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Acute and Long-Term Safety and Tolerability of Risperidone in Children with Autism

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ABSTRACT

Treatment-emergent adverse events (AEs) were monitored during an 8-week, double-blind, placebo-controlled trial of risperidone (0.5–3.5 mg/day) in 101 children and adolescents with a lifetime diagnosis of autistic disorder. In addition, 37 placebo nonresponders received open-label risperidone for another 8 weeks. Of all the risperidone responders (n = 65), 63 entered an open extension of another 16 weeks (6 months total risperidone exposure), and 32 of them were rerandomized to either continued risperidone therapy (n = 16) or gradual replacement with placebo (n = 16) over 8 weeks. We collected the following measures of safety and tolerability: (1) laboratory blood assessments (CBC with differential, electrolytes, and liver function tests) and urinalyses, (2) vital signs, (3) Side Effects Review of AEs thought to be associated with risperidone, (4) sleep records, (5) Simpson Angus Neurological Rating Scale (SARS), (6) Abnormal Involuntary Movement Scale (AIMS), and (7) height and weight. No clinically significant changes were found on the lab tests. During the 8-week acute trial, the most common AEs on the Side Effects Review, scored as moderate or higher, were as follows (placebo and risperidone, respectively): Somnolence (12% and 37%), enuresis (29% and 33%), excessive appetite (10% and 33%), rhinitis (8% and 16%), difficulty waking (8% and 12%), and constipation (12% and 10%). "Difficulty falling asleep" and anxiety actually favored the

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risperidone condition at statistically significant levels. The same AEs tended to recur through 6 months of treatment, although often at reduced levels. Using Centers for Disease Control (CDC) standardized scores, both weight and body mass index (BMI) increased with risperidone during the acute trial (0.5 and 0.6 SDs, respectively, for risperidone; 0.0 and 0.1 SDs, respectively, for placebo) and into open-label extension (0.19 and 0.16 SDs, respectively), although the amount of gain decelerated with time. Extrapyramidal symptoms, as assessed by the SARS, were no more common for drug than placebo, although drooling was reported more often in the risperidone group. There were no differences between groups on the AIMS. Two subjects had seizures (one taking placebo), but these were considered unrelated to active drug. Most AEs were mild to moderate and failed to interfere with therapeutic changes; there were no unanticipated AEs. The side effects of most concern were somnolence and weight gain.

INTRODUCTION

Recent years have witnessed a major increase in the use of all psychotropic medicines, including antipsychotics, in children and adolescents (Zito et al. 2003). This has also been quite noticeable in young people with pervasive developmental disorders, where a 50% increase in psychotropic medicine use has been observed over the last 8–10 years (Aman et al., 2003; Langworthy-Lam et al. 2002). There is a large and growing database on adverse events (AEs) with antipsychotics in adult patients, but the information available from trials with children is quite limited (Stigler et al. 2001).

There are special issues in monitoring AEs in children and adolescents (especially those with disabilities), as discussed by Vitiello et al. (2003). Such patients may have limited verbal capacity to report AEs not visible to the treating clinician, even though detection of AEs may be more important in young patients whose central nervous systems are in the process of maturing. Children and adolescents may be at greater risk for certain side effects (e.g., enuresis) than adults. Uncertain dosing standards and strategies for young patients make vigilance necessary. Because fewer children than adults are treated with most types of psychotropic medicines, the available database is diminished. Finally, there have been reports of apparently increased sensitivity to psychotropic agents in young people with developmental disabilities (Handen et al. 1991).

Ioannidis and Lau (2001) reviewed safety reporting in adult clinical trials and concluded that little space was given in publications to AEs. Greenhill et al. (2003) reviewed safety data in pediatric psychopharmacology studies, and they observed that most reports of multisite clinical trials devoted less than one page to AEs. Recently, the Research Units on Pediatric Psychopharmacology (RUPP) Autism Network (2002) reported clinical (and, briefly, some AE) findings in a sample of 101 children with a lifetime diagnosis of autistic disorder accompanied by tantrums, aggression, and self-injury. These children were followed acutely for 8 weeks of treatment, and 63 clinical responders to risperidone were followed for an additional 4 months (RUPP 2004). In light of risperidone's wide prevalence, we felt that a fine-grained analysis of its side effects is in order, especially as we had data on side effects for 6 months of exposure. In this paper, we report detailed findings for laboratory tests, vital signs, height and weight, a side effects review tailored to risperidone, sleep duration, extrapyramidal symptoms, and dyskinetic movements.

METHOD

Design

Acute double-blind study

Briefly, Protocol I entailed an acute parallel-group, double-blind comparison of matching

placebo and risperidone. Each participant was assessed for inclusionary and exclusionary criteria during a "screen" visit. They were then reassessed on key instruments at baseline (within 4 weeks of screen) and weekly for 8 weeks thereafter. Dosage was titrated individually, based on a schedule determined by the subject's weight and by time in the study. Subjects weighing 20–44.9 kg began risperidone at 0.5 mg at night and were titrated to a maximum dose of 2.5 mg/day (Scahill et al. 2001). Children under 20 kg followed essentially the same schedule, except that dosing was slower. Subjects weighing 45 kg or more were started at 0.5 mg nightly and were titrated to a maximum of 3.5 mg/day in divided doses.

All adverse events instruments and vital signs were assessed weekly for the first 8 weeks. Subjects in the risperidone group who were classified as risperidone responders (see RUPP Autism Network 2002) were invited to participate in Protocol 2. Subjects in the placebo group who were not responders (designated as "Placebo Nonresponders," (PNR)) were offered an 8-week trial of open risperidone with the same dose schedule as during the double blind. Each PNR child who was classified as a risperidone responder in the open-label trial was invited into Protocol 2, along with the responders, to randomly assigned risperidone (Scahill et al. 2001).

Open-label extension with randomized discontinuation

This entailed a 16-week extension on open-label risperidone for all risperidone responders who wished to participate (total exposure to risperidone = 2 months + 4 months, or 6 months total). Following the 16-week extension, participants were rerandomized to either continued risperidone or gradual placebo substitution over 8 weeks. For the placebo substitution group, the risperidone dose was decreased weekly by 25% of the 6-month dose. Children assigned to placebo substitution received placebo only from weeks 4 through 8 of the discontinuation. The participants were assessed every 4 weeks during the 16-week extension and weekly during the 8 weeks that followed rerandomization. Subjects who met preset relapse criteria were withdrawn, and risperidone treatment was resumed (see RUPP Autism Network 2004; Scahill et al. 2001 for further details).

The statistician, in concert with the National Institute of Mental Health (NIMH) Data Safety and Monitoring Board (DSMB), conducted interim analyses after the first 16 and 32 participants were enrolled, with the rationale that we should not continue to randomize subjects if withdrawal of risperidone was shown to cause significant relapse ($p < 0.01$, two-tailed). After 32 subjects completed rerandomization, the interim analysis showed that significantly more children assigned to placebo substitution than risperidone relapsed (62.5% and 12.5%, respectively; Yates' corrected χ^2; = 6.53, $p = 0.01$), and we ceased entering children into the rerandomization from then on. However, all positive responders whose parents were willing continued to be followed for the 16 weeks of the open extension.

Subjects

Double-blind comparison

Briefly, the inclusionary criteria were as follows: (1) Age 5–17 years 2 months; (2) male and female; (3) Aberrant Behavior Checklist (Aman and Singh 1994) Irritability subscale score of at least 18, as completed by a parent; and CGI—Severity (CGI-S; NIMH 1985b) score of at least 4 (see Arnold et al. 2000); (4) *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition (DSM-IV) (American Psychiatric Association, 1994) lifetime diagnosis of autistic disorder; (5) free of all psychotropic drugs at least 2 weeks prior to randomization (4 weeks for antipsychotics and fluoxetine); and (6) for participants with epilepsy, seizure free for at least 6 months and receiving stable antiepileptic dosage for at least 4 weeks. The lifetime diagnosis of autistic disorder was based on a clinical evaluation, which included direct observation of the participants, by an experienced clinical team and DSM-IV interview with a parent. The clinical diagnosis was corroborated by a structured interview of one or more parents, using the Autism Diagnostic Interview—Revised (Lord et al.,

1994). Exclusionary criteria included: (1) Mental age less than 18 months on individually administered IQ tests; (2) positive Beta HCG test for girls; (3) significant medical condition; (4) prior adequate trial with risperidone; (5) past history of neuroleptic malignant syndrome; and (6) because of dosing considerations, weight less than 15 kg. This study was approved by the institutional review boards at all sites, and parents and guardians signed consent forms before the children were enrolled. Subjects received routine electrocardiographs, routine blood and urine laboratory tests, and a physical examination before enrollment.

In all, 101 children and adolescents were randomized to treatment in Protocol 1. Fifty-two (52) were randomly assigned to placebo and 49 to risperidone in the double-blind trial. The mean age was 8.8 years (±2.7); 82 were boys and 19 were girls. Eighty-eight (88) (87%) were prepubertal, based on Tanner Staging. Four (4) subjects (2 in each group) were taking antiepileptic drugs. Three (3) children withdrew from the risperidone group because of lack of efficacy. Seventeen (17) withdrew early from the placebo group before the 8 weeks expired for the following reasons: withdrawal of consent (n = 1), nonadherence (n = 1), loss to follow-up (n = 3), and lack of efficacy (n = 12).

Open-label treatment for placebo nonresponders

In all, 37 of the PNR subjects subsequently received an 8-week trial of open-label risperidone. Their mean age was 8.8 (± 2.6) years.; 29 (78.4%) were boys and 8 (21.6%) were girls. Thirty-one (31) (83.8%) were prepubertal and 6 (16.2%) were postpubertal.

Open-label extension

A total of 63 children showed a positive response to risperidone *and* wished to continue into Protocol 2. Thirty (30) of these were originally in the double-blind risperidone group, and 30 were originally in the PNR group. During the data analysis, we learned that an additional 3 participants were enrolled into Protocol 2, without meeting all response criteria. These 3 children were originally assigned to risperidone. As inclusion of these 3 participants did not alter clinical results for any of the clinical outcome variables (RUPP Autism Network 2004), they were retained for all analyses in this paper. There were no differences in symptom severity or in response between subjects originally assigned to the risperidone group and those in the PNR group. We also compared the 63 subjects who enrolled in Protocol 2 with the 38 who did not and found that they did not differ on any of the primary outcome variables.

The mean age on entry was 8.6 years (±2.8; range, 5.00–17.33 years). The educational placements were as follows: Regular class, 4 (6.4%); regular school/special class, 47 (74.6%); special school, 11 (17.5%); other, 1 (1.6%). Other characteristics of both the children who entered the extension and those who did not are described in detail elsewhere (RUPP Autism Network 2004).

Procedures

All subjects were seen weekly during Protocol 1 (n = 101), every 4 weeks during the 16-week extension, and weekly during the discontinuation. If subjects experienced significant deterioration for 2 successive weeks of the discontinuation, they were withdrawn from the study, and risperidone treatment was resumed if it had been discontinued. All participants were seen by two clinicians. *Blinded clinicians* were not permitted to inquire about adverse events or to be present during breaking of the blind. Their role was exclusively to monitor extent of therapeutic change. *Primary clinicians* were responsible for monitoring adverse events, adjusting dosage, and making clinical recommendations as participants exited the study.

Outcome measures

The following laboratory and side-effect measures were gathered.

Laboratory. This consisted of a complete blood count with automated differential, liver function tests (SGOT, SGPT, total and direct

bilirubin), electrolytes, BUN, creatinine, CPK, and urinalysis (macroscopic and microscopic). These were obtained at screen, after 8 weeks of treatment or the open-label treatment for PNR subjects (all Protocol 1), and after 24 weeks of exposure to risperidone (Protocol 2).

ECGs and prolactin. These were obtained at screen, end of 8 weeks of risperidone treatment (Protocol 1), and after 6 months of exposure to risperidone (Protocol 2). These measures will be the subject of a separate report.

Vital signs. Heart rate (recorded over 30 seconds) and blood pressure were obtained at each visit, preferably with the participant seated and at rest.

Height and weight. These were obtained at each visit. Heights were measured by stadiometer with subjects in their stockings. Weights were obtained to the nearest 0.1 kg on balance scales after subjects removed outer wear and shoes.

Side effects review. A list of 29 adverse events was compiled based on commonly reported events in prior risperidone studies (including those in the package insert) and prior experiences of the investigators. The Side Effects Review Form covered physical and behavioral events commonly related to atypical antipsychotics recorded on a scale ranging from 0 (not present) to 3 (severe, requires immediate intervention). Side effects were reviewed by the primary clinician at each week during acute treatment (8 weeks), 4-weekly during the open-label extension (16 weeks), and weekly during the discontinuation phase. Unlike our original report (RUPP Autism Network 2002), symptoms are reported in this paper if they occurred *at all*. We did not attempt to establish relation of the symptom to treatment on this form, and, hence, previously reported changes (RUPP Autism Network 2002) do not exactly match those printed in this paper.

Sleep log. This form was completed at each visit to record the time at which subjects rose in the morning and fell asleep at night. We used it to calculate sleep duration on and off risperidone.

Simpson-Angus Neurological Rating Scale (SARS). This 10-item scale, which assesses extrapyramidal symptoms, has been shown to be sensitive and reliable in previous studies (Simpson and Angus 1970). Its items assess rigidity, salivation, glabellar reflex, and tremor; the total score was analyzed.

Abnormal Involuntary Movement Scale (AIMS). The AIMS is commonly used to rate neurological side effects, particularly dyskinetic symptoms, including withdrawal dyskinesias and tardive dyskinesia (NIMH 1985a). Its 12 questions cover anatomic location (face, extremities, trunk), global severity, and global judgment of incapacitation and awareness of abnormality. The AIMS includes a clinician-driven interview and a physical examination.

Statistical analyses

Findings for laboratory data were simply tabulated. Results for the Side Effects Review Form were presented by severity and analyzed by chi-square. Interval-level results (blood pressure, heart rate, weight, AIMS scale, SARS, and time spent sleeping) were analyzed by mixed effects linear regression models as a function of drug (risperidone versus placebo), time (baseline and endpoint), the interaction of drug by time, and site. We also looked for possible predictors of weight gain at the end of open-label extension (6 months). This was done by regression analysis in which baseline weight z-score or body mass index (BMI) z-score were entered as covariates, and site was included as a class predictor.

RESULTS

Laboratory findings

The means for the hematology, blood chemistry, and liver function tests appear in Table 1. Statistically (but not clinically) significant

TABLE 1. CLINICAL LABORATORY FINDINGS

						Abnormal**			
	Placebo		Risperidone			PBO		RIS	
Variable	BL (52)	W8 (43)	BL (49)	W8 (46)	p	BL	EP	BL	EP
White blood cell	7.5	7.0	8.0	7.3		1	—	—	—
Red blood cell	4.6	4.7	4.6	4.6	*	—	—	—	—
Platelets	304.1	308.2	313.4	316.1		—	—	—	—
Hemoglobin	13.1	13.1	13.2	13.0		—	—	—	—
Hematocrit	37.9	37.9	38.1	38.0		—	—	—	—
Neutrophil	48.5	48.1	48.5	51.1	*	—	—	—	—
Lymphocyte	39.8	39.7	39.2	36.3	*	—	—	—	—
Monocytes	7.7	7.8	7.9	8.8		—	—	—	—
Eosinophils	3.5	3.5	3.8	3.3		—	—	2	1
Basophils	0.6	0.7	0.5	0.6		—	—	—	—
Sodium	139.4	139.0	139.4	138.1		—	—	—	—
BUN	11.1	11.8	12.3	11.2		—	—	—	—
Potassium	4.0	4.0	3.9	4.0		—	—	—	—
Chloride	103.2	102.8	103.7	102.8		—	—	—	—
Creatinine	0.5	0.5	0.5	0.5		—	—	—	—
AST/SGOT	34.0	33.6	48.0	37.4	*	—	—	—	1
Bilirubin total	0.5	0.5	0.4	0.5		—	—	—	—
Bilirubin direct	0.1	0.1	0.1	0.1		—	—	—	—
CPK	149.8	137.4	152.7	148.6		1	—	1	—
ALT/SGPT	18.1	19.0	18.5	23.7		—	—	—	2

p refers to the probability for the interaction. * $p < 0.05$. Sample sizes for abnormal values: PBO/BL, $n \leq 52$; PBO/W-8, $n \leq 40$; RIS/BL, $n \leq 49$; RIS/W-8, $n \leq 44$. There was only one case with abnormal laboratory findings at the 4-month extension; this was a subject with elevated WBC and neutrophils. ** = extreme values >2 times the normal reference range. BL, baseline; w8, week 8; PBO, placebo; RIS, risperidone.

group-by-drug interaction changes were found for red blood cells, neutrophil, and lymphocyte counts, and for SGPT/SGOT. The last four columns of Table 1 provide the numbers of subjects with extreme values on any of the blood tests, with "extreme" defined as any lab that was greater than twice or more the normal reference range. The low and high reference ranges varied from site to site. Therefore, the overall lowest value was used as the low reference range, and the highest value was cited as the upper reference range for each lab test that was performed. There were few abnormal values that seemed evenly distributed across baseline and drug for risperidone subjects. There was only one case with abnormal laboratory findings at the 4-month extension; this was a subject with elevated WBC and neutrophils at endpoint.

Results from the urinalyses were reviewed. With the exception of one case showing occult 2+ blood at baseline and reduction to 1+ on risperidone at week 8 in the acute trial, no clinically significant changes were observed.

Side effects review

Mild to moderately severe side effects are reported in Table 2. Basal rates of the various symptoms appear under the baseline (BL) column for each drug condition; they are presented for any level of severity (1 (mild), 2 (moderate), or 3 (severe)). These basal rates were often quite high, and no attempt was made to correct for them in this analysis. Results are set out for the placebo group, the randomly assigned risperidone group, and the PNR subjects given an open trial of risperidone. Whereas symptom severity was not presented at baseline (to conserve space), symptoms were classed as either mild (1) or moderate/severe (2/3) during the placebo and risperidone conditions. The following side effects were significantly more common in the risperidone group: Tired during the day ($p < 0.0001$), excessive appetite ($p < 0.0001$), difficulty waking ($p = 0.05$), excessive saliva or drooling ($p = 0.04$), and dizziness or loss of

TABLE 2. PERCENT SIDE EFFECTS APPEARING FOR 8% OR MORE OF SAMPLE IN THE DOUBLE-BLIND COMPARISON AND OPEN 8-WEEK TRIAL FOR PLACEBO NONRESPONDERS (PNR)

	Placebo (n = 52)			*Risperidone* (n = 49)				*PNR* (n = 37)	
		During 8 weeks			*During 8 weeks*			*During 8 weeks*	
Side effect	*BL*	*Mild*	*Mod/Sev*	*BL*	*Mild*	*Mod/Sev*	*p*	*Mild*	*Mod/Sev*
Difficulty falling asleep	50.0	30.8	34.6	32.7	24.5	22.4	0.02	54.1	10.8
Tired during day	23.1	42.3	11.5	14.3	57.1	36.8	*	83.8	2.7
Enuresis	32.7	19.2	28.8	40.8	32.7	32.7	0.11	43.2	0.0
Anxiety	32.7	32.7	15.4	20.4	18.1	14.2	0.05	35.1	2.7
Rhinitis	17.3	36.5	7.7	12.2	38.8	16.3	—	45.9	0.0
Excessive appetite	11.5	28.8	9.6	12.2	49.0	32.6	*	73.0	0.0
Coughing	19.2	21.2	15.4	8.2	40.8	6.1	—	35.1	0.0
Dry mouth	11.5	26.9	1.9	12.2	40.8	2.0	0.15	37.8	0.0
Nausea/vomiting	5.8	23.1	5.8	4.1	36.7	4.0	0.20	27.0	0.0
Diarrhea	9.6	19.2	9.6	8.2	26.5	4.1	—	32.4	0.0
Difficulty waking	19.2	19.2	7.7	14.3	34.7	12.2	0.05	54.1	10.8
Constipation	11.5	13.5	11.5	16.3	28.6	10.2	0.14	18.9	2.7
Skin rash	7.7	15.4	1.9	8.2	24.5	2.0	—	18.9	0.0
Headaches	5.8	11.5	5.8	10.2	18.4	4.1	—	13.5	2.7
Dyspepsia	1.9	11.5	5.8	0.0	10.2	0.0	0.19	8.1	0.0
Excessive saliva	7.7	9.6	1.9	4.1	24.5	4.0	0.04	35.1	0.0
Dizziness/loss of balance	1.9	7.7	0.0	0.0	16.3	6.1	0.04	13.5	2.7
Tachycardia	1.9	7.7	0.0	2.0	6.1	2.0	—	10.8	0.0
Muscles appear stuck	5.8	3.8	1.9	0.0	4.1	4.1	—	5.4	2.7
Tongue movements	3.8	3.8	0.0	4.1	6.1	4.0	—	2.7	0.0

Note. The *p* values are derived from chi-square tests comparing the placebo and risperidone 8-week trials. * $p < 0.0001$. BL = baseline; PNR = placebo nonresponders treated openly with risperidone; Mod/Sev, moderate/severe. Figures under the BL headings represent the "basal" rate for the symptom occurring at time of study entry. The chi-square tests did not adjust for basal levels.

balance ($p = 0.04$). Two problems were significantly *less* common in the risperidone group: Difficulty falling asleep ($p = 0.02$) and anxiety ($p = 0.05$).

Our data were derived from *two* groups who were treated with an identical dosing strategy but under different conditions, namely the originally assigned risperidone subjects ($n = 49$) and the PNR subjects later treated with risperidone ($n = 37$). On average, slightly *more PNR* participants reported mild side effects (mean, 32.4%) than originally assigned risperidone subjects (mean, 26.9%) (summing across all AEs). However, on average, *fewer PNR* subjects reported *moderate/severe* side effects (1.9%) than observed for the originally assigned risperidone group (11.0%).

In Table 3, we have summarized the most common parent-reported side effects that occurred during the open-label 4-month extension of risperidone ($n = 63$). "BL" refers to observations in the 8th week of the blinded trial or the 8th week of open treatment for PNR risperidone responders. There was a fairly constant occurrence of side effects across time until month 4 (equal to 6 months of exposure to risperidone). The sample size decreased from 63 to 57 participants at month 4 (possibly with subjects experiencing the most serious adverse events dropping out). This may explain why several side effects declined at this point. Parents typically reported drowsiness during the day for slightly more than 20% of subjects, excessive salivation for approximately 13%, and a rather low rate of difficulty falling asleep (4.8%–9.5%).

We also plotted side effects as a function of drug condition (placebo, RIS, PNR-RIS) and time. Figures 1, 2, and 3, respectively, show the percentages who: (1) Were tired during the day, and (2) were regarded as having excessive appetite during the acute trial and PNR, and

TABLE 3. SIDE EFFECTS RECORDED DURING OPEN-LABEL EXTENSION (%)

Side effect (n)	*BL* (63)	*Month 1* (63)	*Month 2* (61)	*Month 3* (61)	*Month 4* (57)
Excessive appetite	54.0	60.3	62.3	55.7	49.1
Enuresis	41.3	54.0	44.3	42.6	35.1
Tired during day	22.2	20.6	14.8	23.0	21.1
Dry mouth	20.6	19.0	14.8	19.7	15.8
Coughing	19.0	9.5	19.7	23.0	12.3
Anxiety	19.0	17.5	13.1	16.4	14.0
Rhinitis	15.9	14.3	14.8	14.8	15.8
Excess saliva	12.7	9.5	11.5	16.4	15.8
Nausea/vomiting	6.3	6.3	6.6	13.1	10.5
Difficulty falling asleep	6.3	7.9	6.6	4.9	10.5
Gynecomastia	3.2	4.8	6.6	8.2	7.0
Difficulty waking	4.8	4.8	11.5	1.6	5.3
Diarrhea	6.3	3.2	3.3	11.5	3.5
Constipation	6.3	3.2	6.6	6.6	3.5
Skin rash	1.6	3.2	6.6	6.6	8.8
Muscles "stuck"	3.2	3.2	6.6	6.6	3.5

Note. BL (baseline) refers to the last week of risperidone in the acute trial (originally assigned risperidone subjects) or last week of open-label risperidone for PNR subjects.

"Month 1" = 12 weeks risperidone exposure; "Month 2" = 16 weeks; "Month 3" = 20 weeks; and "Month 4" = 24 weeks of risperidone exposure.

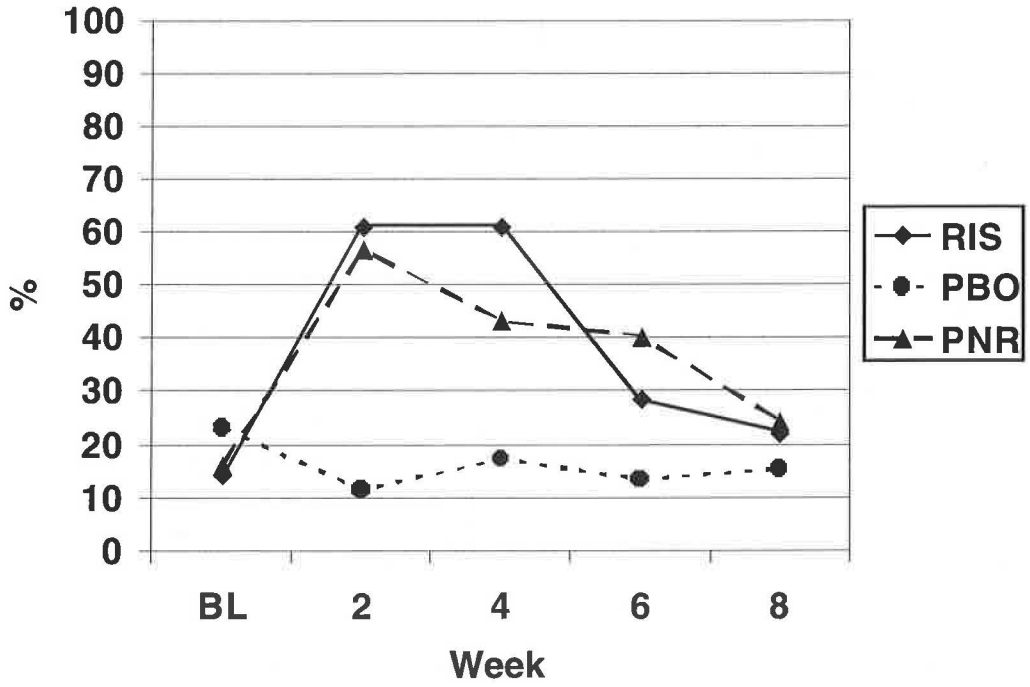

FIG. 1. Percent of participants rated as tired during the day during the double-blind and open-label PNR risperidone intervals. BL, baseline; PBO, placebo; PNR, placebo nonresponder; RIS, risperidone.

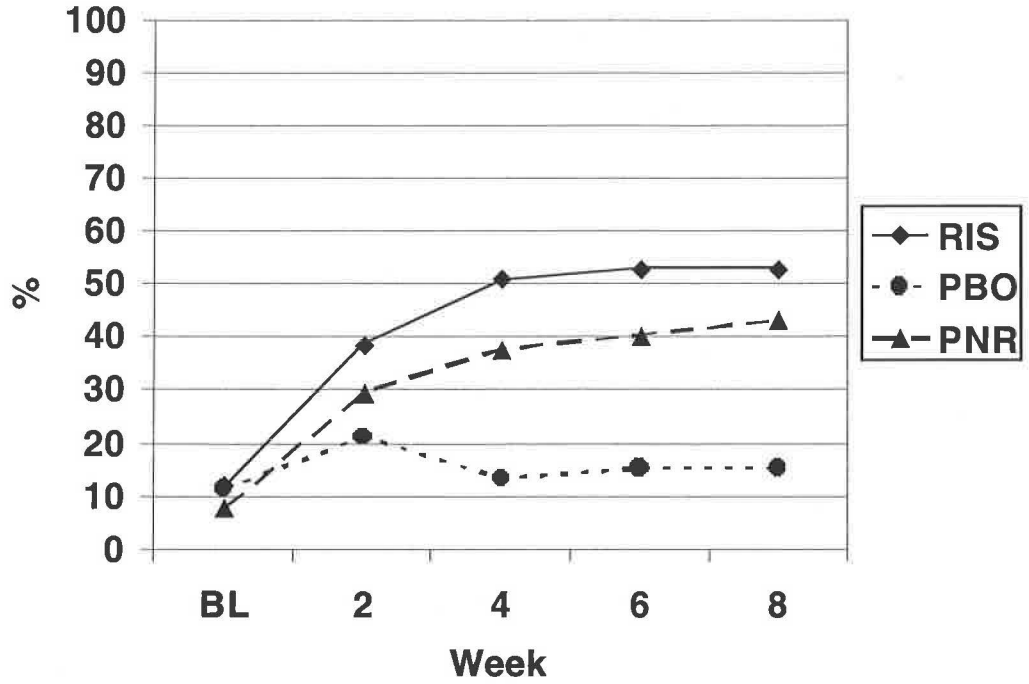

FIG. 2. Percent of subjects reported to have excessive appetite during the double-blind and open-label PNR risperidone intervals. BL, baseline; PBO, placebo; PNR, placebo nonresponder; RIS, risperidone.

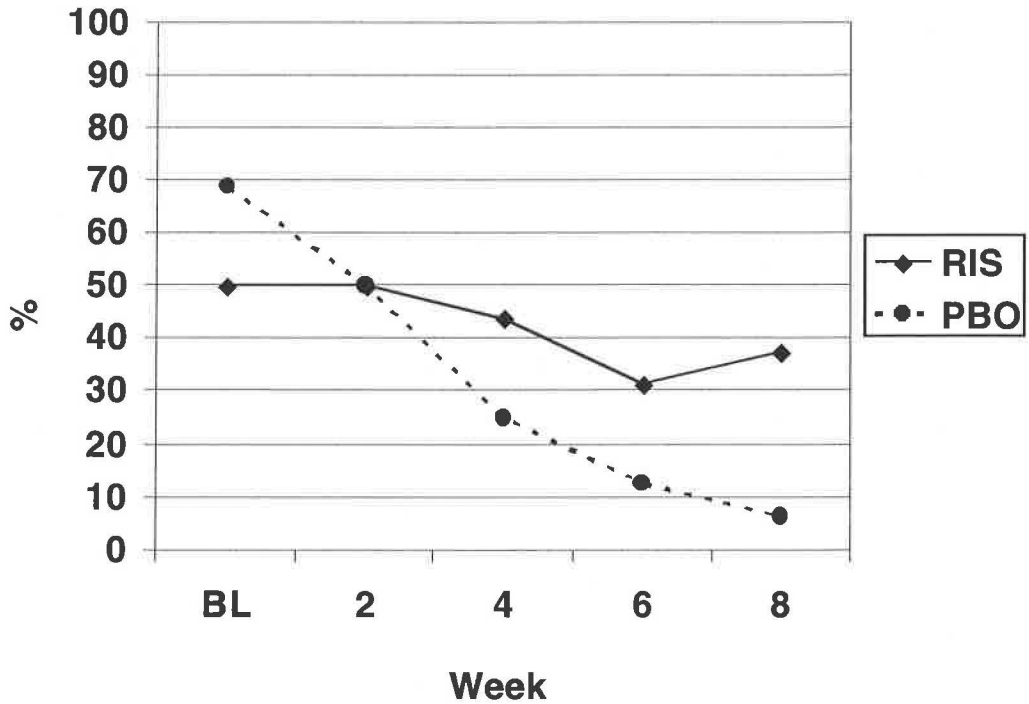

FIG. 3. Percent of subjects reported to have excessive appetite during the randomized discontinuation study ($n = 32$). BL, baseline; PBO, placebo; PNR, placebo nonresponder; RIS, risperidone.

TABLE 4. CDC STANDARD SCORES FOR BMI, WEIGHT, AND HEIGHT (ACUTE TRIAL)

Time		BMI			Weight			Height		
		PBO	RIS	PNR	PBO	RIS	PNR	PBO	RIS	PNR
Baseline	M	0.7	0.4	0.4	0.5	0.3	0.3	−0.1	−0.1	0.0
	SD	1.3	1.4	1.4	1.4	1.3	1.5	1.3	1.2	1.4
Week 2	M	0.7	0.7	0.6	0.5	0.5	0.5	−0.1	−0.1	0.0
	SD	1.3	1.3	1.3	1.4	1.4	1.5	1.4	1.2	1.3
Week 4	M	0.8	0.8	0.8	0.6	0.6	0.6	−0.1	0.0	−0.1
	SD	1.3	1.4	1.2	1.5	1.4	1.4	1.4	1.2	1.3
Week 6	M	0.8	0.9	0.8	0.6	0.7	0.5	−0.1	0.0	−0.1
	SD	1.2	1.3	1.2	1.5	1.3	1.5	1.4	1.1	1.3
Week 8	M	0.8	1.0	0.8	0.5	0.8	0.6	−0.2	0.1	0.0
	SD	1.2	1.3*	1.2	1.5	1.3*	1.4	1.4	1.1	1.4

Note. BMI (body mass index), weight, and height are all standardized scores based on Centers for Disease Control (CDC) norms and are corrected for age and gender. The national mean is 0 and the standard deviation is 1.00. PBO, placebo; RIS, risperidone; PNR, placebo nonresponder in open-label treatment; M, mean; SD, standard deviation; BMI, body mass index. *$p < 0.001$.

(3) showed excessive appetite in the discontinuation study. Figures 1 and 2 show essentially parallel curves for the acute RIS and PNR-RIS conditions. It appears that risperidone-induced drowsiness with antipsychotic treatment did, in fact, dissipate somewhere between weeks 6 and 8 (Fig. 1). Excessive appetite was clearly evident by around week 3 for the RIS and PNR-RIS groups, and it appeared to increase slightly in subsequent weeks (Fig. 2). Figure 3 shows a diminution in excessive appetite during the placebo substitution of the discontinuation phase, whereas appetite was rated fairly consistently for children who continued to receive risperidone.

Weight and height

Centers for Disease Control (CDC) standard scores for BMI, weight, and height appear in Table 4, where the acute trial and PNR risperidone findings are presented. Whereas the weight figures were essentially flat for the placebo condition, there was an increase of 0.6 standard deviation (SD) for BMI and 0.5 SD for weight for subjects receiving acute risperidone. Mixed effects linear modeling revealed significant drug-by-time interaction terms for these measures ($p < 0.001$), indicating significant weight gain within the risperidone group. During the open-label treatment phase, BMI

TABLE 5. CDC STANDARDIZED SCORES FOR BMI, WEIGHT, AND HEIGHT (OPEN-LABEL EXTENSION)

Time (sample size)	BMI*		Weight**		Height†	
	M	SD	M	SD	M	SD
Baseline (62)	1.04	1.13	0.72	1.24	−0.11	0.04
1 month (59)	1.17	1.12	0.85	1.24	−0.17	1.10
2 months (56)	1.19	1.03	0.88	1.22	−0.07	1.10
3 months (54)	1.20	1.03	0.91	1.26	−0.06	1.12
4 months (53)	1.17	1.11	0.89	1.28	−0.04	1.15

Note. BMI (body mass index), weight, and height are all standardized scores based on Centers for Disease Control (CDC) norms and are corrected for age and gender. The national mean is 0 and the standard deviation is 1.00. *$p < 0.009$; **$p < 0.0004$; †$p = 0.25$. BMI, body mass index; M, mean; SD, standard deviation.

"1 month" = 12 weeks of risperidone exposure; "2 months" = 16 weeks; "3 months" = 20 weeks; and "4 months" = 24 weeks of risperidone exposure.

increased 0.4 SD and weight increased by 0.3 SD for the PNR group.

Standardized height and weight measures, based on CDC norms, for the 4-month open-label extension appear in Table 5. Statistical comparisons with baseline were conducted by mixed effects linear model analyses as a function of site and time. Both BMI and weight analyses showed continued weight gain, whereas height showed no changes relative to the norms. The gain in BMI was 0.16 SD, whereas for weight it was 0.19 SD.

We attempted to identify variables that might predict differential weight gain, using multiple regression analyses, with baseline weight and BMI z-scores entered as covariates. The following variables, assessed at baseline, were entered as possible predictors of weight z and BMI scores: IQ (functional level), Tanner stage, age, gender, ABC subscale scores, subscale scores on the Child Symptom Inventory (Gadow et al. 1994), CY-BOCS score, dose, heart rate, and blood pressure. No variable or combination of variables predicted weight gain.

Vital signs

Heart rate, body temperature, and blood pressure did not change as a function of drug condition during: (1) The acute double-blind trial, (2) open-label treatment for placebo nonresponders, or (3) 4-month open-label extension. Heart rate ($p = 0.65$), body temperature ($p = 0.50$), and systolic ($p = 0.15$) and diastolic blood pressure ($p = 0.51$) showed no placebo-risperidone differences in the acute trial.

Simpson Angus Rating Scale (SARS) and AIMS

Ratings failed to change throughout the study. On the SARS, the possible range for the Total score extends from 0.00 to 40.00. Beginning and week 8 values for SARS Total Scores for the acute double-blind trial were as follows (placebo and risperidone, respectively): Baselines, 0.54 (±1.60) and 0.27 (±0.70); week 8, 0.69 (±2.48) and 0.52 (±1.33), $p = 0.43$. Mean SARS Total reached a maximum of 0.71 (±2.67) during the 4-month open-label extension. However, during the acute trial, benztropine mesylate (Cogentin) was prescribed to 1 subject (for motor restlessness), and at least 1 subject had dose-dependent cogwheel rigidity with risperidone. On the AIMS, the possible range on the Total score extends from 0.00 to 28.00. Beginning and week 8 values for AIMS Total scores for the acute trial were (placebo and risperidone, respectively): baseline, 0.23 (±1.02) and 0.36 (±0.99); week 8, 0.22 (±0.73) and 0.17 (±0.57), $p = 0.88$. Mean Total scores never exceeded 0.11 (±0.50) in the open-label extension. Thus, all of these mean Total scores were very low. The drug-by-time interaction was not significant during the acute or open-label phases for SARS Total score ($p > 0.25$) and AIMS Total score ($p = 0.63$).

Sleep log

In the acute double-blind trial, placebo-treated subjects experienced an increased sleep time from 9.42 hours/day to 9.70 hours/day (mean increase of about 17 minutes). The risperidone-treated subjects experienced an increase in sleep time from 9.66 hours/day to 10.33 hours/day (a mean increase of 40 minutes). As assessed by mixed effects linear modeling, average sleep times did not differ between groups during the acute trial. The PNR group experienced a mean increase of 29 minutes of sleep per day after risperidone therapy was instituted. There was essentially no change in duration of sleep (+1 minute) during the 4-month open-label extension.

DISCUSSION

Laboratory tests

The slight increase in neutrophil count, slight decrease in lymphocyte count, and decrease in SGOT with risperidone, although statistically significant, were of no clinical significance. There were a few isolated cases of abnormal lab values, and these occurred equally often at baseline and at week 8.

Side effects review

The most noticeable side effects were tiredness during the day (54% and 94%, *"at all"*; 12% and 37%, *"moderate to severe"*; placebo and risperidone, respectively). These rates exceeded those found by Aman et al. (2002), who assessed risperidone in 118 children and adolescents with borderline IQ or mental retardation and disruptive behavior disorders (DBDs) (including conduct disorder, oppositional disorder, or DBD not otherwise specified). Aman et al. (2002) found rates of somnolence of 10% and 51% (placebo and risperidone), respectively. Snyder et al. (2002) also compared placebo and risperidone in 110 young people with DBDs, using an identical design to that employed by Aman et al. (2002). The observed prevalence of somnolence was 14% and 42%, respectively. An important difference between the current study and the Aman et al. (2002)/Snyder et al. (2002) studies was that we elicited AEs by direct inquiry, whereas the studies of children with DBDs and borderline IQ/intellectual handicap relied on spontaneous caregiver reports. Hence, it is not surprising that higher prevalences were found, both for placebo and risperidone, in our study.

Excessive appetite was observed in 38% of placebo-treated and 82% of risperidone-treated children (10% and 33% at moderate or greater severity, respectively). This compares with 6% and 11% for Aman et al. (2002) and 4% and 15% for Snyder et al. (2002). Other prominent AEs reported in this paper and in the DBD/low IQ studies were as follows: Nausea or vomiting were reported for 29% and 41% (placebo and risperidone, respectively), whereas vomiting (only) was reported for 6% and 20% (Aman et al. 2002) and for 7% and 11% (Snyder et al. 2002). Excessive saliva occurred for 16% and 29% (placebo and risperidone, respectively) and for 2% and 11%, respectively, in Snyder et al. (2002; not reported by Aman et al. 2002). Dizziness/loss of balance was observed for 8% and 22%, respectively, in our study, whereas it was so infrequent that it was not reported by Aman et al. (2002) and Snyder et al. (2002). Interestingly two AEs were reported to *decline* with risperidone in this study: Difficulty falling asleep, 65% and 47% (placebo and risperidone, respectively); and anxiety, 48% and 32%, respectively. It appears that risperidone may have diminished some of the sleep problems often observed in children with autism.

It is possible that the higher rates of side effects may well be accounted for by elicitation (used here) versus spontaneous reporting (used elsewhere). However, it is also possible that young people with autism (many with intellectual handicaps) may be more sensitive to AEs from risperidone than children and adolescents with DBDs and borderline IQ or mental retardation.

Figure 1 shows the changes in sedation. One often hears clinicians assert that antipsychotic-induced sedation is time limited, but we are not aware of previously published data on the issue. Figure 1 clearly indicates that such sedation tends to decline markedly sometime between weeks 6 and 8, provided that the dose-adjustment phase is completed by week 4, as was done in our study. Taken together, Figures 1 and 2 illustrate that the PNR group (which was subsequently given open-label risperidone) "replicated" the AE findings noted for the acutely treated risperidone group. Analysis of AEs is often not very powerful (small sample sizes, low frequency events, or nonparametric statistical methods). This opportunity to replicate findings may enhance our ability to disentangle signal from noise when assessing AEs.

However, there were also some apparent differences in how parents reacted to AEs within the acute-risperidone group and in the PNR risperidone-treated subjects. Whereas the overall rate of reporting AEs was similar for the two groups, there were more mild AEs reported for the PNR group (32% versus 27%) and fewer moderate/severe AEs reported (2% versus 11%, averaged across all AE categories in Table 4). This raises an interesting methodological question, namely whether knowledge of treatment somehow influences the appraisal of AEs as severe or not. An alternative explanation could be that placebo responders tend to experience more severe AEs when given the active drug. Because the randomized risperi-

done group included those who would have been placebo responders, they could have increased the severity of AEs reported in that group relative to the PNR group, which had been purged of placebo responders. On the other hand, the rate of placebo responders was only 10%.

Figure 3 shows a systematic decline in appetite among the 16 subjects assigned to placebo discontinuation, whereas appetite was essentially steady among those assigned to risperidone continuance. The issue arises as to whether weight would eventually return to baseline if medication were permanently withheld. Lindsay et al. (2004) followed 14 subjects, in the DBD studies alluded to above, who discontinued medication either because of excessive weight gain or insufficient clinical response. Although these participants had made excessive weight gains with risperidone, when followed up 12–24 months later, their weights returned to the same (baseline) z-score relative to CDC norms.

Weight and height

In the acute 8-week trial, risperidone-treated children gained approximately 0.6 standardized BMI units, as compared with 0.1 for placebo-treated subjects. PNR risperidone-treated subjects gained approximately 0.4 SD BMI units. During open-label treatment, the maximum BMI increase was 0.16 SDs. There were no significant changes in standardized height scores, either in the acute trial or in the 4-month open-label extension. Standardized weight scores showed significant gains for risperidone-treated children, both in the double-blind trial and in the open-label extension (previously reported by Martin et al. 2004). Whereas the placebo group showed no weight gain, the risperidone group gained 0.5 SD units in weight over 8 weeks. Subjects continued to gain weight in the open-label extension, but the amount of maximum gain (to 4 months following the trial) was only 0.19 SD units. As pointed out in Martin et al. (2004), this suggests decelerating weight gain over time. In the DBD studies mentioned earlier, weight gain over 6 weeks amounted to 0.9 kg for the placebo group and 2.2 kg for the risperidone group (Aman et al. 2002). Snyder et al. (2002) reported a 0.2 kg gain for the placebo group and a 2.2 kg gain for the risperidone group.

Our attempt to predict weight gain using a large variety and number of biological and behavioral measures (beyond those already reported by Martin et al. 2004) failed. We included numerous variables as possible predictors: level of mental retardation (n = 1 variable), ABC subscales (n = 5), Child Symptom Inventory (n = 14), vital signs (3), gender (1), and Tanner stage (n = 1) (25 variables in total). This inability to predict is unfortunate, and it suggests that clinicians will need to be vigilant for excessive weight gain in *all* children treated with risperidone, not just a high-risk subgroup.

Vital signs

Whereas there have been isolated reports of tachycardia with risperidone and other atypical antipsychotics (Tandon 2002; Stigler et al. 2001), no changes were observed in heart rate. However, there was often a high rate of overactivity and/or limited compliance with these assessments, which may have obscured any changes. Other vital signs were unchanged as well.

Extrapyramidal symptoms (EPS)

Tandon (2002) considered risperidone and olanzapine as about equally likely to cause EPSs and more likely than the remaining atypical antipsychotics to cause EPSs. In this trial, there were no differences between the placebo and risperidone conditions on the Simpson-Angus Rating Scale or on the AIMS. In fact, the SARS total mean scores were all less than 1.0, and mean risperidone scores were lower than placebo scores. The mean AIMS scores were also less than 1.0 (maximum possible = 28). In the open-label extension, the AIMS mean total score never exceeded 0.11. Of course, risperidone treatment for 6 months at a mean dose of 2.08 mg/day is not a high exposure. Nevertheless, these observations are somewhat reassuring about short- and medium-term treatment of children with risperidone.

Serious adverse events (SAEs)

Two SAEs occurred in this trial, both involving seizures. One SAE involved a 13-year-old boy with hydrocephalus with severe mental retardation. Shortly after birth, ventriculoatrial shunts were surgically implanted to drain off the fluid. At the age of 10 years (3 years prior to the trial), this boy had one seizure. In the 7th week of the double-blind trial, he had a 10-minute seizure, which coincided with a shunt failure. The valve was replaced surgically, and the boy had no additional seizures. On breaking the blind, it was found that he was taking placebo.

The second SAE occurred in a 9-year-old boy who failed to respond to placebo in the double-blind trial. On entering the open-label risperidone condition, he had a seizure, lasting approximately 1 minute, after his second dose of risperidone (0.5 mg, nightly). No risperidone was given thereafter, and he had a second seizure lasting approximately 2½ minutes, 6 days later. A checkup 1 month later revealed no more recurrences. On reviewing this boy's medical record further, we found that he had taken 0.5 mg/day risperidone for 1–3 months, approximately 1 year before entering this trial. There were no seizures at that time.

Limitations

There were at least two limitations to this investigation. Firstly, although the sample size of 101 children is large for autism clinical trials, the sample was too small to capture infrequent or rare AEs (Vitiello et al. 2003). Secondly, the trial (although longer than most pediatric randomized clinical trials) was still only 6 months in duration. Therefore, although there is interest in the rates of tardive dyskinesia and, currently, much concern about the possibility of obesity and diabetes as possible sequelae of atypical antipsychotics (American Diabetes Association et al. 2004), the time of observation used in this study may be inadequate to assess these issues. We conducted a safety and tolerability follow-up some 20 months after entry to this study, and it is possible that the follow-up will help to address changes that may occur with longer-term treatment.

This 6-month study showed higher rates of AEs than have been reported in other multisite risperidone studies of children with borderline IQ or mental retardation and DBDs. It is likely that this was owing, in large part, to systematic elicitation in this study, but the possibility of greater sensitivity of children with autistic disorder to risperidone cannot be discounted. Most side effects were mild, and they were often time limited. Although somnolence was reported as moderate or severe for 33% of the risperidone group, it largely disappeared between 6 and 8 weeks of treatment. Significantly, two symptoms that appear to be quite common in autism (difficulty falling asleep and anxiety) appeared to decline with risperidone.

As in previous studies, increased appetite and weight were problems for some of our subjects, although the mean amount of weight gain was not large overall. The weight gains were not accompanied by analogous gains in height as witnessed by essentially flat temporal curves for height-standardized scores and by rising scores for BMI with risperidone treatment. Inability to predict weight gain suggests that all children treated with risperidone should be monitored for height and weight during treatment, and, when significant weight gains occur, the patient should be tested for triglycerides and fasting glucose. The best protection from undue weight gain is probably anticipatory guidance, perhaps accompanied by conservative dosing.

CONCLUSIONS

All in all, tolerability was quite good in this study, shown by the fact that only 3 children (6.1%) discontinued risperidone in the acute trial and 6 subjects (9.5%) discontinued in the open-label extension because of AEs. This should be viewed in the context of very substantial reductions in volatile behavior with risperidone (RUPP Autism Network 2002). No unexpected AEs occurred, and the two instances of severe AEs (the 2 boys who had seizures) did not appear to be linked to risperidone.

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