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A Crossover Study of Risperidone in Children, Adolescents and Adults with Mental Retardation

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Risperidone has shown safety and efficacy for aggressive and destructive behaviors in short-term studies. This longer-duration study includes a broad sample. Forty subjects, aged 8–56 years (mean = 22), all with mental retardation and 36 with autism spectrum disorders participated in this 22-week crossover study, with 24 weeks of open maintenance thereafter. Of 40 subjects, 23 (57.5%) responded fully (50% decrease in Aberrant Behavior Checklist-Community Irritability subscale score), while 35 subjects (87.5%) showed a 25% decrease. Gender, mood disorder, and antiseizure medications did not alter response. Increased appetite and weight gain were common. Low dose risperidone was effective for aggressive behavior in persons with MR. More long-term studies are needed, incorporating weight control interventions.

KEY WORDS: Risperidone; mental retardation; aggression; weight gain.

Central nervous system dopamine and serotonin neurotransmitter systems are implicated in aggressive and destructive behaviors. Experiments with rat pups, treated as neonates to deplete dopamine (DA) and then challenged with the DA agonist apomorphine as adult rats, produced an animal model of aggression, self-injury, stereotypy, and hyperactivity (Breese, 2002). In humans, early controlled studies of the dopamine D2 receptor-blocking drug haloperidol in children with autism found significant improvement in aberrant behavior, including anger, mood lability and stereotypy (Anderson *et al.*, 1989, 1984). Early-onset dyskinesias following haloperidol withdrawal were observed, however, producing serious concerns about long-term use (Campbell, *et al.*, 1997). Risperidone is a novel antipsychotic drug designed to resemble haloperidol, while minimizing dyskinesia risks. By design, risperidone exerts a serotonin 5HT2a postsynaptic receptor blocking effect that is approximately 50 times that of its dopamine D2 postsynaptic receptor blocking action (Meltzer, 1995).

Serotonergic measures are abnormal in approximately 30% of persons with autism. Both serum and platelet serotonin are significantly elevated in subjects with autism, and auto-antibodies to their serotonergic neurons have been identified (Cook & Leventhal, 1996). Genetic disequilibrium may occur at the region-encoding site for the serotonin transporter gene (SLC6A4) in autistic disorder (Cook *et al.*, 1997; Kim *et al.*, 2002). The serotonin reuptake inhibitors clomipramine and fluvoxamine showed encouraging results in small preliminary studies in children and

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adults with autism, respectively (Gordon, State, Nelson, Hamburger, & Rapoport, 1993; McDougle *et al.*, 1996).

Two short-term double-blind, placebo-controlled studies found risperidone to be superior to placebo for treating severely problematic behaviors, including repetitive behavior, anxiety, depression, aggression and irritability in adults with autism (McDougle *et al.*, 1998) and for aggression, tantrums and self-injury in children (Research Units on Pediatric Psychopharmacology Autism Network, 2002) with autistic disorder. Two Janssen Pharmaceutica-sponsored multisite studies showed that risperidone was safe and effective for the treatment of children with conduct disorder or oppositional defiant disorder and intelligence ranging from borderline intellectual function to moderate mental retardation (MR), but excluded autism spectrum disorders (ASD) (Aman, De Smedt, Derivan, Lyons, & Findling, 2002; Snyder *et al.*, 2002). Concomitant stimulant treatment was allowed in the Janssen study. We recently published preliminary results of the first 20 subjects in the present study (Zarcone *et al.*, 2001), and a preliminary report on the observed weight gain side effect (Hellings, Zarcone, Crandall, Wallace, & Schroeder, 2001).

The full study is a 46-week placebo-crossover investigation of risperidone efficacy and safety in children, adolescents and adults with all levels of MR and ASD. Persistent aggression, property destruction and self-injury were the treatment targets.

METHOD

Subjects

A board-certified psychiatrist (JH) and the study coordinator (JZ) screened 343 individuals and enrolled 50 subjects in this outpatient study. We obtained approval of the University Human Subjects Committee, informed written consent of each subject's parent or guardian, and when possible subject assent. Referral sources included outpatient clinics, community organizations, residential facilities, and parents or guardians responding to mailings.

Eligibility criteria were age 6–65 years, MR (IQ of less than 70), and at least 6 months' history of aggression, property destruction or self-injury, by caregiver report. In addition, baseline Irritability subscale scores rated on the Aberrant Behavior Checklist-Community (ABC-C) rating scale (Aman, Singh, Stewart, & Field, 1985) were required to be above given norms for age, gender and setting as rated by the primary caregiver. For potential subjects with scores within one standard deviation above the norm for age on the Irritability subscale, inclusion or exclusion was decided by the P.I. and Study Coordinator after reviewing the individual case. Subjects with significant aggression and/or self-injury were then included in the study. Of all 50 subjects, 6 were enrolled with mild elevations. Exclusion criteria were previous risperidone hypersensitivity, history of neuroleptic malignant syndrome, seizures within the past year, degenerative brain disease as assessed by history, and a problematic living situation such as lack of reliable caregiving. Prior treatment with risperidone was not an exclusion criterion. Subjects with epilepsy in remission for at least a year were included in the study ($n = 9$) provided dosages of any antiseizure medications remained constant during the study. For ethical reasons, we recommended against study participation for patients already stable on psychotropic medications. Subjects participating in the study were tapered off existing psychotropic medications prior to the start.

Subjects' IQ testing was updated if not performed in the past 3 years. The Wechsler Adult Intelligence Scale—Revised (Wechsler, 1981) was used for verbal adults, the Wechsler Intelligence Scale for Children—3rd edition (Wechsler, 1991) for verbal children, and the Leiter International Performance Scale (Leiter, 1994) for nonverbal subjects.

Design

At screening, we assessed subjects using all available information to obtain history of the presenting problem, past psychiatric history, family history, developmental, educational and medical and surgical history. A detailed mental status examination was also performed. DSM-IV criteria (American Psychiatric Association, 1994) were used to make all diagnoses. Physical and neurological examinations were performed. The clinical diagnoses arrived at were reviewed for each subject at the study end, when the P.I. had observed subjects' symptoms and signs required for DSM-based diagnoses over the period of the study. This approach pertains also to such difficult comorbid diagnoses as autistic disorder and bipolar disorder.

Eligible subjects were gradually tapered off existing psychiatric medications. A drug-free period lasting at least 2 weeks was necessary prior to beginning the study. Outpatient study visits took

place every second week and at the end of each sub-phase during the acute phase, and monthly during the maintenance phase.

For the blinded phase, the investigational pharmacist randomized subjects to 3, 4, or 5 weeks of the Placebo 1 period. The pharmacist then randomized each subject to start either a low or high dose risperidone phase, and gradually increased the amount of risperidone in the study liquid over 2 weeks to a low or high dose. The dose was then held constant for 4 weeks, after which each dose was switched over to the other. Following this, the subject's dose was gradually tapered down to a 3, 4, or 5 week phase of Placebo 2. We then broke the investigator blind and offered a 24-week maintenance trial of optimal dose of risperidone, adjusted monthly or as needed. (See Fig. 1). After breaking the blind, the optimal effective dose could be identified for each subject, associated with greatest response and fewest side effects, excluding weight gain.

Measures

The ABC-C Irritability subscale score was the main outcome measure, completed weekly by the subject's primary caregiver. The ABC-C is a 58-item standardized problem behavior checklist, and allows item rating on a 4-point scale from zero (not occurring at all) to 3 (severe). The checklist questions comprise 5 subscales: Irritability, Social Withdrawal, Stereotypy, Hyperactivity, and Excessive Speech. The ABC-C Irritability subscale contains 15 items that measure aggression and explosive outbursts. We defined risperidone response as 50% decrease in ABC-C Irritability subscale score, and partial response as 25% decrease in Acute Phase average score.

Dyskinesia side effects were rated by the psychiatrist using the Dyskinesia Identification System Condensed User Scale (DISCUS) (Sprague, Kalachnik, & Shaw, 1989). A designated caregiver filled out the Neuroleptic Side Effects Checklist (NSEC) (Gualtieri, 1984 Unpublished Scale available from the author; Schroeder, Rojahn, & Reese, 1997) at each visit, rating 29 potential side effects. These include gastrointestinal side effects, irritability, sedation, nasal congestion, fever, muscle stiffness, tremor, restlessness, and urinary incontinence and retention.

Routine laboratory tests were checked at baseline, once during the blinded phase and once during the continuation phase: CBC, chemistry profile including liver functions and glucose. Prolactin level, hemoglobin A1c, and lipid profile were measured in a subset of 20 subjects at the time that other tests were obtained. All laboratory tests were non-fasting specimens. The actual time of day as well as specific timepoint in the study phase for drawing of blood tests was not stipulated due to unpredictability of patient compliance. Subjects' weight was measured at each visit.

Study Drug

Liquid study drug and placebo were donated by Janssen Pharmaceutica and dispensed by the investigational pharmacist. The low dose was 1 mg/day for children and adolescents, and 2 mg/day for adults, given on a twice-daily schedule. The pharmacist used subject baseline weight to calculate each subject's target high dose, which was 0.05 mg/kg/day for all age groups.

We built an automatic blinded dose-halving mechanism into the study, to retain subjects in the event of severe side effects, and implemented this on a case-by-case basis where indicated. As an alternative, study drop-out was offered, and chosen by 6 subjects due to sedation and gastrointestinal side effects. The mean high dose for children and adolescents was 2.0 mg/day (range 1.2–2.9 mg/day), and for adults 3.6 mg/day (range 2.4–5.2 mg/day).

Crossover Study

PBO I	T	T	Acute Dose 1	T	T	Acute Dose 2	T	T	PBO II
3, 4 or 5 wks	1 wk	1 wk	4 weeks	1 wk	1 wk	4 weeks	1 wk	1 wk	3, 4, 5 weeks

Maintenance Phase

T	T	24 weeks

T: Drug taper, either gradual increase to a higher dose, or gradual decrease to a lower dose.
Acute Dose 1: High or Low Dose
Acute Dose 2: Low or High Dose

Fig. 1. Study design.

Statistical Analysis

Drug Effect (Acute Phase)

The analyses were conducted using SAS Proc Mixed to compare mean ABC-C Irritability subscale scores in the acute phases of high and low dose to mean ABC-C Irritability scores during Placebo 2. Differences in initial level of aberrant behavior were controlled for by using mean ABC-C Irritability score during Placebo 1 as a covariate.

Initially, overall drug effects were evaluated with a full model to include variables for Study Group (a two-level class variable—the 20 subjects already published and the subsequent 20 subjects), Placebo 1, and Phase (two levels: Placebo 2 and Drug). Analysis using a dichotomous variable for Study determined that data from the above two collection periods could be combined for analysis. The remaining model included the covariate (mean ABC-C during Placebo 1) and Phase with two levels (Drug or Placebo 2).

Dose Effect

Initial analyses showed that data from the two different study groups could be combined. In addition to the Study Group variable, the full model included Placebo 1 as a covariate, and Sequence (order of high versus low dose), Dose (high or low), and interaction between Sequence and Dose. Neither Sequence by Phase interaction nor Sequence were significant, thus, these were dropped from the model.

Drug Effect (Maintenance)

To control for individual differences in problem behavior at presentation, mean ABC-C Irritability subscale score during Placebo 1 was used as a covariate. The data were modeled using SAS Proc Mixed.

Predictors of Response

Characteristics of gender, autism diagnosis, concomitant antiseizure medications, and mood disorder diagnosis were examined dichotomously; these class variables were added individually as predictors into the earlier model for irritability scores across the maintenance phase. The variable "Level of MR" had four categories: mild, moderate, severe, and profound. Age group had three categories: child, adolescent, and adult. These variables were also added individually to the irritability score model for the maintenance phase as a class variable.

Side Effects

Using the NSEC and the DISCUS, a side effect was coded if it occurred on any measurement occasion. Placebo 1 and the acute drug phases (high, low dose) were compared.

McNemar's tests (Siegel & Castellan, 1988) were used to determine if significant numbers of subjects changed from not experiencing each side effect on placebo to experiencing it during acute drug phases, and vice versa. McNemar's test uses information about subjects who changed category and evaluates whether the number of changes in one direction equals the number of changes in the other direction. Rejection of the null hypothesis indicates more changes in one direction, (e.g., from not present in placebo to present during the drug phase). Finally, we used dependent sample *t*-tests to evaluate the mean DISCUS total score difference from Placebo 1 to acute drug phase and also from acute drug phase to Placebo 2.

RESULTS

Subjects

Of 343 patients screened, 50 were enrolled and 40 subjects entered the Placebo I phase of the study. Most screened potential subjects were ineligible. Forty-eight who did not participate were apparently eligible but did not enter the study by choice, or were judged to have too great a problem severity to complete a placebo phase. Fifty subjects enrolled in this study. Ten subjects dropped out prior to receiving the drug, due to problem severity, relocation, medical problems, or electing not to continue in the study. Six subjects dropped out due to side effects in the acute phase. During maintenance, six more subjects dropped out, though none because of side effects: three subjects showed insufficient response, one developed seizure recurrence, and two were lost to follow-up.

The study sample consisted of 23 males and 17 females aged 8 to 56 years (mean age 22.0 years, ±S.D. 13.1). Subject ages were: 13 children (8–12 years); 8 adolescents (13–18 years); and 19 adults (22–56 years). Eighty-five percent (34 subjects) were white, 7.5% (3) African American, 2.5% (1) Hispanic, and 5% (2) were of other races or ethnicities. Levels of MR for the 40 subjects were: 11 mild, 9 moderate, 11 severe, and 9 profound. See Table I for subjects' demographic characteristics. Twenty-eight subjects met DSM-IV criteria for Autistic Disorder,

Table I. Characteristics of the Study Sample

	Age	Sex	MR Level	Topography	Seizure Meds	Dose Reduced[a]
1	8	M	Severe	SIB, Agg	–	–
2	8	M	Mild	Agg	–	√
3	8	F	Moderate	SIB, Agg	–	–
4	9	M	Severe	SIB, Agg	√	–
5	10	M	Moderate	SIB, Agg	–	√
6	10	M	Profound	SIB, Agg	–	–
7	10	M	Mild	SIB, Agg	–	√
8	11	F	Mild	SIB, Agg	–	√
9	11	F	Moderate	SIB, Agg	–	–
10	11	M	Mild	SIB, Agg	–	–
11	12	F	Moderate	SIB, Agg	–	–
12	12	F	Mild	SIB, Agg	–	–
13	12	M	Mild	Agg	√	√
14	13	M	Severe	SIB	–	√
15	14	M	Profound	SIB, Agg	√	–
16	15	M	Severe	SIB, Agg	–	–
17	15	M	Mild	SIB, Agg	–	–
18	15	F	Moderate	SIB, Agg	–	–
19	16	F	Profound	SIB, Agg	√	–
20	16	M	Mild	SIB, Agg	√	√
21	16	M	Severe	SIB, Agg	–	–
22	19	M	Severe	SIB, Agg	–	–
23	20	F	Severe	SIB, Agg	–	–
24	20	M	Moderate	SIB	–	√
25	22	F	Severe	SIB, Agg	–	–
26	23	M	Profound	SIB, Agg	√	–
27	25	M	Mild	SIB, Agg	√	√
28	27	M	Profound	SIB, Agg	–	√
29	30	M	Severe	SIB, Agg	–	√
30	30	F	Mild	Agg	–	–
31	30	F	Mild	SIB, Agg	–	√
32	31	M	Moderate	Agg	–	–
34	31	F	Moderate	SIB, Agg	–	–
33	35	M	Profound	SIB	√	–
35	40	M	Severe	SIB, Agg	–	–
37	43	F	Moderate	SIB	–	–
36	45	F	Profound	SIB, Agg	√	–
38	50	F	Severe	SIB, Agg	–	√
39	51	F	Profound	SIB, Agg	–	–
40	56	F	Profound	SIB	–	–
					$n=9$	$n=13$

Key: SIB: Self-injurious behavior
Agg: Aggression
[a]Dose Reduced refers to dose-halving due to side effects in Acute Phase: √ = yes; – = no.

and 8 met criteria for Pervasive Developmental Disorder, Not Otherwise Specified (PDD-NOS).

Drug Effect—Acute Phase

The results of ABC-C subscale score means are shown for the whole sample in Fig. 2 and Table II and for children and adolescents in Fig. 3. The mean Irritability subscale score decreased from 19.16 (±9.96), in Placebo 1 to 11.15 (±9.28) for the Low dose phase, and 13.31 (±8.92) for the High dose phase. The pattern of results for the children and adolescents was similar. Twenty-three subjects (57.5%) showed a 50% reduction in Irritability subscale score (full response) and 35 subjects (87.5%) showed a 25% decrease. Mean ABC-C Irritability scores across both drug phases were significantly different from mean ABC-C Irritability scores during Placebo 2 controlling for mean Irritability score during Placebo 1 ($F=17.94$; df = 1,31; $p=.0002$).

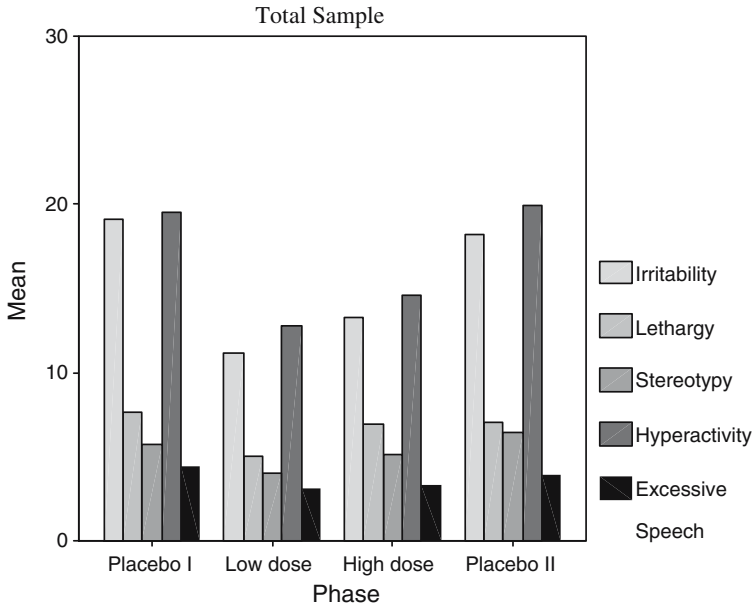

Fig. 2. Mean ABC-C Subscale Scores at the end of each Study Phase: whole Sample.

Dose Effect

Using each subject's ABC-C Irritability total mean score during Placebo 1 as a covariate, we compared low and high dose means (using high dose ratings made prior to any automatic dose-halving reductions). Dose was not significant in the model, indicating that aberrant behavior was not significantly different between the two dose conditions ($F = 2.43$; df = 1,344; $p = .13$). There was no carryover between doses.

Low dose risperidone was as effective as high dose. However, while the differences between mean high and low dosages in each group were not extremely large (3.6 mg vs. 2.0 mg per day for adults, and 2.0 mg vs. 1.0 mg per day for children and adolescents), they had significantly different impacts on adverse events. The mean optimal dose for children and adolescents was 1.67 mg/day, and for adults 1.52 mg/day. It is significant that almost a third of subjects were unable to tolerate gradual dosage increase to 0.05 mg/kg/day (maximum dose 5 mg/day in adults) over a period of 2 weeks for the high dose phase, due to sedation, or gastrointestinal complaints. These intolerable acute side effects were dose-related, since automatic blinded halving of the dose for the rest of that phase resulted in their resolution, and 7 of these 13 subjects then remained in the study.

Table II. Means of ABC-C Subscale Scores for each Study Phase

Phase		Irritability	Lethargy	Stereotypy	Hyperactivity	Excessive Speech
Placebo I	Mean	19.1563	7.6117	5.7192	19.5088	4.4208
	N	40	40	40	40	40
	Std. Deviation	9.96487	6.85336	5.62759	11.09785	3.24738
Low dose	Mean	11.1543	5.0609	4.0694	12.7874	3.1066
	N	39	39	39	39	39
	Std. Deviation	9.27712	5.95749	4.85798	11.37578	3.14898
High dose	Mean	13.3074	6.9778	5.1417	14.5889	3.3519
	N	36	36	36	36	36
	Std. Deviation	8.91781	6.36313	5.50612	12.43913	3.50492
Placebo II	Mean	18.2298	7.0374	6.4672	19.9515	3.9667
	N	33	33	33	33	33
	Std. Deviation	12.355533	7.62312	6.84421	15.04901	3.99945

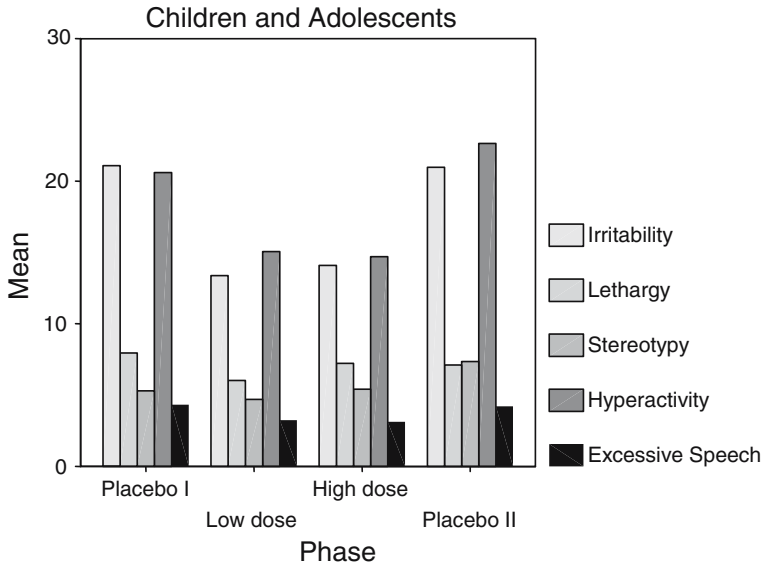

Fig. 3. Mean ABC-C Subscale Scores at the end of each Study Phase: Children and Adolescents.

Drug Effect—Maintenance Phase

Because risperidone doses were being gradually increased again following Placebo 2 in the initial maintenance weeks, week 3 of maintenance was the first data point for maintenance data analysis.

When the initial 2 weeks of maintenance dosage increase are excluded from the analyses, the Irritability score mean is relatively stable as can be seen in Fig. 4 ($n = 32$). The linear decreasing trend in ABC-C Irritability scores over time did approach significance ($F = 2.83$; df = 1,424; $p = .09$).

Predictors of Response

Only maintenance scores were examined for prediction of response. For gender, mood disorder, and concomitant antiseizure medications, all probability levels were not significant (p value ranged from .13 to .31). Level of MR and age group were significant predictors of response. However, these variables are confounded in the current study as only three subjects in the child age group were in the severe or profound MR groups. Thus, these findings require further study in the future. Subjects in the mild MR and profound MR groups showed a greater decrease in mean Irritability scores during maintenance than the other two MR groups, ($F = 3.94$; df = 3,421; $p < .0086$). Age group was a significant predictor of mean Irritability scores across the maintenance phase ($F = 32.41$; df = 2.28; $p < .0001$). Children had significantly higher mean maintenance Irritability scores than did adolescents and adults, and responded worse overall. Adolescents and adults did not differ significantly in this respect.

Side Effects

The last column in Table 1, "Dose Reduced" shows the 13 subjects in whom dose-halving was necessary due to side effects, notably sedation and gastrointestinal disturbance including nausea and abdominal discomfort. Dependent sample t-tests were used to evaluate whether the mean DISCUS total score

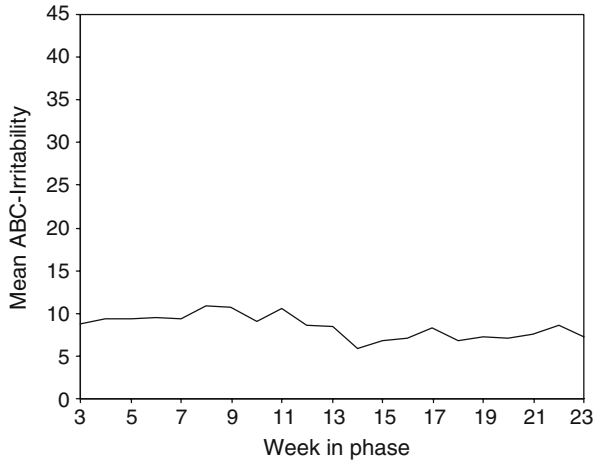

Fig. 4. Maintenance Phase Irritability Subscale Mean Scores ($n = 32$).

differed from Placebo 1 to the acute drug phase, and from the acute drug phase to Placebo 2. The mean DISCUS score did not change significantly in either analysis ($t = 2.01$; df = 36; $p = .052$; and $t = -.71$; df = 32; $p = .482$). The number of items scored positively on the DISCUS was extremely small in all phases; Placebo 1 (2.38 ± 5.11), acute drug (1.18 ± 3.25), and Placebo 2 (1.48 ± 3.62).

McNemar's tests demonstrated that only 8 of the 29 side effects were significant at the .05 level: drowsiness ($\chi^2 = 20.05$), increased weight gain ($\chi^2 = 15.43$), appetite ($\chi^2 = 14.45$), too quiet ($\chi^2 = 8.64$), not themselves ($\chi^2 = 6.86$), tremor ($\chi^2 = 6.75$), lack of spontaneity ($\chi^2 = 6.75$), and nasal congestion ($\chi^2 = 5.79$).

Clinical Observations of Side Effects

Sedation and gastrointestional complaints, in the high dose acute phase were intolerable in 13 of the 40 subjects, as mentioned above and shown in Table 1, but remitted on halving of the drug dose for the rest of that study phase, in the 7 of these subjects who remained in the study. One adult male developed severe akathisia with dangerous climbing on and jumping off furniture, which persisted after halving of the drug dose, and resulted in drop-out. Another adult male exhibited a significant increase in motor restlessness and lost 12.3 kg in weight during the acute phase. This subject's guardian chose for him not to proceed into the maintenance phase.

An adult male developed recurrent oculogyric crisis early in maintenance. This resolved after dividing the original risperidone dose of 1.5 mg/day into smaller doses of 0.5 mg given eight hourly. Neuroleptic malignant syndrome and tardive dyskinesia were not observed.

Weight gain greater than 3 kg occurred in 28 of 40 subjects (70%) during the study. Mean weight gain over the 46 weeks was 7.9 kg for children, 8.3 kg for adolescents, and 6.0 kg for adults (see Table III). Tapering off in weight gain was observed in only 10 of the 40 subjects during maintenance. While CDC norms of natural growth are not used for comparison of the expected weight gain during growth of children and adolescents, the weight gain recorded is clearly excessive. Laboratory test results showed no cases of significant liver enzyme elevation, nor of elevated glucose. Measures of hemoglobin A1c and serum lipids remained normal in the subgroup of 20 subjects.

Prolactin findings will be published separately (Hellings *et al.*, 2005).

DISCUSSION

We present a longitudinal study, comparing risperidone to placebo in the treatment of aberrant behaviors in children, adolescents, and adults with MR. Risperidone was significantly more effective than placebo, acutely for 22 weeks, and for an additional 6 months. Over half (57.5%) of subjects met criteria for full response, while 87.5% met criteria for partial response. Mean irritability levels during maintenance were significantly higher in children than in adolescents or adults.

Gender, diagnosis of autism, mood disorder diagnosis, or concomitant seizure medications did not alter response. Level of MR merits further study, since the groups were small. Although comorbid diagnosis was made using DSM-IV criteria as closely as possible, many subjects met criteria for multiple comorbid Axis I diagnoses. It was not possible to achieve the statistical power necessary to examine response according to diagnostic comorbidity; a large multicenter study would be necessary to examine this.

The heterogeneity of the study sample in terms of age groups, comorbidity, levels of MR, living situations, previous epilepsy and ASD, in part renders the findings applicable to a broad clinical population. In addition, half of the subjects were in severe and profound MR categories. Also the relatively long study duration, comprising a 22-week acute trial with a 24-week follow-up, allowed observation for tardive dyskinesia and chronic side effects including weight gain.

Limitations

Since the sample was heterogeneous, subgroups were relatively small for examining predictors of response. Rater blinding can be compromised by a crossover design, since subjects receive the drug at somewhat predictable stages, and drug response and side effects may be obvious to a single rater. The unusual design of this study may render results more difficult to interpret. However, recent analysis of placebo-controlled drug studies showed that so-called blinded raters could predict subjects' medication or placebo status most of the time, and that this is a common problem of unblinding that occurs in drug studies in general (Vitiello, 2002). The broad age-group range may be another limitation, however it is important to compare drug response and side effects in different age groups. Another limitation is that IQ

Table III. Weight (kg) and Total Change in Weight Each Study Phase End

	Age	Baseline/ PBO Wt.	Drug	Placebo 2	Acute Phase Change[a]	Maint.	Maint. Phase Change[b]	Total Change
Children								
1	8	NA	31.8	29.5	NA	34.8	3	3
2	8	29.5	36.3	36.5	6.8	39.3	3	9.8
3	8	24.1	25.5	24.5	1.4	26.8	1.8	2.7
4	9	38.6	41.3	39	2.7	50	8.7	11.3
5	10	32.3	36.3	35.9	4	36.3	0	4
6	10	35.4	39.1	37.3	3.6	39	0	3.6
7	10	28.2	30.9	32.7	2.7	37.3	6.4	9.1
8	11	33.2	40	41.4	6.8	50.9	10.9	17.7
9	11	74.1	70.9	NA	−3.2	NA	NA	NA
10	11	45.2	44.7	45	−0.5	45	0.3	0.3
11	12	43.6	53.2	51.4	9.6	59	5.8	15.4
12	12	24.1	29.1	29.1	5	NA	NA	NA
13	12	45.5	53	53.6	7.5	55.9	2.7	10.2
Mean		37.8	40.9	38	3.9	43.1	3.9	7.9
Standard deviation		13.7	12.3	8.8	3.6	9.9	3.6	5.6
Adolescents								
14	13	unreliable						
15	14	32.7	35.4	NA	2.7	38.2	2.8	5.5
16	15	42.3	40.9	44	−1.4	NA	NA	NA
17	15	34.1	37.3	38.6	3.2	42.5	5.2	8.4
18	15	39.5	42.3	43.2	2.8	NA	NA	NA
19	16	46.5	46.8	45.4	0.3	44.5	−2.3	2.6
20	16	71	78.6	77.5	7.6	87.7	9	16.6
21	16	unreliable						
Mean		44.3	46.9	49.7	2.5	53.2	3.7	8.3
Standard deviation		14	16	15.7	3	23.1	4.7	6
Adults								
22	19	67.3	70	71.8	2.7	70.9	0.9	3.6
23	20	57.5	63	62	5.6	63	0	5.6
24	20	NA	92.7	NA	NA	NA	NA	NA
25	22	56.4	57.2	NA	0.8	62.2	5	5.8
26	23	70	65.4	NA	4.5	65.4	0	4.5
27	25	76	0.8	78	3.6	80.9	0.9	4.5
28	27	55	55	58.2	0	62.3	7.2	7.2
29	30	68	55.2	55.6	−12.8	NA	NA	NA
30	30	98	101.8	101.8	3.8	103.6	1.8	5.6
31	30	57.2	59	39.5	1.8	57.3	2.8	4.6
32	31	90.4	92.3	92.3	1.8	102.5	8.9	10.7
33	31	69.5	73.1	70	3.6	NA	NA	NA
34	35	61.8	63.8	60.6	2	59.5	4.31	6.31
35	40	68	64	NA	4	NA	NA	NA
36	43	62.2	60.4	60	−1.8	64.5	4.1	2.3
37	45	69.5	74.1	74.1	4.5	79.1	5.3	9.6
38	50	48.6	53.4	52.7	4.8	54	0.6	5.4
39	51	84.1	87.7	NA	3.6	92.2	4.5	8.1
40	56	103.2	108.4	105.2	5.2	108	0.2	5.4
Mean		70	68.3	70	2.1	75	3.2	6
Standard deviation		15	23.3	18.9	4.2	18.3	3	2.4

[a]Acute Phase Change: Weight change from baseline to end of Acute Blinded Phase.
[b]Maintenance Phase Change: Weight change from Baseline to end of Maintenance.

testing was only performed if not completed within the past 3 years: 12 of the 40 subjects were retested. Autism spectrum disorders were diagnosed by clinical history and mental status using DSM-IV criteria, rather than autism diagnostic scales, another potential methodological weakness.

Clinical Implications

In terms of safety, the most significant side effects ($p < .001$) were increased appetite, weight gain and drowsiness. As noted, we found it necessary to modify the study design to diminish serious drowsiness and gastrointestinal side effects. Increased appetite was noted within the first 4–6 weeks of the study, primarily manifesting as a lack of satiation in most subjects. The mean weight gain was significant, notably 7.9 kg for children, 8.3 kg for adolescents, and 6.0 kg for adults (See Table III). Individuals with MR, with less autonomy and ability to take control of the weight gain side effect, are at greater risk than the general population for experiencing ongoing weight gain and its serious medical consequences. Since drug treatment of aberrant behavior is most often chronic, the feasibility and effectiveness of concomitant diet and exercise merit urgent study. Although weight control strategies were not part of the study design, weight gain was halted in 1 subject in whom dietary restriction was introduced by her parents for the duration of the maintenance phase. An additional 9 subjects did not gain further weight. Serious health risks of long-term obesity include increased rates of stroke, cardiovascular disease, diabetes, hyperlipidemia, arthritis, and carcinoma (Kawachi, 1999), as well as sleep apnea and right-sided cardiac failure.

There were no cases of tardive dyskinesia or neuroleptic malignant syndrome in the study lasting almost a year. Ocular dystonia, in the form of oculogurus, occurred in 1 male subject. This subject's problem responded to dose division into 3 smaller doses of 0.5 mg each. Two young male subjects manifested significant akathisia. Overall, very few items were scored positively on the DISCUS. Seizure recurrence developed in one of nine subjects with a history of epilepsy; no other subjects developed seizures.

CONCLUSIONS

Risperidone was significantly more effective than placebo for treating serious problematic behaviors in children, adolescents and adults with all levels of MR, for up to 46 weeks. Low doses were equally effective but better tolerated than high doses. Increased appetite, ongoing weight gain, and sedation were significant side effects. More studies are warranted that examine prolactin level systematically, and incorporate early weight control strategies. Weight gain associated with risperidone treatment may be greater in this population than for non-developmentally disabled individuals.

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