Tolerability, Safety, and Benefits of Risperidone in Children and Adolescents with Autism: 21-Month Follow-up After 8-Week Placebo-Controlled Trial

Michael Aman, PhD,¹ Mallikarjuna Rettiganti, PhD,² Haikady N. Nagaraja, PhD,³ Jill A. Hollway, PhD,¹
James McCracken, MD,⁴ Christopher J. McDougale, MD,⁵ Elaine Tierney, MD,⁶ Lawrence Scahill, MSN, PhD,⁷
L. Eugene Arnold, MEd, MD,¹ Jessica Hellings, MD,¹ David J. Posey, MD,⁵ Naomi B. Swiezy, PhD,⁵
Jaswinder Ghuman, MD,⁶ Marco Grados, MD,⁶ Bhavik Shah, MD,⁴ and Benedetto Vitiello, MD⁸

Abstract

Objective: Risperidone has demonstrated efficacy for acute (8 week) and intermediate length (6 month) management of severe irritability and aggression in children and adolescents with autism. Less is known about the long-term effects of risperidone exposure in this population. We examined the tolerability, safety, and therapeutic benefit of risperidone exposure over a 1–2 year follow-up period.

Methods: In a naturalistic study, 84 children and adolescents 5–17 years of age (from an original sample of 101) were assessed an average of 21.4 months after initial entry into a placebo-controlled 8 week trial of risperidone for children and adolescents with autism and severe irritability. They were assessed at baseline and at follow-up on safety and tolerability measures (blood, urinalysis, electrocardiogram [ECG], medical history, vital signs, neurological symptoms, other adverse events), developmental measures (adaptive behavior, intelligence quotient [IQ]), and standardized rating instruments. Treatment over the follow-up period, after completion of protocol participation, was uncontrolled. Statistical analyses assessed outcome over time with or without prolonged risperidone therapy.

Results: Two-thirds of the 84 subjects continued to receive risperidone (mean 2.47 mg/day, S.D. 1.29 mg). At follow-up, risperidone was associated with more enuresis, more excessive appetite, and more weight gain, but not more adverse neurological effects. No clinically significant events were noted on blood counts, chemistries, urinalysis, ECG, or interim medical history. Regardless of drug condition at follow-up, there was considerable improvement in maladaptive behavior compared with baseline, including core symptoms associated with autism. Height and weight gains were elevated with risperidone. Social skills on Vineland Adaptive Behavior Scale (VABS) improved with risperidone. Parent-rated Aberrant Behavior Checklist (ABC) Irritability subscale scores were reduced in those taking risperidone at follow-up. Several other measures of maladaptive behavior (some related to socialization) also showed improved functioning in association with risperidone on the ABC or on the Modified Real Life Rating Scale.

Conclusions: Increased appetite, weight gain, and enuresis are risks associated with long-term risperidone. Our data suggest that these risks were balanced by longer-term behavioral and social benefits for many children over 1.8 years of ongoing treatment.

¹Nisonger Center, Ohio State University, Columbus, Ohio.

²Biostatistics Program, Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock, Arkansas.

³Biostatistics, College of Public Health, Ohio State University, Columbus, Ohio.

⁴Department of Psychiatry and Behavioral Sciences, David Geffen School of Medicine UCLA - Semel Institute, University of California, Los Angeles, California.

⁵Department of Psychiatry, Indiana University School of Medicine, Indianapolis, Indiana.

⁶Kennedy Krieger Institute, Baltimore Maryland.

⁷Marcus Autism Center, Atlanta, Georgia.

⁸National Institute of Mental Health, Bethesda, Maryland.

Statistical Consultants: Haikady N. Nagaraja and Mallikarjuna Rettiganti.

Funding: This project was supported by funds from the National Institute of Mental Health (NIMH), National Institutes of Health (NIH), under contracts N01MH80011 (PI: Michael G. Aman), N01MH70010 (PI: James T. McCracken), N01MH70001 (PI: Christopher J. McDougale), and N01MH70009 (PI: Lawrence Scahill). This research was also supported by the NIH/National Center for Research Resources (NIH/NCRR) General Clinical Research Centers grants at Indiana University, M01 RR00750; Johns Hopkins University, M01RR00052; Ohio State University, M01 RR00034; and Yale University, M01 RR06022, Korczak Foundation (Dr. Scahill), and by grant MH01805 from NIMH (Dr. McCracken).

Introduction

THE USE OF PSYCHOTROPIC MEDICATIONS as one component of treatment for children with autism spectrum disorder (ASD) has grown rapidly, with surveys indicating that ~ 50% of individuals with ASD take psychotropic drugs or supplements intended to address impairing behaviors (Aman et al. 2005b; Coury et al. 2012). Whereas much use of psychotropic agents in ASD is off label and guided by limited empirical evidence, two agents have United States Food and Drug Administration (FDA) indications for serious behavior problems in children with autistic disorder. In 2006, the FDA approved risperidone for managing serious behavioral problems, and in 2009, similar approval was given for the use of aripiprazole. Although such agents have acceptable efficacy and safety for short- or intermediate-term exposures, less systematic evidence is available to evaluate safety and benefits over longer periods. This report presents data obtained from a 1–2 year follow-up of the sample from one of the pivotal trials that earned FDA approval for risperidone.

Greenhill et al. (2003b) and Vitiello et al. (2003) reviewed safety assessment issues in trials of psychotropic drugs in children and adolescents. Greenhill et al. (2003b) identified 196 reports, from two decades of psychopharmacological research in children, which addressed adverse events (AEs). They classified method of elicitation of AEs as primarily laboratory based or primarily from patient reports, and the latter were further classified as being based on general queries or on drug-specific checklists. Greenhill et al. found that 33% of studies used general queries with no formal method, whereas 23% used drug-specific checklists and 44% primarily used laboratory test methodology. They decried the lack of standardized AE measures and commented on the limited space (usually less than one page) given to AEs in most published reports. Vitiello et al. (2003) noted that, compared with adults, pediatric patients pose additional concerns with psychotropic exposure, including effects on growth, timing of puberty, brain development, and cognitive effects. There is evidence suggesting that children are more prone than adults to weight gain with atypical antipsychotics (Ratzoni et al. 2002; Correll et al. 2009; Hellings et al. 2010). Vitiello et al. (2003) recommended systematic prospective naturalistic studies of young people who are treated long term. Similarly, recommendations from a National Institute of Mental Health workshop on long-term safety of psychotropic use in children included the need to monitor benefits and harm from psychotropic drugs (Greenhill et al. 2003a).

Despite these reports, there continue to be relatively few long-term safety studies of second generation antipsychotics in children, with a few exceptions (Marcus et al. 2011b; Kent et al. 2013). Safety issues vary according to the class and even the specific agent within a medication class (McCracken 2005). One major concern with risperidone and almost all newer antipsychotics in children is excessive weight gain (Correll et al. 2009). A host of retrospective, prospective, and comparator studies documented excessive weight gain occurring in the majority of children and adolescents receiving a variety of atypical antipsychotics, with few exceptions (Maayan and Correll 2011). This raises significant health questions concerning long-term use, given potential obesity-related health outcomes such as cardiovascular disease, diabetes, and other conditions.

Similarly, earlier reports documenting high rates of withdrawal dyskinesias in 33.9% of children with autism who were prospectively monitored during haloperidol discontinuance raised the prospect that children, especially those with ASD, may be more at risk for antipsychotic-related abnormal motor sequelae such as tardive dyskinesias (Campbell et al. 1997). Other concerns lacking

substantial long-term follow-up data include possible effects on other organ systems, cardiac function, behavioral and cognitive AE, and drug dosing requirements.

Data on the *durability of therapeutic effects* of common antipsychotic medications in children and adolescents are also scarce. Issues such as maturation, growth in height and weight, and the possibility of the development of tolerance are all relevant threats to long-term efficacy. For example, in one study of 80 children with a pervasive developmental disorder (PDD), autistic disorder, Asperger's disorder, or PDD not otherwise specified, 34% of those treated with risperidone were nonresponders within 6 months and 47% were nonresponders by 1 year (Lemmon et al. 2011). Similarly, a 52 week follow-up of aripiprazole for irritability in autism reported that only 60% completed the naturalistic study and many required the addition of concomitant medications (Marcus et al. 2011a).

The Research Units on Pediatric Psychopharmacology Autism Network (RUPP) (2002) reported on a sample of 101 children with autistic disorder who were enrolled in a placebo-controlled trial of risperidone. We conducted a comprehensive assessment at study baseline, which served as the baseline for this follow-up study. Subjects who showed a positive response in the acute trial were offered up to 4 more months of continued risperidone, for a total exposure of 6 months; a subset of 32 also participated in an additional 2 month randomized placebo-controlled discontinuation phase (Research Units on Pediatric Psychopharmacology Autism Network 2005). Subsequently, all subjects were referred to usual care. In this article, we discuss the longer-term outcome for 83% of the enrolled children, who were re-contacted and reassessed at 7–38 months from their original assessment at study entry (mean duration, 21.4 months).

This follow-up study had three primary aims. Our first aim was to evaluate the safety and tolerability associated with risperidone treatment over the 21 month follow-up. To do so, we assessed findings from laboratory tests, physical examinations, electrocardiograms (ECGs), a standardized list of 28 side effects, and clinician-elicited AEs. We predicted greater weight gain and higher body mass index (BMI) in subjects with greater exposure to risperidone over the follow-up period. Second, regardless of patient history, we examined other behavioral, adaptive skill, and intelligence quotient (IQ) outcomes over the 21-month interval to describe the course of illness of these children.

Third, we were interested in the subsequent treatment histories for these participants, including how many remained on risperidone, and compared subjects with greater risperidone exposure with those with less exposure during the follow-up period. We predicted that children with greater exposure to risperidone, especially those receiving risperidone at time of the follow-up, would have lower rates of behavior problems, suggesting continued benefits. Our primary hypothesis regarding risperidone was that greater exposure and current treatment with the drug would be associated with improved scores on the Aberrant Behavior Checklist (ABC) (Aman et al. 1985a,b) Irritability subscale and on the Clinical Global Impressions–Severity (CGI–S) scale (National Institute of Mental Health 1985). The ABC Irritability subscale and CGI–Improvement (CGI–I) score were primary outcome measures of the original controlled trial.

Methods

This study was approved by the institutional review boards of the collaborating universities, and the parents or guardians of all participants signed consent forms.

Design

Participants in the original risperidone study (Research Units on Pediatric Psychopharmacology Autism Network 2002) were invited to participate by mail and were subsequently phoned by study coordinators. Despite an effort to perform reassessments at a uniform 18 month follow-up interval from original study entry, follow-up intervals varied from 7 to 38 months (mean = 21.40 ± 4.32 months, median = 20 months, mode = 19 months) primarily because of difficulty in contacting subjects and delays in scheduling. However, the 10th percentile was 18 months and the 90th percentile was 27 months, indicating reasonable consistency in lag of follow-up for most participants.

Subjects

At initial enrollment, all children were required to meet full *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., Text Revision (DSM-IV-TR) criteria for autistic disorder according to an evaluation by a licensed clinician (American Psychiatric Association 2000) corroborated by the Autism Diagnostic Interview-Revised (Lord et al. 1994) with a parent or caregiver, and associated with severe parent-rated irritability (≥ 18 on the ABC Irritability subscale). Eligible participants then entered an 8 week double-blind, parallel group, placebo-controlled trial of risperidone (see Research Units on Pediatric Psychopharmacology Autism Network 2002, 2005 for more details). Positive responders to risperidone (those with ABC Irritability subscale reductions $>25\%$ from baseline and CGI-I ratings of much or very much improved) were eligible to continue risperidone for an additional 4 months. Subjects randomized to placebo and not improved were offered open-label risperidone following the same dosing schedule and response criteria as those used in the double-blind trial. At the end of the 8 week open label trial, positive responders were also eligible to continue risperidone for 4 additional months. A total of 63 subjects entered the 4 month open-label phase, and 52 completed 6 months of risperidone treatment under the protocol; a subgroup of 32 went on to participate in a randomized placebo-controlled drug discontinuation phase of up to 8 weeks (Research Units on Pediatric Psychopharmacology Autism Network 2005).

Procedure

All 101 families who participated in the original RUPP risperidone protocol were asked to return for ~ 5 –6 hours of assessment. Study personnel gathered information using the same procedures that were performed in the original study (Research Units on Pediatric Psychopharmacology Autism Network 2002) (i.e., blinded clinician [with medication status unknown], primary clinician, project coordinator).

Outcome measures

Direct subject assessments. These included 1) clinical nonfasting laboratory tests for complete blood count (CBC) with differential, blood chemistries, liver functions, triglycerides, glucose, and HgbA1C; 2) urinalysis; 3) ECG; 4) vital signs; and 5) height and weight. Other assessments included 6) a Side Effects Review Form [which included the 28 most common AEs associated with risperidone] (Aman et al. 2005a); 7) The Simpson-Angus Rating Scale (Simpson and Angus 1970) for extrapyramidal symptoms; 8) the Abnormal Involuntary Movement Scale (AIMS) (Guy 1976); 9) a physical examination; and 10) a medical history assessing health since departure from the acute trial. To enable the subjects to consume some food before assessment, we developed breakfast and

lunch “Nutrition lists” that resulted in ~ 70 g of carbohydrate and a minimum amount of fat (7–10 g). Also included was an IQ test (employing the same instrument used at enrollment): The Wechsler Intelligence Scale for Children (Wechsler 1992), Leiter International Performance Scale—Revised (Roid et al. 1997), or Mullen Scales of Early Learning (Mullen 1995).

Parent interviews. These included the VABS (Sparrow et al. 1984) and the Children’s Yale-Brown Obsessive Compulsive Scale Modified for PDD (CY-BOCS-PDD) (Scahill et al. 1997, 2006). The VABS was employed to assess the child’s usual performance on everyday activities in the realms of Social Skills, Communication Skills, and Activities of Daily Living. The CY-BOCS-PDD rates the severity on 0–4 Likert scales for 1) time spent engaged in repetitive behavior, 2) interference with ongoing events, 3) distress experienced if compulsions were prevented, 4) subject’s level of resistance to repetitive behaviors, and 5) subject’s control over repetitive behaviors. Following all other parent interview measures, inspection of parent rating forms, and observation of the child, clinicians rated participants on the CGI-S scale (Arnold et al. 2000, National Institute of Mental Health 1985). The scores on the CGI-S range from 1 (Normal) through 4 (Moderately ill) to 7 (Among the most ill patients); the RUPP network adopted the convention that presence of pure autism (no additional pathology) defaulted to a score of 3, significant behavioral or emotional problems beyond that resulted in scores ranging from 4 through 7. To be enrolled in the initial study, subjects had to have a score of at least 4.

Parent ratings. These included the ABC (Aman et al. 1985a) and the Modified Real Life Rating Scale for Autism (M-RLRS) (Freeman et al. 1986, McDougle et al. 2005). The ABC is a reliable and valid 58 item scale empirically developed to assess treatment effects in individuals with developmental disabilities. Its subscales are designated as Irritability (15 items), Social Withdrawal (16 items), Stereotypic Behavior (7 items), Hyperactivity/Noncompliance (16 items), and Repetitive Speech (4 items) (Aman 1985a,b, 1987). The M-RLRS was a modification of an observational system developed by Freeman and colleagues (1986). We altered the 47 items of the observational tool into narrative statements to be rated by the children’s parents (see McDougle et al. 2005). Items were rated on a 4 point Likert scale ranging from 0 (“never occurs”) through 3 (occurs “almost always”). The subscale names and typical items are: I. Sensory Motor Behaviors (7 items; e.g., “hand flapping,” “rocking”); II. Social Relatedness (7 items; e.g., “appropriate response to interaction attempts”); III. Affectual Responses (5 items; e.g., “crying,” “temper outbursts”); IV. Sensory responses (16 items; e.g., “rubbing surfaces,” “sniffing self or objects”); and V. Language (10 items; e.g., “initiation of communication”). Higher mean scores denote worse symptoms of autism.

Concurrent and intercurrent medications. Parents were asked about any new or additional medications, especially psychotropic medicines used since the child left the acute trial. The process was aided by a list (containing both generic and brand names) of 50 common psychotropic drugs, together with color photocopies of the drugs taken from the *Physicians’ Desk Reference* (2007). All instances of starting and stopping medications were collected.

Standardization and reliability

All measures were administered in a standard fashion by trained raters to ensure consistency across sites and examiners. Standard

procedures for assessing heart rate, blood pressure, weight, and CGI-S were specified in our operations manual. The five participating sites trained all raters to acceptable standards for interrater reliability before the follow-up for clinician scales (CGI-S, CY-BOCS-PDD).

Data analyses

Computation of risperidone exposure. To quantify the amount of risperidone taken from the end of the acute clinical trial to follow-up, we tallied all reported periods of risperidone exposure in days as well as exposure to other antipsychotics (haloperidol [$n=1$], quetiapine [$n=4$], and ziprasidone [$n=2$]). Collectively, exposure (expressed in days) to other antipsychotics accounted for only 3.79% of all antipsychotic exposure. Exposure in days was then divided by the time from end of the acute trial (i.e., week 8), to the day of the follow-up visit to give the “percentage of antipsychotic (mainly risperidone) exposure” variable.

Follow-up subjects versus participants lost to follow-up. To determine if there were differences between subjects who returned for the follow-up study and those who did not, we conducted t tests for independent groups with correction for unequal variances. Chi square tests were used to assess differences on categorical variables. As an additional comparison, we examined responder status for the 84 participants in the follow-up and for the 17 subjects who did not participate. Of the 84 subjects in the follow-up, 61 were risperidone responders, 12 were nonresponders, and 11 were “indeterminate,” meaning that their responder status was not resolved in the acute study (e.g., subjects who were assigned to and did not respond to placebo but did not continue within protocol to determine response to risperidone). Of 17 subjects who did not volunteer for the follow-up, 8 were responders, 1 was a nonresponder, and 8 were indeterminate. Significantly more of subjects

not followed up were found to be indeterminate during the acute study (47% vs. 13%, $p=0.003$, by Fisher Exact Test). However, of the 82 participants whose risperidone responder status was known, there was no significant difference between the proportion of positive responders among those who were followed up and those who were not (84% vs. 89%, $p=1.0$, by Fisher Exact Test).

Changes caused by time (maturation) and medication condition. To examine AEs at follow-up visits, we employed Fisher’s Exact Test to compare participants who were taking risperidone with those who were not in the 4 weeks prior to the follow-up. The ordinal-level AE score at baseline was subtracted from the follow-up AE score, and all subjects showing no change versus those showing an increase in side effects were compared for the risperidone and non-risperidone groups. To assess interval-level changes caused by history and maturation (the passage of time alone), we conducted paired t tests. Examination of the data from the follow-up indicated that all subjects except one could be classified as either taking risperidone or not taking risperidone for the month prior to follow-up (one subject took risperidone for the last 15 days of the month and was classified as taking risperidone).

In order to look at the effects of medication over time, for continuous responses, we used analysis of covariance (ANCOVA) with the final value as the response, its baseline value as a covariate, and “days of risperidone exposure” and the indicator of recent use (i.e., 1 month before follow-up) as independent variables in two separate models. We used Spearman’s rank correlation to determine whether lag of the follow-up was associated with follow-up score. If lag of follow-up was found to be significantly associated with follow-up score, we then used the lag as an additional covariate in the analysis described.

As the total risperidone exposure and its recent use were highly associated (see Fig. 1 where the frequency distribution of percent

FIG. 1. Frequency distribution of percent of time of exposure to risperidone during the period from Week 8 in the acute risperidone trial to follow-up (21.4 months later, on average). Subgroup variable is the indicator of use of risperidone in the last 4 weeks before follow-up (red=recent use; blue=recent nonuse). Percent value indicated below each bar is the midpoint of values in that bin except for 0 and 100, where bars represent only those numbers.

exposure as separated by the recent use status is displayed), they were not used *simultaneously* as predictors in our ANCOVA models. Significant findings as a function of *risperidone exposure* can be interpreted as reflecting incremental effects of risperidone over the 1.8 years of the follow-up. Significant findings as a function of *recent use* can be conceptualized as reflecting the more immediate effect of the medicine given before the follow-up assessments. In earlier exploratory analyses, we also included response status (acute risperidone responder/nonresponder) in the analyses as an independent variable. However, responder status contributed nothing to the outcomes and, therefore, is not discussed further.

Of the 81 subjects for whom the CGI-S change score was available, 38% had no change and 47% had a decrease of 1; overall 58% improved and 42% did not. Therefore, we converted CGI-S score change to a binary variable based on whether or not there was improvement on the follow-up score compared with the baseline score (i.e., CGI-S decrease at follow-up). It was analyzed by logistic regression analysis as a function of risperidone exposure (i.e., days of risperidone exposure) or recent use (i.e., last 4 weeks), and the baseline value. The *p* values for risperidone exposure and for recent use are reported. For *safety* issues, a Type II error is more problematic than a Type I error; therefore, we set α at $p \leq 0.10$, two tailed, in the evaluation of AEs using an ordinal measure derived from the Side Effects Review Form. When we assessed potential AEs as continuous variables (e.g., weight gain), we set α at $p \leq 0.05$, without correction for multiplicity, given the exploratory nature of the analysis. For CGI-S and ABC Irritability subscales (primary outcome variables), we set α at $p \leq 0.025$, two tailed, to account for multiple testing. For the remaining analyses, we set $p \leq 0.01$, two tailed. *P* values between 0.02 and 0.05 are treated as exploratory. The *p* value associated with the CGI-S regression model is based on the Wald test. SAS JMP Version 8 and SAS 9.1.3 (SAS Institute, Cary NC) were used for statistical analyses.

Results

Subjects

Eighty-four of the originally studied 101 participants (83.2%) were successfully assessed for at least some measures. Sixty-seven participants (79.8%) were boys and 17 (20.2%) were girls. At enrollment (acute trial baseline), these subjects had a mean ABC Irritability subscale score of 26.01 (SD, 7.45), compared with 26.20 (SD, 7.9) for the entire sample of 101 subjects. Mean age at baseline was 8.82 years (SD=2.69) and at follow-up it was 10.61 years (SD, 2.74). Other characteristics of the subjects at baseline and at follow-up are presented in Table 1.

Of the subjects who did not participate in the follow-up assessment, 15 (88.2%) were boys and 2 (11.8%) were girls, which was not significantly different from the follow-up group. We also compared the participants successfully followed ($n=84$) with those not followed ($n=17$) on baseline CGI-S, ABC Irritability subscale, chronological age, and IQ. As assessed by *t* tests, with correction for unequal variances, all comparisons were nonsignificant, as follows: 1) CGI-S, t (22.77)=0.71, $p=0.49$; 2) ABC Irritability, t (21.75)=0.75, $p=0.46$; 3) age, t (22.30)=0.34, $p=0.73$; and 4) IQ, t (19.11)=0.44, $p=0.67$. Therefore, the subjects who participated in the follow-up assessment did not differ significantly from those who did not participate, on these severity and demographic variables.

There were two pathways to being regarded as risperidone responders in the previous clinical trials: 1) Original assignment to risperidone and having good clinical response; or 2) original as-

TABLE 1. SAMPLE CHARACTERISTICS AT BASELINE AND FOLLOW-UP

Characteristic	Baseline		Follow-up	
	n	%	n	%
CGI Severity [†]				
2. Borderline mentally ill			1	1.22
3. Mildly ill			7	8.54
4. Moderately ill	14	16.9	39	47.56
5. Markedly ill	45	54.2	23	28.05
6. Severely ill	23	27.7	8	9.76
7. Among most extremely ill	1	1.2	4	4.88
Ethnicity				
White, not of Hispanic Origin	57	67.9	—	—
Black, not of Hispanic Origin	10	11.9	—	—
Asian, Pacific Islander	6	7.1	—	—
Hispanic	5	6.0	—	—
Other	6	7.1	—	—
Functional level*				
Normal IQ	6	9.4	10	21.3
Mild intellectual disability (ID)	18	28.1	2	4.3
Moderate ID	13	20.3	15	31.9
Severe/Profound ID	27	42.2	20	42.5
Class assignment				
Regular class	6	7.2	6	7.2
Special ed., regular school	61	73.5	54	65.1
ID/DD	14	16.9	13	15.7
Other	2	2.4	10	14.4
Residential setting				
Parental home	76	90.5	74	89.2
Relative's home	4	4.8	5	6.0
Foster home	2	2.4	2	2.4
Group home	0	0.0	1	1.2
Other	2	2.4	1	1.2
Primary caregiver education				
High school diploma or less	18	21.4	—	—
Technical/trade school	6	7.1	—	—
Some college	22	26.2	—	—
University diploma	26	31.0	—	—
Advanced degree	12	14.3	—	—

[†]Paired *t* test statistic for CGI-Severity score is -6.78 , $df=82$, $p<0.0001$.

*Data available only on 64 (baseline) and 47 (follow-up) subjects.

CGI, Clinical Global Impressions; IQ, intelligence quotient; DD, developmental delay.

signment to placebo with nonresponse to placebo, and subsequent positive response to risperidone in 8 week open-label treatment. There were three pathways to being determined as risperidone nonresponders (or indeterminate responders) in the earlier trials: 3) Being assigned to placebo and responding to it; 4) being assigned to double-blind risperidone and not responding; and 5) being assigned to placebo, not responding to it, and subsequently not responding to 8 week open-label risperidone. The resulting treatment outcomes for our 84 participants were as follows: 1) Double-blind risperidone responder, $n=33$ (39.3%); 2) placebo nonresponders, who responded to open-label risperidone, $n=36$ (42.9%); 3) double-blind placebo responders, $n=5$ (6.0%); 4) double-blind risperidone nonresponders, $n=8$ (9.5%); and 5) placebo nonresponders, subsequently risperidone nonresponders, $n=2$ (2.4%).

Table 1 also shows changes that occurred on the CGI-S over the 21 month interval. Overall, the sample showed reductions in global severity ($p<0.0001$), although ratings for three participants

TABLE 2. PSYCHOTROPIC MEDICATIONS TAKEN ON AT LEAST 24 OF LAST 30 DAYS OF THE FOLLOW-UP

Drug name	Frequency	% of Sample
No drug	15	17.86
Antipsychotics		
Risperidone	53	64.00
Quetiapine	2 ^a	2.38
Haloperidol	1	1.19
Mood stabilizers		
Divalproex/valproate	4	4.76
Carbamazepine	2	2.38
Oxcarbazepine	1	1.19
Gabapentin	2	2.38
Alpha 2 adrenergic agonists		
Clonidine	2	2.38
Guanfacine	4	4.76
Psychostimulants		
Methylphenidate	3 ^b	3.57
Dextroamphetamine	1	1.19
Antidepressants		
Citalopram	2	2.38
Paroxetine	2	2.38
Sertraline	3	3.57
Imipramine	1	1.19
Other		
Buspirone	1	1.19
Diphenhydramine	1	1.19
Melatonin	3	3.57

Frequencies and percentages add to greater than totality because some subjects were taking multiple drugs. A total of 27 participants were taking no antipsychotics during the month before the follow-up.

^aOne participant received olanzapine for part of the interval.

^bTwo participants received long-acting forms of methylphenidate.

worsened to “among the most extremely ill” (7) designation. Substantial improvement in CGI-S scores was observed, with eight participants reported as having “borderline” (2) or “mild” (3) illness at follow-up (i.e., less severe) (Table 1).

Medication status at follow-up

On the day of the follow-up, 56 participants were taking an antipsychotic (risperidone [$n=55$] or quetiapine [$n=1$]). The mean dose of risperidone was 2.47 mg (SD, 1.29). Risperidone accounted for 96.21% of all antipsychotic use over the follow-up interval. Figure 1 shows the highly positive association between the percent of antipsychotic exposure during follow-up and recent use of risperidone (point biserial correlation = 0.82).

Psychotropic medications recorded for at least 24 of the last 30 days before the follow-up are listed in Table 2. A total of 53 participants (63.1%) were taking risperidone in the month leading up to the follow-up; mood stabilizers ($n=9$), antidepressants ($n=8$), and α agonists ($n=6$) were also common at follow-up. Stimulants ($n=4$) and melatonin ($n=3$) were fairly uncommon.

Adverse events

(P was set at 0.10 significance for nonparametric analyses). AEs that were reported present for $\geq 9\%$ of the risperidone or non-risperidone groups at time of the follow-up are summarized in Table 3. In general, the rates of potential AE were quite similar between the groups. Forty-two percent of risperidone-treated

TABLE 3. SIDE EFFECTS THAT EXCEEDED BASELINE SEVERITIES FOR RISPERIDONE ($N=57$) AND NON-RISPERIDONE ($N=27$) GROUPS (RATES $\geq 9\%$ OF RISPERIDONE OR NON-RISPERIDONE GROUPS)

Side effect	Risperidone		No risperidone		p value (Fisher exact test)
	n	%	n	%	
Sleep Problems	6	10.5	2	8.0	1.00
Tired during the day	13	23.2	7	28.0	0.78
Difficulty awakening	7	12.3	6	24.0	0.20
Constipation	5	8.9	5	20.0	0.28
Diarrhea, loose stools	9	15.8	1	4.0	0.27
Dyspepsia	5	8.9	2	8.0	1.00
Nausea or vomiting	6	10.6	2	8.0	1.00
Anxiety	7	12.3	7	28.0	0.13
Excessive saliva, drooling	10	17.5	2	8.0	0.33
Excessive appetite	24	42.1	5	20.0	0.08
Dry mouth, increased beverage intake	6	10.6	4	16.0	0.48
Urinary problems (enuresis)	11	19.6	0	0.0	0.01
Rhinitis (runny nose)	7	12.5	2	8.0	0.71
Skin rash	3	5.4	3	12.0	0.37
Peculiar eating habits	4	7.1	3	12.0	0.67

Side effects are reported only if they exceeded severity reported at baseline of the acute risperidone study (Research Units on Pediatric Psychopharmacology Autism Network 2002). The following side effects, experienced by $<8\%$ of either group, had the following frequencies (risperidone vs. not risperidone, respectively): Shakiness in limbs (3, 0); twisting or repetitive tongue movements (2, 0); muscles stiff or stuck (0, 1); eyes stuck in one position (0, 0); headaches (3, 2); dizziness/loss of balance (4, 0); blurred vision (0, 1); trouble emptying bladder (1, 0); gynecomastia (3, 1); galactorrhea (0, 0); menstrual problems (0, 1); coughing (4, 1); tachycardia (2, 1); seizures (2, 0); skin rash (3, 3); and tinnitus (0, 0).

participants had excessive appetite, as compared with 22% of those not taking risperidone ($p=0.08$). The risperidone group also had a higher incidence of “urinary problems” (enuresis) ($p=0.02$). Nonsignificantly fewer risperidone subjects (9%) reported constipation than occurred among the non-risperidone group (20%). Two participants in the risperidone group (3.7%) reported seizures, whereas no seizures were reported for the non-risperidone group (nonsignificant). These cases were new seizures, not previously reported, for the risperidone group. Among the spontaneously reported AEs, the following were reported: Weight gain for three participants (5.5%) taking risperidone; metatarsal necrosis (one participant taking risperidone); mouth trembling (one not taking risperidone); and throat clearing (one not taking risperidone). Uncommonly reported side effects appear in the note to Table 3.

Laboratory values. We conducted laboratory tests on 72 of the 84 participants (86% of the current sample); 12 subjects either refused blood draws or were unable to undergo venipuncture.

CBC. No hematological abnormalities were observed.

Lipid panel. We had nonfasting triglyceride levels for 61 of the 84 subjects (73%). Six subjects taking risperidone ($n=42$) and four not taking risperidone ($n=19$) had abnormal values. Three taking risperidone and three not taking risperidone had elevated cholesterol. Three and two, respectively, had elevated low-density

lipoprotein (LDL); two and two, respectively, had low high-density lipoprotein (HDL). None of these differences (or their collective totals) indicated statistically increased risk for subjects currently taking risperidone ($p > 0.10$, one tailed).

Glucose and HgbA1c. We collected 68 nonfasting glucose and 64 HgbA1c samples. Eight glucose levels from the risperidone group ($n=46$) and one from the non-risperidone group ($n=22$) were high (potentially clinically significant; $p=0.26$, Fisher's exact test). All of the HgbA1c results were normal.

Urinalysis. Urinalyses were available for 64 of the 84 participants (76%). Two of the samples from the risperidone group ($n=43$) were cloudy, as were two from the non-risperidone group ($n=19$). One from each group had abnormal ketones and presence of protein. Two from the risperidone group and one from the non-risperidone group had occult blood.

ECG data. Out of 84 follow-up subjects, 66 (79%) had ECGs. The ECG of one subject not taking risperidone was reported with findings of an abnormal superior vector, the ECG of another taking risperidone had left axis deviation, and another who was not taking risperidone had incomplete right bundle branch block. QTc was calculated by machine, followed by cardiologist review. Borderline prolonged QTc was reported in two subjects (one taking risperidone, one not), and borderline prolonged QT or TU fusion was reported in another three subjects taking risperidone. Suboptimal ECG tracings were reported in five subjects, four of whom were taking risperidone.

Medical history. Medical histories were recorded for 55 participants taking risperidone and 23 not taking risperidone in the month before follow-up. Fifteen subjects taking risperidone (27.3%) and 12 not taking risperidone (52.2%) had medical events recorded as having occurred between our baseline and follow-up. The events appeared minor and unrelated to medication exposure (20%). Five (9%) of the subjects taking risperidone reported constipation, versus five of the subjects (19%) not taking risperidone. As assessed by Fisher's exact test, this difference was nonsignificant at $p=0.28$, two tailed test. No other events were reported by >5% of either group, nor were any comparisons significantly different in frequency (stomachache, esophageal reflux, hemorrhoids, diarrhea, and heartburn).

Change in clinical status with time alone (irrespective of drug)

Table 4 shows changes that occurred for the complete group of subjects over the 22 months in 1) vital signs, 2) abnormal movements, 3) growth indices, 4) IQ, 5) VABS standard scores, 6) CY-BOCS, 7) ABC subscales, and 8) M-RLRS. No changes were found in vital signs (except for a minor reduction in temperature), IQ, and VABS. Although age and sex standard scores were used to correct for developmental changes, weight ($p < 0.0001$) and BMI ($p < 0.0001$) increased significantly relative to norms over the 2 years. The increase for weight and BMI were 0.43 and 0.39 standard score units above the population mean, respectively. At follow-up, both weight and BMI were almost a full standard unit above the norm.

On the CY-BOCS, scores declined from 15.51 to 12.11, a significant difference of 3.30 (effect size, Cohen's $d=0.79$) (Cohen 1992). All ABC subscale scores showed major declines, with all

$ps < 0.001$. The effect sizes for the subscales were as follows: 1) I. Irritability, $d=1.08$; 2) II. Social Withdrawal, $d=0.85$; 3) III. Stereotypic Behavior, $d=0.82$; 4) Hyperactivity/Noncompliance, $d=1.07$; and 5) Inappropriate Speech, $d=0.41$.

All five M-RLRS subscales showed declines with passage of time (all $ps < 0.0001$): 1) Sensory Motor ($d=0.52$); 2) Social Relationships ($d=1.20$); 3) Affectual Responses ($d=0.98$); (d) Sensory Responses ($d=1.11$); and (e) Language ($d=0.78$).

Change in clinical status as a function of risperidone exposure

Findings for the separate ANCOVAs and the binary logistic regressions are reported in Table 5. One can view the p values associated with "risperidone exposure" as reflecting the incremental effect of medication, whereas the p values associated with "last 4 weeks" reflects the more immediate effect of risperidone at follow-up. The sign (+/−) affixed to total exposure indicates the direction of the relationship. A (+) affixed to total exposure indicates that more exposure to risperidone was associated with higher outcome scores. Likewise, a (−) affixed to "last 4 weeks" signifies higher exposure being associated with lower outcome scores.

Safety, tolerability, and developmental indices. ($P < 0.05$ was used for continuous safety measures).

The physical variables, Simpson–Angus Scale Total and AIMS were not associated with total risperidone exposure or with the marker of recent use. An increase in weight z score was associated with risperidone being given in the last month before follow-up ($p=0.03$), and height z scores were associated with *both* risperidone total exposure and medication in the last month. Surprisingly, BMI scores were *not* associated with percent exposure or medication in the last month. To get a clinical feel for the weight changes, we classified subjects having had less than or greater than 50% of days of risperidone exposure over the follow-up interval. Those with <50% exposure had a mean exposure of 11.9% of days to risperidone; those with >50% exposure had a mean exposure of 95.8%. We then computed how many subjects "crossed over" from ≤85th percentile to ≥90th percentile in each group. For those with <50% risperidone exposure, 3 of 16 subjects (18.8%) with baseline weights ≤85th percentile crossed over. For those with >50% risperidone exposure, 5 of 28 subjects (17.9%) with baseline weights in ≤85th percentile crossed over (n.s., $p=0.91$, by contingency analysis). We repeated this analysis with BMI, and exactly 25% of each group (risperidone and non-risperidone) crossed over the 90th percentile.

Developmental indices. Use of risperidone was not associated with changes in IQ. Significant gains on the VABS Social Skills Standard score were associated with presence of risperidone in the preceding 4 weeks *and* marginally with greater percent exposure to risperidone ($p=0.05$; exploratory).

Standardized behavior ratings. Except for CGI-S and ABC Irritability scores, p was set at ≤0.01, two tailed, for statistical significance on all rating scale variables. CGI-S score improvements (co-primary hypothesis) were not associated with risperidone over the follow-up interval (p for exposure=0.68; p for recent use=0.26). Conversely, on the ABC Irritability subscale, improvements were associated with recent use of risperidone ($p=0.01$). Of the remaining ABC subscales, parent ratings showed significant improvements on Social Withdrawal and Hyperactivity/

TABLE 4. COMPARISON OF PHYSICAL AND BEHAVIORAL ASSESSMENTS AT BASELINE AND FOLLOW-UP REGARDLESS OF TREATMENT

Variables	Baseline		Follow-up		Paired t	p value	Effect size
	Mean	SD	Mean	SD			
Vital Signs							
Systolic BP	106.21	13.46	107.66	13.33	0.81 ^a	0.4191	0.1066
Diastolic BP	68.21	10.32	67.6	8.19	-0.43 ^a	0.6702	-0.0562
Heart rate (bpm)	95.84	17.42	95.62	13.97	-0.10 ^b	0.9184	-0.0130
Temperature	97.65	1.17	97.29	0.91	-2.21 ^b	0.0310	-0.2805
Abnormal Involuntary Movement Scale							
Total Body Score	0.30	1.10	0.15	0.59	-1.47 ^c	0.1452	-0.1624
Severity of Movement	0.07	0.34	0.04	0.19	-1.00 ^c	0.3203	-0.1104
Incapacitation	0.01	0.11	0.00	0.00	-1.00 ^c	0.3203	-0.1104
Subject's Awareness	0.00	0.00	0.04	0.19	1.00	0.3262	0.1890
Simpson-Angus Neurological Scale	2.02	5.47	0.71	2.19	-2.32 ^c	0.0228	-0.2564
Growth							
Height Standard Score	0.12	1.33	0.26	1.48	1.19 ^a	0.2400	0.1427
Weight Standard Score	0.49	1.44	0.95	1.31	5.13 ^d	<0.0001	0.6045
Body Mass Index Standard Score	0.50	1.42	0.99	1.18	4.36 ^e	<0.0001	0.5284
IQ	49.24	25.66	47.75	26.77	-1.20 ^a	0.2354	-0.1561
Vineland Adaptive Behavior Scale							
Communication	43.25	15.55	43.83	19.20	0.50 ^f	0.6220	0.0568
Daily Living Skills	36.88	17.56	39.92	20.59	1.67 ^f	0.0996	0.1913
Socialization	47.86	13.97	48.61	16.25	0.52 ^f	0.6021	0.0601
Adaptive Behavior Composite	40.22	15.17	39.99	16.18	-0.58 ^f	0.5646	-0.0668
CY-BOCS	15.51	3.19	12.11	4.53	-7.10 ^g	<0.0001	-0.7932
CGI-Severity	5.14	0.68	4.48	0.96	-6.78 ^c	<0.0001	-0.7535
Aberrant Behavior Checklist							
I. Irritability	25.98	7.44	15.79	9.31	-9.78 ^c	<0.0001	-1.0800
II. Social Withdrawal	16.86	8.96	10.02	7.76	-7.75 ^c	<0.0001	-0.8509
III. Stereotypic Behav.	9.99	4.72	6.25	4.70	-7.41 ^c	<0.0001	-0.8233
IV. Hyperactivity	32.52	9.11	19.45	11.03	-9.38 ^f	<0.0001	-1.0690
V. Inapprop. Speech	5.67	3.94	4.28	3.48	-3.69 ^c	0.0004	-0.4055
Ritvo-Freeman M-RLRS							
1. Sensory Motor	1.04	0.67	0.75	0.53	-4.64 ^g	<0.0001	-0.5190
2. Social Relationships	0.72	0.48	0.16	0.44	-10.78 ^g	<0.0001	-1.2050
3. Affectual Resp.	1.95	0.65	1.22	0.63	-8.74 ^g	<0.0001	-0.9770
4. Sensory Responses	1.28	0.56	0.76	0.45	-9.94 ^g	<0.0001	-1.1118
5. Language	0.31	0.41	0.05	0.38	-6.95 ^g	<0.0001	-0.7773

^adf=57,58; ^bdf=61,62; ^cdf=80-82; ^ddf=71; ^edf=64-69; ^fdf=74-76; ^gdf=79.

BP, blood pressure; IQ, intelligence quotient; CY-BOCS, Children's Yale-Brown Obsessive Compulsive Scale; CGI, Clinical Global Impressions; M-RLRS, Modified Real Life Rating Scale for Autism.

Noncompliance associated with risperidone use in the month before follow-up (i.e., risperidone use associated with lower [improved] scores). Change on Inappropriate Speech reached exploratory significance ($p=0.04$) for the last 4 weeks. On the M-RLRS Sensory Response score, improvements were associated with markers of recent use; Affectual Response reached exploratory levels of significance.

Summary

There were 17 variables that were capable of reflecting possible benefits (including VABS and IQ) and 6 variables able to show possible safety/tolerability concerns (Table 5). Of the 17 variables related to benefit, there were 4 (24%) that suggested significant benefits associated with recent risperidone use, 2 (VABS Social Skills and ABC Social Withdrawal) reflected possible increases in social relatedness, one (M-RLRS, Sensory Responses) reflected improvements in how subjects interacted with others and the environment, and another (ABC Irritability) reflected fewer aggression/

self-injury problems. Five variables could reflect adverse drug effects (AIMS [two variables], Simpson-Angus, weight, BMI), and, of these, only weight gain (20%) was associated with recent risperidone use. We treated height as neutral (neither an index of tolerability nor of therapeutic change).

Discussion

These data, with comprehensive follow-up assessments, form an important addition to the limited knowledge base on longer exposures to antipsychotics in children and adolescents. Overall, we were successful in following a large portion of 83% of the 101 subjects in the original RCT for a mean of 21.4 months (1.8 years) after their participation in our acute study of risperidone. An impressive proportion (67.9%) of the follow-up sample remained on treatment with an antipsychotic (predominately risperidone) in the month leading up to follow-up, despite the fact that most of the treatment received after protocol participation was naturalistic. Additions of other medication groups (mood stabilizers, α agonists,

TABLE 5. COMPARISON OF SUBJECTS AFTER TWO YEARS OF TREATMENT AS A FUNCTION OF RISPERIDONE EXPOSURE (NUMBER OF DAYS) AND RECENT TREATMENT

Variable name	p total exposure	n	Non-risperidone group		n	Risperidone group		p last 4 weeks (1)
			Baseline	Follow-up		Baseline	Follow-up	
			Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
AIMS								
1. Q1 to Q7 Total	NA	25	0.52 (1.29)	0.32 (0.99)	57	0.26 (1.01)	0.07 (0.26)	NA
2. Q8 (Severity)	NA	25	0.16 (0.47)	0.0 (0.0)	57	0.04 (0.26)	0.05 (0.23)	NA
Simpson–Angus Scale								
1. Simpson Total	0.6763	25	2.28 (4.72)	1.20 (3.03)	57	1.91 (5.81)	0.49 (1.69)	0.1862
Weight and height								
1. Weight score <i>z</i>	0.3759	24	0.19 (1.74)	0.47 (1.63)	48	0.64 (1.25)	1.18 (1.06)	0.0304 ⁺
2. Body mass index <i>z</i>	0.8705	24	0.38 (1.60)	0.85 (1.28)	44	0.56 (1.33)	1.06 (1.13)	0.6206
3. Height <i>z</i>	0.0112 ⁺	24	−0.12 (1.62)	−0.38 (1.69)	45	0.26 (1.15)	0.60 (1.25)	0.0052 ⁺
CY-BOCS								
1. Total Score (0–20) [‡]	0.9810	25	16.00 (3.29)	13.08 (4.60)	55	15.29 (3.15)	11.67 (4.48)	0.3000
Intelligence quotient								
1. IQ	0.9699	20	46.74 (30.57)	45.85 (32.22)	39	50.52 (23.07)	48.73 (23.92)	0.7586
Vineland Adaptive Behavior Scales								
1. Communication	0.921	24	44.21 (17.43)	45.21 (21.09)	52	42.81 (14.75)	43.19 (18.45)	0.8296
2. Daily Living Skills	0.2215	24	33.25 (15.20)	38.54 (21.60)	52	38.56 (18.44)	40.56 (20.30)	0.5804
3. Social Skills	0.0516 ⁺	24	48.83 (18.19)	44.21 (18.07)	52	47.40 (11.71)	50.63 (15.10)	0.0110 ⁺
4. Motor Skills	0.0826 [−]	16	56.88 (24.63)	63.06 (27.17)	32	60.34 (19.86)	61.94 (15.72)	0.5432
5. Adaptive Behavior C.	0.8091	24	38.58 (15.38)	38.96 (18.02)	51	41.55 (15.63)	40.25 (15.51)	0.7090
Clinical Global Impressions (CGI)								
1. CGI Severity [†]	0.6799	26	5.23 (0.65)	4.65 (1.09)	55	5.09 (0.7)	4.40 (0.89)	0.3004
Aberrant Behavior Checklist								
1. Irritability	0.9738	27	23.44 (7.24)	17.78 (10.82)	55	27.22 (7.28)	14.82 (8.40)	0.0147 [−]
2. Social Withdrawal	0.4005	27	18.52 (9.72)	13.33 (8.73)	56	16.05 (8.55)	8.43 (6.77)	0.0130 [−]
3. Stereotypic Behavior	0.8034	25	8.84 (5.22)	6.76 (5.37)	56	10.50 (4.43)	6.02 (4.40)	0.0866 [−]
4. Hyperactivity/Noncompliance	0.2152	24	28.58 (10.40)	23.38 (12.06)	53	34.30 (7.95)	17.68 (10.16)	0.0020 [−]
5. Inappropriate Speech	0.9494	27	5.59 (4.03)	5.15 (4.24)	56	5.71 (3.93)	3.86 (3.01)	0.0433 [−]
M-RLRS								
1. Sensory Motor	0.4966	25	4.76 (2.98)	4.20 (3.42)	55	6.95 (4.28)	4.67 (3.06)	0.3721
2. Social Relationships	0.6485	25	6.28 (4.32)	2.40 (3.16)	55	6.55 (4.29)	1.02 (4.23)	0.0723 [−]
3. Affectual Responses	0.3049	25	5.20 (1.94)	4.04 (1.88)	55	6.13 (1.90)	3.49 (1.88)	0.0455 [−]
4. Sensory Responses	0.0920 [−]	25	19.24 (8.80)	14.80 (7.08)	55	20.96 (9.06)	11.02 (7.10)	0.0007 [−]
5. Language	0.8099	25	4.92 (4.65)	1.96 (4.30)	55	2.67 (4.31)	−0.15 (3.99)	0.3123

Non-risperidone group comprises subjects not taking risperidone in last 4 weeks before follow-up; risperidone group comprises subjects receiving risperidone prior to follow-up.

All analyses were by ANCOVA, except for the CGI-S, tagged with [†], where logistic regression was used and *p* values for Wald tests are reported. This ordinal variable was converted into a binary variable based on whether improvement was observed or not during the follow-up period relative to the baseline. In both analyses, baseline value was used as a covariate (always significant) and only one of the predictor variables was used. The signs that accompany the *p* values < 0.10 correspond to the direction of association between the response and the corresponding predictor. The mean percent of risperidone exposure for the 28 patients who had not been taking risperidone in the past 4 weeks was 18.98%, and for the 56 patients who were taking risperidone in the past week it was 88.86%.

NA, complete separation of data points observed in logistic regression.

[‡]For CY-BOCS total score, lag follow-up was also included as a covariate in the ANCOVA models. Lag had no effect on all remaining variables.

The sign (+/−) affixed to total exposure indicates the direction of the relationship.

AIMS, Abnormal Involuntary Movement Scale; CY-BOCS, Children's Yale-Brown Obsessive Compulsive Scale; M-RLRS, Modified Real Life Rating Scale for Autism.

and stimulants) were reported but at lower rates compared to other long-term follow-up studies (e.g., Marcus et al. 2011a).

Findings showing continued benefit.

First, although these follow-up data represent uncontrolled, naturalistic observations of individuals with ASD in community care, the high rate of continued risperidone treatment suggests that sustained benefits were perceived by parents and prescribers for up

to 21 months. This interpretation is bolstered by other observations, such as parent ratings of reduced maladaptive behaviors, reduced ASD symptoms, and even possible gains in VABS social skills in those with the greatest and most recent risperidone exposure. Our primary hypothesis, that CGI-S and ABC Irritability scores would be improved in association with risperidone treatment, proved to be correct for ABC Irritability for recent use (*p* = 0.01). CGI-S may be “too blunt an instrument” (especially when dichotomized as “improved” vs. “not improved”) to detect changes in a follow-up

such as this. Because CGI-S ratings were dichotomized, we were forced to use a nonparametric statistic that was lacking in power. Inspection of the range of other behavioral measures suggests broad improvements associated with risperidone use in the previous month ($p \leq 0.01$), but not significantly with percentage of use across time, suggesting benefit temporally associated with current risperidone use rather than residual benefit.

Findings showing possible facilitation of social/autism variables

Although not representing *a priori* hypotheses, it is of clear interest to note a number of improvements on variables related to social functioning and autistic symptoms, including improvements on VABS Social Skills domain ($p = 0.004$), Social Withdrawal subscale on the ABC ($p = 0.0002$), and M-RLRS Sensory Responses ($p = 0.0012$). Therefore, *current* use of risperidone was associated with improved parent report of some social behaviors, although association of such improvements with *cumulative* exposure almost always failed to reach statistical significance. Marrus et al. (2014) obtained serial parent-rated Social Responsiveness Scale (SRS) ratings from children treated with risperidone for mean durations of 4.4–5.2 years (depending on the type of comparison obtained). Total SRS scores actually increased in risperidone-treated subjects, indicating worsening of core autism symptoms. Although our findings and those of Marrus et al. appear to contradict one another, there were important differences in methodology, subject characteristics, follow-up time, and assessment procedures between the two studies. For example, it is possible that over the more extended time (4–5 years), the most favorable responders found that they no longer needed risperidone whereas the more severe cases continued it.

Findings regarding AEs

Although no unexpected AEs emerged from our data on follow-up, weight gain associated with risperidone remains a significant associated AE and health concern with extended exposure. Relative to Centers for Disease Control norms, height and weight increased significantly over the average 1.8 year follow-up interval. BMI increased by nearly 0.54 standard units over this time. However, BMI gain with risperidone exceeded height gain by a mean of 0.20 standardized units, which is of questionable clinical significance. Our study was limited by not examining fasting measures of glucose or lipids; nor did we obtain the current recommended measure of waist circumference. Nevertheless, laboratory abnormalities were uncommon, and tolerability for risperidone appeared to be good. This can be inferred in part from the large number of subjects who reported risperidone exposures of >80% of the entire follow-up period.

Although several AEs were commonly reported, few appeared strongly associated with risperidone exposure, and most were of minor or no medical significance (e.g., allergies, gastrointestinal symptoms). Constipation, listed as an adverse effect in the risperidone package insert, was no greater with risperidone than without. Perhaps more importantly, we saw no statistical evidence of abnormal movements, dyskinesias, or other signs of extrapyramidal symptoms, despite our use of multiple structured assessments for these signs. We did observe more excessive appetite (42.1% vs. 20.0%) and more enuresis/urinary problems (19.6% vs. 0.0%) among the subjects taking risperidone. The higher percentage of children with excessive appetite (42%) is consistent with the literature and with weight gain findings in other studies (Martin et al. 2004; Aman et al. 2005a; Correll et al. 2009; Hellings et al. 2010).

Case reports have noted enuresis with risperidone (both daytime and nocturnal) in children with PDDs (Hergüner and Mukaddes 2007; Ghanizadeh et al. 2008; Cop et al. 2011), and there is at least one report of enuresis associated with aripiprazole as well (Bozkurt and Abali 2011). The frequency of this associated event (especially in patients with developmental disabilities) suggests that clinicians should anticipate the possibility, discuss it with parents, and monitor explicitly for such changes. Finally, two children in the predominately risperidone group experienced seizures. In our previous AE study (Aman et al. 2005a), we reported two other participants who experienced seizures, one while taking placebo and one with risperidone treatment. Hedges et al. (2003) reviewed the evidence on antipsychotic induction of seizures and concluded that clozapine was the second-generation antipsychotic most frequently associated with seizures whereas risperidone appeared to have relatively low risk. Nevertheless, given that seizures often accompany autism, clinicians should be vigilant for their occurrence, and further data on any association with risperidone treatment would be helpful.

Time-related (maturational) changes

In all, there were 14 measures of behavioral change; 4 derived by clinician interview (VABS, CY-BOCS, and CGI-S) and 10 derived from parent ratings. The clinician-derived CY-BOCS showed significant improvements in compulsions over the 1.8 years, as did all the 10 parent-derived ratings on the ABC and M-RLRS. These are grounds for optimism, and this pattern is consistent with much of the previous follow-up literature in children with autism.

The ABC contains two subscales (Lethargy/Social Withdrawal and Stereotypic Behavior) relevant to autism symptomatology, and all five of the M-RLRS subscales are similarly relevant to autism. Collectively, these changes suggest a substantial decline in severity of symptoms over time. Most of the participants entered the study with high scores on these, and we had no control groups with whom to compare the changes. It is unknown if these changes were developmental effects, reflecting regression to the mean as has been seen in ADHD research (Milich et al. 1980), or are the result of some combination of these influences. These optimistic findings are consistent with much of the follow-up literature (Seltzer et al. 2004; Shattuck et al. 2007), although the signal in this study may be somewhat stronger than in previous studies.

Limitations

We are encouraged by observations that current risperidone use was associated with reductions in a range of maladaptive behaviors (aggression, agitation, hyperactivity) and parent ratings of improved social behaviors after nearly 2 years of exposure. Nevertheless, we acknowledge significant limitations to our ability to interpret these data with certainty. These limitations include absence of a control group free of treatment, inadequate control for developmental effects, and limitations of rating instruments for assessing core domains of ASD. It is possible that expectation of benefit may have biased parent report for the participants taking risperidone in the 4 weeks prior to assessment, as all statistically significant improvement was seen in parent-rated measures. We did not obtain information from outside informants or from direct observations, which could have shed light on other important impacts of risperidone on outcome. The lack of fasting glucose and lipid measures and of currently recommended waist circumference was previously mentioned. Finally, there was a difference between participants who enrolled in the follow-up compared with those who declined, with significantly more indeterminate responders in

the latter group. Hence, the beneficial changes seen in this evaluation may have been accentuated by a relatively good response rate in the participants who were successfully followed.

Conclusions and Clinical Significance

Our longer-term treatment data add to the information available to clinicians on durability of benefits and health risks associated with risperidone treatment of children and adolescents with ASD. At 1.8 years after starting risperidone, 67% of young people with autism continued to receive the drug. A pattern of continued benefits across broad areas of related symptomatology was observed in association with ongoing risperidone exposure, supporting the likely continued therapeutic benefits of treatment, even after extended exposure in many individuals. Lower rates of targeted symptoms of irritability/aggression and reductions in hyperactivity were seen in association with current risperidone exposure. AEs included excessive appetite, weight gain, and enuresis, all of which can form significant challenges for adherence and safe long-term use.

It is important to note that these children and adolescents started treatment because of extreme irritability, and any benefits may depend upon this indication. Clearly, not all subjects benefited from risperidone, as suggested by one third ceasing such treatment by the time of follow-up (alternatively, some may no longer have needed treatment). Finally, it is important for practitioners to monitor for enuresis and for increased appetite and weight, and (where indicated) markers of metabolic syndrome in such subjects.

Disclosures

Dr. Michael Aman has received research contracts for, consulted with, served on advisory boards for, or conducted investigator training for Biomarin Pharmaceuticals, Bristol-Myers Squibb, CogState Clinical Trials, Ltd., Confluence Pharmaceuticals, Coronado Biosciences, Forest Research, Hoffman-LaRoche, Johnson and Johnson, MedAvante, Inc., Novartis, Pfizer, ProPhase LLC, and Supernus Pharmaceuticals. Dr. L. Eugene Arnold has received research funding from CureMark, Forest, Lilly, Shire, and Young Living; advisory board honoraria from Biomarin, Novartis, Noven, Roche, Seaside Therapeutics, and Shire; consulting fees from Gowlings, Pfizer, Tris Pharma, and travel support from Noven. Dr. Jaswinder Ghuman has received past funding from the NIMH for a K-23 career development grant, the Health Resources and Services Administration–Maternal and Child Health (HRSA-MCH) for the University of Arizona Leadership Education in Neurodevelopmental Disabilities Program (AZLEND), the Arizona Institute for Mental Health Research, and from Bristol-Myers Squibb for a clinical trial in autistic disorder. Dr. Jessica Hellings has been an Investigator for Forest, Shire, Sunovion, and Young Living; she has had authorship collaborations with Roche.

Dr. Jill A. Hollway has received research funding from Forest Research Institute and Sunovion Pharmaceuticals. Dr. James McCracken has received consultant income research contract support from Roche. Dr. Lawrence Scahill has served as a consultant for Bracket, Coronado, MedAdvante, Neuren, Roche, and Shire Pharmaceuticals. Dr. Elaine Tierney has received funding or material support from Alcobra, Autism Speaks, Biomarin Pharmaceuticals, Forest, Lundbeck, Neurim, Otsuka Purdue, Pfizer, Roche Pharmaceuticals, Smith Lemli Opitz Foundation, Solace Nutrition, Sunovion, and SynueRx. The following authors have no financial relationships to disclose: Dr. Marco Grados, Dr. Christopher J. McDougle, Dr. Haikady N. Nagaraja, Dr. David J. Posey,

Dr. Mallikarjuna Rettiganti, Dr. Bhavik Shah, Dr. Naomi B. Swiezy, and Dr. Benedetto Vitiello.

References

- Aman MG, Arnold LE, McDougle CJ, Vitiello B, Scahill L, Davies M, McCracken JT, Tierney E, Nash PL, Posey DJ, Chuang S, Martin A, Shah B, Gonzalez NM, Swiezy NB, Ritz L, Koenig K, McGough J, Ghuman JK, Lindsay RL: Acute and long-term safety and tolerability of risperidone in children with autism. *J Child Adolesc Psychopharmacology* 15:869–843, 2005a.
- Aman MG, Lam KSL, Van Bourgondien ME: Medication patterns in patients with autism: Temporal, regional, and demographic influences. *J Child Adolesc Psychopharmacology* 15:116–126, 2005b.
- Aman MG, Singh NN, Stewart AW, Field CJ: The Aberrant Behavior Checklist: A behavior rating scale for the assessment of treatment effects. *Am J Ment Deficiency* 89:485–491, 1985a.
- Aman MG, Singh NN, Stewart AW, Field CJ: The psychometric characteristics of the Aberrant Behavior Checklist. *Am J Mental Deficiency* 89:492–502, 1985b.
- Aman MG, Singh NN, Turbott SH: Reliability of the Aberrant Behavior Checklist and the effect of variations in instructions. *Am J Ment Deficiency* 92:237–240, 1987.
- American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., Text Revision. Washington, DC: American Psychiatric Association; 2000.
- Arnold LE, Aman MG, Martin A, Collier-Crespin A, Vitiello B, Tierney E, Bell-Bradshaw F, Freeman BJ, Gates-Ulanet P, McCracken JT, McDougle CJ, McGough JJ, Posey DJ, Scahill L, Swiezy NB, Ritz L, Volkmar FR: Assessment in autism multisite randomized clinical trials (RCT)s. *J Autism Dev Disord* 30:99–111, 2000.
- Bozkurt H, Abali O: Aripiprazole-induced enuresis in a child with autistic disorder. *Arch Neuropsychiatry* 48:164–166, 2011.
- Campbell M, Armenteros JL, Malone RP, Adams PB, Eisenberg ZW, Overall JE: Neuroleptic-related dyskinesias in autistic children: A prospective, longitudinal study. *J Am Acad Child Adolesc Psychiatry* 36:835–843, 1997.
- Cohen J. A power primer. *Psychol Bull* 112:155–159, 1992.
- Cop E, Oner P, Oner O: Risperidone and double incontinence in a child with autism. *J Child Adolesc Psychopharmacol* 21:647–648, 2011.
- Correll CU, Manu P, Olshansky V, Napolitano B, Kane JM, Malhotra AK: Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA* 302:1765–1773, 2009.
- Coury DL, Anagnostou E, Manning-Courtney P, Reynolds A, Cole L, McCoy R, Whitaker A, Perrin JM: Use of psychotropic medication in children and adolescents with autism spectrum disorders. *Pediatrics* 130(Supplement 2):S69–S76, 2012.
- Freeman BJ, Ritvo ER, Yokota A, Ritvo A: A scale for rating symptoms of patients with the syndrome of autism in real life settings. *J Am Acad Child Adolesc Psychiatry* 25:130–136, 1986.
- Ghanizadeh A, Kianpoor M: Cessation in risperidone-induced incontinence by valproate in a child with pervasive developmental disorder. *Prim Psychiatry* 15:32–34, 2008.
- Greenhill LL, Vitiello B, Abikoff H, Levine J, March JS, Riddle MA, Capasso L, Cooper TB, Davies M, Fisher P, Findling RL, Fried J, Labellarte MJ, McCracken JT, McMahon D, Robinson J, Skrobala A, Scahill L, Varipatis E, Walkup JT, Zito JM: Developing methodologies for monitoring long-term safety of psychotropic medications in children: Report on the NIMH conference, September 25, 2000. *J Am Acad Child Adolesc Psychiatry* 42:651–655, 2003a.
- Greenhill LL, Vitiello B, Riddle MA, Fisher P, Shockey E, March JS, Levine J, Fried J, Abikoff H, Zito JM, McCracken JD, Findling RL, Robinson J, Cooper TB, Davies M, Varipatis E, Labellarte MJ,

- Scahill L, Walkup JT, Capasso L, Rosengarten J: Review of safety assessment methods used in pediatric psychopharmacology. *J Am Acad Child Adolesc Psychiatry* 42:627–633, 2003b.
- Guy W: ECDEU Assessment Manual for Psychopharmacology: Revised (DHEW publication number ADM 76-338). Rockville, MD: US Department of Health, Education and Welfare, Public Health Service, Alcohol Drug Abuse and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs, 1976. Pp 534–537.
- Hedges D, Jeppson K, Whitehead P: Antipsychotic medication and seizures: a review. *Drugs Today (Barc)* 39:551–557, 2003.
- Hellings J A, Cardona AM, Schroeder SR: Long-term safety and adverse events of risperidone in children, adolescents, and adults with pervasive developmental disorders. *J Ment Health Research Intellectual Disabil* 3:132–144, 2010.
- Hergüner S, Mukaddes NM: Risperidone-induced enuresis in two children with autistic disorder. *J Child Adolesc Psychopharmacol* 17:527–530, 2007.
- Kent JM, Hough D, Singh J, Karcher K, Pandina G: An open-label extension study of the safety and efficacy of risperidone in children and adolescents with autistic disorder. *J Child Adolesc Psychopharmacol* 23:676–686, 2013.
- Lemmon ME, Gregas M, Jeste SS: Risperidone use in autism spectrum disorders: A retrospective review of a clinic-referred patient population. *J Child Neurol* 26:428–432, 2011.
- Lord C, Rutter M, LeCouteur A: Autism Diagnostic Interview-Revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord* 24:659–685, 1994.
- Maayan L, Correll CU: Weight gain and metabolic risks associated with antipsychotic medications in children and adolescents. *J Child Adolesc Psychopharmacology* 21:517–535, 2011.
- Marcus RN, Owen R, Manos G, Mankosi R, Kamen L, McQuade RD, Carson WH, Corey-Lisle PK, Aman MG: Aripiprazole in the treatment of irritability in pediatric patients (aged 6–17 years) with autistic disorder: Results from a 52-week, open-label study. *J Child Adolesc Psychopharmacol* 21:229–236, 2011a.
- Marcus RN, Owen R, Manos G, Mankosi R, Kamen L, McQuade RD, Carson WH, Findling RL: Safety and tolerability of aripiprazole for irritability in pediatric patients with autistic disorder: A 52-week, open-label, multicenter study. *J Clin Psychiatry* 72:1270–1276, 2011b.
- Marrus N, Underwood-Riordan H, Randall F, Zhang Y, Constantino JN: Lack of effect of risperidone on core autistic symptoms: Data from a longitudinal study. *J Child Adolesc Psychopharmacol* 24:513–518, 2014.
- Martin A, Scahill L, Anderson GM, Aman M, Arnold LE, McCracken JT, McDougle CM, Tierney E, Huang S, Vitiello B: Weight and leptin changes among risperidone-treated youths with autism: Six-month prospective data. *Am J Psychiatry* 161:1125–1127, 2004.
- McCracken JT: Safety issues with drug therapies for autism spectrum disorders. *J Clin Psychiatry* 66 (Suppl 10):32–37, 2005.
- McDougle CJ, Scahill L, Aman MG, McCracken JT, Tierney E, Davies M, Arnold LE, Posey DJ, Martin A, Ghuman JK, Shah B, Chuang SZ, Swiezy NB, Gonzalez NM, Hollway J, Koenig K, McGough J, Ritz L, Vitiello B: Risperidone for the core symptom domains of autism: Results from the study by the Autism Network of the Research Units on Pediatric Psychopharmacology. *Am J Psychiatry* 162:1142–1148, 2005.
- Milich R, Roberts MA, Loney J: Differentiating practice effects and statistical regression on the Conners Hyperkinesis Index. *J Abnorm Child Psychol* 8:549–552, 1980.
- Mullen EM: Mullen Scales of Early Learning. Los Angeles: Western Psychological Services; 1995.
- National Institute of Mental Health: Special Feature: Rating scales and assessment instruments for use in pediatric psychopharmacology research. *Psychopharmacol Bull* 21:1077–1080, 1985.
- Physicians Desk Reference*: 61st ed. Montvale, NJ: 2007.
- Ratzoni G, Gothelf D, Brand-Gothelf A, Reidman J, Kikinzon L, Gal G, Phillip M, Apter A, Weizman R: Weight gain associated with olanzapine and risperidone in adolescent patients: A comparative prospective study. *J Am Acad Child Adolesc Psychiatry* 41:337–343, 2002.
- Research Units on Pediatric Psychopharmacology Autism Network (Aman MG, Arnold LE, Lindsay R, Nash P, Hollway J, McCracken JT, McGough J, Shah B, Cronin P, Hong D, McDougle CJ, Posey D, Swiezy N, Kohn A, Scahill L, Martin A, Koenig K, Volkmar F, Carroll D, Lancor A, Tierney E, Ghuman J, Gonzalez NM, Grados M): Risperidone treatment of autistic disorder: Longer term benefits and blinded discontinuation after six months. *Am J Psychiatry* 162:1361–1369, 2005.
- Research Units on Pediatric Psychopharmacology Autism Network (McCracken JT, McGough J, Shah B, Cronin P, Hong D, Aman MG, Arnold LE, Lindsay R, Nash P, Hollway J, McDougle CJ, Posey D, Swiezy N, Kohn A, Scahill L, Martin A, Koenig K, Volkmar F, Carroll D, Lancor A, Tierney E, Ghuman J, Gonzalez NM, Grados M, Vitiello B, Ritz L, Davies M, Robinson J, McMahon D): A double-blind, placebo-controlled trial of risperidone in children with autistic disorder. *New Engl J Med* 347:314–321, 2002.
- Roid GH, Miller LJ: Leiter-R: Leiter International Performance Scale—Revised—Examiners Manual. Chicago: Stoelting; 1997.
- Scahill L, McDougle CJ, Williams S, Dimitropoulos A, Aman MG, McCracken J, Tierney E, Arnold LE, Lam KL, Vitiello B: The Children's Yale-Brown Obsessive-Compulsive Scales modified for pervasive developmental disorders. *J Am Acad Child Adolesc Psychiatry* 45:1114–1123, 2006.
- Scahill L, Riddle MA, Hardin MT, Ort SI, King RA, Goodman WK, Leckman JF: Children's Yale-Brown Obsessive Compulsive Scale: Reliability and validity. *J Am Acad Child Adolesc Psychiatry* 36:844–852, 1997.
- Seltzer MM, Shattuck PT, Abbeduto L, Greenberg JS: Trajectory of development in adolescents and adults with autism. *Ment Retard Dev Disabil Res Rev* 10:234–247, 2004.
- Shattuck PT, Seltzer MM, Greenberg JS, Orsmond GI, Bolt D, Kring S, Lounds J, Lord C: Change in autism symptoms and maladaptive behaviors in adolescents and adults with an autism spectrum disorder. *J Autism Dev Disord* 37:1735–1747, 2007.
- Simpson GM, Angus JW: A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand* 21:11–19, 1970.
- Sparrow S, Balla D, Cicchetti D: Vineland Adaptive Behavior Scales. Circle Pines, MN: American Guidance Service; 1984.
- Vitiello B, Riddle MA, Greenhill L, March JS, Levine J, Schachar RJ, Abikoff H, Zito JM, McCracken JT, Walkup JT, Findling RL, Robinson J, Cooper TB, Davies M, Varipatis E, Labellarte MJ, Scahill L, Capasso L: How can we improve the assessment of safety in child and adolescent psychopharmacology? *J Am Acad Child Adolesc Psychiatry* 42:634–641, 2003.
- Wechsler D: Manual for the Wechsler Intelligence Scale for Children, 3rd ed. San Antonio: Psychological Corporation; 1992.

Address correspondence to:
 Michael Aman, PhD
 The Nisonger Center UCEDD
 Ohio State University
 581 Dodd Drive
 Columbus, OH 43210-1257

E-mail: aman.1@osu.edu