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Risperidone Improves Behavioral Symptoms in Children with Autism in a Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract Subgroup analysis of children (5–12 years) with autism enrolled in an 8-week, double-blind, placebo-controlled trial of risperidone for pervasive developmental disorders. The primary efficacy measure was the Aberrant Behavior Checklist-Irritability (ABC-I) subscale. Data were available for 55 children given risperidone ($n = 27$) or placebo ($n = 28$); mean baseline ABC-I (± SD) was 20.6 (8.1) and 21.6 (10.2). Risperidone [mean dose (± SD): 1.37 mg/day (0.7)] resulted in significantly greater reduction from baseline to endpoint in ABC-I versus placebo [mean change (± SD): –13.4 (1.5) vs. –7.2 (1.4), $P < 0.05$; ES = –0.7]. The most common adverse effect with risperidone was somnolence (74% vs. 7% with placebo). Risperidone treatment was well tolerated and significantly improved behavioral problems associated with autism.

Keywords Autism · Risperidone · Behavioral symptoms · Hyperactivity · Irritability · Safety

Introduction

Autism, a type of pervasive developmental disorder (PDD), is one of the most disabling pediatric psychiatric conditions. A recent survey of children aged 3–10 years in a large US metropolitan area estimated the prevalence of PDDs (autistic disorder, PDD-Not Otherwise Specified, and Asperger's syndrome) at 3.4 per 1,000 children (Yeargin-Allsopp et al., 2003). Among PDDs, autism is the most common, with a conservative estimate of the prevalence of autism being 1 per 1,000 children (Fombonne, 2003). Autism is characterized by impaired social interaction and communication, along with restricted or stereotyped behaviors (American Psychiatric Association, 2000). Associated behavioral problems include aggression, impulsivity, self-injurious behavior, tantrums, and hyperactivity.

Existing treatments target symptom control of maladaptive behaviors and may not alter the course of the disorder (Masi, 2004; Posey & McDougle, 2000). Educational and behavioral therapies are key components of treatment and may be effective in many cases (Horner, Carr, Strain, Todd, & Reed, 2002). However, when persistent maladaptive behaviors inhibit therapeutic progress, pharmacological therapy may be considered as a treatment option. Pharmacological therapy focuses on targeting problem behaviors and treating with a symptom-based approach (Chez, Memon, & Hung, 2004). Numerous studies have evaluated a variety of medications for reducing different behavioral problems in subjects with PDD (Posey & McDougle, 2000). Hyperactivity and attention disorders in children with PDD have been targeted by psychostimulants (e.g., methylphenidate), atypical antipsychotics (e.g., risperidone, olanzapine), and alpha agonists (e.g., guanfacine, clonidine) (Aman, 2004). Aggressive or self-injurious behavior has been predominantly targeted by both typical and atypical antipsychotic medications (e.g., haloperidol, risperidone) (Chez et al., 2004). For many

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of these compounds, controlled, large-scale, long-term studies are not available, making it difficult to reach concrete conclusions on their efficacy and tolerability in treating PDD. Among the atypical antipsychotics tested in children with PDD, risperidone has been the most extensively studied.

Risperidone has been shown to safely and effectively reduce behavioral symptoms in autism and PDD in several double-blind and open-label studies (Arnold et al., 2003; Gagliano et al., 2004; Malone, Maislin, Choudhury, Gifford, & Delaney, 2002; Masi, Cosenza, Mucci, & Brovedani, 2003; McCracken et al., 2002; Nicolson, Awad, & Sloman, 1998; Shea et al., 2004). The Research Units on Pediatric Psychopharmacology (RUPP) Autism Network recently conducted a large (N = 101), 8-week, double-blind trial of risperidone in children with autistic disorder (McCracken et al., 2002). Data showed that risperidone-treated subjects had significant improvement in their global condition, as well as improvement in serious behavioral problems, such as aggression, tantrums, or self-injurious behavior (McCracken et al., 2002). Problems frequently cited as those of most concern to parents (tantrums, aggression, hyperactivity, and stereotypy) were significantly reduced with risperidone treatment after 4 and 8 weeks of treatment (Arnold et al., 2003). More recent analyses of the RUPP data also demonstrated that, compared with placebo, risperidone treatment significantly reduced the core autism symptoms of stereotypic and obsessive compulsive behaviors, as measured on the Ritvo–Freeman Real Life Rating Scale and the Children's Yale-Brown Obsessive Compulsive Scale (McDougle et al., 2005).

The current analysis was conducted to further evaluate the efficacy and safety of risperidone in the treatment of children with autism. Data reported here represent a secondary analysis of the data from a larger study of children with autism and other PDDs (Shea et al., 2004). The original study was designed to test the hypothesis that risperidone would significantly reduce disruptive behavior in children with PDD (Shea et al., 2004). The current secondary analysis evaluated the same behavior and clinical assessment measures included in the RUPP autism study (McCracken et al., 2002), and also included assessments for each subject's most troublesome symptom to evaluate the specific autism symptoms that most need treatment.

Methods

This is a subgroup analysis of children with autism included in an 8-week, multicenter, randomized, double-blind, placebo-controlled study conducted in Canada, which evaluated risperidone for treating behavioral problems in children with PDD (Shea et al., 2004). Before initiation of this study, the protocol and written informed consent were approved by local Independent Ethics Committees. This study was conducted in accordance with good clinical practice and the Declaration of Helsinki. Informed consent was obtained from the parents or guardians of every subject prior to study enrollment.

Participants

Physically healthy children (aged 5–12 years) diagnosed with autistic disorder according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, were included if they had a baseline Childhood Autism Rating Scale (CARS) total score ≥ 30, representing at least mild autism (Schopler, Reichler, DeVellis, & Daly, 1980). Children with concomitant schizophrenia or other psychotic disorders were excluded. Children were also excluded if they had a history of drug or alcohol abuse, tardive dyskinesia, neuroleptic malignant syndrome, seizure within the previous 3 months, or previous intolerance or unresponsiveness to risperidone.

Study design

Prior to treatment, all subjects were evaluated with standardized measures of behavioral disturbances and general function, including the parent- or caregiver-rated Aberrant Behavior Checklist (ABC) (Aman, Singh, Stewart, & Field,1985), Nisonger-Child Behavior Rating Form (N-CBRF) parent version (Aman, Tassé, Rojahn, & Hammer 1996; Tassé, Aman, & Rojahn, 1996), the Visual Analog Scale for the most troublesome symptom (VAS-MS), which was reported by the parent or caregiver and rated from 0 (not troublesome) to 100 (extremely troublesome), the Vineland Adaptive Behavior Scale (VABS) (Carter et al., 1998; Sparrow & Cicchetti, 1985), and investigator-rated Clinical Global Impression (CGI). Standard IQ testing was performed. In patients whose intellectual abilities precluded administration of standard IQ testing, other cognitive tests, such as Leiter International Performance scales or Raven's Progressive Matrices, were completed.

After completing baseline assessments, subjects were randomized to treatment with an oral solution of risperidone (1.0 mg/ml) or placebo every morning. Risperidone was initiated at 0.01 mg/kg/day, increased to 0.02 mg/kg on day 3. Starting from treatment day 8

on, weekly dosage adjustment was determined by the investigator, based on efficacy and tolerability, which were assessed by the same investigator. Risperidone could be increased by up to 0.02 mg/kg/day steps, to a maximum total daily dosage of 0.06 mg/kg/day. In addition, subjects reporting drowsiness could have medication administered as a single nightly dose or divided into twice-daily dosing.

Concomitant use of medication and behavioral therapy during the trial are described more fully elsewhere (Shea et al., 2004). Briefly, antipsychotics other than the study medication, or medications used to treat psychiatric disorders or extrapyramidal symptoms were to be discontinued at the time of entry into the trial. During the trial, anticholinergics could be initiated to treat emergent extrapyramidal symptoms after completion of the Extrapyramidal Symptom Rating Scale (ESRS). Medications for pre-existing organic disorders were allowed, provided the dose and schedule of administration were kept as constant as possible.

Outcome measures

Efficacy measures were assessed at treatment weeks 1, 2, 3, 5, 7, and 8. The primary efficacy measure was the Irritability subscale of the ABC, which includes questions about aggressive and self-injurious behaviors, tantrums, agitation, or unstable mood. Secondary efficacy measures included other ABC subscale scores and N-CBRF subscale scores, VAS-MS, and CGI-Change (CGI-C) as described previously (Shea et al., 2004). To allow comparison of results with those of previous trials, the effect size was calculated for the primary efficacy measure. As a post-hoc analysis, treatment response was determined by identifying composite responders defined individuals using criteria previously employed in the RUPP trial [McCracken et al., 2002; ≥ 25% improvement in the ABC-Irritability (ABC-I) subscale plus CGI-C score ≤ 2—much/very much improved].

Safety and tolerability measures were also recorded throughout treatment. Spontaneously reported adverse events (AEs), vital signs, and weight were recorded. Biochemistry, hematology, urinalysis, and electrocardiograms (EKGs) were recorded at screening and end point.

At each clinical evaluation, the presence of drug-induced extrapyramidal symptoms was regularly assessed by means of the ESRS (Chouinard, Ross-Chouinard, Annable, & Jones, 1980), representing the patient's/caregiver's verbal report and subjective rating of extrapyramidal symptoms, and clinical examination of parkinsonism, akathisia, dystonia, and dyskinesia.

Data analysis

Efficacy was assessed in all subjects who received at least one dose of study drug and had a baseline assessment, and at least one post-baseline assessment. Response rates and CGI-C scores were compared using a Fisher's exact test or Cochran–Mantel–Haenszel test, controlling for investigator site. Between-group differences in changes from baseline for all other efficacy measures were analyzed using an analysis of covariance.

Safety was assessed in all subjects who received at least one dose of study drug (intention-to-treat population). Safety and tolerability measures were compared using descriptive statistics. Between-group differences in changes in ESRS were evaluated with an analysis of covariance.

Results

Participants

A total of 80 PDD subjects were enrolled and randomized at seven investigational sites for the original study (Shea et al., 2004). Of these, 55 subjects from six sites met the DSM-IV diagnosis for autistic disorder (risperidone, $n = 27$; placebo, $n = 28$). Demographics and disease characteristics were similar between groups, with the exception of IQ, where there were more subjects in the placebo group with an IQ > 84 (Table 1). The mean CARS baseline score for both treatment groups reflected severe illness. Within this sample, the mean modal risperidone dosage [± standard deviation (SD)] was 1.37 ± 0.7 mg/day; dose range, 0.5–4.2 mg/day. Eight weeks of treatment were completed by 92.6% ($n = 25$) of subjects receiving risperidone and 85.7% ($n = 24$) receiving placebo. Reasons for discontinuation in the risperidone group were extrapyramidal disorder ($n = 1$) and insufficient response ($n = 1$), and, in the placebo group, reasons for discontinuation were overdose ($n = 1$), insufficient response ($n = 2$), and withdrawal of consent ($n = 1$).

Efficacy

Mean changes at end point in ABC subscales scores for Irritability, Lethargy/Withdrawal, Stereotypic Behavior, and Hyperactivity/Noncompliance favored risperidone versus placebo (Table 2). Mean reduction in ABC-I subscale score was significantly greater with risperidone than with placebo at week 2 and at each subsequent evaluation point ($P < 0.05$) (Fig. 1). The effect size on the ABC-I subscale was –0.7. Mean changes at end point

Table 1 Subject demographics and disease characteristics

Variable	Risperidone (n = 27)	Placebo (n = 28)	P-value
Mean age, years (SD)[a]	7.4 ± 2.4	7.1 ± 2.1	0.537
Sex, n (%)[b]			0.172
Male	19 (70.4)	24 (85.7)	
Female	8 (29.6)	4 (14.3)	
Race, n (%)[b]			0.524
Caucasian	16 (59.3)	18 (64.3)	
Black	4 (14.8)	6 (21.4)	
Other	7 (25.9)	4 (14.3)	
IQ level,[c] n (%)[b]			0.020
≤ 84	19 (100)	18 (75)	
> 84	0 (0)	6 (25)	
Mean IQ (SD)[a,c]	50.8 (19.8)	60.1 (26.9)	0.213
Mean VABS (SD)[a]	44.6 (13.8)	46.7 (19.7)	0.653
Mean total CARS (SD)[a]	40.1 (5.4)	40.9 (6.6)	0.605

CARS Childhood Autism Rating Scale, *IQ* intelligence quotient, *SD* standard deviation, *VABS* Vineland Adaptive Behavior Scale

[a] P-values associated with analysis of variance

[b] P-values associated with Cochran–Mantel–Haenszel test for general association

[c] n = 19 for risperidone, n = 24 for placebo

in N-CBRF Conduct Problem, Hyperactive, and Overly Sensitive subscale scores showed significantly more improvement with risperidone than placebo (Table 2).

Visual Analog Scale for the most troublesome symptom data were available for 53 subjects. Symptoms rated as most troublesome by caregivers included: aggression (n = 15), tantrums/negative mood (n = 11), defiance/disobedience (n = 9), hyperactivity (n = 7), obsessive/repetitive behaviors (n = 5), impaired concentration (n = 3), communication dysfunction (n = 2),

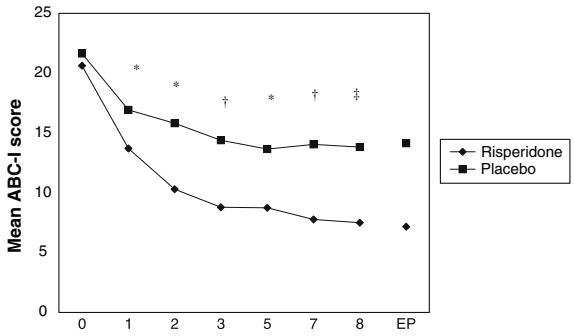
Table 2 Mean subscale scores for ABC, N-CBRF, and VAS-MS at baseline and end point (standard deviation)

Efficacy	n	Risperidone		n	Placebo		P[a]	ES[b]
		Baseline	End point		Baseline	End point		
ABC								
Irritability	24	20.6 (8.1)	7.2 (5.9)	28	21.6 (10.2)	14.1 (11.3)	0.002	–0.7
Lethargy/withdrawal	26	14.0 (6.8)	4.7 (4.4)	28	13.6 (8.6)	8.2 (8.9)	0.020	–0.5
Stereotypic behavior	25	8.4 (5.8)	3.9 (4.2)	28	9.4 (5.5)	6.9 (6.9)	0.053	–0.4
Hyperactivity/noncompliance	25	29.2 (9.5)	13.3 (8.7)	27	33.6 (6.8)	26.4 (12.8)	0.001	–0.8
Inappropriate speech	26	4.5 (3.7)	1.9 (2.2)	28	4.5 (3.7)	3.1 (3.5)	0.058	–0.4
N-CBRF								
Adaptive/social	26	3.8 (2.3)	5.3 (2.4)	28	3.9 (2.0)	4.3 (2.4)	0.072	
Compliant/calm	25	6.8 (2.7)	8.7 (3.3)	26	6.2 (2.4)	6.9 (2.9)	0.072	
Conduct problem	26	17.2 (8.0)	6.5 (5.7)	28	21.5 (10.7)	15.5 (11.9)	0.005	
Hyperactive	25	17.7 (5.6)	9.4 (5.4)	28	19.6 (5.2)	14.9 (8.4)	0.021	
Insecure/anxious	26	6.3 (6.7)	3.2 (4.3)	28	8.7 (6.7)	5.4 (4.8)	0.217	
Overly sensitive	26	6.7 (3.4)	2.8 (2.3)	28	6.6 (3.4)	4.3 (3.3)	0.029	
Self-injury/stereotypic	26	4.5 (4.4)	2.2 (3.1)	28	4.1 (4.4)	2.8 (3.9)	0.183	
Self-isolated/ritualistic	26	7.3 (4.0)	2.4 (2.5)	28	7.8 (4.2)	4.5 (5.5)	0.078	
VAS-MS								
Aggression	7	86.0 (14.5)	22.3 (20.0)	8	88.3 (9.0)	63.4 (37.3)	0.056	
Defiance/disobedience	4	75.0 (47.0)	60.0 (12.1)	5	84.8 (19.6)	65.2 (25.0)	0.872	
Hyperactivity	3	68.7 (28.6)	39.7 (19.7)	4	96.3 (4.2)	80.5 (14.2)	0.040	
Obsessive/repetititve	3	86.3 (19.4)	70.0 (16.8)	2	98.0 (0)	48.0 (63.4)	0.612	
Tantrums/negative mood	6	80.8 (10.1)	28.0 (20.9)	5	81.2 (13.9)	43.4 (28.8)	0.496	

ABC Aberrant Behavior Checklist, *N-CBRF* Nisonger-Child Behavior Rating Form, *VAS-MS* Visual Analog Scale for the most troublesome symptom

[a] P-value for mean change between-group difference at end point (analysis of covariance, model including treatment center, and baseline as covariate)

[b] Effect size (ES) was calculated using mean change difference at end point divided by pooled end point standard deviation



	Wk 0	Wk 1	Wk 2	Wk 3	Wk 5	Wk 7	Wk 8	EP
RIS Mean	20.6	13.7	10.3	8.8	8.8	7.8	7.5	7.2
(SD)	(8.1)	(9.1)	(7.6)	(7.3)	(7.2)	(6.2)	(6.4)	(5.9)
PLA Mean	21.6	16.9	15.8	14.4	13.7	14.0	13.8	14.1
(SD)	(10.2)	(10.7)	(10.8)	(11.7)	(11.1)	(11.8)	(12.2)	(11.3)

Fig. 1 Mean ABC-I subscale scores. Baseline is represented as treatment week 0. Mean score change was significantly greater for risperidone: $^{*}P < 0.05$; $^{\dagger}P < 0.01$; $^{\ddagger}P = 0.001$. *ABC-I* Aberrant Behavior Checklist-Irritability, *EP* end point, *PLA* placebo, *RIS* risperidone, *SD* standard deviation, *Wk* week

and social withdrawal/passivity ($n = 1$). The change from baseline to end point in VAS scores (least squares mean estimate ± SE) was –40.2 ± 6.6 in the risperidone group compared with –24.9 ± 6.4 in the placebo group (between-group difference: $P = 0.066$). Scores for individual symptoms with between-group analyses are shown in Table 2. Statistical significance between groups was noted for hyperactivity ($P = 0.04$).

Clinical Global Impression-Change scores showed significantly more improvement at most time points and at end point with risperidone compared with placebo ($P = 0.001$). At end point, composite response (≥ 25% ABC-I subscale improvement plus CGI-C of ''much'' or ''very much'' improved) was achieved by significantly more subjects receiving risperidone than those receiving placebo ($P = 0.008$). There were a total of 14 composite responders with risperidone (58.3%) versus 6 composite responders with placebo (21.4%).

Safety and tolerability

Adverse events were reported for 100% of subjects treated with risperidone and 71% with placebo. The most common AE was somnolence, which occurred more frequently with risperidone (74%) than placebo (7%); though most cases of somnolence were mild and resolved either spontaneously or were managed effectively by dose adjustments. Other AEs that occurred in more than 10% of risperidone-treated subjects were: upper respiratory infection (41% vs. 18% with risperidone and placebo, respectively); rhinitis (26% vs. 7%); fever (26% vs. 18%); increased saliva (15% vs. 4%); coughing (15% vs. 11%); vomiting (11% vs. 21%); increased appetite (11% vs. 4%); anorexia (11% vs. 4%); and influenza-like symptoms (11% vs. 4%). Most AEs were mild in severity.

Weight increase was reported as an AE by two risperidone and no placebo subjects. Mean change in weight was numerically, though not statistically, greater for subjects treated with risperidone ($P = 0.276$). Mean weight at baseline and end point, respectively, was 30.4 ± 11.8 and 32.8 ± 12.6 kg for risperidone and 27.3 ± 8.9 and 28.4 ± 9.8 kg for placebo.

There were few reports of AEs related to movement disorders. One case of hyperkinesia and one case of extrapyramidal disorder were reported in subjects receiving risperidone. The latter was reported in a subject who had received an accidental medication overdose and was treated with benztropine, discontinued the study, and recovered without residual effects. Other reported movement disorders in risperidone subjects were dyskinesia, hyperkinesia, hypokinesia, involuntary muscle contractions ($n = 1$ for each), and tremor ($n = 2$). Tardive dyskinesia and involuntary muscle contractions were reported by subjects receiving placebo ($n = 1$ for each). Mean ESRS scores, including scores on the subscales for the overall subjective rating, and the physician's exams for parkinsonism, dyskinesia, akathisia, and dystonia were very low throughout the trial.

There were no clinically relevant differences between the mean hematology or chemistry values in each treatment group. Urinalysis results were also similar for risperidone and placebo. There were no significant differences in vital signs with treatment. Changes noted in EKG measurements were not considered clinically relevant, except in one case of tachycardia with risperidone.

Discussion

Autism is a particularly devastating disorder, with no curative therapies available. Treatment focuses on targeting problem behaviors with medication and behavioral interventions. Among pharmacological therapies, risperidone is the best-studied medication for treatment of the disruptive symptoms associated with autism.

This secondary analysis of a large, randomized, double-blind study of PDD presents a homogenous group of children with autism, treated with risperidone or placebo for 8 weeks. This analysis adds to the

growing body of controlled data supporting the efficacy and safety of risperidone for the treatment of autism and underscores the consistency among published data. The current findings are noteworthy because of the increased interest in this disorder in the past years and relative paucity of available controlled data.

Treatment with risperidone for 8 weeks resulted in significantly greater reduction in ABC subscales scores for Irritability, Lethargy/Social Withdrawal, and Hyperactivity, compared with placebo. These findings suggest that risperidone can be an effective treatment for behavioral problems such as aggression, tantrums, self-injurious behavior, and hyperactivity in children with autism. Moreover, the present findings are consistent with the results of the RUPP randomized, double-blind, placebo-controlled trial (McCracken et al., 2002). In the current study, combined improvement in ABC-I and CGI-C was achieved by 58 and 21% of risperidone and placebo subjects, respectively, compared with 69% versus 12% in the RUPP study (McCracken et al., 2002). In addition, hyperactivity and aggression, identified by caregivers as the most troublesome symptoms in the present study, were improved with risperidone treatment. Although group comparisons were precluded due to sample size limitations, these observations are consistent with findings in the reanalysis of the RUPP data (Arnold et al., 2003). Taken together, the present data support the superiority of risperidone over placebo for amelioration of severe behavioral problems in children with autism.

It should also be noted that in this study risperidone was effective at mean dose of 1.37 mg/day, which is consistent with risperidone doses used in the general pediatric population. This dose was lower than the dose of 1.8 mg/day used in the RUPP trial, and one possible explanation for this is the differences in severity of autism between the two studies. For instance, the mean score on the ABC-I subscale at baseline was numerically higher in the RUPP trial, compared with the present analysis (26 vs. 21, with a higher score indicating greater severity), but this is likely due to the fact that a minimum score on the ABC-I subscale was required for entry into the RUPP study, but not the current study.

The current analysis showed that the treatment of irritable behavior with risperidone was well tolerated in children with autism. While AEs were commonly reported, risperidone was associated with few discontinuations due to AEs and few reports of movement disorders over the 8-week study period. Somnolence appeared to be transient, particularly with adaptation of drug administration. Weight gain was low with both risperidone and placebo, and the difference in weight gain was not statistically significant.

Treatment with risperidone has been associated with endocrine and metabolic events, such as a hyperprolactinemia, hypercholesterolemia, and glucose dysregulation. Although these measurements were not obtained in the current study, they should be evaluated on an individual patient basis per clinical practice. Hyperprolactinemia is usually transient in nature (Findling et al., 2003), but should be closely monitored because of its potential impact on growth and sexual maturation. A recent meta-analysis, however, concluded that there was no evidence of statistically or clinically significant growth failure or delay in pubertal onset or progression in children during risperidone treatment for up to 1 year (Dunbar, Kusumakar, Daneman, & Schultz, 2004). Metabolic AEs such as glucose dysregulation or lipid abnormalities can be related to weight gain or occur independently. Recent data in children with disruptive behavior disorders treated with low doses of risperidone suggests that weight gain occurs over the initial 12 weeks of treatment after which it plateaus (Reyes, Buitelaar, Toren, Augustyns, & Eerdekens, 2006). Guidelines for addressing these issues have been published by the American Diabetes Association and the American Psychiatric Association, though little information is available regarding appropriate measures to be taken in the pediatric population (American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity, 2004).

The current study is limited by the relatively brief study duration and small sample size. This study evaluated 8-week treatment response, but did not assess long-term maintenance of response. Despite low sample numbers, significant between-group differences were observed on several measures. Consistent with recent recommendations that clinical trials of autism should use general behavioral assessments, along with evaluations of core features of autism (Aman et al., 2004), this study included both clinician- and caregiver-rated measures of general clinical status (CGI), adaptive behavior (VABS), and assessment of behavioral symptoms of PDD (N-CBRF and ABC).

In summary, this secondary analysis showed that risperidone (1.37 ± 0.7 mg/day) was well tolerated and significantly improved irritable behavior as well as hyperactivity, as measured by improvements in both clinician-rated and caregiver-rated measures. This improvement plus a general clinical impression of improvement occurred in over half of the children with autism receiving risperidone compared with one-fifth of those receiving placebo. The efficacy and safety findings are consistent with other reports and suggest

that risperidone may have an important role in the management of behavioral problems in children with autism.

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