ORIGINAL ARTICLE

Randomized, Controlled, Crossover Trial of Methylphenidate in Pervasive Developmental Disorders With Hyperactivity

Research Units on Pediatric Psychopharmacology (RUPP) Autism Network

Context: Hyperactivity and inattention are common symptoms in children with autistic disorder and related pervasive developmental disorders, but studies of stimulants in these conditions have been inconclusive.

Objectives: To determine the efficacy and safety of methylphenidate hydrochloride in children with pervasive developmental disorders and hyperactivity.

Design: Double-blind, placebo-controlled, crossover trial followed by open-label continuation.

Setting: Five academic outpatient clinics.

Participants: Seventy-two drug-free children, aged 5 to 14 years, with pervasive developmental disorders accompanied by moderate to severe hyperactivity.

Interventions: Prior to randomization, subjects entered a 1-week test-dose phase in which each subject received placebo for 1 day followed by increasing doses of methylphenidate (low, medium, and high doses) that were each given for 2 days. The low, medium, and high doses of methylphenidate hydrochloride were based on weight, and they ranged from 7.5 mg/d to 50.0 mg/d in divided doses. Subjects who tolerated the test dose (n=66) were assigned to receive placebo for 1 week and then 3 methylphenidate doses in random order during a double-blind, crossover phase. Children responding to methylphenidate then entered 8 weeks of open-label treatment at the individually determined best dose.

Main Outcome Measures: The primary outcome measure was the teacher-rated hyperactivity subscale of the Aberrant Behavior Checklist. Response was defined as "much improved" or "very much improved" on the Clinical Global Impressions Improvement item coupled with considerable reductions in the parent-rated and/or teacher-rated Aberrant Behavior Checklist hyperactivity subscale score.

Results: Methylphenidate was superior to placebo on the primary outcome measure, with effect sizes ranging from 0.20 to 0.54 depending on dose and rater. Thirty-five (49%) of 72 enrolled subjects were classified as methylphenidate responders. Adverse effects led to the discontinuation of study medication in 13 (18%) of 72 subjects.

Conclusions: Methylphenidate was often efficacious in treating hyperactivity associated with pervasive developmental disorders, but the magnitude of response was less than that seen in typically developing children with attention-deficit/hyperactivity disorder. Adverse effects were more frequent.

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Author Affiliations: A list of the participants of the Research Units on Pediatric Psychopharmacology Autism Network and their affiliations appears at the end of this article.

AUTISTIC DISORDER (AUTISM) and other pervasive developmental disorders (PDDs) are increasingly being diagnosed, with recent prevalence estimates reaching as high as 1 in 160 preschool children.[1] These children often present with interfering hyperactivity, distractibility, and impulsiveness requiring treatment.[2] By nosological convention, these symptoms are not diagnosed as comorbid attention-deficit/hyperactivity disorder (ADHD).[3] This partly reflects the assumption that inattention occurring in children with PDD may be secondary to the underlying autistic symptoms and/or mental retardation, as well as the assumption that treatment response may be different.[4] However, the use of this diagnostic convention is a matter of continued debate.[5]

Early studies[6,7] examining the effects of stimulants on children with PDDs in heterogeneous samples described negative results. To our knowledge, only 2 small randomized controlled trials of methylphenidate hydrochloride in autism have been published. In the first of these,[8] methylphenidate was more efficacious than placebo for 10 subjects treated in a 4-week, double-blind, placebo-controlled, crossover study. In another 3-week, double-

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blind, placebo-controlled, crossover study,[9] 8 of 13 subjects were described as responding to methylphenidate based on a 50% reduction in the Conners Hyperactivity Index score. Adverse effects were common in both studies and included irritability and social withdrawal.

Despite these encouraging findings in 2 small studies, the magnitude of benefit from stimulants and their tolerability in the treatment of PDDs remain uncertain. In a recently published retrospective study[10] of 195 youths with PDDs, stimulants were ineffective or poorly tolerated more often than not. However, community surveys suggest a steady rise in the use of these agents in children with PDDs.[11] With these contradictory results in mind and questions of safety unanswered, the Research Units on Pediatric Psychopharmacology Autism Network chose to study methylphenidate in a larger sample of children with PDDs. We hypothesized that methylphenidate would be more efficacious than placebo in reducing hyperactivity and impulsiveness in children with PDDs, and that IQ, diagnosis, age, and weight might act as moderators of response. Furthermore, we hypothesized that adverse effects of methylphenidate would be dose related.

METHODS

DESIGN

This was a randomized, placebo-controlled, crossover trial of methylphenidate. It included a 1-week test-dose phase to check tolerability, a 4-week randomized-order, placebo-controlled, double-blind crossover phase to assess efficacy, and an 8-week open-label continuation phase for responders.

The purpose of the test-dose phase was to determine whether subjects could tolerate all of the doses of methylphenidate prior to randomization to the crossover phase. The purpose of the crossover phase was to compare methylphenidate with placebo and to identify the best dose of methylphenidate for each child. A crossover design was chosen over a parallel design to minimize sample size and because the quick onset and short duration of action of methylphenidate lend themselves well to this type of study. During the continuation phase, subjects were maintained on the best dose for an additional 8 weeks to evaluate the stability of response and tolerability.

PARTICIPANTS

Subjects were recruited for participation in a multisite protocol executed at 5 centers forming the Research Units on Pediatric Psychopharmacology Autism Network funded by the National Institute of Mental Health, Bethesda, Md. The sites were Indiana University, Indianapolis; the Kennedy Krieger Institute at Johns Hopkins University, Baltimore, Md; The Ohio State University, Columbus; the University of California, Los Angeles; and Yale University, New Haven, Conn. All of the subjects were outpatients at the time of study participation. The study was approved by the institutional review board at each site, and written informed consent was obtained from a parent or guardian of each subject prior to enrollment. Protocol adherence and subject safety were monitored by each site independently, with additional oversight using weekly conference calls, annual site visits, and an independent data- and safety-monitoring board.

Subject eligibility criteria included boys and girls aged 5 to 14 years, inclusive, with a diagnosis of autistic disorder, Asperger disorder, or PDD not otherwise specified (NOS) based on the criteria set forth in the *DSM-IV*.[12] All of the subjects had to have interfering symptoms of hyperactivity and/or impulsiveness that were present for at least 6 months and began prior to the age of 7 years. The severity was confirmed by a Clinical Global Impressions (CGI)[13] severity subscale score of 4 or higher (rated "moderately ill," taking into account all of the symptoms) and a total score of 27 or higher (item mean, 1.50 on a 0-3 metric) on both a parent-rated and teacher-rated Swanson, Nolan, and Pelham–version IV ADHD scale (items 1-18),[14] with a score of at least 10 on the hyperactivity-impulsivity subscale (items 10-18). Subjects were also eligible for entry if the hyperactivity-impulsivity subscale score on the Swanson, Nolan, and Pelham–version IV ADHD scale (items 10-18) was at least 15 (item mean, 1.67), even in the absence of notable inattentiveness. This entry criterion attempted to deal with the challenge of assessing attention in lower-functioning, nonverbal children.

Other eligibility criteria were the following: (1) no concurrent psychotropic medications for at least 1 to 3 weeks (1 week for stimulants and clonidine hydrochloride; 2 weeks for antidepressants except fluoxetine and citalopram hydrobromide; 3 weeks for fluoxetine, citalopram hydrobromide, or antipsychotics) prior to baseline visit; (2) mental age of at least 18 months as determined by intelligence testing; (3) no other neuropsychiatric disorders that might require alternative medical management; (4) for subjects with a tic disorder, tic severity had to be mild or less on a CGI–severity subscale rating pertaining to tics only; (5) no significant medical condition, such as heart or liver disease, that could make treatment with methylphenidate unsafe; (6) for subjects with a seizure disorder, no seizures in the past 6 months and a stable anticonvulsant dose for at least 1 month; (7) no hypertension; (8) no treatment with an adequate trial of methylphenidate hydrochloride (0.4 mg/kg per dose given at least twice daily for a minimum of 2 weeks) within the past 2 years; and (9) no history of severe adverse response to methylphenidate.

Screening and baseline assessments included complete medical and psychiatric history, mental status examination, height, weight, vital signs, and physical examination. Diagnostic and laboratory studies included urinalysis, complete blood cell count with differential, electrolyte, renal, liver, and thyroid function tests, urine pregnancy test (when indicated), and an electrocardiogram. All of the subjects were given the Slosson Intelligence Test[15] to allow for a single measure to compare IQ among subjects. Adaptive behavior was measured with the Vineland Adaptive Behavior Scales.[16]

The Autism Diagnostic Interview–Revised[17] was administered to corroborate the *DSM-IV* diagnosis of autistic disorder based on clinical interview and examination. Since the Autism Diagnostic Interview–Revised does not have specific criteria for Asperger disorder or PDD NOS, these diagnoses followed the *DSM-IV* and took into account all of the available information.

TREATMENT

Medication

Medication and placebo capsules were compounded by a Food and Drug Administration–approved pharmacy at the University of Iowa, Iowa City, and shipped to the investigational pharmacist at each site. Dosage levels were varied depending on the weight of the child (**Table 1**). The low, medium, and high dosage levels approximated dosage levels of 0.125, 0.250, and 0.500 mg/kg per dose. Each dose was received 3 times daily (8 AM, 12 PM, and 4 PM), with the third dose sculpted to be approximately half of the earlier doses.

Test-Dose Phase

On day 1, the capsules contained placebo; this was followed by 2 days each of the 3 different dosage levels (low, medium, and

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Table 1. Weight-Dependent Methylphenidate Dosing at Each Dosage Level

Subject Weight Class, kg	Mean ± SD Observed Weight, kg	Low Dose, mg (Mean ± SD Dose, mg/kg per Dose*)†	Medium Dose, mg (Mean ± SD Dose, mg/kg per Dose*)†	High Dose, mg (Mean ± SD Dose, mg/kg per Dose*)†
16 to <24 (n = 29)	20.6 ± 2.1	2.5, 2.5, 2.5 (0.123 ± 0.013)	5.0, 5.0, 2.5 (0.246 ± 0.026)	10.0, 10.0, 5.0 (0.493 ± 0.054)
24-34 (n = 20)	28.2 ± 3.3	5.0, 5.0, 2.5 (0.180 ± 0.020)	10.0, 10.0, 5.0 (0.359 ± 0.041)	15.0, 15.0, 10.0 (0.511 ± 0.057)
>34 (n = 17)	49.7 ± 15.1	5.0, 5.0, 2.5 (0.108 ± 0.027)	10.0, 10.0, 5.0 (0.216 ± 0.054)	20.0, 20.0, 10.0 (0.428 ± 0.112)

*Calculated using the 8 AM or 12 PM methylphenidate hydrochloride dose divided by weight.
†Values indicate doses received at 8 AM, 12 PM, and 4 PM, respectively.

high) of methylphenidate in stepwise fashion. During the test-dose phase, the subject's caregiver was called nightly and asked about specific adverse events. Clinical response was then rated on the CGI global improvement (CGI-I) item. Subjects who experienced a severe adverse event and those who were rated as "much worse" or "very much worse" on the CGI-I item at the low or medium dosage level were excluded from further participation in the study. If a severe adverse event or clinical worsening occurred on only the high dose, the subject could still be randomized to a modified crossover schedule that omitted the high dose and substituted an additional week of the medium dose.

Double-blind Crossover Phase

Subjects tolerating methylphenidate during the test-dose phase then entered into the 4-week crossover phase. Each subject received placebo and 3 different dosage levels (Table 1) of methylphenidate in random order. There were 2 exceptions to the completely randomized design: (1) subjects who could not tolerate the high dosage level of methylphenidate received the medium dose twice (1 of which replaced what would have been the high dose) during the crossover phase, and (2) the high dose could not follow the placebo so as to avoid an abrupt exposure to a high dose of methylphenidate that might cause adverse effects.

Randomization was balanced by site to avoid repeating the treatment order within the site. Randomization lists were generated centrally and were held by an investigational pharmacist at each site. Subjects were seen at the end of each week of treatment by a prescribing clinician and by a rating clinician who was kept blind to adverse effects. The prescribing clinician could drop the 4 PM dose to reduce insomnia if it occurred. Clinicians, the patient, and the caregiver were blind to treatment assignment during this phase.

Open-Label Continuation Phase

Subjects meeting the criteria for positive response during 1 or more weeks in the crossover phase underwent a best-dose determination (described later) at the completion of the final blinded, crossover-week visit. The prescribing clinician then broke the blind for that week only, which allowed the rating clinician to remain blind to the results. Responders whose best dose was methylphenidate were then entered into the 8-week open-label continuation phase at that dosage, with a visit at 4 weeks and a visit at 8 weeks. The prescribing clinician could adjust the dosage of methylphenidate based on clinical judgment to improve symptoms and limit adverse effects during the continuation phase.

MEASURES OF EFFICACY

Outcome measures were double-blind during the crossover phase and were unblinded during the test-dose and continuation phases. The rating clinician was also kept blinded to any information about adverse events or changes in vital signs or weight.

The primary outcome measure of the study was the 16-item hyperactivity subscale embedded in the 58-item Aberrant Behavior Checklist (ABC)[18,19] that was rated by the teacher. An important secondary measure was the parent-rated ABC hyperactivity subscale. The hyperactivity subscale of the ABC included 16 items rated on a 4-point scale: 0 (not at all a problem) through 3 (the problem is severe in degree). The items assessed inattentiveness, hyperactivity, impulsiveness, and noncompliance. The ABC also included these additional subscales: irritability (15 items assessing aggression, self-injury, tantrums, etc), lethargy/social withdrawal (16 items assessing social withdrawal, inactivity, emotional unresponsiveness, etc), stereotypy (7 items assessing stereotypical and repetitive movements), and inappropriate speech (4 items assessing loud, excessive, or repetitive speech).

The CGI-I subscale score was determined by the rating clinician at each visit, who took into account all of the sources of information except for adverse events and changes in vital signs and weight. It included a 7-point scale of change ranging from 1 (very much improved) through 7 (very much worse).

The CGI-I subscale was combined with the parent-rated and teacher-rated ABC hyperactivity subscales into an overall definition of response. A patient was considered a responder if he or she was rated as much improved or very much improved on the CGI-I subscale and showed a 30% decrease in hyperactivity on the parent-rated *or* teacher-rated ABC or showed a 25% decrease in hyperactivity on the parent-rated *and* teacher-rated ABC.

BEST-DOSE DETERMINATION

In subjects who showed a positive response during only 1 week of treatment, that dose would be labeled the best dose. If a subject responded during more than 1 week of treatment, then the prescribing and rating clinicians ranked the weeks of response in order from best to worst. The prescribing clinician then broke the blind for this best dose. If the best dose was active methylphenidate, the subject then entered the 8-week open-label continuation phase. Subjects showing no response at any week and subjects responding best to placebo exited the study.

SAFETY

At each visit, the parent completed a survey of possible adverse effects. This form was reviewed by the prescribing clinician with the parent or caregiver to record and classify any adverse events. Height, weight, blood pressure, pulse, and body temperature were also recorded.

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STATISTICAL ANALYSIS

Sample size calculation for the crossover phase took into account an estimated within-subject correlation of 0.6 based on data from 3 methylphenidate crossover studies[20-22] involving subjects with developmental disabilities. The proposed sample of 60 subjects had 99% statistical power to detect a moderate effect size (0.50) at the level of *P* being less than .05. The statistical power to detect a small effect size (0.30) was 72%.

Sample characteristics among the 5 sites were compared using the χ^2 test or analyses of variance. Response rates among dosage levels were compared using the McNemar χ^2 test. Continuous measures were analyzed with an intent-to-treat, mixed-effects, linear model. Fixed-effects stratification factors were site (5 levels), dose (4 levels), and the interaction of site × dose. Random effects were the intercept and the slope of the regression of response on dose of methylphenidate.

The IQ of the subjects was a prespecified moderator (2 levels: less than 50 vs 50 or higher). We also examined 3 exploratory moderators: age (2 levels: younger than 6.7 years vs 6.7 years or older), diagnosis (2 levels: autism vs Asperger disorder or PDD NOS), and assigned weight class (3 levels: 16 to less than 24 kg, 24 to 34 kg, and greater than 34 kg). For the moderator analyses, the intent-to-treat, mixed-effects model was reapplied, with each candidate moderator included as a main effect and in interaction with dose. The differential effects of a moderator on response were tested using the moderator × dose interaction term. We used analytic and graphic methods to examine the interaction of dose at each level of moderator in the presence of a significant interaction.

Descriptive statistics are given as the mean ± SD. Effect sizes for continuous measures were calculated using the difference between ratings on methylphenidate vs placebo divided by the pooled SD. The frequencies of adverse effects in each treatment group were compared using the McNemar χ^2 test for paired samples.

RESULTS

TEST-DOSE PHASE

One hundred seventeen subjects were screened, and 72 subjects participated from November 14, 2001, through September 5, 2003 (**Figure 1**). Six subjects (8%) had intolerable adverse effects with more than 1 methylphenidate dosage level during the test-dose phase, and they exited the study per protocol. Sixteen of the remaining 66 subjects had intolerable adverse effects at the highest dose of methylphenidate, and they were randomized to a modified crossover phase that omitted the highest dose.

DOUBLE-BLIND CROSSOVER PHASE

Sixty-six subjects (59 boys, 7 girls) were randomized to the crossover phase. Subject characteristics (**Table 2**) were similar among the 5 sites. No subjects receiving anticonvulsants were enrolled. The mean ± SD weight of subjects was 30.4 ± 14.3 kg. The mean weights by weight class and calculated dose (milligrams per kilogram per dose) are shown in Table 1.

One of the 66 children randomized to the crossover phase withdrew consent just prior to receiving the study drug. Seven subjects withdrew from the study owing to intolerable adverse effects during the crossover phase (3 subjects receiving a high dose; 3 subjects receiving a medium dose; and 1 subject receiving a low dose); 58 subjects completed the crossover.

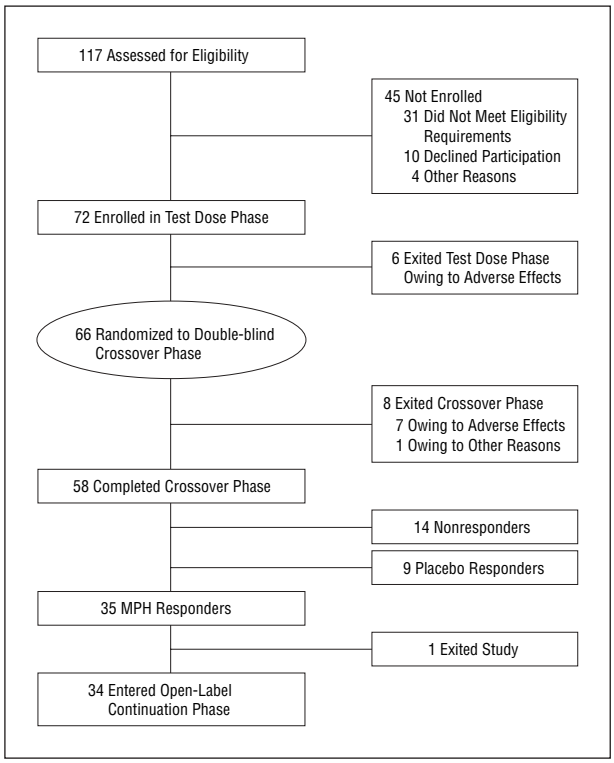

Figure 1. Diagram of subject screening, enrollment, and flow through all of the phases of methylphenidate hydrochloride (MPH) treatment.

Consistent with intent-to-treat principles, all of the data from those subjects receiving 2 medium doses (owing to the inability to tolerate a high dose) were analyzed. No significant differences were found between these 2 weeks of receiving the medium dose, so the data were combined.

The ABC hyperactivity subscale scores during the crossover phase are presented in **Table 3**. There was a statistically significant main effect of dose on the ABC hyperactivity subscale score as rated by both teacher ($F = 4.02$; $P = .009$) and parent ($F = 6.10$; $P < .001$). In pairwise comparisons, all of the methylphenidate dosage levels were statistically superior to placebo. Effect sizes ranged from small to medium, and they favored the medium dose for parent ratings and high dose for teacher ratings. Effect sizes were greater at the optimal dose of methylphenidate (defined as the dose at which the ABC hyperactivity subscale score was lowest for each individual participant).

Forty-four (76%) of 58 subjects responded during at least 1 of the 4 treatment conditions. A best-dose determination was made to choose a dose for continued treatment in the 8-week open-label continuation phase. The distribution of best doses among the subjects was as follows: 9 (20%) placebo, 11 (25%) low, 14 (32%) medium, and 10 (23%) high.

Sixteen subjects were randomized to receive a medium dose twice, which led to 77 distinct trials of the medium dose in 62 subjects. The response rate at each dose, regardless of whether the subject completed the crossover, was as follows: placebo (12 [20%] of 61 subjects), low (20 [33%] of 61 subjects), medium (27 [35%] of 77 subjects), and high (18 [38%] of 47 subjects). Response

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Table 2. Demographics and Baseline Characterization of Subjects Randomized During Crossover Phase

Variable	Total Across All of the Sites (n = 66)
Age, mean (SD; range), y	7.5 (2.2; 5.0-13.7)
Male, No. (%)	59 (89.4)
Race/ethnicity, No. (%)	
White	48 (72.7)
Black or African American	9 (13.6)
Asian	6 (9.1)
Hispanic or Latino	3 (4.6)
Diagnosis, No. (%)	
Autistic disorder	47 (71.2)
Asperger disorder	5 (7.6)
Pervasive developmental disorder NOS	14 (21.2)
Prior medications, No. (%)	18 (27.3)
Stimulant	6 (9.1)
α_2-adrenergic agonist	5 (7.6)
Antipsychotic	3 (4.6)
SSRI	3 (4.6)
Other	4 (6.1)
Mother's educational level, No. (%)	
High school graduate/GED or less	8 (12.1)
Some college or post–high school	25 (37.9)
College/advanced graduate or professional degree	33 (50.0)
Employed mother, No. (%)	44 (66.7)
Employed father, No. (%)	59 (89.4)
Married, n (%)	53 (80.3)
Clinical Global Impressions, severity subscale rating, No. (%)	
Moderately ill	20 (30.3)
Markedly ill	35 (52.0)
Severely ill	11 (16.7)
Slosson IQ, mean (SD; range)	62.6 (32.9; 16-135)
Vineland scale score, mean (SD; range)	
Communication	62.8 (21.8; 20-126)
Daily living skills	54.4 (19.8; 20-110)
Socialization	61.7 (16.7; 20-109)
Motor skills	69.2 (17.8; 44-113)
Adaptive behavior composite	56.2 (21.0; 20-109)
Maladaptive behaviors total	29.2 (9.2; 13-51)
Parent-rated ABC score, mean (SD; range)	
Irritability	16.9 (10.1; 0-41)
Lethargy/social withdrawal	12.1 (8.9; 0-33)
Stereotypy	7.6 (5.9; 0-21)
Hyperactivity	33.2 (8.7; 2-47)
Inappropriate speech	6.0 (4.1; 0-12)
Teacher-rated ABC score, mean (SD; range)	
Irritability	16.1 (9.4; 0-43)
Lethargy/social withdrawal	15.5 (10.9; 0-42)
Stereotypy	7.6 (5.1; 0-19)
Hyperactivity	30.9 (7.9; 16-45)
Inappropriate speech	5.8 (3.6; 0-12)

Abbreviations: ABC, Aberrant Behavior Checklist; GED, General Education Diploma; NOS, not otherwise specified; SSRI, selective serotonin reuptake inhibitor.

rates among doses were compared using the McNemar χ^2 test. There was a statistical trend favoring high dose over placebo (χ^2=3.20; P=.07). There was no significant difference between the low dose and placebo (χ^2=1.81; P=.18).

Two χ^2 tests were performed for medium-dose–placebo comparisons since those subjects randomized to modified dosing received a medium dose of methylphenidate twice. Both comparisons included those subjects randomized to a medium dose of methylphenidate only once during the crossover phase. The first comparison included the first medium dose that the subjects with modified dosing received. The second comparison included the second medium dose that the subjects with modified dosing received. The response rate to the medium dose of methylphenidate was statistically superior to placebo (χ^2=3.85; P=.05) for the first comparison, and the response rate showed a statistical trend favoring the medium dose of methylphenidate (χ^2=3.52; P=.06) for the second comparison. Comparisons between active doses of methylphenidate were not significantly different.

OPEN-LABEL CONTINUATION PHASE

The 35 subjects for whom an active dose of methylphenidate was chosen as the best dose represented 49% of the original 72 subjects who enrolled in the study. Thirty-four of these 35 subjects received open-label methylphenidate for an additional 8 weeks. One placebo responder (who also responded equally as well to methylphenidate) was allowed to enter this phase of the study as well, which led to a total of 35 subjects entering the continuation phase. Thirty-two (91%) of the 35 subjects completed the continuation phase. Reasons for the 3 early terminations were adverse effects, lack of efficacy, and "declined further study participation." The response to methylphenidate was maintained during the 8-week continuation phase (**Figure 2**).

ASSOCIATED SYMPTOM RESPONSE

In secondary analyses, we examined changes in other symptom domains as assessed by the other 4 subscales (irritability, lethargy/social withdrawal, stereotypy, and inappropriate speech) of the ABC. Parent-rated lethargy/social withdrawal subscale scores during the high dose of methylphenidate were significantly worse than during placebo (P=.004; effect size=0.37). A statistically significant improvement was seen in the parent-rated stereotypy (P=.02; effect size=0.22) and inappropriate speech (P=.02; effect size 0.27) subscale scores at the medium dose of methylphenidate as compared with placebo. Parent-rated irritability subscale scores and none of the other 4 teacher-rated subscale scores were significantly different from placebo. After Bonferroni correction for multiple measures (α=.05/5=.01), only the worsening in the lethargy/social withdrawal subscale scores associated with the high dosage level remained statistically significant.

MODERATORS OF RESPONSE

None of the 4 candidate moderators (age, IQ, diagnosis, or weight) had an effect on teacher-rated or parent-rated ABC hyperactivity subscale scores. This was true even when relaxing the significance level to a P value of less than .20 to take into account the study being underpowered to detect moderator interactions.

However, there was a nonsignificant trend for diagnosis to have a moderating effect on the categorical rating of response. Namely, those subjects diagnosed with

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Table 3. Parent-Rated and Teacher-Rated Aberrant Behavior Checklist Hyperactivity Subscale Scores During Crossover Phase

Dosage Level	Sample Size*		Hyperactivity Subscale Score, Mean (SD)†		*P* Value‡		Effect Size§	
	Parent-Rated	Teacher-Rated	Parent-Rated	Teacher-Rated	Parent-Rated	Teacher-Rated	Parent-Rated	Teacher-Rated
Placebo	60	46	26.0 (9.90)	26.0 (11.66)				
Low Dose	62	45	23.0 (11.29)	22.9 (12.84)	.03	.03	0.29	0.25
Medium Dose	63	52	20.6 (10.27)	23.6 (12.53)	<.001	.008	0.54	0.20
High Dose	47	33	22.1 (9.67)	20.3 (11.94)	.003	.002	0.40	0.48
Optimal Dose‖	64	58	17.2 (9.87)	20.1 (12.40)	<.001	<.001	.89	.48

*Change in sample size owing to missing data and modified dosing (see text). The medium dose scores for subjects randomized to modified dosing were averaged.

†For comparison, mean (SD) baseline parent-rated and teacher-rated hyperactivity subscale scores were 33.2 (8.7) and 30.9 (7.9), respectively.

‡Pairwise comparisons with placebo.

§Effect sizes calculated as (placebo – active dose) ÷ pooled SD.

‖Optimal dose defined as the dose at which the Aberrant Behavior Checklist hyperactivity subscale score was lowest for each individual participant.

Asperger disorder and PDD NOS were more likely to be classified as responders to both placebo and methylphenidate than those subjects with autism ($P=.07$). The response rates of subjects with Asperger disorder and PDD NOS (n=19) during treatment with placebo and with low, medium, and high doses of methylphenidate were 6 (32%) of 19 subjects, 7 (37%) of 19 subjects, 7 (37%) of 19 subjects, and 6 (32%) of 19 subjects, respectively. This contrasted with the lower response rates seen at each respective dosage level in subjects with autism (n=47): 6 (13%) of 47 subjects, 13 (28%) of 47 subjects, 15 (32%) of 47 subjects, and 12 (26%) of 47 subjects, respectively. In additional McNemar χ^2 tests, response to each dose of methylphenidate was superior to placebo for the autism subgroup ($P<.001$), but not for the Asperger/PDD NOS subgroup ($P>.05$).

ADVERSE EVENTS

Six of the original 72 subjects exited the study during the test-dose phase owing to inability to tolerate the 2 highest doses of methylphenidate. An additional 7 subjects exited during the crossover phase (1 at low, 3 at medium, and 3 at high doses) owing to intolerable adverse effects. These 13 subjects represented 18% of the original 72 subjects. The symptom of irritability was the primary reason for discontinuation in 6 subjects. **Table 4** shows the frequency of adverse effects at each dosage level of methylphenidate compared with placebo.

COMMENT

Methylphenidate was consistently more efficacious in improving inattention, distractibility, hyperactivity, and impulsivity than placebo was, as rated by the ABC hyperactivity subscale. The effect sizes ranged from 0.20 to 0.54, suggesting a small to medium magnitude of response.

On the categorical rating of responder vs nonresponder, medium-dose methylphenidate was statistically superior to placebo for 1 of 2 analyses. There were statistical trends ($.05<P<.10$) for the medium dose (in the other analysis) and the high dose to be better than placebo in terms of overall response. Overall, 35 (49%) of the original sample of 72 subjects responded best to an active dose of methylphenidate. The response to methylphenidate was maintained for at least 8 weeks in the majority of responders. This indicates that the test-dose and crossover phases selected a sample of subjects who would tolerate and continue to do well with methylphenidate in the short term.

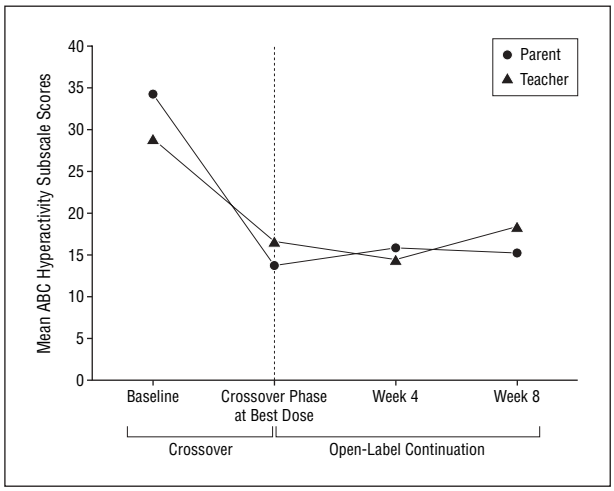

Figure 2. Mean Aberrant Behavior Checklist (ABC) hyperactivity subscale scores as rated by teachers and parents at baseline, at the best dose of methylphenidate during the crossover phase, and during the methylphenidate hydrochloride open-label continuation phase. Linear slopes were used to examine the change in the primary outcome measure over time during the 8-week open-label continuation phase. Parent-rated (F=1.09; $P=.30$) and teacher-rated (F=3.01; $P=.10$) ABC hyperactivity subscale score slopes were not significantly different from 0, suggesting a maintenance of response.

These results are consistent with the 13-subject study in PDD described by Di Martino et al.[23] Di Martino and colleagues gave subjects a single test dose of 0.4 mg/kg, which was between our medium and high doses, and they found that 5 subjects could not tolerate it, showing increased hyperactivity, stereotypy, dysphoria, or tics within 1 hour. Of the remaining 8 subjects, 6 improved when treated, constituting an overall response rate of 46%.

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Table 4. Adverse Effects During Each Dose of Methylphenidate* Compared With Placebo

Adverse Effects†	Subjects Receiving Placebo, No. (%) (n = 66)	Subjects Receiving Low Dose, No (%) (n = 66)	Subjects Receiving Medium Dose, No. (%) (n = 66)	Subjects Receiving High Dose, No. (%) (n = 50)
Appetite decrease	2 (3.0)	3 (4.6)	16 (24.2)‡	12 (24.0)§
Difficulty falling asleep	1 (1.5)	7 (10.6)‖	12 (18.2)§	8 (16.0)‖
Stomach or abdominal discomfort	1 (1.5)	2 (3.0)	5 (7.6)	6 (12.0)
Irritability	2 (3.0)	5 (7.6)	8 (12.1)‖	5 (10.0)
Emotional outburst	0	5 (7.6)	9 (13.6)§	5 (10.0)
Anxiety	2 (3.0)	3 (4.6)	1 (1.5)	4 (8.0)
Depression	0	1 (1.5)	3 (4.6)	4 (8.0)
Repetitive behaviors and thoughts	2 (3.0)	2 (3.0)	4 (6.1)	3 (6.0)
Self-injury	2 (3.0)	1 (1.5)	3 (4.6)	3 (6.0)
Headache	0	2 (3.0)	1 (1.5)	3 (6.0)
Diarrhea	4 (6.1)	3 (4.6)	3 (4.6)	2 (4.0)
Social withdrawal	0	2 (3.0)	4 (6.1)	2 (4.0)
Increased motor activity	1 (1.5)	4 (6.1)	1 (1.5)	1 (2.0)
Bradycardia	4 (6.1)	3 (4.6)	0	0
Tiredness or fatigue	0	1 (1.5)	4 (6.1)	0

*Methylphenidate was administered as methylphenidate hydrochloride.
†Only adverse effects reported at 5% or greater are shown.
‡$P \leq .001$.
§$P \leq .01$.
‖$P \leq .05$.

Methylphenidate did not improve irritability, lethargy/social withdrawal, stereotypy, or inappropriate speech ABC subscale ratings. The finding of increased social withdrawal with higher doses of methylphenidate is consistent with adverse events described in previous studies.[9]

Methylphenidate treatment was associated with an 18% rate of discontinuation owing to adverse events. Irritability was a frequent reason for discontinuation. This finding, coupled with the fact that the irritability subscale on the ABC was not helped, differs dramatically from the finding in the National Institute of Mental Health Collaborative Multisite Multimodal Treatment Study of Children With ADHD (the MTA study).[24] In their initial 1-month titration, the symptom of irritability was better with methylphenidate as compared with placebo in typically developing children with ADHD.[24] Other adverse events that were significantly more frequent with methylphenidate as compared with placebo included decreased appetite, difficulty falling asleep, and emotional outbursts.

Methylphenidate is a first-line treatment for ADHD. Our response rate of 49% is less than the previously described response rates of 70% to 80% seen in typically developing children with ADHD.[24] In the MTA study, typically developing children with ADHD were also treated with placebo and 3 different dosages of methylphenidate (in a randomized daily switching procedure) over 4 weeks.[25] The highest dose of methylphenidate given in that study approached 0.8 mg/kg per dose as compared with 0.625 mg/kg per dose in our study. In the MTA study, 198 (69%) of 289 subjects randomized to medication were rated as responders to methylphenidate[24]; the rate of adverse events was much lower in the MTA study, with only 4 (1.4%) of 289 subjects discontinuing medication owing to adverse events as compared with 13 (18%) of 72 subjects in our PDD sample. On outcome measures assessing ADHD symptoms, effect sizes for the optimal dose in our study ranged from 0.48 to 0.89, compared with 0.35 to 1.31 in the MTA study. Finally, the placebo response (32 [12.5%] of 256 completers) in the MTA study was comparable to the placebo response (9 [15.5%] of 58 completers) seen in our sample. Thus, methylphenidate is less efficacious and is associated with more frequent adverse effects in children with PDD than in typically developing children with ADHD.

In our study, IQ as well as exploratory moderators of age and weight did not affect the primary outcome measure or categorical rating of response. Diagnosis may have a moderating effect on the categorical rating of response. Subjects with autistic disorder, but not those with Asperger disorder and PDD NOS, were significantly less likely to respond to placebo than to methylphenidate. The failure to find IQ moderator effects contrasts with the results found by Aman et al[20,26] that in the general population of mental retardation, an IQ of 45 seems to provide a threshold for favorable methylphenidate effect. Perhaps this is partly explained by the generally low rate of favorable response in our PDD sample, which did not allow much room to show moderator effect. Future analyses are planned to explore moderator effects on secondary outcome measures.

There are limitations to this study. It is possible that 1 week of treatment of each methylphenidate dose was not long enough to determine efficacy. The 4-week crossover phase did well in identifying subjects who maintained their response at 8 weeks of treatment. However, the long-term maintenance of this response was not tested. In addition, our study examined the use of methylphenidate in drug-free children with PDD. A retrospective study has raised the interesting possibility that the use of psychostimulants added to another psychotropic medication may be associated with a greater rate of response

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than when used alone.[10] For example, persons with autism already receiving an antipsychotic medication might be protected to some extent from adverse effects associated with psychostimulants (eg, irritability, insomnia, loss of appetite). This might be examined in future studies.

This study did not explore high doses of methylphenidate because of previous studies finding disproportionately more frequent adverse events in children with developmental disabilities.[27] This decision was supported in part by our findings; despite using relatively low dosages, we still found a high rate of discontinuation owing to adverse events (most commonly with medium and high doses of methylphenidate). However, it is also possible that certain individuals may require even higher dosages of methylphenidate to achieve response. On the other hand, our rate of adverse events may be an underestimate of that seen in clinical settings since we excluded subjects who had previously had an adverse response to methylphenidate. One final limitation is our use of the test-dose phase to quickly exclude those subjects who experienced worsening on methylphenidate. While ethically sound, this could have partially influenced parent blinding.

Our findings with methylphenidate may not be generalized to the use of other psychostimulants (eg, dextroamphetamine sulfate) in the treatment of PDD. In addition, it is unknown whether longer-acting stimulants are associated with a better or worse response in children with PDD and hyperactivity. Research on this topic may also be warranted. In fact, additional research on the phenomenology and optimal treatment of this symptom cluster in PDD is greatly needed.

This study has 2 main clinical implications. First, about half of the children with PDD and hyperactivity respond to methylphenidate treatment, but this response is less than that seen in the treatment of typically developing children with ADHD. Second, methylphenidate treatment of children with PDD and hyperactivity is frequently associated with adverse effects severe enough to lead to discontinuation.

At present, methylphenidate is a reasonable choice to target hyperactivity in the context of PDDs, given modest group effects and a response rate that approaches 50%. However, caregivers should be cautioned about the strong possibility of adverse effects. In addition, practitioners should be prepared to suspend treatment if considerable adverse effects are reported. Further secondary analyses are planned to better delineate individual responses and other moderators of response, including genotype.

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Correspondence: David J. Posey, MD, Riley Hospital for Children, Room 4300, 702 Barnhill Dr, Indianapolis, IN 46202 (dposey@iupui.edu).
Research Units on Pediatric Psychopharmacology (RUPP) Autism Network Participants: Michael G. Aman, PhD (principal investigator), L. Eugene Arnold, MEd, MD, Yaser Ramadan, MD, Andrea Witwer, BS, and Ronald Lindsay, MD, The Ohio State University, Columbus; Christopher J. McDougle, MD (principal investigator), David J. Posey, MD, Naomi Swiezy, PhD, and Arlene Kohn, BA, Indiana University, Indianapolis; James T. McCracken, MD (principal investigator), Bhavik Shah, MD, Pegeen Cronin, PhD, James McGough, MD, and Lisa Sea-Yun Lee, BA, University of California, Los Angeles; Lawrence Scahill, MSN, PhD (principal investigator), Andres Martin, MD, Kathleen Koenig, MSN, Deirdre Carroll, MSN, Christopher Young, MD, and Allison Lancor, BA, Yale University, New Haven, Conn; Elaine Tierney, MD (principal investigator), Jaswinder Ghuman, MD, Nilda M. Gonzalez, MD, and Marco Grados, MD Kennedy Krieger Institute, Baltimore, Md; Benedetto Vitiello, MD (principal investigator), and Louise Ritz, MBA, National Institute of Mental Health, Bethesda, Md; statistical analysis: Shirley Chuang, MS, and Mark Davies, MPH, Columbia University, New York, NY; and data management: James Robinson, MEd, and Don McMahon, MS, Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY.
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