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Cognitive Effects of Risperidone in Children with Autism and Irritable Behavior

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Abstract

Objective: The objective of this research was to explore the effects of risperidone on cognitive processes in children with autism and irritable behavior.
Method: Thirty-eight children, ages 5–17 years with autism and severe behavioral disturbance, were randomly assigned to risperidone (0.5 to 3.5 mg/day) or placebo for 8 weeks. This sample of 38 was a subset of 101 subjects who participated in the clinical trial; 63 were unable to perform the cognitive tasks. A double-blind placebo-controlled parallel groups design was used. Dependent measures included tests of sustained attention, verbal learning, hand-eye coordination, and spatial memory assessed before, during, and after the 8-week treatment. Changes in performance were compared by repeated measures ANOVA.
Results: Twenty-nine boys and 9 girls with autism and severe behavioral disturbance and a mental age ≥18 months completed the cognitive part of the study. No decline in performance occurred with risperidone. Performance on a cancellation task (number of correct detections) and a verbal learning task (word recognition) was better on risperidone than on placebo (without correction for multiplicity). Equivocal improvement also occurred on a spatial memory task. There were no significant differences between treatment conditions on the Purdue Pegboard (hand-eye coordination) task or the Analog Classroom Task (timed math test).
Conclusion: Risperidone given to children with autism at doses up to 3.5 mg for up to 8 weeks appears to have no detrimental effect on cognitive performance.

Introduction

Literature focusing on the cognitive effects of atypical antipsychotics in children and adolescents is exceptionally sparse. The bulk of the literature currently comes from studies of adults with schizophrenia; in addition there are a few investigations with patients having Alzheimer's disease. Given that antipsychotics often cause sedation, many investigators and clinicians have wondered if cognitive blunting and/or sedation accompanying early treatment may impair cognition (Ernst et al. 1998; Aman 1984; Aman et al. 1991). The possibility of cognitive impairment seems likely in the short term, as somnolence is a frequent side effect of atypical antipsychotics, especially early in treatment. However, a detailed analysis of adverse events from risperidone treatment in children with autism indicated that reports of somnolence usually dissipated between 2 and 4 weeks after the last dose adjustment of risperidone (Aman et al. 2005). Thus

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it seems that the time of greatest "risk" of cognitive impairment would be in the earliest weeks of treatment.

Literature from adult trials in schizophrenia, have provided us with some insight into the cognitive effects of these drugs. Keefe et al. (1999) conducted a review of 15 studies in which adult patients with schizophrenia were assessed for cognitive effects while taking atypical antipsychotics (AAPs). Contrary to cognitive impairment, they reported improvements in attention, executive function, and visuospatial processes. Purdon (1999) found a handful of studies reporting beneficial effects of AAPs in verbal fluency, verbal learning, and visuomotor tracking. In both reviews, the authors suggested that the results of the studies be interpreted with caution, as many studies lacked sufficient controls (e.g., placebo control, double-blind status, and baseline scores). In a few of the studies that did have baseline scores, there was some uncertainty regarding medication status at baseline.

In a more recent review of 26 studies, Stip et al. (2005) analyzed the effects of AAPs on cognitive-motor functioning in adults with schizophrenia. This review concluded that a variety of AAPs (risperidone, clozapine, quetiapine) improved attention in six studies but showed no change in nine. Please note that summaries often do not total to 26, because not all studies addressed all possible cognitive-motor domains and some studies included more than one relevant measure on the domain under discussion. The authors reported one study of clozapine in which attention was negatively affected. In the area of verbal and working memory, the authors reported that clozapine, olanzapine, quetiapine, and risperidone improved functioning in 12 comparisons while showing no change in 17. Finally, when the authors reviewed the research on motor performance, they found that treatment with the atypicals risperidone, clozapine, and olanzapine was associated with improved motor functioning in four studies and no change in four others. The findings of these adult trials suggest that the atypical antipsychotics do not have an adverse effect on cognitive-motor functioning. Indeed, there is some evidence that AAPs may even enhance function.

Recently a few studies have assessed cognitive effects of risperidone in children with severe behavioral disturbance. Günther et al. (2006) assessed open-label risperidone in 23 children with attention-deficit/hyperactivity disorder (ADHD) and disruptive behavior disorders (DBDs) and in normal controls matched for age and IQ. No effect of medication was found on three tests of sustained and selective attention (continuous performance, divided attention, and Go/No-Go tasks). Troost et al. (2006) tested 24 children with autism spectrum disorders [autism, pervasive developmental disorder not otherwise specified (PDD—NOS), Asperger's disorder] and found 12 (50%) to be testable on focused attention and divided attention tasks. All participants were shown to be responders to risperidone in a previous clinical trial, and risperidone was withdrawn and gradually replaced with placebo for half of the participants after 24 weeks of treatment. Troost et al. found that performance on the divided attention task (considered to be an index of working memory) deteriorated significantly for subjects receiving placebo substitution in comparison to those maintained on risperidone.

Although, rarely considered in clinical trials, it has been established that environmental variables can influence the effects of pharmacotherapy (Yoo et al., 2003). In their study of two doses of risperidone and tangible reinforcement, Yoo et al. (2003), found that risperidone caused a decrease in response rate and an increase in response time when compared with placebo on a timed visual matching discrimination task. However, these changes were much smaller when tangible reinforcement was added to the risperidone alone condition. The investigators suggested that the added reinforcement had a protective effect on the rate decreasing effects of risperidone.

Pandina et al. (2007) reported on the 6-week acute effects of risperidone and placebo in 228 children with DBDs and subaverage IQ ($\leq$84). The cognitive tasks were a continuous performance task (CPT) and a Children's Verbal Learning Task modified from the California Children's Verbal Learning Test (Delis et al. 1994). The design was a 6-week, parallel-group, comparison of placebo and risperidone (0.02 to 0.06 mg/kg/d). There were no drug-group differences in cognitive functioning in the acute trials.

Finally Aman et al. (in press) assessed 16 children maintained on risperidone (mainly for DBDs) on a computer-controlled cognitive-motor test battery. Subjects were assessed on their regular dose of risperidone and then assigned to one of two drug orders: placebo-risperidone or risperidone-placebo, each of which lasted 2 weeks. Assessments included a Match-To-Sample Memory task, a Short-Term Recognition Memory (STM) test, a Continuous Performance Task (CPT), performance on the Graduated Holes Task (index of static tremor), and seat activity electronically recorded during the memory and CPT tasks. Response time was significantly shorter with risperidone on the STM task, seat activity was significantly lower with risperidone during the STM task, and static tremor was significantly lower with risperidone than placebo on the Graduated Holes Task.

Thus, on balance, most variables failed to show significant changes due to drug condition in these studies with children. However, when they did occur, changes favored risperidone in the Troost et al. (2006) study (working memory) and in the Aman et al. (2007) study (response time, seat activity, static tremor). The present study was designed to test whether risperidone has an effect on cognitive performance in children with autism accompanied by serious behavior problems. This was an exploratory comparison, as no data were available with AAPs in children with autism at the time of the trial. The null hypothesis is that there would be no differences between placebo and risperidone.

Method

Design

This was a multi-site investigation that was conducted at five medical centers. This study used an acute, double blind, placebo controlled, parallel groups design. After being assessed at the screen visit, participants who met inclusion criteria for the study were then reassessed with clinical instruments at baseline and weekly for the next 8 weeks. Matched placebo and risperidone were provided by the manufacturer (Janssen Pharmaceutica) in tablet form. A flexible dosing schedule was based on the participant's weight, time in the study, clinical response, and emergence of adverse events (see Research Units on Pediatric Psychopharmacology [RUPP] Autism Network, 2002). Cognitive assessments were

conducted at baseline, 4 weeks, and 8 weeks. For any participant who terminated either condition prematurely, the last observation was carried forward to endpoint. Participants' parents or legal guardians provided written informed consent as approved by institutional review boards of the five participating universities.

Study participants

Participant characteristics, study design, and outcome measures have been described in detail in previous publications (Arnold et al., 2000; RUPP Autism Network, 2002; Scahill et al., 2001). Study participants were male and female children or adolescents, ages 5 to 17 years 2 months, with mental ages ≥18 months who had autism and severe behavioral disturbance. To be enrolled in the study, participants received a score of ≥18 on the Irritability subscale of the Aberrant Behavior Checklist (ABC) (Aman and Singh 1994). In addition, participants must have been rated with a Clinical Global Impressions-Severity (CGI-S) score of ≥4 by an experienced clinician (CGI-S; NIMH 1985, Arnold et al. 2000), and according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (American Psychiatric Association, 1994) a lifetime diagnosis of autistic disorder. The diagnosis of autism was based on a clinical evaluation that included a DSM-IV interview with a parent and direct observation of the participants. The clinical diagnosis was corroborated by structured interview with one or more parents acting as informants, using the Autism Diagnostic Interview—Revised (Lord et al. 1994).

Exclusion criteria included positive Beta HCG test for girls; significant medical condition; past history of neuroleptic malignant syndrome; and, because of dosing considerations, weight less than 15 kg. Originally, 52 children and adolescents were randomly assigned to placebo and 49 to risperidone, for a total of 101 study participants. The total number of subjects who had scorable cognitive measures at baseline and at lease one subsequent visit was 38 (37.6%) and, depending on which test was administered, the sample sizes ranged from 8 subjects to 30. Eighteen of the 38 subjects were assigned to placebo and 20 to risperidone. The remaining 63 (62.4%) subjects were not testable either due to the severity of their cognitive impairment and/or disruptive behavior.

Procedures

Any participants receiving psychotropic medicines before the study went through a washout for at least 2 weeks prior to randomization (4 weeks for antipsychotics or fluoxetine). Cognitive assessments were done at Baseline, Week 4 and Week 8. Participants were started at either 0.25 or 0.50 mg with gradual adjustments over the first four weeks. Maximum dose for smaller subjects (15—45 kg) was 2.5 mg/day, whereas the maximum dose for larger participants (>45 kg.) could be as high as 3.5 mg/day.

Outcome measures

The following cognitive measures were obtained.

California Verbal Learning Task–Children's Version (VLT-C) and Modified VLT-C (MVLT-C) (Delis, Kramer, Kaplan, & Ober, 1994). The VLT-C and the MVLT-C measure verbal memory over brief and intermediate periods of time. Respondents were presented with a 10- (MVLT-C) or 15-item (VLT-C) list of nouns on five separate learning trials; most participants were tested with the MVLT-C. The subjects were asked to recall the words in any order after each trial (measuring Immediate Free Recall). Once the Trial 5 responses were recorded, the examiner administered the Cancellation Task (see below). This took approximately 10 minutes and prevented subjects from rehearsing the original verbal learning list. Following the Cancellation Task, subjects were asked to recall as many of the words as possible (Long Delay Free Recall). Finally, we administered one Recognition Trial to the respondents, in which previously-presented and new words were used. Subjects then had to determine whether they had heard the word prior to the recognition trial by indicating "yes" or "no" to the examiner.

The dependent measures for the MVLT-C included the total number of words correctly recalled on learning Trials 1-5 (reflecting verbal memory with exposure and practice), the total number of words correctly recalled after the 10-minute delay (i.e., Long Delay Free Recall), and Recognition Score (by taking the sum of the number of correctly-recognized words and the number of non-list words correctly rejected divided by the total number of words).

The Visuospatial Memory Test ("Dot Test") (Keefe et al. 1997). The spatial memory test has been shown to be sensitive to pharmacological treatment in adults having schizophrenia or Alzheimer's disease. It tests the ability to recall the location of a black dot on a blank sheet of 8.5 by 11 inch paper immediately or following a 10-second delay. The test has 20 trials. Participants were asked to reproduce the position of the dot on a blank page. Participants sat at a desk in front of a stack of paper that had the numbers 1 to 20 on the back. Trials 1-8 consisted of the no-delay trials and trials 9-20 were the delayed trials (i.e., 10 seconds). During the delayed condition, participants were required to name pictures of common objects taken from the Peabody Picture Vocabulary Test—Revised (Dunn et al. 1981) to prevent verbal rehearsal.

Using a metric ruler and a transparent scoring template, and a scoring sheet the examiner measured in millimeters the difference between the stimulus dot and the respondent's dot on each of the 20 trials. The dependent measures for this protocol included the average no-delay distance, the average 10-second delay distance, and the difference between the two conditions (i.e., averaged delayed recall distance minus the no-delay distance).

Cancellation Task (Barkley, 1991). In this commonly-used test of attention span, the participant was required to scan rows of geometric figures (circles, triangles, stars, diamonds, and squares) and to cancel the target figure, which was a square. All other figures were to be left un-cancelled. Participants were given 5 minutes in which to cancel 6 pages of stimuli. Correct detections, failures to mark squares (errors of omission), and cancellation of non-targets (errors of commission) were recorded as dependent variables.

Purdue Pegboard Task (Tiflin, 1968; Tiflin and Asher, 1948). Our modified version of the original Purdue Pegboard Test was a measure of hand-eye coordination. It re-

quired the participant to insert as many pins as possible into a column of holes on a wooden pegboard. Each trial lasted 40 seconds. The assessment entailed one practice trial, followed by three test trials with each hand. The total number of pins correctly inserted was recorded. Study participants alternated between their dominant and non-dominant hands, and the examiner left all pins in place until both the dominant and non-dominant hands had been tested. The examiner then counted and recorded the number of pins inserted by each hand. Dependent measures for this protocol consisted of the total number of pegs inserted for each hand and the total number of "drops" for each hand.

Classroom Analogue Task (Handen et al., 1990). Prior to giving the Analogue Classroom Task, the child's math ability was determined by the Wide Range Achievement Test (WRAT) (Wilkinson, 1993). The WRAT was given only once and was used solely to determine the participant's math capability and the level at which to conduct testing. The Classroom Analogue Task involved presenting participants with numerous ability-appropriate math problems. These problems ranged from very basic [matching numbers to the size of sets (e.g., finding the correct numeral from 2, 3, 4, 5 when a set of 3 ducks was presented)] to more conventional addition and subtraction. Seven-minute work samples were derived from each participant. The task has been extensively used in ADHD research and in work with developmentally disabled patients (Handen et al. 1990), and it has been found to be sensitive to the use of psychostimulant medication (Aman and Pearson, 1999). The dependent measures consisted of the total number of math problems that the participant attempted and total number correctly calculated. The Analogue Classroom Task took 7 minutes to administer.

Consensus rulings on mastery and valid data

Prior to data analysis, the cognitive assessors from each site prepared operational criteria for judging ambiguous responses and for determining whether subjects had mastered the tasks or were simply responding randomly. For example, on the Cancellation Task we determined that the pencil mark had to actually touch the geometric form in order to be counted (rather than to merely be in its proximity). We also determined that direction of cancellations (left to right and vice versa) did not invalidate performance on this task, although it might influence the count of omission errors (Written consensus operational rules available on request from MGA or JAH.)

Statistical analyses

Analyses were carried out for the children who had valid task measures. Mastery was determined by a set of operational principles applied by the tester at each site, in consultation with all other testers, before the blind was broken. The first analyses were *t*-tests and ChiSquare tests to determine if children with mastery differed from those who did not on the following variables: Age, IQ, Irritability subscale score on the ABC, gender, and CGI-Severity score at baseline. Cognitive data were analyzed as a function of Drug (2 levels; placebo vs. risperidone) and by Time (3 levels, within participants). The General Linear Models package in SPSS was used to analyze the results with repeated measures ANOVA tests (SPSS, 2003). Effect sizes (partial eta squared, η_P^2) were provided in addition to p values. Partial eta squared is the proportion of the effect plus the error variance that is attributable to the effect in the sample. It is not additive as is the squared correlation ratio and according to Keppel and Wickens (2004), it is often the most useful measure of effect for within subject designs. In all tests, p values $\leq .05$ were used to indicate statistical significance.

Results

Subjects

Of the 101 participants in the clinical trial of risperidone vs. placebo, 38 (37.6%) were able to provide valid cognitive measures. Of these 38 participants, 12 (31.6%) were risperidone responders, 8 (21%) were risperidone nonresponders and 18 (47.4%) were randomized to placebo. Of the 63 (62.4%) participants who were unable to complete valid cognitive measures, 22 (34.9%) were risperidone responders, 7 (11.1%) were risperidone non-responders and 34 (54%) were randomized to placebo. Characteristics of the 38 participants including functional level, ethnicity, class placement, and parent educational level are presented in Table 1. The modal functional level was mild intellectual disability (n = 18), with average/borderline (n = 8) and moderate intellectual disability (n = 8) also quite common. Ethnically, the large majority was white, and educationally most participants were assigned to special classes. Educational levels of the primary caregivers were quite high, with 19 parents having a university degree or higher and only one parent without a high school diploma (Table 1). When these participants were compared with those who failed to achieve mastery, the following differences were found: (a) IQ was higher for the Mastery group [t (86) = 5.11, $p \leq .001$ (M = 62.6 and 39.6, respectively)]; (b) age was higher for the Mastery group [t (99) = 2.05, p = .04 (M = 9.0 and 7.9, respectively)]. No differences were found for ABC Irritability score, CGI-Severity score, or gender, although Irritability scores and CGI-Severity tended to be nonsignificantly higher (worse) for the non-Mastery group.

Cognitive measures

Table 2 shows the outcome means (and SDs) for Drug by Time on the Cancellation Task, Analogue Classroom Task, and the Verbal Memory Test. The table shows the outcome means (and SDs) and partial eta values (η_P^2) for Baseline, Week 4 and Week 8, for Time and the Drug by Time interaction. Analysis of variance indicated two significant effects attributable to Drug (i.e., the interaction of Time and Drug). Risperidone resulted in more correct detections than placebo on the Cancellation Task [F (1, 17) = 3.18, p = .05, η_P^2 = .16] and more correct recognitions than placebo on the Verbal Learning Task, [F (1, 13) = 4.42, p = .05, η_P^2 = .20]. Immediate recall on the Verbal Learning Task in both drug conditions showed a significant effect of Time (suggesting a significant practice effect).

Table 3 shows the outcome means (and SDs) for Drug by Time on the Purdue Pegboard Test and the Visuospatial Memory Test. On the Purdue Pegboard, dominant hand insertions showed a significant effect over time for *both* treatments (i.e., a practice effect). Results indicated no significant

TABLE 1. SAMPLE CHARACTERISTICS (N = 38)*

Age, yr, mean ± SD (range)	9.42 ± 2.96 (5–17 yrs)
Sex, no. (%)	
Male	29 (76.3)
Female	9 (23.7)
Race, no. (%)	
White	31 (81.57)
Black	2 (5.26)
Asian/Pacific Islander	3 (7.89)
Hispanic	2 (5.26)
Functional level, no. (%)**	
Average/low average ability	8 (21.05)
Mild intellectual disability	18 (47.36)
Moderate intellectual disability	8 (21.05)
Severe intellectual disability	1 (2.63)
Profound intellectual disability	2 (5.26)
Daily dose risperidone (mg), mean ± SD***	1.12 ± 0.44
Class placement, no. (%)	
Regular school class	4 (10.53)
Special class	30 (78.94)
MRDD school	4 (10.53)
Primary caregiver education level, no. (%)	
Graduate degree	8 (21.05)
University degree	11 (28.95)
Some college	7 (18.42)
Trade school	3 (7.89)
High school	8 (21.05)
<High School	1 (2.63)

*There were 63 children who could not be successfully assessed. Testable participants had a significantly higher IQ (23 points higher) and higher mean age (9.0 vs. 7.9 years) than the untestable subjects.
**IQ score unavailable for one subject.
***Range = 0.5–2.0 mg/day.

effect attributed to drug (i.e., the Time by Drug interaction). The Visuospatial Task (Dot Test) showed a significant effect of Drug by Time favoring risperidone on the difference score between immediate recall of the dot's placement (average distance) and the delayed recall of the dot's placement (average distance–delay), [F (1,6) = 5.22, p = .05, η_p^2 = .46]. We noted a significant baseline difference (p = .05) by t-test, so we reanalyzed this variable by analysis of covariance (ANCOVA). With this comparison, the interaction term was no longer significant [F (2,5) = 3.29, p = .12].

Discussion

As noted earlier we were able to evaluate the cognitive performance of 38 children with autism. These 38 participants were similar to the remaining 63 (those unable to perform the cognitive tests) on CGI-Severity score, ABC Irritability score, and gender. Not surprisingly, the participants who could be tested had higher IQs (about 23 points, on average), and they were older (9.0 vs. 7.9 years). Thus, there were important differences in presumed cognitive ability and maturity, but they were similar in terms of symptom severity and gender. However, of those assigned to risperidone, similar proportions of responders and nonresponders could perform the cognitive tests. These findings have implications for generalizability of the findings, a point that we return to later.

No declines, significant or otherwise, were indicated in the measures of attention (i.e., Cancellation Task, timed math test), hand-eye coordination (Purdue Pegboard), or short term verbal memory (verbal learning task). Conversely, significant improvement occurred with risperidone in two areas of cognitive processing, namely on the Cancellation Task (correct detections) and on the Verbal Learning Task (correct recognitions); improvement occurred equivocally on the Spatial Memory Task (Dot Test, difference score). Whereas this stability of cognitive performance may appear to be at odds with reported tiredness with risperidone (Aman et al., 2005), the two are not necessarily inconsistent. For example risperidone caused a large reduction in irritable/disruptive behavior (E.S. = 1.20) and hyperactivity (E.S. = 1.00), which may have enabled the participants to perform as well or better, even if somnolence were present.

Purdon's (1999) review of atypical antipsychotic studies in adults with schizophrenia suggested enhancement in the areas of verbal fluency and attention, although he cautioned that some investigations used open-label designs. In our study, subjects taking risperidone showed significant improvement compared with controls on verbal learning *recognition* performance but not on short-term or delayed recall.

TABLE 2. FINDINGS FOR CANCELLATION, ANALOGUE CLASSROOM, AND VERBAL LEARNING TASKS

	Placebo Mean (SD)			*Risperidone Mean (SD)*			*ANOVA Results*		
Cognitive Assessments	*Baseline*	*Week 4*	*Week 8*	*Baseline*	*Week 4*	*Week 8*	*F Time*	*F Drug x Time*	η_P^2 *Drug x Time*
Cancellation Task									
Correct Detections	110.71 (56.3)[a]	76.43 (63.9)	95.29 (59.7)	126.75 (46.9)[b]	131.33 (40.3)	138.50 (59.7)	2.10	3.18*	.16
Commissions	2.29 (4.3)	5.29 (5.6)	4.09 (9.7)	6.50 (22.2)	0.00 (0.0)	0.08 (0.3)	.23	1.03	.06
Omissions	19.00 (20.3)	29.57 (35.5)	27.57 (33.8)	11.75 (22.6)	5.83 (9.8)	10.00 (19.3)	.22	1.24	.07
Analogue Classroom Task									
Number Attempted	31.63 (11.0)[c]	29.25 (13.6)	32.50 (15.7)	22.88 (14.7)[d]	19.63 (9.3)	24.50 (5.8)	.74	.03	.00
Number Correct	24.50 (10.5)	21.38 (13.8)	26.63 (18.0)	19.25 (11.4)	17.75 (8.8)	20.50 (6.6)	.81	.08	.01
Verbal Learning Task									
Immediate Recall	25.00 (8.8)[e]	28.00 (11.4)	29.88 (8.9)	28.50 (11.9)[f]	31.92 (12.4)	31.92 (11.6)	5.48**	.28	.015
Delayed Recall	4.67 (2.9)[g]	6.33 (8.4)	4.83 (2.9)	6.20 (4.6)[h]	4.80 (3.8)	7.40 (2.7)	.15	1.31	.09
Recognition	81.00 (11.6)[i]	66.33 (9.0)	75.00 (14.0)	77.89 (19.1)[j]	85.23 (16.5)	83.17 (15.4)	.60	4.42*	.25

Sample sizes differ because many of the participants could not do all cognitive tasks and, in some cases, subjects could not perform all parts of the given task. [a]n = 7. [b]n = 12. [c]n = 8. [d]n = 8. [e]n = 8. [f]n = 12. [g]n = 6. [h]n = 10. [i]n = 5. [j]n = 10.

* $p \leq 0.05$, ** $p \leq 0.01$.

TABLE 3. FINDINGS FOR PURDUE PEGBOARD AND SPATIAL MEMORY TASKS

	Placebo Mean (SD)			*Risperidone Mean (SD)*			*ANOVA Results*		
Cognitive Assessments	*Baseline*	*Week 4*	*Week 8*	*Baseline*	*Week 4*	*Week 8*	*F Time*	*F Drug x Time*	η_P^2 *Drug x Time*
Purdue Pegboard									
Dominant hand insert	24.08 (10.5)[a]	27.61 (13.0)	28.38 (13.9)	32.76 (17.4)[b]	32.82 (19.2)	34.59 (16.0)	3.13*	1.06	.04
Nondominant hand insert	22.38 (9.9)	26.00 (7.3)	24.23 (10.3)	26.82 (18.4)	29.23 (17.4)	29.53 (14.7)	.14	.80	.01
Dominant hand drops	2.77 (2.4)	3.08 (2.3)	3.00 (2.6)	2.35 (1.9)	3.76 (3.4)	4.00 (3.4)	1.86	.94	.03
Nondominant hand drops	2.31 (2.4)	3.77 (3.2)	3.54 (2.9)	3.24 (3.0)	2.59 (2.0)	4.00 (3.0)	1.25	1.53	.05
Both hands inserts	46.46 (19.5)	51.62 (19.2)	52.62 (23.2)	59.59 (35.3)	62.06 (36.1)	64.12 (30.0)	2.91	.47	.02
Both hands drops	5.08 (4.3)	6.85 (4.9)	6.54 (4.9)	5.59 (4.0)	6.35 (4.8)	8.00 (5.5)	2.10	.52	.02
Dot Test									
Average Distance	3.52 (1.8)[c]	2.47 (.79)	2.90 (1.3)	2.40 (1.0)[d]	2.75 (.96)	2.57 (1.3)	.74	2.75	.31
Average Distance - Delay	4.95 (2.2)	6.12 (2.8)	5.27 (2.6)	7.19 (2.34)	5.19 (3.0)	5.08 (2.4)	.64	2.28	.27
Difference	1.43 (1.5)	3.65 (2.4)	2.38 (2.9)	4.79 (2.0)	2.44 (2.2)	2.52 (2.0)	.51	5.22*	.46

Sample sizes differ because many of the participants could not do all cognitive tasks. [a]n = 13. [b]n = 17. [c]n = 4. [d]n = 4.
* $p \leq 0.05$.

Current literature is mixed regarding the effect of risperidone on spatial memory. Results from Reilly, Harris, Keshaven and Sweeney (2006), in subjects with schizophrenia, showed worsening of deficits in the maintenance of spatial working memory. In contrast, a comparison of clozapine and risperidone in patients with schizophrenia conducted by McGurk et al. (2005) found improvements in spatial memory with risperidone and worsening with clozapine. Our study suggests an equivocal improvement in delayed spatial memory for the risperidone group compared to placebo controls. (Loss of significance with the ANCOVA may have been due merely to reduced degrees of freedom, given the smallness of the sample.)The "significant" finding was based on a difference score between no-delay and delay conditions, and only 8 participants could conduct the task. As the finding of improvement with risperidone can result from worsening in the no-delay or improvement in the delay condition with risperidone (or the opposite with placebo), this "significant" outcome needs replication.

The choice of cognitive-motor tasks in children with developmental disabilities has varied greatly, and results have also differed across cognitive constructs. Results of the cancellation task used in this study suggest that the risperidone-treated participants were more task oriented than placebo-treated subjects. This is not consistent with the Günther et al. (2006) study, which found no risperidone effects on attention in adolescents with ADHD. However, in Troost et al. (2006) and in the present study, aspects of memory and attention did improve (Troost et al., characterized their divided attention task as an index of working memory.) Findings for the Verbal Learning test differed from the Pandina (2007) study in that we observed enhanced word recognition with risperidone, but Pandina et al. did not. (However, Pandina et al. did report improvements in uncontrolled one year open-label extension studies.) We are not aware of any other study with children having pervasive developmental disorders in which the Visuospatial Memory Task has been used. This is not surprising in that it proved to be very difficult to convey instructions to these children on how to perform the Dot Test.

Children with autism and accompanying irritable behavior are exceptionally difficult to assess for cognitive change. Troost et al. (2006) commented that a testable rate of 50% of children with PDDs was "very favorable" and "would have been lower if a larger proportion of the children . . . had an autistic disorder." (pg. 571) Indeed, only 2 of 14 participants (14.3%) in the Troost et al. study had a diagnosis of autism, whereas the remainder had PDD—NOS or Asperger's disorder. Our study was conducted exclusively with children having autistic disorder accompanied by serious behavior problems. Furthermore, the large majority of the original sample (83%) had intellectual disability. Collectively, these features made this group of children very challenging to test. As such, our data may provide important information on the selection of cognitive-motor tasks in this population. The Purdue Peg Board task was clearly the easiest for these youngsters to understand. By contrast, the "Dot Test" was remarkably difficult for them to grasp. The MVLT-C, Cancellation Task, and Analogue Classroom Task were of intermediate difficulty. It is easy to see how all of these latter tests may reflect important skills that are relevant to learning in traditional classroom settings. The advantages of being able to sustain attention better over time (as in the Cancellation task) and to be more capable of recognizing previously-heard words would seem apparent both in academic settings and in real life. Likewise, enhanced memory for location (Visuospatial Task) would seem to carry advantages in real-life settings as well. As partial eta squared ranged from .16 to .46, this indicates that the drug condition actually accounted for substantial amounts of variance in these outcome variables. Nevertheless, it is also somewhat reassuring that there were no indications of risperidone-associated deterioration on any of the other variables.

Limitations

This study has several limitations that caution against over-embracing the statistically-significant (and one equivocal) findings. First, given the exploratory nature of this work (there is only one other study of atypical antipsychotics in children with PDDs), we adopted the .05 level for alpha. Had we corrected for multiple comparisons, *none* of the comparisons would have exceeded alpha. Second, only a minority of our participants were able to perform these tasks. This resulted in (a) small sample sizes and (b) the observation that the testable group had a higher IQ and was older than the untestable group. This indicates that the findings may not be fully representative of what would be observed if all the 101 clinical trial participants were testable. However, as reported by others (Troost et al. 2006), children with autism and irritable behavior are very challenging to assess with such cognitive tests, and the proportion of participants assessed was probably quite respectable under the circumstances. Third, we have already stated our reservations about the "significant" drug finding for the Dot test in that only a small number of participants could perform it.

Despite these obvious limitations, the findings are noteworthy for several reasons. First, autistic disorder is often coupled with substantial cognitive disability. Therefore, it is important that pharmacotherapy not increase any functional handicap that is already present. We did not see evidence of risperidone-induced deficits in performance, and there was some indication of enhancement on some variables. Second, the magnitude of change, assessed by partial eta squared, suggests sizable gains in adaptive skills if upheld by future studies. Third, it is worth noting that the data were gathered across multiple sites under double-blind conditions, which may help to discount any individual examiner effects (i.e., unintended bias). Finally, the mechanism of any improvement is unknown. These were performance tests which tapped what the participant was able to achieve on test days. At this stage, it is unknown whether the participants were simply more compliant (i.e., the changes were a secondary consequence of suppressed irritable behavior) or whether risperidone affected true cognitive ability at a more basic level.

Clinical implications

The results reported here are reassuring to clinicians prescribing risperidone for school children with autistic disorder. It does not appear to impair academic ability or cognitive-motor performance. However, at the current state of knowledge, clinicians should not conclude that risperidone can be counted on to improve cognitive-motor performance

or even that it is innocuous. The main value of these findings is to reduce one, and only one, of several safety concerns, with the serious possibilities of metabolic and neurological risks remaining. Further research will be needed to determine the robustness and extent of any favorable effects on cognitive performance.

Disclosures

Dr. Aman has affiliations with Bristol-Myers Squibb Co., Forest Research Institute, Johnson and Johnson, Neuropharm, and Supernus. Dr. Arnold has affiliations with Shire, Neuropharm, Lilly, Novartis, Organon, Janssen, and McNeil. Dr. Ghuman has affiliations with Bristol-Myers Squibb Co. Dr. McDougle has affiliations with Bristol-Myers Squibb Co., Eli Lilly and Co., Forest Research Institute, Janssen Pharmaceutica, and McNeil Pediatrics. Dr. Scahill has affiliations with Janssen Pharmceutica, Bristol-Myers Squibb Co., Neuropharm and Supernus. Dr. Posey has affiliations with Bristol-Myers Squibb Co., Eli Lilly and Co., Forest Research Institute, and Shire. Dr McCracken has affliations with Bristol Myers Squibb, Eli Lilly, McNeil Pediatrics, Janssen Pharmaceutica, Pfizer, Shire, UCB, Wyeth, and Novartis. Dr. P. Cronin, Ms. A. Gavaletz, Ms. J. Hollway, Ms. K. Koenig, Ms. L. Ritz, Dr. Swiezy, Dr. Tierney, Dr. Vitiello, and Ms. Wheeler have no affiliations.

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