

Randomized, Placebo-Controlled, Crossover Study of Methylphenidate for Attention-Deficit/Hyperactivity Disorder Symptoms in Preschoolers with Developmental Disorders

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Abstract

Objective: The aim of this study was to investigate the short-term efficacy and safety of methylphenidate (MPH) to treat attention-deficit/hyperactivity disorder (ADHD) symptoms in an understudied population of preschoolers with pervasive developmental disorder (PDD) or intellectual disability (ID).

Methods: Fourteen preschoolers with developmental disorders (DD, $n = 14$; PDD, $n = 12$; ID, $n = 2$) underwent MPH titration in a single-blind manner followed by a 4-week double-blind crossover phase. Each child was administered placebo for 2 weeks and “optimal dose” for 2 weeks. The primary outcome measure was the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) ADHD subscale of the Conners’ Parent Rating Scale-Revised (CPRS-R-DSM-IV-ADHD).

Results: MPH improved parent-rated ADHD symptoms of the preschoolers; 50% were rated as responders. The CPRS-R-DSM-IV-ADHD subscale was significant for the PDD subgroup ($p = 0.005$, Cohen $d = 0.97$) and marginally significant for the entire DD sample ($p = 0.08$, Cohen $d = 0.50$). Half of the preschoolers experienced side effects with MPH, including reports of increased stereotypic behavior, upset stomach, sleep-related difficulties, and emotional lability. One child discontinued during titration due to side effects.

Conclusion: The predominant direction of response in these preschoolers with both ADHD and PDD/ID favored MPH, even though the response was more subtle and variable than in older and typically developing children. Due to high rates of adverse effects, preschoolers should be monitored closely.

Introduction

CHILDREN WITH DEVELOPMENTAL DISORDERS (DD), including pervasive developmental disorder (PDD) and intellectual disability (ID), often have symptoms of attention-deficit/hyperactivity disorder (ADHD) that limit the effectiveness of educational, behavioral, and other interventions (American Psychiatric Association 2000; Lecavalier 2006). Stimulants are considered standard pharmacological treatment in typically developing school-age children with ADHD (AACAP 2007). The response rate is reported to be lower in

school-age children with PDD and/or ID (50–60%) compared to typically developing children with ADHD (70–90%) (Elia et al. 1991; Spencer et al. 1996; Aman et al. 2003; RUPP Autism Network 2005).

Stimulant response in typically developing preschoolers with ADHD is also reported to be less robust and their response rate is reported to be lower compared to school-age children (Greenhill et al. 2006; for review, see Ghuman et al. 2008). Information about stimulant response in preschoolers with PDD and/or ID is limited. There are a few reports of small, controlled, or open-label stimulant studies in

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preschoolers with PDD (Campbell et al. 1972; Campbell et al. 1976; Hoshino et al. 1977; Birmaher et al. 1988; Mayes et al. 1994) or studies that have included preschoolers along with school-age children with PDD or other developmental disorders (Mayes et al. 1994; RUPP Autism Network 2005), and findings indicate mixed results with more side effects. Of the four controlled studies, the Mayes et al. (1994) methylphenidate (MPH) study included both school-age children ($n = 55$) and preschoolers ($n = 14$), and both inpatients and outpatients. The 14 preschoolers had a heterogeneous mix of diagnoses (4 preschoolers had ADHD only and 10 preschoolers had various neurodevelopmental diagnoses); details regarding the specific neurodevelopmental diagnoses were not provided. Given the diagnostically heterogeneous sample of preschoolers with DD and general lack of details, it is difficult to draw conclusions from the Mayes et al. (1994) paper.

The RUPP Autism Network (RUPP Autism Network 2005) conducted a study in 5- to 14-year-old children with PDD and symptoms of hyperactivity and reported improvement with MPH compared to placebo. However, no specific details are provided as to how the preschoolers responded to MPH. The other two controlled amphetamine studies, conducted more than 30 years ago, were in preschool inpatients with a *Diagnostic and Statistical Manual of Mental Disorders*, 2nd edition (DSM-II) (American Psychiatric Association 1968) diagnosis of early infantile autism, schizophrenia with autistic features, and organic brain syndrome (not selected for ADHD). One study reported improvement in hyperactivity in 5 of the 7 children with ADHD symptoms (Campbell et al. 1976), while the other open-label study reported no improvement (Campbell et al. 1972). Because of the differences in the DSM-II and the current *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text-Revision (DSM-IV-TR) (American Psychiatric Association 2000) nomenclatures, it is difficult to determine if the findings from children with "schizophrenia with autistic features" can be generalized to children with the DSM-IV-TR diagnosis of PDD. The only report of a placebo-controlled MPH study in preschoolers with ID (preschoolers with PDD were excluded) reported improvement in ADHD symptoms in 8 of the 11 preschoolers (Handen et al. 1999). Adverse effects included social withdrawal, increased crying, and irritability, especially at the higher 0.6 mg/kg per dose administered twice a day (b.i.d.).

Despite limited empirical support regarding efficacy and guidance on use of stimulants and increased rate of stimulant side effects in preschoolers with PDD or ID, 6–20% of preschoolers with autism are reported to be taking psychostimulants (Aman et al. 1995; Oswald and Sonenklar 2007). In a survey of medication use in autism, 6% of the children in the age range of "zero through 6 years" were taking stimulants among the surveyed individuals (Aman et al. 1995; Aman et al. 2005). MPH was the most commonly prescribed stimulant. Stimulants were one of the three psychotropic medications that the caregivers were most satisfied with (Aman et al. 1995). Given that no controlled trials have investigated the efficacy and safety of MPH in preschoolers with PDD, only one randomized controlled trial (RCT) has been conducted in preschoolers with ID, and a high rate of stimulant use was reported in preschoolers with PDD and/or ID without empirical guidance, we conducted this study to investigate the short-term efficacy and safety of immediate-release MPH to

treat ADHD symptoms in preschoolers with PDD and/or ID. We hypothesized that MPH would be more efficacious than placebo in reducing ADHD symptoms in such preschoolers and that it would produce more side effects.

For the purposes of this study, we defined preschool age prior to starting formal schooling, i.e., first grade. The Food and Drug Administration (FDA) provides additional demarcation for children younger than 6 years. Most of the pharmacological agents for treatment of ADHD are approved by the FDA only for children at least 6 years (with the exception of amphetamines), and their use in children younger than 6 years is considered as "offlabel" by the FDA. Our definition of preschool age appears to be consistent with recent pharmacological studies conducted in preschool children with ADHD (Handen et al. 1999; Greenhill et al. 2006).

Methods

Study population

Participants were recruited through referrals from pediatricians, preschool teachers, and interested parents in response to study flyers, media advertising, and word of mouth. Participants were 3- to 5-year-old preschoolers who met the DSM-IV-TR criteria for autistic disorder (AD), Asperger disorder, or PDD Not Otherwise Specified (NOS) supported by the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS), or for developmental delays defined by intelligence quotient (IQ) and/or Vineland Adaptive Behavior Scales (VABS) composite score of below 70 ± 5 . Subjects were included only if they exhibited impairing symptoms of hyperactivity and impulsivity in multiple settings (e.g., home, school, or other community places, such as Sunday school, library, restaurant) for at least 6 months. The preschoolers also had to meet severity criteria based on the Hyperactive-Impulsive subscale T-score of 65, 1.5 standard deviation (SD) (93rd percentile) above the age- and sex-adjusted mean on either the Conners' Parent Rating Scale-Revised or Conners' Teacher Rating Scale-Revised (CPRS-R or CTRS-R) (Conners 2001). Impairment criteria included a score of 60 or below on the Children's Global Assessment Scale (CGAS) (Shaffer et al. 1983) and a score of moderate or above on the Clinical Global Impressions-Severity (CGI-S) scale (Guy 1976). Exclusion criteria were: (1) Prior failed treatment with MPH defined as a minimum of 5 weeks of MPH at 15 mg/day for children weighing ≤ 18.0 kg and 20 mg/day for children weighing > 18.0 kg at the time of entering the study; (2) concurrent medications having central nervous system (CNS) effects (including any psychotropic medications); (3) history of tics; (4) major medical condition that could be affected negatively by MPH; and (5) diagnosis of bipolar disorder, psychosis, significant suicidality, or other psychiatric disorders requiring treatment with additional medication.

The study was conducted at the University of Arizona and was approved by the Institutional Review Board. Caregivers/legal guardians provided written informed consent prior to study participation. Because the FDA has not approved MPH use in children younger than 6 years or in children with PDD or ID, we submitted an Investigational New Drug application to the FDA and were granted an exemption for the study.

Fourteen children (mean age 4.8 ± 1.0 years [range 3.0–5.9 years]) completed the crossover phase; 3 children were 3 years

old, 4 children were 4 years old, and 7 children were 5 years old. There were 13 boys (92.9%) and 1 girl, 9 children (64.3%) were Caucasian and 5 were Hispanic. Nine children lived with both parents, 3 children lived with a single parent, and 2 children were adopted. Mean age of the primary caregiver was 36.8 ± 10.0 years (range = 26–69 years). One family received public assistance; mean Hollingshead socioeconomic status (Hollingshead 1975) of the sample was 39.2 ± 6.9 (range = 30.5–52.5).

Associated current or past medical conditions included chronic diarrhea or constipation in 3 children (21.4%), and club foot, bilateral cataracts and hearing loss, microcephaly, Fragile X syndrome, staring spells and hand tremor, premature birth at 32 weeks, low birth weight (2 pounds and 14 ounces), and high lead level and anemia in 1 child (7.1%) each. Delayed speech development was present in 13 children (92.9%) and delayed motor milestones (started walking ≥ 18 months) in 4 children (28.6%). Only 3 children (21.4%) were fully toilet trained on entering the study.

Co-morbid psychiatric disorders included oppositional defiant disorder (ODD) in 3 children (21.4%), separation anxiety disorder in 2 children (14.3%), and adjustment disorder in 1 child (7.1%). Six children (42.9%) had received past trials of psychotropic medications ($\alpha 2$ agonists, $n = 4$; stimulants, $n = 3$; atomoxetine, $n = 2$; and quetiapine, $n = 1$), including polypharmacy in 3 children (21.4%) with 2, 3, or 4 psychotropic medications in 1 preschooler each. Due to adverse effects or lack of response, parents had discontinued medications prior to study participation. Of the 3 children with past stimulant trials, 1 child was treated with MPH. However, the caregiver discontinued the medication after 4 days due to nonresponse with 2.5 mg b.i.d. of MPH. Concurrent medications during the trial included a 2-day course of prednisone and albuterol inhaler for asthma, flonase nasal spray for nasal congestion, and atropine eye drops for lazy eye in 1 child each. Melatonin was added during the study for sleep problems in 3 children. Adjunctive services during the trial included special education services ($n = 10$, 71.4%), speech therapy ($n = 10$, 71.4%), occupational therapy ($n = 5$, 35.7%), physical therapy ($n = 2$, 14.3%), and behavior therapy ($n = 2$, 14.3%). These services were stable for at least 3 months prior to entering the study and were continued unaltered while the children took part in this trial.

Study design

This was a randomized, double-blind, placebo-controlled, crossover trial of immediate-release MPH conducted in an outpatient setting. Potentially eligible preschoolers were screened for categorical diagnosis, dimensional rating scale threshold, and functional impairment threshold to determine eligibility. A brief behavioral instruction to teach children to swallow pills by practicing swallowing increasing sizes of cake decorations (Ghuman et al. 2004) was provided if the child was not experienced with swallowing pills. Each subject participated in a 1-week single-blind placebo lead-in phase; the dimensional and clinician ratings were repeated 1 week later at the baseline visit. Children still meeting inclusion criteria were considered eligible to continue in the study. Medication phases included a single-blind, flexible, stepwise titration of MPH followed by a 4-week double-blind randomized crossover phase. MPH was administered

in gel capsules and was initiated at 1.25 mg b.i.d.; subsequent dose adjustments were made weekly during clinic visits based on clinical impression until an optimal dose that produced the maximal effect with minimal side effects was reached. Sometimes, the dose was titrated at a slower rate if the preschooler experienced moderate adverse events (AEs). The maximum allowed dose was 10 mg b.i.d. The optimal dose determinations were based on clinical impression and were conducted by the same clinician (J.K.G.) for all the study participants.

Following the single-blind titration, each child entered a 4-week double-blind crossover phase with 2 weeks of placebo and 2 weeks of the child's "best dose" in random order—either placebo-MPH or MPH-placebo. The placebo and active medication were administered in identical capsules. Pre-treatment efficacy and safety assessments were conducted at baseline and repeated weekly during the study.

Measures

The ADI-R (Rutter et al. 2003) and ADOS (Lord et al. 2002) were administered to support a diagnosis, if present, of autistic disorder or PDD-NOS. A complete psychiatric history was obtained from the caregivers to establish impairing symptoms of hyperactivity and associated co-morbidities. Each child was administered the Differential Abilities Scale (DAS) (Elliott 1990) and VABS (Sparrow et al. 1984) for an estimate of general cognitive ability and adaptive functioning. Two children were administered the Bayley Scales of Infant Development (Bayley 1993) because they were unable to complete the DAS. Each child's language level was assessed with the Preschool Language Scale-4 (PLS-4) (Zimmerman et al. 1992).

The outcome measures, CRS-R, Nisonger Child Behavior Rating Form (NCBRF) (Aman et al. 1996), CGAS (Shaffer et al. 1983), and CGI (Guy 1976) were obtained at screen, baseline, and at the weekly medication monitoring visits. Items on the primary efficacy measure, the CPRS-R-DSM-IVADHD subscale, are based on DSM-IV ADHD diagnostic criteria. If the child attended preschool or was in daycare, the CTRS-R ratings were also obtained. Parents and teachers, if available, completed the NCBRF (Aman et al. 1996). The NCBRF items measure problem and positive social behaviors and are rated from 0 to 3, with higher scores indicating more severe behavior problems but more prosocial behaviors (there is reverse scoring with prosocial items). The NCBRF has shown good internal consistency, interrater reliability, and validity and was developed in 3- to 16-year-old children with developmental disabilities (Aman et al. 1996).

The CGAS is a clinician-rated instrument based on information obtained from the parents and other informants about the child's functioning. The scale is rated from 1 to 100, with lower scores reflecting poorer adjustment. The CGI-S is rated on a 7-point scale ranging from 1 (normal) to 7 (extremely ill). The CGI-I, completed at every medication-monitoring visit, was rated relative to the child's condition at baseline on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). All clinical assessments (psychiatric history, CGAS, and CGI) were conducted by a board-certified child and adolescent psychiatrist (J.K.G.) experienced in working with preschool children with developmental disorders (DD).

Safety Assessments

Each child had a physical examination (PE), baseline blood work up, and a 12-lead electrocardiogram (ECG) before initiating MPH. PE and ECG were repeated at the end of the study. Height, weight, blood pressure (BP), pulse rate, AE, and concomitant medications and treatments review were conducted by the psychiatrist at baseline and at the weekly monitoring visits via open-ended interview with the caregiver. Additionally, parents completed a psychostimulant Side Effects Rating Scale (SERS) (Barkley and Edwards 1998). The SERS is a 4-point scale, with higher scores reflecting higher severity of the side effect (none = 0, through severe = 3). Parents also completed the Stereotyped Behavior Scale (SBS) (Rojahn et al. 2000) because psychostimulants have been shown to precipitate and/or worsen preexisting stereotypic movements (Roffman and Raskin 1997). The SBS yields a frequency score and a severity score; higher scores reflect higher frequency and higher severity of the stereotyped behaviors. The Yale Global Tic Severity Scale (YGTSS) (Storch et al. 2005) was completed by the clinician because dopamine agonist action of MPH may unmask, trigger, or exacerbate irreversible tics or Tourette disorder (Lowe et al. 1982); higher scores reflect higher severity of tics. The DD version of the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS), addressing compulsive behavior only because of language handicap in such children (Scahill et al. 2006), was completed by the clinician after interviewing the parents to monitor development or worsening of preexisting compulsive, ritualistic repetitive behavior.

Data analysis

Descriptive statistics were used to characterize the baseline subject features and outcome and safety variables. Efficacy and safety analyses were conducted for all the children who completed the titration phase and were randomized to the crossover phase ($n = 14$). Separate analyses were also conducted for the preschoolers who had PDD ($n = 12$). Results for primary outcomes are reported for both the entire DD sample and the PDD subgroup. The results for secondary outcomes, MPH dose, and safety outcomes are reported for the entire DD sample unless the results were different for the overall sample and the PDD subgroup. Repeated-measures analysis of variance (RM-ANOVA) was used to compare the baseline scores with scores for the second week of placebo and MPH conditions on the parent-rated Conners' and NCBRF subscales, CGI-S, CGI-I, and CGAS ratings, with drug order as the between-subject factor, to determine whether there was a significant change with treatment over the three time points. We used the second-week ratings for each drug condition to avoid carry-over effects. *Post hoc* planned comparisons with the Fisher protected least significant difference (Fisher PLSD) were performed to examine whether MPH was likely to have an effect compared to placebo (Hilton and Armstrong 2006). To evaluate the clinical significance of the impact of treatment on outcome, empirically based effect sizes (Cohen d) were calculated as $d = MC/SD\text{-placebo}$, where MC was the difference between the means for the outcome measure scores for the placebo and MPH, and SD-placebo was the standard deviation of the placebo condition (Rosenthal et al. 2000). A two-tailed sign test (Rosner 2006) was conducted to examine the null hypothesis that there was an equal probability of

improvement with MPH and placebo for all outcome measures.

Results

Baseline characteristics

Parents of 46 children gave written consent for their child's participation in the study; 16 of the 46 parents withdrew consent for various reasons (inability to attend weekly visits, reservations about medication for their child, or lost contact). Of the remaining 30 children, 7 children did not meet study eligibility criteria, and caregivers of 6 children declined further study participation. Seventeen children met study eligibility criteria and entered the 1-week placebo lead-in phase. Clinician and caregiver ratings were repeated at the baseline visit to reconfirm study eligibility criteria. All 17 children were eligible to continue study participation and initiated treatment with MPH. However, 3 of the 17 children dropped out during the titration phase: One due to AEs, 1 due to difficulty swallowing capsules, and 1 failed to return. Fourteen children completed the single-blind titration phase and were randomized into the crossover phase. Seven children received placebo followed by MPH and the other 7 children received MPH followed by placebo during the crossover phase.

There were no significant differences in the age, gender, or CPRS-R-DSM-IV-ADHD subscale scores between the 14 children who completed the crossover phase compared to the 32 children who did not. Baseline sample characteristics are presented in Table 1.

Primary outcomes

Results for primary outcome measures are presented in Table 2. The CPRS-R-DSM-IV-ADHD scores improved from baseline for both the placebo and MPH conditions, favoring MPH ($F[2,13] = 8.3, p = 0.002$) for the entire DD sample. The mean difference between placebo and MPH CPRS-R-DSM-IVADHD subscale scores was statistically significant ($p = 0.005$) for the PDD subgroup ($n = 12$), and was not statistically significant ($p = 0.08$) for the entire DD sample ($n = 14$). The hyperactive subscale of the parent-rated NCBRF (NCBRF-P-Hyperactive) indicated a significant advantage for MPH over placebo for the PDD subgroup as well as for the entire DD sample ($p = 0.003$ and $p = 0.03$, respectively). No drug order effects were observed in the analyses.

The CGI-I scores improved from baseline for both the placebo and MPH conditions ($F[2,13] = 15.60, p \leq 0.0001$). *Post hoc* planned comparisons between placebo and MPH CGI-I scores showed significantly lower scores with MPH ($p = 0.02$ for both PDD subgroup and the entire DD sample). The CGAS scores improved from baseline for both the placebo and MPH conditions, favoring MPH. The difference between MPH and placebo CGAS scores was statistically significant ($p = 0.03$) for the PDD subgroup and was not statistically significant ($p = 0.11$) for the entire DD sample. The placebo and MPH CGI-S ratings were not significantly different for the PDD subgroup and the entire DD sample ($p = 0.07$ for both).

We calculated response rate in 10–20% increments based on improvement in the CPRS-RDSM-IV-ADHD subscale using the formula: (Placebo–MPH)/Placebo as first reported by (Aman et al. 2003). Table 3 shows the rates of clinical response for various criteria (20% improvement, 30% improvement,

TABLE 1. BASELINE CHARACTERISTICS OF THE METHYLPHENIDATE DEVELOPMENTAL DISORDERS PRESCHOOL STUDY SAMPLE SUBJECT VARIABLES (N = 14)

Child assessment variables	Range	
Developmental Disorder, N (%)		
Autistic disorder	5 (35.71)	
Pervasive developmental disorder, not otherwise specified	7 (50.00)	
Intellectual disability only	2 (14.29)	
Differential Abilities Scale, mean (SD), [range]		
Verbal score	74.4 (13.87)	[50–92]
Nonverbal score	81.9 (22.76)	[43–121]
General cognitive ability score (<i>n</i> = 11) ^{1,2}	74.9 (18.55)	[44–105]
Vineland Adaptive Behavior Scale (VABS) Standard Score, mean (SD), [range] ³		
VABS communication score	62.4 (21.93)	[14–99]
VABS socialization score	60.4 (18.22)	[12–89]
VABS composite score	61.0 (14.74)	[38–94]
VABS daily living skills score	58.9 (20.00)	[19–99]
Preschool Language Scale-4 (PLS-4) Standard Score, mean (SD), [range] ⁴		
Expressive communication score ⁵	65.1 (14.36)	[50–87]
Auditory comprehension score	66.4 (16.78)	[50–93]
PLS-4 composite score	68.2 (17.11)	[50–89]

¹DAS scores are available on only 11 children as one child was untestable due to extreme inattention, lack of cooperation and very low functioning, and 2 children were tested with the Bayley Scales of Infant Development (BSID) as they were low functioning. They had developmental quotient scores of 27 and 33 (BSID developmental age/chronological age).

²One child was not able to complete all subtests within his age range due to extreme distractibility and difficulty comprehending task demands.

³VABS scores were computer-generated.

⁴*n* = 13 as one child was untestable due to extreme inattention and lack of cooperation.

⁵One child completed 84% of the PLS-4 expressive communication items and then refused to continue.

etc.) for the entire DD sample. Using *a priori* definition of 25% or more reduction in the CPRS-R-DSM-IV-ADHD subscale scores and a CGI-I rating of Much Improved or Very Much Improved (RUPP Autism Network 2005), 7 children (50%) with DD were rated as responding positively to MPH and

1 child (7.1%) responded positively to placebo. The estimated effect sizes (Cohen *d*) relative to placebo for the CPRS-R-DSM-IV-ADHD subscale, NCBRF-P-Hyperactive subscale, CGI-I, CGI-S, and CGAS for the entire DD sample were 0.50, 0.54, 0.95, 0.65, and 0.43, respectively (see Table 2).

TABLE 2. PRIMARY OUTCOME MEASURES COMPARING PLACEBO AND METHYLPHENIDATE SCORES IN PRESCHOOLERS WITH DEVELOPMENTAL DISORDERS AND SYMPTOMS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (N = 14)

Outcome measure	Baseline		Placebo		Methylphenidate		Within subject effects ¹			Methylphenidate & Placebo		Effect size
	Mean	SD	Mean	SD	Mean	SD	df	<i>f</i>	<i>p</i>	Mean difference	<i>p</i> ²	Cohen's <i>d</i> ³
Conners' Parent Rating Scale-Revised-DSM-IV-ADHD Subscale												
PDD Subgroup = 12	34.83	7.33	30.75	9.18	21.83	8.06	2,11	10.454	0.001	8.92	0.005	0.97
Entire DD sample = 14	34.86	7.15	27.57	11.77	21.71	8.78	2,13	8.255	0.002	5.86	0.08	0.50
Nisonger Child Behavior Rating Form-Parent-Hyperactive Subscale												
PDD Subgroup = 12	20.25	4.52	15.75	5.80	10.50	3.83	2,11	16.835	<0.0001	5.25	0.003	0.90
Entire DD sample = 14	20.00	4.21	14.14	6.75	10.50	3.78	2,13	18.199	<0.0001	3.64	0.03	0.54
Clinical Global Impressions (CGI)-Global Improvement score-Clinician												
PDD Subgroup = 12	4.08	0.90	3.00	1.04	1.75	1.14	2,11	12.322	0.0003	1.25	0.02	1.20
Entire DD sample = 14	4.07	0.83	2.79	1.12	1.71	1.07	2,13	15.600	<0.0001	1.07	0.02	0.95
CGI- Severity of Illness score-Clinician												
PDD Subgroup = 12	5.25	0.45	5.00	0.74	4.42	0.79	2,11	3.649	0.045	0.58	0.07	0.79
Entire DD sample = 14	5.21	0.43	4.86	0.77	4.36	0.74	2,13	5.150	0.014	0.50	0.07	0.65
Children's Global Assessment Scale												
PDD Subgroup = 12	46.42	7.00	49.50	5.05	54.33	6.85	2,11	8.522	0.002	4.83	0.03	0.96
Entire DD sample = 14	46.57	6.52	51.86	7.62	55.14	6.63	2,13	9.354	0.001	3.29	0.11	0.43

¹Repeated measures ANOVA comparing baseline, 2nd week placebo and methylphenidate scores.

²Fisher's Protected Least Significant Difference pairwise post hoc comparisons between methylphenidate and placebo.

³Cohen's *d* = Mean difference in the 2nd week outcome measure scores for the placebo and MPH conditions ÷ Standard deviation of the placebo group.

TABLE 3. PERCENTAGE OF DRUG RESPONDERS AS FUNCTION OF DEGREE OF CHANGE IN THE PRIMARY OUTCOME MEASURE (N = 14)

Extent of change ^{1,2}	Number of subjects	% of subjects	Cumulative % of subjects
≥51% improvement	1	7.14	7.14
41–50% improvement	2	14.29	21.43
31–40% improvement	1	7.14	28.57
21–30% improvement	3	21.43	50.00
1–20% improvement	6	42.86	92.86
No change/Worse	1	7.14	100.00

¹Change was calculated using formula $([\text{Placebo-MPH}] \div \text{Placebo})$ as first reported by (Aman et al. 2003).

²Score on Conners' Parent Rating Scale-Revised-DSM-IV-ADHD subscale.

Secondary outcomes

The results for secondary outcomes were similar for the PDD subgroup and the entire DD sample with two exceptions (NCBRF-P Calm/Compliant and parent CGI-S subscales). The secondary CPRS-R and NCBRF-P subscale scores improved from baseline for both the placebo and MPH conditions (favoring MPH). The difference between placebo and MPH conditions was not statistically significant for any of the secondary CPRS-R and NCBRF-P subscales for the entire DD sample (p values ranged from 0.08 for the NCBRF-P Compliant/Calm subscale to 0.95 for the CPRS-R Social Problems subscale). For the PDD subgroup, the difference between placebo and MPH NCBRF-P Calm/Compliant subscale scores was statistically significant ($p = 0.02$).

Comparisons between placebo and MPH parent CGI-I scores ($n = 10$) showed significantly lower scores with MPH (MPH mean score = 2.42 ± 1.1 , placebo mean score = 3.64 ± 1.6 , $p = 0.014$, Cohen $d = 0.74$). The difference between placebo and MPH parent CGI-S ratings ($n = 14$) marginally failed to reach

traditional levels of significance (MPH mean score = 3.64 ± 1.2 , placebo mean score = 4.2 ± 1.3 , $p = 0.06$, Cohen $d = 0.46$) for the entire DD sample, and was statistically significant for the PDD subgroup (MPH mean score = 3.67 ± 1.07 , placebo mean score = 4.42 ± 1.24 , $p = 0.02$, Cohen $d = 0.6$). Overall, all of the 16 outcome measure subscale scores (7 CPRS-R and 6 NCBRF-P subscales, CGI-I, CGI-S, and CGAS) showed more improvement with MPH compared to placebo; this was significant by the two-tailed sign test ($p < 0.0001$) (Rosner 2006).

Methylphenidate dose

Table 4 shows the weight, dose, and duration of medication phase for each individual child in chronological order. The mean MPH morning and noon doses for the crossover phase were 7.32 ± 2.3 mg and 7.14 ± 2.37 mg or 0.40 ± 0.15 mg/kg and 0.39 ± 0.15 mg/kg, respectively (range 2.5–10 mg or 0.14–0.58 mg/kg for both the morning and noon doses). Three children completed titration and were stabilized in 5 visits, 4 in 6 visits, 4 in 7 visits, and 1 each in 8, 10, and 11 visits (mode of 6 visits). The mean duration for the medication phase (flexible titration phase + crossover phase) was 12.7 ± 2.8 weeks (range = 8–18 weeks).

Safety outcomes

One child (diagnosed with AD) discontinued the study during titration due to dysphoria, crying, and whining on MPH 5 mg b.i.d. with no improvement in the AEs when the dose was reduced. Because this child did not participate in the crossover phase, his SERS scores are not included in the following placebo and MPH comparisons. RM-ANOVAs showed no difference in the second-week MPH and placebo SERS scores for all, except one, side effects categories. The mean second-week MPH SERS score for the buccal-lingual movements category (1.36 ± 0.63) was significantly worse than the placebo score (1.07 ± 0.27 , $p = 0.04$). Figure 1 shows the frequency of moderate or severe side effects endorsed on

TABLE 4. AGE, WEIGHT, DOSE, AND MEDICATION PHASE DURATION FOR INDIVIDUAL PRESCHOOL CHILDREN WITH DEVELOPMENTAL DISORDERS AND SYMPTOMS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (N = 14)

Variable	Child Characteristics														Summary	
	AA	BB	CC	DD	EE	FF	GG	HH	II	JJ	KK	LL	MM	NN	N/Mean	%S
Age in months ¹	36.5	40.4	46.2	51.2	51.7	55.9	57.2	63.0	63.6	66.6	69.3	69.7	70.3	71.6	58.08	11.55
Weight ² in kg	16.1	12.8	15.3	17.6	20	17.4	17.3	17.3	19.5	22.4	19.8	19.9	34.7	16.05	19.01	5.12
Total daily methylphenidate dose in mg ³	10.0	15.0	10.0	20.0	15.0	20.0	5.0	20.0	12.5	10.0	20.0	15.0	15.0	15.0	14.46	4.62
Total daily methylphenidate dose mg/kg ³	0.62	1.17	0.65	1.14	0.75	1.15	0.29	1.16	0.64	0.45	1.01	0.75	0.43	0.93	0.80	0.30
Duration of medication phase in weeks ⁴	18	13	9	17	15	11	10	11	14	15	11	13	8	12	12.66	2.79

¹Children presented in chronological order, AA through GG are younger (3- and 4-year-olds) and HH through NN are older (5-year-olds).

²Weight at the 2nd week of MPH crossover phase.

³Dose during crossover phase \div Weight at the 2nd week of MPH crossover phase.

⁴Titration phase + crossover phase.

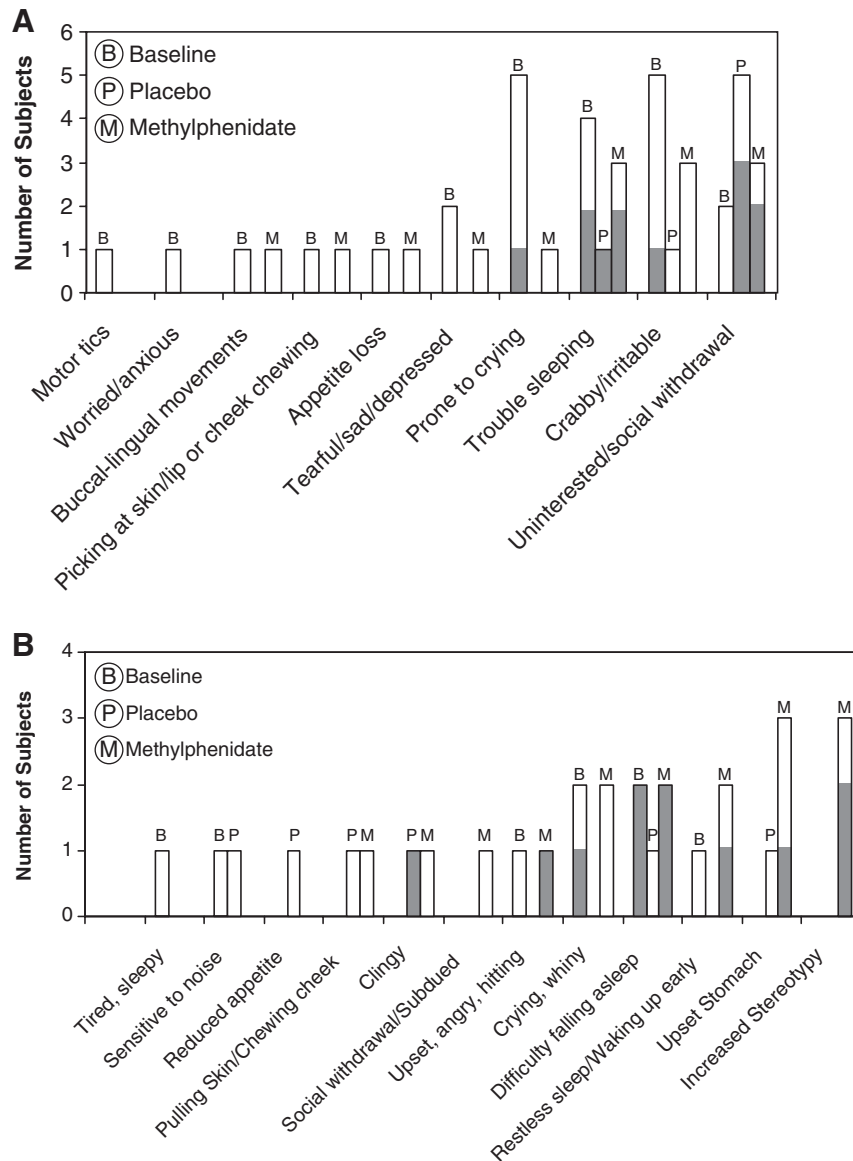


FIG. 1. (A) Safety outcome: Side effect rating scale parent ratings ($n = 14$). The shaded portions of the columns indicate severe side effects. (B) Safety outcome: Spontaneously reported adverse events ($n = 14$). The shaded portions of the columns indicate moderate severity of the adverse events.

the SERS and spontaneously reported AEs at baseline and at the end of the second week of the placebo and MPH conditions. It is interesting that parents rated as many or more children to have moderate or severe side effects at baseline as in the MPH condition. The second-week MPH SERS scores indicated that 4 children (28.6%) either had a new occurrence of a side effect or had an increase in the severity of a side effect relative to the baseline or the placebo condition, although no statistically significant differences between placebo and MPH conditions were detected. Figure 1A shows frequency of moderate and severe side effects on the SERS at baseline and during the second week of the placebo and MPH conditions.

Either new occurrence or increase in severity from the baseline or placebo conditions in the spontaneously-reported AEs occurred in 7 children (50%) during the second week of MPH condition; 3 children had one AE, 2 children had two

AEs, and 1 child had three and four AEs each. Figure 1B shows frequency of spontaneously-reported AEs of mild and moderate severity. None of the parents reported severe AEs.

Repetitive behaviors, as measured by the clinician-rated CYBOCS scores and the parent-rated NCBRF Self Isolative/Ritualistic subscale scores, were slightly worse with MPH than placebo; however, the difference between placebo and MPH conditions was not significant ($p = 0.43$ and 0.75 , respectively). There was a slightly larger decline in the stereotypic behaviors as measured by the parent-rated SBS frequency and severity subscales and NCBRF-P Self Injury/Stereotypy subscale scores with MPH compared to placebo; however, the differences were not significant ($p = 0.20$, 0.92 , and 0.40 , respectively) (see Table 5). The YGTSS indicated presence of motor tics in 4 children at baseline, and 2 of these children continued to have motor tics during the second week of the MPH and placebo conditions; there was a slightly larger

TABLE 5. REPETITIVE AND STEREOTYPED BEHAVIORS COMPARING PLACEBO AND METHYLPHENIDATE SCORES IN PRESCHOOL CHILDREN WITH DEVELOPMENTAL DISORDERS AND SYMPTOMS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (N = 14)

Outcome measure	Baseline		Placebo		Methylphenidate		Within subject effects			Placebo & Methylphenidate		Effect size
	Mean	SD	Mean	SD	Mean	SD	df	f	p	Mean difference	P ²	Cohen's d ³
Stereotyped behaviors												
Stereotyped Behavior Scale (SBS)												
SBS Frequency Score (N = 10)	32.00	21.17	24.50	15.92	20.30	13.22	2, 9	10.14	0.001	4.20	0.20	0.26
SBS Severity Score (N = 9)	19.33	15.39	8.89	5.53	8.56	6.37	2, 8	6.95	0.008	0.33	0.92	0.06
Nisonger Child Behavior Rating Form Parent (N-CBRF-P) Self Injury/Stereotypy Subscale	2.43	2.38	0.93	1.27	0.64	0.74	2,13	7.50	0.003	0.29	0.40	0.23
Repetitive behaviors												
Children Yale-Brown Obsessive Compulsive Scale	13.29	4.68	11.43	4.47	11.93	3.95	2,13	5.43	0.011	-0.50	0.43	-0.11
N-CBRF-P Self Isolative Ritualistic Subscale	7.43	5.10	5.43	3.65	5.71	4.86	2,13	4.13	0.029	-0.29	0.75	-0.08

¹Repeated measures ANOVA comparing baseline, placebo and methylphenidate scores.

²Fisher's Protected Least Significant Difference pair-wise post hoc comparisons.

³Cohen's d = $\frac{\text{Mean difference in the outcome measures scores for the 2nd week of the Placebo and MPH conditions}}{\text{Standard deviation of the placebo condition}}$

decline in the YGTSS severity scores with MPH compared to placebo (9 and 13 for one preschooler and 3 and 5 for the second preschooler, respectively).

No significant changes were observed in the children's weight (baseline = 19.3 ± 5.6 kg, placebo = 20.9 ± 6.8 kg, MPH = 19.0 ± 5.1), height (baseline = 107.7 ± 7.5 cm, placebo = 109.2 ± 8.5 cm, MPH = 109.4 ± 8.2), pulse (baseline = 107 ± 17.0, placebo = 105 ± 10.0, MPH = 102 ± 13.4), BP (systolic BP at baseline = 94 ± 12.3 mmHg, on placebo = 91 ± 12.6 hg and on MPH = 96 ± 11.7, and diastolic BP at baseline = 60 ± 9.95 mmHg, on placebo = 63 ± 7.0 mmHg and on MPH = 64 ± 9.2), and ECG parameters at endpoint compared to the baseline values.

Discussion

To the best of our knowledge, this is the first double-blind, randomized, placebo-controlled MPH trial in a highly exceptional and understudied population, namely preschoolers with PDD, and is the second RCT to include preschoolers with ID. In general, MPH improved parent-rated ADHD symptoms of preschoolers diagnosed with PDD and/or ID; 50% of the preschoolers responded positively to MPH. MPH scores on the primary outcome measure, CPRS-R-DSM-IV-ADHD subscale were significantly better in the PDD subgroup ($p = 0.005$, Cohen $d = 0.97$) and were marginally better than placebo ($p = 0.08$, Cohen $d = 0.50$) in the entire DD sample. MPH response was significantly better than placebo for the parent-rated NCBRF-P for both the PDD subgroup and the overall sample ($p = 0.003$ and 0.03 , Cohen $d = 0.90$ and 0.54 ,

respectively), and for the clinician- and parent-rated improvement on the CGI-I. Overall, MPH was associated with improvement more often than placebo, reflected by a significant sign test ($p = 0.0002$).

The rate and degree of clinical response with MPH in ADHD symptoms in the current trial (>25% reduction in the primary outcome measure) in 50% of the DD preschoolers is similar to the report of 49% response rate in school-age children (RUPP Autism Network 2005), but is less than reported in children with ID. In low-IQ children, a reduction of ≥30% in the primary outcome measure was reported in 44% of school-age children (Aman et al. 2003) compared to 29% of the DD preschoolers in the current trial; and a reduction of ≥40% in 73% of preschool-age children with ID (Handen et al. 1999; Aman et al. 2003) compared to 21% of the DD preschoolers in the current trial 16 (see Table 5).

Lower dosage, more side effects and co-morbidity may account for some of the differences in response. The effect size of 0.50 for the parent-rated primary outcome measure was similar to the MPH effect size of 0.39 for parents and 0.57 for teachers in school-age children with low IQ and ADHD (Aman et al. 2003), and 0.20 to 0.54 in school-age children with PDD (RUPP Autism Network 2005). It is interesting to note that the effect sizes in the current study are similar to the MPH effect size of 0.56 in typically developing preschoolers with ADHD who had 2 co-morbid disorders in addition to ADHD (Ghuman et al. 2007). The preschoolers in the current study could be considered to have two or more "co-morbid disorders," namely PDD and/or ID and communication disorder, in addition to their "ADHD." Higher co-morbidity also re-

duces treatment response in school-age children with ADHD (MTA 1999).

Both parents and clinicians rated the children's improvement on the CGI-I as significantly better with MPH than placebo. The change in children's overall impairment on the CGI-S was not significantly different. The discrepancy between improvement and impairment ratings may be due to the multiple psychiatric, behavioral, and developmental comorbidities exhibited by the study participants. Even though parents and clinicians may detect improvement with MPH in the children's overt behaviors relative to their baseline behaviors, the children may still be significantly impaired and may remain symptomatic in many other areas.

Half of the children experienced spontaneously reported AEs with MPH during the second week of the crossover phase. The AEs included reports of increased stereotypic behavior, upset stomach, sleep-related difficulties, and emotional lability. One child with AD discontinued the study during the titration phase due to dysphoria, crying, and whining. This is similar to the report of irritability leading to discontinuation of MPH in school-age children with PDD (RUPP Autism Network 2005). Report of increased stereotypies in 3 children (21.4%) in the current study is consistent with the report of increased stereotypies after a single test dose of MPH in older children with PDD (Di Martino et al. 2004). The frequency and profile of AEs in the current trial were similar to the AEs seen with older children with PDD and/or ID (Aman et al. 2003; RUPP Autism Network 2005) and preschoolers with ID (Handen et al. 1999). Adverse effects in the Handen et al. (1999) study included social withdrawal, increased crying, and irritability, especially at 0.6 mg/kg dose. High rates of emotional lability were also reported in typically developing preschoolers treated with MPH (Greenhill et al. 2006).

The mean "optimal dose" of 0.76 ± 0.3 mg/kg per day during the crossover phase was lower than the 1.12 mg/kg per day dose in the Handen et al. (1999) study; the preschoolers with PDD and/or ID in the current trial were not able to tolerate the higher doses such as reported by Handen et al. (1999). For example, further dose adjustments had to be stopped due to AEs in 9 of the 14 preschoolers in the current study. Nevertheless, parents were able to detect MPH effects and were pleased with the change in their children's behavior, however modest it might have been; and more than two thirds of the parents (71%) wanted their child to continue taking MPH at the end of the study.

The small sample size precluded a meaningful statistical analysis of the effect of IQ on MPH response; nevertheless, an attempt to compare responders by IQ level failed to show a significant pattern in this small sample.

Limitations

This study had several limitations. First, the study sample size was small. As a result, it is possible that drastic variability within a small number of participants overly influenced the results. For example, parent ratings during the crossover phase varied greatly from one visit to the next for one child with ID only; the mother, who was recuperating from surgery at that time, avoided contact with the child lest her wound be aggravated. Additionally, the small sample size limited any meaningful statistical comparisons between younger and older preschoolers, boys and girls, and ethnic, IQ, or diag-

nostic subgroups, and also limits the generalizability of the findings. Despite the limitations of the small sample size, it is important to note that this is the only MPH trial for ADHD symptoms in such an exceptional and understudied population of PDD preschoolers. The findings from this study need replication with larger samples. Second, the MPH doses used in the study were low; immediate-release MPH was used and was administered b.i.d. instead of the once-a-day longer-acting preparations that are currently preferred in clinical practice. However, due to the fact that empirical guidance for the use of any stimulants is virtually nonexistent and there are reports of increased side effects in preschoolers with PDD or ID, we felt that it was important first to establish guidelines regarding dosage, safety, and efficacy of immediate-release preparations. This is also congruent with the authors' clinical experience with DD preschoolers. In clinical practice, we initiate treatment with short-acting stimulant preparations and may switch to longer-acting preparations if desired by the caregivers once optimal dose, effectiveness, and tolerability have been determined. The b.i.d. dosing of the immediate-release MPH also meant that there was limited medication coverage for the afternoon hours that most preschoolers usually spend with their caregivers, and hence may not have provided sufficient support to the parents/caregivers to help manage their child's ADHD symptoms. However, we used a conservative dosing regimen based on our clinical experience with this population and reports of increased MPH sensitivity in typically developing preschoolers with ADHD (Birmaher et al. 1988; Ghuman et al. 2001; Greenhill et al. 2006) and in developmental disorders (Handen et al. 1999). More aggressive dosing may have yielded a higher response rate (and possibly more side effects). Finally, preschool children were included in the current study based on a dimensional rating scale threshold on either the parent or the teacher scores. Every attempt was made to get teacher ratings for the children who were in a structured preschool or a daycare setting. However, many preschoolers were either not attending preschool or were enrolled in the study during a school break, making it difficult to obtain teacher ratings on a consistent basis. Hence, it is possible that some participants may not have had ADHD symptoms in a preschool setting. Moreover, lack of consistent teacher data limited our ability to assess preschoolers' response to MPH in school settings.

Conclusion

Preschoolers with PDD and/or ID showed modest improvement with MPH; 50% responded positively to MPH. MPH response in the preschool participants was more subtle and variable compared to typically developing ADHD children. However, the predominant direction of change (by sign test) favored MPH over placebo. Both preschoolers and children with PDD and/or ID seemed more sensitive to the side effects of MPH, and they tolerated lower doses, required a slower rate of titration, and needed close monitoring for side effects.

Disclosures

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