. *Global improvement in patients with autism or pervasive developmental disorder not otherwise specified who were given risperidone or placebo for 12 weeks, as measured on the Clinical Global Impression (CGI) Scale global improvement item (see the "Rating Scales" section for an explanation of the scoring). Asterisk indicates $F_{1,27} = 8.93$, $P<.006$; dagger, $F_{1,27} = 9.67$, $P<.004$; and double dagger, $F_{1,27} = 15.07$, $P<.001$ (risperidone vs placebo, analysis of covariance). Variance bars represent SE.*

negative symptoms of schizophrenia.[11,12] Because of its improved profile of extrapyramidal effects and putative mechanism of therapeutic action, the use of risperidone in patients with PDDs has received increasing attention.

Results from the open-label use of risperidone in the treatment of children and adolescents,[13-22] as well as adults[23-26] with PDDs, have been reported. Typically, these studies have described reductions in irritability, impulsivity, hyperactivity, self-injury, aggression, and interfering repetitive behavior, along with improvement in some elements of social function and communication.

To our knowledge, no controlled studies of risperidone treatment of children, adolescents, or adults with PDDs have been published. The present 12-week randomized, double-blind, placebo-controlled investigation was conducted to determine the safety and short-term efficacy of risperidone for the treatment of adults with autistic disorder and PDD not otherwise specified (NOS). It was hypothesized that risperidone would be better than placebo for reducing repetitive behavior and aggression and for improving some aspects of social relatedness. In addition, it was hypothesized that the extrapyramidal and other adverse effects associated with risperidone would be only minimally greater than those of placeo.

RESULTS

Additional clinical characteristics of the risperidone and placebo groups are given in the Table. No significant differences were seen in age, sex distribution, diagnostic subtype distribution, full-scale IQ score, treatment setting, or optimal dose of risperidone between groups.

GLOBAL TREATMENT RESPONSE

Ratings on the CGI global improvement item showed risperidone superior to placebo as evaluated by the drug × time interaction (mean ± SE, 4.00 ± 0.00 to 2.54 ± 1.27 vs 4.00 ± 0.00 to 4.00 ± 0.79; $F_{3,84} = 7.80$, $P<.001$, intent-to-treat sample, n = 30 [$F_{3,84} = 6.43$, $P<.002$; completers, n = 24]). Subsequent ANCOVAs determined that risperidone was superior to placebo beginning at week 4 ($F_{1,27} = 8.93$, $P<.006$) and continuing at weeks 8 ($F_{1,27} = 9.67$, $P<.004$) and 12 ($F_{1,27} = 15.07$, $P<.001$) (**Figure 1**).

Eight (57%) of 14 of the risperidone-treated patients were categorized as responders compared with none of 16 in the placebo group ($\chi^2 = 9.72$, $P<.002$). Treatment response was not related to diagnostic subtype (autistic disorder, 5 of 8; PDD NOS, 3 of 6), sex, or treatment setting or correlated with age, full-scale IQ, baseline measures of repetitive behavior (Y-BOCS compulsion subscale score), aggression (SIB-Q total score), or dose of risperidone. A trend toward a significant correlation was found for treatment response and baseline level of overall autistic behavior (Ritvo-Freeman scale overall score) ($r = 0.31$, $P<.09$).

Nine (60%) of the 15 patients treated with open-label risperidone after completing the double-blind placebo phase were categorized as responders (autistic disorder, 7 of 8; PDD NOS, 2 of 7). Ratings on the CGI Scale showed that risperidone treatment resulted in a statistically significant global improvement in symptoms over time in these patients (4.00 ± 0.00 to 2.47 ± 1.06; $F_{3,42} = 11.60$, $P<.001$).

RESPONSE OF REPETITIVE BEHAVIOR

Risperidone was superior to placebo in the treatment of interfering repetitive behavior (16.15 ± 3.58 to 12.77 ± 3.63 vs 14.29 ± 3.50 to 14.35 ± 3.02; $F_{3,84} = 8.73$, $P<.001$ [$F_{3,84} = 7.26$, $P<.002$]). This effect began at week 4 ($F_{1,27} = 11.08$, $P<.003$) and continued through weeks 8 ($F_{1,27} = 8.31$, $P<.008$) and 12 ($F_{1,27} = 6.77$, $P<.02$). For the 15 patients who received treatment with open-label risperidone, the drug also resulted in a significant reduction in Y-BOCS scores over time (14.27 ± 2.92 to 11.47 ± 3.64; $F_{3,42} = 4.41$, $P<.03$).

RESPONSE OF AGGRESSIVE BEHAVIOR

As measured by the total score on the SIB-Q, risperidone was superior to placebo in reducing self-injurious behavior, physical aggression toward others, and property destruction (47.8 ± 19.5 to 24.2 ± 9.5 vs 37.7 ± 11.9 to 32.8 ± 15.0; $F_{3,84} = 9.22$, $P<.001$ [$F_{3,84} = 6.51$, $P<.005$]). This effect began at week 4 ($F_{1,27} = 5.61$, $P<.02$) and continued through weeks 8 ($F_{1,27} = 7.92$, $P<.009$) and 12 ($F_{1,27} = 7.16$, $P<.01$). For the 15 patients who were given open-label risperidone, the drug treatment also resulted in a significant reduction in aggressive behavior over time (32.43 ± 15.89 to 23.07 ± 13.45; $F_{3,42} = 3.07$, $P<.05$).

RESPONSE ON RITVO-FREEMAN REAL-LIFE RATING SCALE

Subscale I: Sensory Motor Behaviors

Risperidone resulted in a statistically significant improve ment in subscale I scores compared with placebo (0.79 ± 0.65 to 0.38 ± 0.38 vs 0.71 ± 0.58 to 0.64 ± 0.49; $F_{3,84} = 5.92$, $P<.004$ [$F_{3,84} = 4.16$, $P<.02$]). This effect be-

gan at week 4 ($F_{1,27}$ = 17.66, P<.001) and continued through weeks 8 ($F_{1,27}$ = 10.19, P<.004) and 12 ($F_{1,27}$ = 8.69, P<.007). For the 15 patients who received treatment with open-label risperidone, a significant reduction in subscale I scores over time also occurred (0.68 ± 0.48 to 0.44 ± 0.31; $F_{3,42}$ = 3.21, P<.04).

Subscale II: Social Relationship to People

Risperidone treatment did not result in a statistically significant improvement in subscale II scores compared with placebo. Similarly, for the 15 patients who received treatment with open-label risperidone, no statistically significant change in subscale II scores over time occurred.

Subscale III: Affectual Reactions

Symptoms within subscale III were significantly reduced by risperidone treatment compared with placebo (1.02 ± 0.39 to 0.35 ± 0.37 vs 0.78 ± 0.49 to 0.82 ± 0.57; $F_{3,84}$ = 8.78, P<.001 [$F_{3,84}$ = 7.48, P<.001]). This effect was present at week 4 ($F_{1,27}$ = 10.17, P<.004) and continued through weeks 8 ($F_{1,27}$ = 8.55, P<.007) and 12 ($F_{1,27}$ = 10.40, P<.003). For the 15 patients who were administered open-label risperidone, a statistically significant improvement in subscale III scores over time also occurred (0.75 ± 0.53 to 0.33 ± 0.28; $F_{3,42}$ = 5.95, P<.007).

Subscale IV: Sensory Responses

Risperidone treatment did not result in a statistically significant improvement in subscale IV scores compared with placebo for the intent-to-treat sample. In the analysis of the 24 completers, however, risperidone was found to be superior to placebo on this measure ($F_{3,66}$ = 3.48, P<.02). For the 15 patients who were treated with open-label risperidone, a statistically significant improvement in subscale IV scores over time occurred (0.70 ± 0.38 to 0.44 ± 0.36; $F_{3,42}$ = 5.67, P<.004).

Subscale V: Language

Treatment with risperidone did not result in a statistically significant improvement in language usage compared with placebo as measured by subscale V. Similarly, no statistically significant improvement in subscale V scores over time occurred in the 15 patients treated with open-label risperidone.

Ritvo-Freeman Scale Overall Score

Risperidone treatment resulted in a significant improvement in the overall behavioral symptoms of autism as measured by the overall score on the Ritvo-Freeman scale compared with placebo (0.60 ± 0.44 to 0.32 ± 0.27 vs 0.53 ± 0.41 to 0.45 ± 0.41; $F_{3,84}$ = 4.19, P<.02 [$F_{3,84}$ = 4.42, P<.01]). This effect first became evident at week 4 ($F_{1,27}$ = 10.51, P<.003) and remained significant at weeks 8 ($F_{1,27}$ = 4.54, P<.04) and 12 ($F_{1,27}$ = 4.03, P<.05)

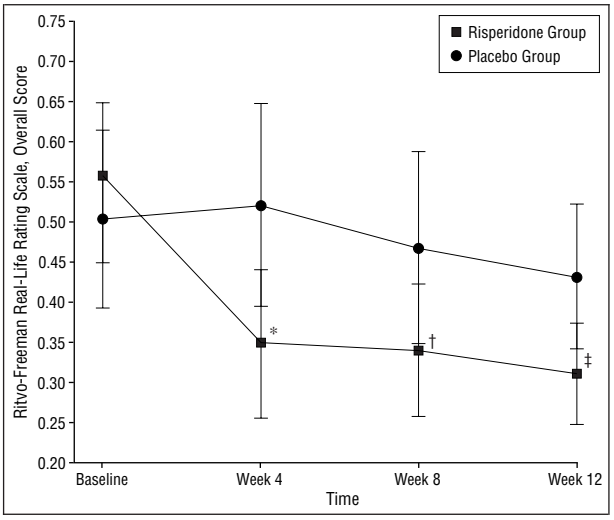

Figure 2. *Change in severity of the overall behavioral symptoms of autism in patients with autism or pervasive developmental disorder not otherwise specified who were given risperidone or placebo for 12 weeks, as measured by the overall score on the Ritvo-Freeman Real-Life Rating Scale (range, –0.42 to 2.58). Asterisk indicates $F_{1,27}$ = 10.51, P<.003; dagger, $F_{1,27}$ = 4.54, P<.04; and double dagger, $F_{1,27}$ = 4.03, P<.05 (risperidone vs placebo, analysis of covariance). Variance bars represent SE.*

(**Figure 2**). For the 15 patients treated with open-label risperidone, a significant improvement in the Ritvo-Freeman scale overall score over time also occurred (0.50 ± 0.38 to 0.27 ± 0.33; $F_{3,42}$ = 5.50, P<.003).

RESPONSE ON CLINICIAN-RATED VISUAL ANALOG SCALES

On the 10 clinician-rated visual analog scales, risperidone treatment resulted in significant changes in measures of "anxious or nervous" (decreased) (70.4 ± 16.4 to 42.3 ± 28.0 vs 66.6 ± 22.1 to 60.0 ± 28.5; $F_{3,84}$ = 4.14, P<.02 [$F_{3,84}$ = 3.57, P<.03]), "depressed" (decreased) (23.8 ± 17.6 to 8.5 ± 11.4 vs 23.1 ± 28.1 to 19.4 ± 25.4; $F_{3,84}$ = 3.38, P<.03 [$F_{3,84}$ = 2.58, P<.08]), and "irritable" (decreased) (51.8 ± 23.2 to 21.8 ± 20.4 vs 31.5 ± 24.4-22.3 ± 24.9; $F_{3,84}$ = 4.33, P<.01 [$F_{3,84}$ = 4.47, P<.01]), as evaluated by the drug × time interaction. No statistically significant differences over time were identified for the measures of "calm," "eye contact," "happy," "restless," "social interaction," "talkative," or "tired." For the 15 patients who received open-label risperidone, statistically significant changes over time occurred in measures of "anxious or nervous" (decreased) (62.67 ± 26.04 to 37.93 ± 29.95; $F_{3,42}$ = 3.91, P<.02), "calm" (increased) (26.67 ± 22.25 to 46.60 ± 24.01; $F_{3,42}$ = 4.37, P<.01), "irritable" (decreased) (27.33 ± 23.75 to 14.13 ± 16.27; $F_{3,42}$ = 3.03, P<.05), and "restless" (decreased) (54.67 ± 28.25 to 27.00 ± 22.82; $F_{3,42}$ = 3.69, P<.03). No statistically significant changes over time occurred in measures of "depressed," "eye contact," "happy," "social interaction," "talkative," or "tired."

ADVERSE EFFECTS

Adverse effects associated with risperidone administration are presented in the Table. No clinically significant

changes in blood pressure, heart rate, respiratory rate, or temperature were recorded, and no acute extrapyramidal effects (other than possibly the development of an abnormal gait in 1 patient), seizures, or cardiac events occurred. In general, risperidone was well tolerated, with the most prominent adverse effect being mild transient sedation during the initial phase of drug administration.

COMMENT

Risperidone was significantly more effective than placebo for decreasing many of the interfering behavioral symptoms of adults with autism and PDD NOS. Specifically, risperidone was effective in reducing interfering repetitive behavior, as well as aggression toward self, others, and property. While risperidone was more effective than placebo for decreasing the overall behavioral symptoms of autism, as measured by the Ritvo-Freeman scale overall score, this finding was largely accounted for by significant changes in sensory motor behaviors, affectual reactions, and to some extent, sensory responses. Significant differences between risperidone and placebo were not captured on subscales II and V of the Ritvo-Freeman scale, which measure social relationships to people and language, respectively. For many patients, however, clinicians, parents, and other members of the treatment team had the impression that anxiety associated with social interactions was reduced, allowing for enhanced social function. It may be that the rating scales used to assess social relatedness in this study were not sensitive enough to detect changes in this complex aspect of behavior.

In general, risperidone was well tolerated. Thirteen (87%) of 15 patients randomly allocated to risperidone treatment had at least 1 adverse effect—although this included only mild, transient sedation in 5 patients—compared with 5 (31%) of 16 patients given placebo (agitation in all 5 cases). Importantly, the weight gain observed with risperidone in the treatment of some children and adolescents with autism and other PDDs[21] did not occur to the same degree in this study of adult patients.

The pattern of symptomatic change in this study of adults with autism is similar to that observed in a previous systematic investigation of open-label risperidone use in children and adolescents with autism and other PDDs.[21] That risperidone is effective in both children and adolescents, as well as adults with autism, contrasts with controlled studies of the use of fluvoxamine that demonstrated efficacy and tolerability for autistic adults[9] but significant increases in agitation, aggression, insomnia, and other forms of behavioral activation and limited efficacy in the pediatric sample (C.J.M., J.P.H., D.J.C., L.H.P., unpublished data, 1998). These disparate results may be due to different influences of brain development on serotonin$_2$ receptors and the serotonin transporter protein, respectively.

Because of recent reports of possible tardive dyskinesia in children treated with risperidone,[38] continued close monitoring of the drug and longer-term follow-up studies are warranted. Double-blind, placebo-controlled studies are needed to determine the safety and efficacy of risperidone in adults with other subtypes of PDD, such as Asperger disorder, as well as in children and adolescents with the broad range of these profound disorders.

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