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Risperidone in Preschool Children with Autistic Spectrum Disorders: An Investigation of Safety and Efficacy

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ABSTRACT

Introduction: **Early intervention in autism spectrum disorders (ASDs) appears promising and may represent a window of opportunity for more effective treatment. Whereas the safety and efficacy of risperidone have been established for children aged 5 and older, they has not been adequately tested in preschool children.**

Methods: **A randomized placebo-controlled study of risperidone in preschool children was conducted in a sample of young children, most of whom were also undergoing intensive behavioral treatment.**

Results: **Preschool children tolerated low-dose risperidone well with no serious adverse effects observed over a 6-month treatment period. Weight gain and hypersalivation were the most common side effects reported, and hyperprolactinemia without lactation or related signs was observed. Significant differences between groups found at baseline complicated the analyses; however, controlling for some of these differences revealed that preschoolers on risperidone demonstrated greater improvements in autism severity. The change in autism severity scores from baseline to 6-month follow up for the risperidone group was 8% compared to 3% for the placebo group. Notably, both groups significantly improved over the 6-month treatment period.**

Conclusions: **Study findings suggest that risperidone is well tolerated in preschoolers over a 6-month period, but that only minimally greater improvement in target symptoms was evident in the risperidone group, possibly due to the differences between groups at baseline or due to the small sample size. Although these findings are not sufficient to direct treatment, they suggest that larger-scale, double-blind, placebo-controlled investigations of risperidone in preschoolers with ASDs should now be conducted.**

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INTRODUCTION

AUTISM SPECTRUM DISORDERS (ASDs) are a group of chronic disorders characterized by early childhood onset of profound impairment in social relatedness, delayed and deviant communication, and a markedly restricted repertoire of behavior and interests. These core symptoms are often accompanied by behavior disturbances, including hyperactivity, poor adaptability, anxiety, aggression, irritability, sterotypies, and self-injurious behavior. These nonspecific behavioral problems are disruptive, impeding remediation of core symptoms as well as daily living skills. A recent epidemiological study reported a prevalence rate for ASD of 4 cases per 1,000 children (Bertrand et al. 2001). Substantially higher rates, 6.7 cases per 1,000, are reported when milder forms of ASDs are accounted for. Because autism can be diagnosed in early childhood and autistic individuals are expected to have a normal life span, Gerlai and Gerlai (2004) recently noted that the number of 'patient years' associated with autism is second only to Alzheimer's disease.

The mainstay treatment for autism for more than a decade has been intensive behavioral intervention. A number of treatment programs based on this fundamental approach are available and have demonstrated effectiveness (for review, see Schreibman, 2000). Importantly, several studies now suggest that intensive intervention before the age of 5 years provides a window of opportunity for more effective treatment using this modality (for review, see Dawson et al., 2000). Early intervention during the preschool period (or earlier) appears to be the most promising, resulting in substantially better outcomes than later intervention (Faja and Dawson, 2006). This finding, taken together with basic neurodevelopmental research demonstrating greater neuroplasticity during the first 5 years of life, suggest that a similar window of opportunity might exist for pharmacologic interventions as well.

Pharmacological treatment of autism has been guided by the demonstrated effectiveness of medications in the treatment of psychiatric symptoms exhibited by individuals with ASDs. Along these lines, treatment to date has targeted the reduction of specific associated behavioral problems such as aggression and hyperactivity as opposed to improving the core deficits of autism. Typical antipsychotics were among the first medications to be studied systematically in autistic children and have been widely used for the control of agitation, aggression, and self-harming behaviors (McDougle et al. 2003). A suboptimal risk–benefit ratio related to untoward side effects, such as sedation, weight gain, and the risk of tardive dyskinesia, has catalyzed the search for new and better medications in this class.

Newer atypical antipsychotics have been used effectively in the treatment of adults and older children with autism (McCracken et al. 2002). Compared to conventional antipsychotics, these medications have a reduced risk of extrapyramidal and sedating side effects. The latter is particularly important when treating children for whom social learning is still actively developing, albeit atypically. Among atypical antipsychotics used for the treatment of ASDs, risperidone has been the most well-studied agent. Studies have demonstrated that children with ASDs treated with risperidone display decreased aggression and self-injurious behavior (e.g., McCracken et al. 2002). As a result, risperidone has now been identified as the only evidence-based pharmacological treatment for autism (McClellan and Werry 2003). Although multiple studies have demonstrated decreases in impulsivity, aggression, and self-harm (and even stereotypic behavior) with use of risperidone, there is considerably less evidence that the core social impairments of autism can be reduced through the use of risperidone or similar agents in children over 6 years old (McCracken et al. 2002; Shea et al. 2004; McDougle et al. 2005).

Despite lack of controlled data supporting their safety and efficacy, preschool age children in general (and presumably those with ASDs) are being treated with antipsychotics at very high rates in the community (Zito et al. 2000). Witwer and Lecavalier (2005) reported that nearly 10% of children with ASDs under the age of 7 were treated with antipsychotic medications in the previous year. Pharmacologic treatment at this early point in development could pose unique promise or unique

risk on the basis of greater neuroplasticity of the brain during the preschool period (Vitiello 1998). For this reason, as well as known high rates of prescribing in this age group, studies focusing on the safety and efficacy of atypical antipsychotics specifically in preschool age children are needed.

Despite the promising findings on early intervention in ASDs, information on the effectiveness of risperidone in the treatment of ASDs among preschool age children is limited to case descriptions and open-label studies. Masi and colleagues (2001) conducted the largest available open-label trial of risperidone for preschool children aged 3.9–6.6 years with ASDs and found improvement in the global severity of autistic symptoms. Notably, the core social impairments of the disorder improved, with gains seen in the ability to relate to people, increased verbal and nonverbal communication, and reduced social withdrawal. The authors hypothesized that the unique and promising improvements in social behaviors, which most previous studies in school age samples had failed to demonstrate, may have been related to the subjects having received treatment earlier in life. These findings, while promising, are limited by the use of an open-label design and the inherent lack of a control group.

To date, only two double blind, placebo-controlled studies investigating the efficacy of risperidone for the treatment of ASDs are available (McCracken et al. 2002; Shea et al. 2004). Although findings from both studies demonstrated efficacy for the amelioration of disruptive symptoms of the disorder in children ranging in age from 5 to 17 years, the study by Shea and colleagues also found improvements in scales measuring inappropriate speech and lethargy/social withdrawal. Another limitation of the available database is that the treatment duration of most trials is relatively short, typically 8–16 weeks. Longer duration of treatment is desirable for mimicking real-life practice and providing a more rigorous test for placebo effects, which may occur early and appear robust and sustained over the short term, particularly in this population, but do not endure over time (Sandler and Bodfish 2000). In addition, longer treatment dura-

tion is necessary to monitor for adverse effects such as weight gain, metabolic changes, and tardive dyskinesias.

The goal of the present study was to examine the safety and effectiveness of risperidone in the treatment of preschool children with ASDs over a 6-month period. Of interest was whether the medication was safe and well tolerated and whether it ameliorated the associated disruptive behavioral features and/or the core social deficits of the disorder when this early intervention was applied. Unique features of this investigation were the very young sample and the implementation of a randomized, double blind, placebo-controlled design for an extended duration of treatment. The majority of the study sample was receiving varying amounts of Applied Behavior Analysis (ABA) because it is a mandated treatment through the local public school district for eligible children. Therefore, the efficacy of risperidone was tested in the context of a population in which many children were undergoing an intensive behavioral intervention. To our knowledge, this investigation is the first double-blind, placebo-controlled trial in a preschool-age ASD population, including preschoolers with Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS). The inclusion of those with PDD-NOS and those undergoing behavioral treatments have been noted to be particularly important because they mimic real world practice (Troost et al. 2005).

MATERIALS AND METHODS

Setting and patients

This 6-month, randomized, double blind, placebo-controlled trial was conducted in a psychiatric outpatient clinic at Washington University School of Medicine (WUSM) in St. Louis between November, 1999, and November, 2002. The study protocol was approved by the WUSM Institutional Review Board, and written informed consent was obtained from a parent or legal guardian prior to enrollment. Parents were specifically informed about the experimental use of the drug for ASDs, as well

as the lack of data on safety in younger children (e.g., effects on growth and development).

Twenty four (n = 24) preschool children between the ages of 2.5 and 6.0 years who met *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition (DSM-IV) criteria for autism or PDD-NOS (American Psychiatric Association 1994), previously diagnosed and referred by a clinician, were recruited for participation. Subjects were ascertained from the child psychiatry outpatient clinic, offices of pediatricians and neurologists, and the special education department of local public school districts. All subjects were randomized, n = 12, to each treatment group. Other inclusion criteria at the time of enrollment included: (1) absence of other known significant central nervous system (CNS) disorders; and (2) absence of significant medical problems or other psychiatric disorders requiring pharmacotherapy. A complete physical exam was performed on all study participants by a board-certified pediatrician to rule out neurological and medical illness. In addition, participating families were strongly encouraged to minimize the use of adjunctive medications and/or supplements (hormones, vitamins, diets) over the duration of treatment.

Protocol schedule and design

Patients were consecutively assigned by an unblinded child psychiatrist (J.L.) to risperidone or placebo treatment using a randomization table obtained from the WUSM pharmacy and derived using a standard software package. Parents and raters who conducted all standardized assessments were blind to treatment group. Due to the exploratory nature of this study and to assure safety in this very young study population, the treating child psychiatrist (J.L.) was unblended and conducted regular clinical assessments over the 6-month period as follows: A baseline visit, weekly visits during the first study month, biweekly visits during the second month, followed by monthly visits for months 3–6. A thorough psychiatric and medical history, mental status exam, as well as physical exam were conducted at baseline.

Structured diagnostic assessments of autism symptoms were conducted at baseline, 2 months, 4 months, and 6 months. Standardized measures were used to assess general cognitive and socio-emotional functioning at baseline and after 6 months. Assessments were completed over 2 half-day periods, including multiple breaks and rewards to elicit maximum performance from children. Due to limited data regarding the effects of risperidone on growth and development in young children, height and weight and potential adverse events were carefully monitored at each study visit. In addition, electrocardiograms and a battery of laboratory tests (including prolactin and leptin) were performed at baseline, 2 months, and 6 months. Data about other medical, educational and developmental interventions (including hours of ABA weekly) were obtained through parental interview or the child's medical record.

Baseline assessment and efficacy measures

The central diagnostic outcome measures included the Childhood Autism Rating Scale (CARS) (Schopler et al. 1988), a 15-item behavior rating on a 7-point Likert scale based on clinician observation of the core social and behavioral symptoms of autism; and the Gilliam Autism Rating Scale (GARS) (Gilliam 1995), a rating scale completed by the clinician based on parent report and direct observation of the child's behavior that assessed frequency of DSM-IV autistic symptoms, including communication, social interaction, stereotypic behavior, and developmental regression, all yielding a total Autism Quotient. These were administered at baseline, 2, 4, and 6 months by raters blinded to treatment group status.

The following measures were administered at baseline and 6-month endpoint. Socialization and general adaptive development were assessed with the Vineland Adaptive Behavior Scales, Interview Edition (VABS) (Sparrow et al. 1984), a semistructured parent interview assessing communication, social skills, daily living skills, and motor development. The Childhood Behavior Checklist 1.5–5 (CBCL) (Achenbach and Edelbrock 1995) was com-

pleted by parents to assess behavior and emotion problems. Patients completed the Preschool Language Scale, Third Edition (PLS-3) (The Psychological Corporation, 1992), a standardized measure to assess receptive and expressive language development. Patients underwent an additional comprehensive developmental assessment using standardized and experimental cognitive, neuropsychological, and observational measures.

Medication dosing

Risperidone was administered in low doses and titrated by the unblinded child psychiatrist on the basis of the individual subject's progress and side-effect profile. The dosing range used in the study population was narrow and low (0.5–1.5 mg total daily dose). Medication was administered twice daily when doses greater than 0.5 mg were administered. Adjustments in dose were made as needed, depending upon treatment response and side effects, based on the clinical judgment of the unblinded child psychiatrist. Placebo dosing was also "titrated" to better maintain the blind design.

Most patients in the active medication group (90.9%) started risperidone at 0.5 mg once daily (91.7% of placebo patients were dispensed 0.5-mg daily doses) and mean starting dose was 0.03 mg/kg/day. Mean starting dose in the risperidone and placebo group were similar [0.50 mg (SD 0.15) risperidone versus 0.54 mg (SD 0.14) placebo]. With weekly dose escalation, 81.8% of risperidone and 66.7% of placebo patients took 1 mg (0.5 mg twice daily) after 4 weeks; 27.3% of risperidone and 33.3% of placebo patients were dispensed total daily doses of 1.5 mg after 8 weeks (2 months), whereas all others received total daily doses of 1 mg. Most patients were maintained on this schedule for the remainder of the study. Only 1 patient in the risperidone group was tapered from 1 mg at 4 months to 0.5 mg at 6-month endpoint. The final risperidone mean dose was 0.05 mg/kg/day. Mean daily final dose was 1.14 mg (SD 0.32) risperidone versus 1.38 mg (SD 0.57) placebo, which was comparable.

Safety monitoring

Treatment and side effects, including any occurrences of adverse events, were monitored at each study visit by the child psychiatrist who was not blind to the treatment condition, to assure safety in this very young study sample. All standardized baseline and outcome assessments were, however, administered by raters blind to the treatment conditions as described above. Physical and physiological parameters potentially affected by treatment were assessed including height, weight, and serum leptin and prolactin levels (known to be elevated in older children and adults on this medication).

Data analyses

Preliminary analyses were conducted to examine the possibility of differences between the two study groups (i.e., treatment and control groups) in relation to several demographic variables. To test for these differences, t tests, Mann–Whitney U tests, or Chi-square analyses were performed. To test for the effects of treatment over the course of four time points as well as the potential interactions between treatment and time, repeated measures analyses of variance (ANOVA) were conducted. Because the study groups significantly differed in autism severity at baseline, several methods were used to adjust for these differences. Specifically, covariates were entered into factorial or repeated measures ANOVAs to reduce the effect of the differences in autism severity between the two groups at baseline. To account further for the differences in autism severity at baseline, in several analyses CARS change scores were used as the dependent variable. CARS change scores were created by subtracting a child's baseline CARS score from their final CARS score obtained during the last assessment. The overall treatment effects were then estimated by comparing change scores between the risperidone and placebo groups with independent t-tests or Mann–Whitney U tests (for ordinal scale data). Additional analyses using covariates in these nonparametric tests were also conducted.

RESULTS

Sample characteristics

Twenty four children 2.5–6 years of age with a diagnosis of an ASD participated in a 6-month treatment trial; $n = 23$ of these children were included in the analyses that follow. One child did not meet the threshold for an ASD on the CARS or GARS at baseline, despite having been referred with a clinical diagnosis, and was excluded from analyses. From the total sample, $n = 11$ children were randomly assigned to the risperidone [mean age 49.0 months (4.1 years), SD 10.9 months] treatment group and $n = 12$ preschool-age children were assigned to the placebo group [mean age 48.1 months (4 years), SD 13.2]. The demographic and clinical characteristics of the sample at baseline are illustrated in Table 1. The two groups did not differ significantly in age, gender, or maternal education. The groups did also not differ significantly with regard to the ABA treatment. The mean number of weekly ABA treatment hours was 21.2 for the risperidone group and 11.3 for the placebo group. This difference in treatment intensity was, however, not significant ($p = 0.13$).

Baseline differences between study groups

Despite using conventional methods (e.g., random digits table) to randomize the assignment of children to each treatment group, preschoolers in the risperidone group displayed significantly greater severity of autism symptoms at baseline as measured by the CARS ($t = -2.34$, df $= 21$, $p = 0.03$). In addition, the risperidone group had significantly poorer language skills as measured by the PLS-3 and poorer motor skill development as measured by the VABS Motor

TABLE 1.   BASELINE CHARACTERISTICS OF PRESCHOOL STUDY SAMPLE: RISPERIDONE VERSUS PLACEBO GROUP

	Risperidone (n = 11)	Placebo (n = 12)	Test of significance
Age in months: Mean (SD)	49.0 (10.9)	48.1 (13.2)	$p = 0.86$, $t = -0.18$, df = 21
Gender (M/F)	9/2	8/4	$p = 0.64$, Fisher's exact
Weight in kg: Mean (SD)	19.2 (3.3)	18.1 (4.2)	$p = 0.49$, $t = -0.70$, df = 21
Ethnicity-Caucasian	91%	92%	$p = 0.37$, $\chi^2 = 2.01$, df = 2
Household income: Median[a]	2.0	3.0	$p = 0.09$, U = 43.00,
>$60,000	46%	83%	$p = 0.12$, $\chi^2 = 4.30$, df = 2
Maternal Education: Median[b]	6.0	6.0	$p = 0.66$, U = 59.00
range	4–8	4–8	
ABA hours per week	21.2 (14.8)	11.3 (15.1)	$p = 0.13$, $t = -1.60$, df = 21
CARS Total Score: Mean (SD)*	37.6 (4.0)	33.3 (4.9)	$p = 0.03$, $t = -2.34$, df = 21
CARS Category: Median	2.0	1.0	$p = 0.15$, U = 44.5
Nonautistic (Cat 1)	0 (0%)	3 (25%)	$p = 0.19$, $\chi^2 = 3.36$, df = 2
Mild–moderate (Cat 2)	5 (46%)	5 (42%)	
Severe (Cat 3)	6 (56%)	4 (33%)	
GARS Autism Quotient SS[c]	91.6 (9.5)	91.3 (9.3)	$p = 0.94$, $t = -0.08$, df = 21
Object Assembly Scaled Score:			
>3 years Mean (SD) (n = 10/10)	5.5 (3.8)	8.1 (4.6)	$p = 0.19$, $t = 1.38$, df = 18
PLS-3 Total SS*	57.3 (10.1)	73.5 (19.4)	$p = 0.02$, $t = 2.48$, df = 21
VABS Communication SS	65.5 (18.5)	73.2 (8.8)	$p = 0.23$, $t = 1.26$, df = 21
VABS Daily Living Skills SS	64.7 (14.8)	74.6 (15.9)	$p = 0.14$, $t = 1.54$, df = 21
VABS Socialization SS	66.3 (16.3)	72.0 (16.4)	$p = 0.41$, $t = 0.84$, df = 21
VABS Motor Skills SS	73.1 (18.7)	86.9 (13.4)	$p = 0.05$, $t = 2.05$, df = 21

CARS = Childhood Autism Rating Scale; GARS = Gilliam Autism Rating Scale; PLS-3 = Preschool Language Scale, Third Edition; VABS = Vineland Adaptive Behavior Scales, Interview Edition.

[a]1 = $0–$29,999, 2 = $30,000–$59,999, 3 = ≥$60,000.

[b]1 = some grade school, 2 = completed grade school, 3 = some high school, 4 = high school diploma, 5 = some college or 2-year degree, 6 = 4-year college degree, 7 = some years beyond college, 8 = graduate or professional degree.

[c]SS = Standard Score (mean 100, SD 15).

*$p < 0.05$.

Skills Scale (see Table 1). To account for these baseline differences in symptom severity and developmental impairment between groups, these key developmental variables were entered as covariates in subsequent analyses as appropriate. It should be noted that treatment groups did not differ significantly in autism severity on the GARS or IQ as measured by a nonverbal reasoning and problem-solving task (Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) Object Assembly). Thus, it was not necessary to control for the effects of these variables in the analyses that follow.

Safety of risperidone

No deaths or serious treatment-related adverse events occurred during the 6-month study period for any subject. Risperidone was well tolerated at the low doses administered. No clinically significant changes in EKG were detected for any subject from baseline to follow-up. The most common adverse events that occurred were transient sedation ($n = 5$), increased appetite ($n = 6$), and hypersalivation ($n = 2$). Constipation was reported by the parent of one study participant taking risperidone. Notably, no dystonic or dyskinetic movements were observed over the 6-month period for any participant on risperidone.

One participant on risperidone demonstrated transient staring spells (lasting several seconds) and periods of apparent waxy flexibility. These episodes were described by the parent and teacher and reportedly occurred over a 48-hour period after a minor head injury with visible bruising on her head but without loss of consciousness. An additional clinic visit was scheduled, during which time the subject was afebrile and no abnormalities were observed on AIMS evaluation. Although the episode was not deemed attributable to the medication, the dose

was lowered as a precautionary measure and a pediatric exam was recommended. The episodes spontaneously resolved within 48 hours.

It was notable that subjects on placebo also were reported by their parents to be experiencing transient sedation ($n = 4$) and increased appetite ($n = 3$). One subject on placebo dropped out of the study after 5 days due to a parental report of severe hyperactivity after placebo was started.

Physiologic findings

Changes in physiological measures within study groups and analyses of group differences in change scores are summarized in Table 2. Increases in prolactin serum levels were noted for both study groups from baseline to endpoint, with changes significantly higher [$\lambda = 0.66$, $F (1, 15) = 7.61$, $p < 0.05$] in the risperidone group from mean baseline levels of 8.11 ng/ml (SD 4.56 ng/ml) to mean endpoint levels of 41.49 ng/ml (SD 18.30 ng/ml) [vs. from 9.29 ng/ml (SD 4.06 ng/ml) to 20.40 ng/ml (SD 18.09 ng/ml) in the placebo group]. There was a trend ($p = 0.05$) for a higher increase in mean leptin serum levels in the risperidone group from 3.09 mg/L (SD 0.79) at baseline to 5.16 mg/L (SD 4.21) at 6 months versus from 4.34 mg/L (SD 2.75) to 3.81 mg/L (SD 2.18) in the placebo group. Most notably, children on risperidone gained significantly more, $F (1, 21) = 8.67$, $p < 0.01$, weight than children in the placebo group, with a mean weight gain of 2.96 kg from baseline versus 0.61 kg in the placebo group.

Effectiveness in amelioration of autism symptoms: Comparing the risperidone and placebo groups at four time points

Results of primary outcome measures during all four assessment points (baseline, 2, 4,

TABLE 2.   MEAN CHANGE SCORES OF PHYSIOLOGICAL MEASURES FROM BASELINE TO ENDPOINT

Measure	Risperidone		Placebo		Statistics	
	M	SD	M	SD	t (df)	p
Weight change in kg	2.96	2.53	0.61	1.10	−2.94 (21)	0.008
Leptin change in mg/L	0.66	0.97	−0.35	0.91	−2.15 (14)	0.050
Prolactin change in ng/ml	33.38	14.48	11.11	18.74	−2.76 (15)	0.015

and 6 months) are provided in Table 3. A repeated measures ANOVA across all four time points indicated that all participants' CARS Total Scores improved significantly over time within the risperidone and placebo groups combined [$\lambda = 0.37$, $F(3, 19) = 10.61$, $p < 0.001$]. However, the degree of improvement was not statistically different between the risperidone and placebo groups. To minimize the potential effect of group differences in autism symptom severity at baseline, the two developmental variables that differed between groups at baseline (PLS-3 Total Language and VABS Motor Skills scores) were used as covariates in follow-up analyses. Results from the repeated measures ANCOVA revealed no significant differences between the risperidone and placebo groups when the effects of preschoolers' language and motor development were controlled for statistically (see Table 3).

Effectiveness in treatment of autism symptoms: Risperidone versus placebo at baseline and 6-month follow up

When differences in baseline developmental characteristics were accounted for, results indicated no statistically significant differences between the risperidone and placebo groups on any of the outcome measures of interest when examining all four time points. However, when the total number of intervals being examined was reduced from four to two points (i.e., baseline and final assessment), and when baseline differences in motor development between groups were accounted for, repeated measures analyses of autism symptom scores on the CARS over these two time points (baseline to 6-month study endpoint) revealed significant differences between the study groups [$\lambda = 0.74$, $F(1,21) = 6.92$, $p < 0.05$] with a large effect size of $d = 0.95$. Specifically, children treated with risperidone demonstrated greater improvement in autism symptom ratings when compared to placebo controls (see Table 4). Accordingly, the risperidone group mean CARS Total scores dropped from the "Severely Autistic" to the "Mildly to Moderately Autistic" range at endpoint, whereas severity classification did not change in the placebo group. The change in CARS total

scores from baseline to 6-month follow up for the risperidone group was 8% compared to 3% for the placebo group. In addition, results from a repeated measures ANCOVA revealed a significant difference [$\lambda = 0.78$, $F(1,20) = 5.50$, $p < 0.05$] between the risperidone and placebo groups on the CARS Emotional Response subscale when VABS Motor Skills was included as a covariate (see Table 4).

Additional related outcome measures of interest (e.g., CARS Adaptation, CARS Fear and Nervousness, GARS Total, and VABS Socialization scores), expected to differ significantly between the groups, revealed no significant time-by-treatment interaction, even when baseline language and motor development were included in the equations as covariates.

Effectiveness of risperidone versus placebo on anxiety: Baseline to 6-month follow up

A trend toward differences in change of anxiety symptoms was found between the risperidone and placebo groups using the CBCL. This trend emerged despite a smaller sample size due to missing data at follow up. Although no differences were found between the groups in the CBCL Internalizing T composite scores, results from an ANOVA indicated that differences between the two study groups' mean scores on the CBCL Anxious/Depressed subscale approached significance [$F(1,13) = 4.42$, $p = 0.056$]. Covariates were not included in these analyses because there were no differences between the study groups in these areas (e.g., motor skills, CARS scores, etc.) when only the means for the reduced number of subjects included in the analyses were calculated (the sample sizes were reduced due to missing data as described above).

DISCUSSION

The current study aimed to determine whether risperidone was well tolerated and safe in preschool aged children with ASDs. It also aimed to investigate the short-term and 6-month efficacy of low-dose risperidone in the early treatment of ASDs during the preschool period of development. The findings demon-

TABLE 3.   TREATMENT EFFECTS AND COVARIATES OVER FOUR TIME POINTS ON PRIMARY OUTCOME MEASURES

Outcome	Baseline		Week 8		Week 16		Week 24		Time		Time × treatment interaction		Between subjects	
	M	SD	M	SD	M	SD	M	SD	F	p	F	p	F	p
CARS Total[a]									10.61	<0.01*	1.43	0.26	3.99	0.059
Risperidone	37.6	4.0	32.6	4.8	32.6	4.3	33.0	4.0						
Placebo	33.3	4.9	29.6	3.4	29.6	3.9	31.5	5.1						
With VABS motor covariate									0.233	0.87	0.85	0.49	2.76	0.12
With PLS-3 language covariate									0.213	0.89	1.37	0.19	0.299	0.67

CARS = Childhood Autism Rating Scale; VABS = Vineland Adaptive Behavior Scales; PLS = Preschool Language Scale.
[a]CARS total score: 15–29.99 "Non Autistic"; 30–36.99 "Mildly-Moderately Autistic"; 37.0–60 "Severely Autistic."
*p < 0.05

TABLE 4.   EFFICACY OF PRIMARY AND SECONDARY OUTCOMES FROM BASELINE TO 6-MONTH FOLLOW UP

Outcome	Baseline		Endpoint		Time × treatment interaction	
	Mean	SD	Mean	SD	F	p
CARS total[a]						
Risperidone (n = 11)	37.6	4.0	33.0	4.0	2.73	0.114
Placebo (n = 12)	33.3	4.9	31.5	5.1		
With VABS Motor					6.92	0.16*
With PLS-3 Language					2.82	0.109
CARS Emotional Response						
Risperidone (n = 11)	3.0	0.6	2.4	0.8	2.16	0.157
Placebo (n = 12)	2.3	0.8	2.2	0.5		
With VABS Motor					5.50	0.029*
With PLS-3 Language					1.24	0.278

CARS = Childhood Autism Rating Scale; VABS = Vineland Adaptive Behavior Scales; PLS = Preschool Language Scale.

[a]CARS Total Score: 15–29.99 "Non Autistic"; 30–36.99 "Mildly-Moderately Autistic"; 37.0–60 "Severely Autistic."

*$p < 0.05$.

strated that risperidone appeared safe and well tolerated in this young sample over a 6-month treatment period, with the most common enduring side effects including weight gain, hypersalivation, and elevations in prolactin levels (with no clinical lactation in any study subject). Low levels of sedation were observed; however, all observed sedation was transient and spontaneously resolved after several days. It was notable that no serious adverse side effects deemed attributable to the medication were observed during the 6-month trial. There were no occurrences of extraprymadial movements, and no subjects dropped out due to side effects of risperidone. There was a trend toward greater elevations in leptin levels among subjects on risperidone. All of these side effects are well known from investigations of risperidone in older children and adults. These data suggest that low-dose risperidone can be given over a 6-month period and is well tolerated by preschool children.

The finding that differences between the study groups were detected in the baseline to 6 month comparison and not in the four time point repeated measures comparison is based on the fact that the former tests are specific to a single change, namely 6-month improvement. By comparison, the repeated measures tests involving all four time points are sensitive to many possible differences across time and therefore are less powerful at detecting any specific change.

The etiology of the weight gain as well as potential remedies, which could be used to minimize this, should be the focus of future study. The use of an unblinded clinician may have diminished the occurrence of adverse events; however, the fact that medication dosage was lowered for only 1 subject at only one study visit minimizes this possibility.

Study findings suggest that preschool children treated with low-dose risperidone displayed greater improvements in global measures of autism symptoms compared to those treated with placebo. These findings emerged only when baseline differences in development between the two study groups were accounted for. Specifically, differences between study groups in CARS autism symptom scores of a large effect size became evident when baseline differences in motor skills were controlled. Although these findings were statistically significant, the possibility of a Type I (or Type II) error cannot be ruled out due to the small sample size and the severity differences between groups at baseline that complicated the analyses. Therefore, although findings overall are promising and suggestive of treatment effects, we do not believe they should be used for direct clinical practice. Instead, these study findings suggest that fur-

ther study with larger samples and longer treatment durations is warranted.

The original study hypothesis was that risperidone, when used at very early points in development, would allow for greater improvements in the core symptoms of autism, including communicative language, restricted interests, stereotypies, as well as social competence and reciprocity. Although global autism scores appeared to improve, this study did not detect evidence of more specific improvement in autism core symptoms as a function of treatment group. This finding is consistent with results from double-blind treatment trials of risperidone in older children with ASDs, which demonstrated that despite improvements in nonspecific disruptive behavior and autism-related stereotypic behavior, the core social and language impairments were not affected by medication treatment (McCracken et al. 2002). More recently available data from the multisite trial (Research Units on Pediatric Psychopharmacology Autism Network, RUPP) of older autistic children has also shown that whereas improvements in restricted, repetitive, and stereotypic behaviors were detected, no significant improvement in social skills or communication emerged (McDougle et al. 2005).

In contrast to the current findings, Shea and colleagues (2004) found children treated with risperidone for 8 weeks showed greater improvement in the core symptoms of inappropriate speech and lethargy/social withdrawal in addition to decreases in stereotypic and disruptive behaviors. Given that the final mean dose of both the Shea et al. study and the current study were similar (0.05 mg/kg/day), and the fact that the current study was of longer duration, suggests that the failure of the current study to detect differences in core autistic features could be due to lack of statistical power related to the relatively small sample size.

Although parents and treatment providers have held out great hope that a medication such as risperidone might have a primary ameliorating effect on the core symptoms of autism, the more restricted improvements observed could be expected based on the fact that the medication was developed as an anti

psychotic to treat debilitating impairments in emotional and behavioral control. These symptoms, while viewed as more peripheral to autism, are still quite disabling and, therefore, an important treatment target.

It was notable that both study groups improved significantly over the study period, a finding that could have been related to the ongoing developmental therapies in both groups applied during this young age. Furthermore, positive effects of both medication and placebo were evident in both groups early in the study; however, notably, the risperidone treated group sustained gains over the 6-month period. The important clinical implication here is that, if monitored adequately, the beneficial effects of risperidone over placebo should be evident after 6 months of treatment. Although this study was only continued for 6 months, the effects gained were maintained throughout that time. Pertinent to and extending this finding, a blinded discontinuation arm of the RUPP Autism Network demonstrated that risperidone showed sustained efficacy and tolerability over a 6-month treatment period and that discontinuation resulted in a reversal of these gains (RUPP Autism Network 2005). Further studies are needed to address whether or not there are ongoing improvements in behavior symptoms over longer durations in autism samples treated during the preschool period.

When baseline differences between groups were controlled, some significant differences in symptom improvement were evident between groups. Although the findings are not robust, they must be viewed in light of the fact that many study subjects also were undergoing an intensive behavioral intervention. This would suggest that differences between groups could have been more pronounced in a similar study group that was not also undergoing this intensive treatment. Whereas these findings may reflect some level of improvement among all children receiving risperidone, another possibility is that only a small number of children treated with risperidone demonstrated improvement in symptoms beyond those resulting from intensive intervention. Thus, one interpretation of the findings might be that risperidone would be most judi-

ciously used in those children who fail to make significant gains despite intensive psychosocial and educational treatment. Additional double-blind, placebo-controlled treatment trials in larger samples of preschool children with ASDs, including careful safety monitoring, are necessary before clinical use in this age group can be recommended with confidence.

Limitations

The clinical significance of the changes observed are difficult to determine on the basis of the lack of any objective measures of functioning beyond symptom manifestations. Therefore, further study is still needed to determine if the benefits outweigh the risks of this medication in preschool aged children with ASDs. These investigations should make direct comparisons of preschoolers in ABA treatment with and without medication augmentation. It is also unclear whether the dosing schedules used by the unblinded clinician were comparable to those implemented in similar studies of this medication in older children or were too low to produce more detectable changes.

The findings of greater severity of ASD symptoms and greater developmental impairments in the risperidone treatment group were limitations of the study. This, as well as the relatively small sample size, increases the possibility of Type I and/or Type II errors. Furthermore, the absence of corrections for multiple tests for outcome analyses are another clear limitation of the findings. The lack of a more comprehensive observational assessment and structured clinical interview of autism, such as the Autism Diagnostic Observation Schedule (ADOS) and Autism Diagnostic Interview-Revised (ADI-R), was also a study limitation. In addition, although safety of the medication over the 6-month period was established on the basis of measures of growth and development and physiology used, the longer-term effects of the medication on the developing brain remain unknown and should be the focus of future studies. Furthermore, other metabolic measures such as insulin resistance, now known to be important in atypical antipsychotic medications, were not measured

in this investigation and should be included in future clinical trials of risperidone in children.

DISCLOSURES

Drs. Luby, Mrakotsky, Belden, Heffelfinger, and Spitznazel and Ms. Stalets and Williams have no conflicts of interest or financial relationships to disclose.

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