ADVANCES IN PRESCHOOL PSYCHOPHARMACOLOGY

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Methylphenidate Effects on Functional Outcomes in the Preschoolers with Attention-Deficit/Hyperactivity Disorder Treatment Study (PATS)

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ABSTRACT

Objective: **The purpose of this study was to examine the effects of methylphenidate (MPH) on functional outcomes, including children's social skills, classroom behavior, emotional status, and parenting stress, during the 4-week, double-blind placebo controlled phase of the Preschoolers with Attention Deficit/Hyperactivity Disorder (ADHD) Treatment Study (PATS).**

Methods: **A total of 114 preschoolers who had improved with acute MPH treatment, were randomized to their best MPH dose (M = 14.22 mg/day; n = 63) or placebo (PL; n = 51). Assessments included the Clinical Global Impression-Severity (CGI-S), parent and teacher ver-**

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sions of the Strengths and Weaknesses of ADHD-Symptoms and Normal Behaviors (SWAN), Social Competence Scale (SCS), Social Skills Rating System (SSRS), and Early Childhood Inventory (ECI), and Parenting Stress Index (PSI).

Results: **Medication effects varied by informant and outcome measure. Parent measures and teacher SWAN scores did not differentially improve with MPH. Parent-rated depression ($p < 0.02$) and dysthymia ($p < 0.001$) on the ECI worsened with MPH, but scores were not in the clinical range. Significant medication effects were found on clinician CGI-S ($p < 0.0001$) and teacher social competence ratings (SCS, $p < 0.03$).**

Conclusions: **Preschoolers with ADHD treated with MPH for 4 weeks improve in some aspects of functioning. Additional improvements might require longer treatment, higher doses, and/or intensive behavioral treatment in combination with medication.**

INTRODUCTION

The diagnosis of attention-deficit/hyperactivity disorder (ADHD) is most commonly made in middle childhood, although onset during preschool years is typical. In contrast to an extensive treatment literature regarding the efficacy of psychostimulants in elementary school-aged children with ADHD, only a small number of such studies have been conducted with preschoolers. The efficacy of psychostimulants in reducing ADHD symptoms in preschoolers was first reported in the 1970s (Conners 1975; Schleifer et al. 1975). With few exceptions (Cohen 1981; Barkley et al. 1984), subsequent placebo-controlled studies, although varying in design, quality, and size, have confirmed medication effects on symptoms of ADHD. Monteiro-Musten et al. (1997) found that stimulants increased preschoolers' attention and decreased impulsiveness. Byrne et al. (1998) reported that stimulants improved behavior and significantly reduced errors of omission on visual and auditory vigilance tests. Short et al. (2004) found a clinically significant reduction in ADHD symptoms in 82% ($n = 28$) of preschoolers treated with stimulants. Findings from the National Institute of Mental Health (NIMH) multisite Preschoolers with ADHD Treatment Study (PATS) indicated that immediate release methylphenidate (MPH-IR), delivered in 2.5-, 5.0-, and 7.5-mg doses three times a day (t.i.d.), yielded significant reductions on ADHD symptom scales compared to placebo (Greenhill et al. 2006).

School-aged and preschool children with ADHD share not only a common symptom profile, but also a similar pattern of associated functional deficits and impairments (Sonuga-Barke et al. 2003). Both age groups have deficits in social skills, especially in social cooperation (Merrell and Wolfe 1998) and friendships (Lahey et al. 1998). They also experience problematic interactions with their parents and other relatives (DuPaul et al. 2001; Daley et al. 2003) that contribute to high levels of familial stress, which in turn exacerbate mental health problems among family members (DeWolfe et al. 2000).

Notably, functional impairments, especially in social functioning and parent–child interactions, as well as deficient regulation of emotions and problematic classroom behavior, typically result in clinic referrals in children with ADHD. Medication has been shown to improve these functional domains in elementary school-aged children with ADHD (MTA Cooperative Group 1999; Abikoff et al. 2004; Hechtman et al. 2004); however, information regarding medication effects on these aspects of functioning in preschoolers with ADHD is sparse and inconclusive. Acute MPH treatment has been reported to reduce the observed frequency of controlling and dominating peer interactions in 4–6 year olds with ADHD in a simulated classroom setting (Cunningham et al. 1985). Barkley (1988) reported that stimulants improved the quality of interactions between preschoolers and their mothers, whereas Monteiro-Musten et al. (1997) found that, although stimulants improved adjustment, they did not increase compliance with parental requests.

In recognition of the need to characterize the impact of stimulants on clinically relevant aspects of functioning in preschoolers with ADHD, the PATS trial evaluated the effects of MPH on children's social skills, classroom behavior, emotional status, and parenting stress. We hypothesized that medication effects in preschoolers with ADHD would parallel those found in school-aged children. Specifically, it was hypothesized that: (1) compared to children randomized to placebo (PL), preschoolers randomized to their "best dose" of MPH would show significant improvements in classroom behavior, social, and emotional functioning; and (2) parents of children receiving MPH would show significant reduction in parenting stress compared to parents of children on PL.

METHODS

Detailed descriptions of the PATS design and methods are provided elsewhere (Greenhill et al. 2006; Kollins et al. 2006); therefore, only key study features are presented here.

Subjects

Participants had to meet the following criteria: Stimulant-naive children of both sexes, ages 3–5.5 years with a *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV) consensus diagnosis of ADHD (American Psychiatric Association, 1994), combined or predominantly hyperactive subtype, based on the Diagnostic Interview Schedule for Children IV–Parent Version (DISC-IV-P) (Shaffer et al. 1996) and semistructured interview; an impairment scale score $\leq$55 on the Children's Global Assessment Scale (C-GAS) (Shaffer et al. 1983); hyperactive-impulsive subscale T score of 65 (1.5 SD above age- and sex-adjusted means) on both the Conners Revised Parent (CPRS) (Conners et al. 1998a) and Teacher (CTRS) (Conners et al. 1998b) Rating Scales; full scale intelligence quotient (IQ) $>$ 70 on the Differential Ability Scales (DAS; Elliott 1990); participation in a preschool, day-care group setting or other school program at least 2 half-days per week with at least 8 same-age peers; and the same primary caretaker for at least 6 months prior to screening.

Exclusion criteria included current evidence of adjustment disorder, pervasive developmental disorders, psychosis, significant suicidality, or other psychiatric disorder that required treatment with additional medication; current stimulant or cocaine abuse in a relative living in the home; a confounding medical condition; inability of the parent to understand or follow study instructions; or history of bipolar disorder in both biological parents.

Study design

The PATS design consisted of several phases, detailed in Kollins et al. (2006). Briefly, 183 preschoolers who failed to improve significantly after parent participation in a 10-week parent training program, and whose parents consented to a medication trial for their youngsters, entered an open-label, lead-in phase to determine if they could tolerate doses of MPH used in the subsequent double-blind phases. Children (n = 165) who tolerated the lead-in doses entered the study's 5-week double-blind, within-subject, placebo-controlled, crossover-design, titration phase, and 147 children were randomized to, and completed, all five sequences of active MPH (1.25, 2.5, 5, 7.5 mg) and PL administered t.i.d.. At the end of each week, school and home behavior and side effects ratings were obtained from teachers and parents. At the conclusion of the 5-week trial, these weekly ratings were reviewed by two independent clinicians, blind to dosing information, who generated a consensus decision regarding each child's best dose. Following this crossover phase, children went on to participate in the between-subjects, randomized, 4-week, double-blind, parallel design study phase of the PATS trial, wherein they were randomized to either their best dose of MPH or PL. The parallel-design phase, unlike the preceding titration phase, included assessments of functional outcomes. Findings on these outcomes are reported here.

The study protocol and parental informed consent forms were approved by the institutional review boards at the six recruiting sites. The study was monitored by the Data and Safety Monitoring Board of the National Institute of Mental Health.

Table 1. Demographic and Clinical Characteristics of the Sample at Baseline

Variable	*Best dose* (n = *61*)	*Placebo* (n = *53*)
Age, years mean (SD)	4.39 (0.72)	4.45 (0.67)
Male, *n* (%)	49 (80.33)	36 (67.92)
Ethnicity, *n* (%)		
White	36 (59.02)	38 (71.70)
Black or African American	12 (19.67)	7 (13.21)
Hispanic or Latino	12 (19.67)	7 (13.21)
Other	1 (1.64)	1 (1.19)
High school graduate, *n* (%)		
Mother	58/60 (96.67)	49/51 (96.08)
Father	48/49 (97.96)	43/44 (97.73)
Employed, *n* (%)		
Mother	48/59 (81.36)	32/51 (62.75)
Father	44/58(75.86)	36/51 (70.59)
Welfare, *n* (%)	5/53 (9.43)	2/45 (4.44)
Married, *n* (%)	35/60 (58.33)	33/52 (63.46)
Hollingshead SES, mean (SD)	46.65 (9.17)	48.75 (9.76)
Family Composition, *n* (%)		
2 Parents	50 (81.97)	42 (79.25)
1 Parent	11 (18.03)	11 (20.75)
CTRS, mean (SD)		
Inattention	15.00 (5.41)	14.65 (6.29)
Hyperactivity[a]	21.44 (4.12)	19.51 (5.12)
Total	36.56 (8.08)	34.24 (9.60)
CPRS, mean (SD)		
Inattention	16.95 (5.09)	18.34 (5.17)
Hyperactivity	22.00 (3.57)	22.62 (3.40)
Total	39.02 (7.31)	41.02 (7.62)
DAS IQ, mean (SD)	98.86 (16.84)	95.75 (15.17)
C-GAS Impairment Scale, mean (SD)	47.15 (4.42)	47.55 (3.93)
ADHD Subtype, *n* (%)		
Hyperactive-Impulsive	18 (29.51)	11 (20.75)
Combined	43 (70.49)	42 (70.25)

CTRS = Conners Teacher Rating Scale; CPRS = Conners Parent Rating Scale; DAS = Differential Ability Scale; C-GAS = Children's Global Assessment Scale; SD = standard deviation; IQ = intelligence quotient; SES = socio-economic status.

[a]$p < 0.04$, all other comparisons nonsignificant.

Participants

A total of 114 children participated in the parallel design study phase of the PATS: 61 were randomized to MPH and 53 to PL. Their characteristics are summarized in Table 1.

Domains and measures

ADHD behavior. Strengths and Weaknesses of ADHD-Symptoms and Normal Behaviors. The common occurrence of ADHD behaviors in preschoolers results in over-estimates of such behaviors with conventional ADHD rating scales. The SWAN's 7-point metric (from −3 "far above average" to +3 "far below average") of strengths and weaknesses of ADHD-Symptoms and Normal Behaviors (SWAN) was designed to protect against over-estimates of ADHD behaviors, and yields ratings of preschool children's ADHD behaviors that are normally distributed, such that average, unaffected children would receive ratings of "0," which indicates no particular attentional or impulsive/motor problems compared to other children of the same age. Teacher and parent versions of the SWAN were used in the study (Swanson et al. 2001; Cornish et al. 2005).

Social behavior. Social Skills Rating System. The Social Skills Rating System (SSRS) is a standardized scale that assesses social functioning. Preschool and School-age parent (SSRS-P) and teacher (SSRS-T) versions are available (Gresham and Elliott 1990). The SSRS-P comprises 70 items, 60 of which assess prosocial skills and 10 assess problem behaviors. Fifty of the proso-

cial items overlap with the SSRS-T and the other 10 address social situations at home. The Total Social Skills score served as the study outcome measure, with higher scores indicating better functioning. Reliability and validity have been established (Gresham and Elliott, 1990).

Social Competence Scale. The 12-item parent (SCS-P) and teacher (SCS-T) versions of the Social Competence Scale Scale assess frustration tolerance, peer relationships, communication skills, and empathy (Conduct Problems Prevention Research Group 1992). The Total score served as the study outcome measure, with higher scores indicating more competence. The scale has demonstrated sensitivity to treatment effects in preschoolers (Webster-Stratton 1998).

Parental stress. Parenting Stress Index. The Parenting Stress Index (PSI) is a 101-item, 5-point Likert scale that measures stressful child, parental, relational, and situational characteristics (Abidin 1995). The Total score on the Parent Domain, which taps depression, attachment, restriction of role, sense of competence, social isolation, relation with spouse, and parent health, served as the outcome measure. Internal consistency and concurrent and discriminant validity have been documented. The scale has been shown to be sensitive to treatment effects in children with conduct disorders (Kazdin and Whitley, 2003).

Mood. Early Child Inventory. The Early Child Inventory (ECI) is a 108-item inventory that has been normed on preschool children, and the parent (ECI-P) and teacher (ECI-T) versions have acceptable reliability and validity data (Gadow and Sprafin, 1996; Sprafkin et al. 2002). The items assess behaviors and symptoms associated with a wide-range of childhood mental disorders. Scores on the two Mood Scales, Dysthymic Disorder and Major Depressive Disorder, served as outcome measures.

Severity of illness. Clinical Global Impressions–Severity. The Clinical Global Impressions–Severity (CGI-S) is a clinician completed 7-point rating scale (1 = not at all ill to 7 = among the most extremely ill) that assesses the child's current level of severity of illness (Guy 1976). The scale has adequate psychometric properties (American Psychiatric Association, 2000) and is one of the most widely used outcome measures in psychopharmacology trials.

Data analyses

Measures were obtained at baseline at the beginning of the PATS trial (prior to initiation of medication) and at the end of the 4-week, double-blind, parallel design study phase. For participants who did not complete the 4-week phase, efforts were made to obtain outcome scores at the time of dropout. Data analysis was based on intent-to-treat, last observation carried forward (LOCF) procedures. Analyses of covariance of fixed effects, using baseline scores as the covariate, were conducted to evaluate medication effects on the study measures. Effect sizes (ES), using Cohen's *d*, were calculated for each outcome measure by dividing the difference between the post-treatment group means by the pooled SD.

The CGI-S, completed by the clinician at the end of each subject's participation in the parallel-design phase, was obtained on the full sample. Data on other measures were missing from some parents, and to a greater extent, from teachers. An *a priori* decision was made to analyze measures for which scores were available on at least half of the sample that entered the double-blind (DB) efficacy trial. Consequently, the teacher-completed ECI, which was unavailable on 60% of the sample (38 in the MPH group [62.6 %] and 30 in the PL group [56.6 %]) and the teacher-completed SSRS, missing for 51% of the sample (31 in the MPH group [50.8 %] and 27 in the PL group [50.1%]), were not analyzed. Descriptive statistics, analysis of covariance (ANCOVA) results and effect sizes are presented in Table 2.

RESULTS

Sample retention

Of the 114 children who entered the 4-week parallel-design phase, 36 (32%) dropped out. Of these, 33 had behavioral deterioration [24 were in the PL group (24/53, 45%), and 9 in the MPH group (9/61, 15%)], 2 declined study participation, and 1 had medication related ad-

Table 2. Comparison of Treatment Groups on Study Outcome Measures at Immediate Posttreatment

Outcome measure	N	Best dose (n = 61)		Placebo (n = 53)			ANCOVA treatment effect		
		Baseline mean (SD)	Posttreatment mean (SD)	n	Baseline mean (SD)	Posttreatment mean (SD)	$F_{(NDF,DDF)}$	p <	Effect size
SWAN Parent[a]									
Total ADHD	48	1.66 (0.65)	1.09 (0.72)	38	1.83 (0.61)	1.41 (0.77)	$2.09_{(1, 78)}$	NS	0.43
Inattention	48	1.37 (0.82)	0.92 (0.81)	37	1.63 (0.72)	1.28 (0.86)	$1.51_{(1, 77)}$	NS	0.43
Hyp-Imp	47	1.92 (0.62)	1.26 (0.81)	38	2.04 (0.74)	1.52 (0.79)	$1.41_{(1, 77)}$	NS	0.32
SWAN Teacher[a]									
total ADHD	32	1.39 (0.58)	1.09 (0.80)	32	1.41 (0.79)	1.35 (0.77)	$2.20_{(1, 56)}$	NS	0.32
Inattention	31	1.10 (0.59)	0.85 (0.88)	32	1.31 (081)	1.14 (0.81)	$0.86_{(1, 55)}$	NS	0.34
Hyp-Imp	32	1.70 (0.71)	1.35 (0.87)	33	1.53 (0.95)	1.58 (0.89)	$3.37_{(1, 57)}$	0.08	0.27
Parent ECI[a]									
MDD	35	4.00 (2.36)	5.53 (2.85)	26	4.71 (2.86)	4.06 (2.46)	$6.52_{(1, 53)}$	0.02	0.55
Dysthymic	35	3.04 (1.85)	4.49 (2.56)	26	3.83 (2.49)	2.98 (1.74)	$12.22_{(1, 53)}$	0.001	0.67
CGI-S[a]	61	4.77 (0.59)	3.74 (1.09)	53	4.68 (0.51)	4.47 (0.89)	$18.85_{(1, 106)}$	0.001	0.73
PSI–Total Stress[a]	45	75.27 (27.36)	67.29 (32.84)	33	82.27 (23.77)	76.70 (24.76)	$0.82_{(1, 70)}$	NS	0.32
SCS–Parent[b]	50	1.16 (0.55)	1.43 (0.62)	37	1.23 (0.59)	1.36 (0.57)	$1.44_{(1, 79)}$	NS	0.13
SCS–Teacher[b]	31	1.14 (0.59)	1.56 (0.82)	31	1.31 (0.72)	1.27 (0.63)	$5.17_{(1, 54)}$	0.03	0.39
SSRS Parent[b]	44	84.48 (12.42)	89.41 (13.66)	31	81.52 (16.38)	87.39 (15.75)	$0.00_{(1, 67)}$	NS	0.14

[a]Lower scores indicate better outcome.

[b]Higher scores indicate better outcome.

SWAN = Strengths and Weaknesses of ADHD-Symptoms and Normal Behaviors; Hyp-Imp = Hyperactive/Impulsive scale; ECI = Early Child Inventory; MDD = major depressive disorder; CGI-S = Clinical Global Impressions-Severity; PSI = Parenting Stress Index; SCS = Social Compentence Scale; SSRS = Social Skills Rating System; ADHD = attention-deficit/hyperactivity disorder; SD = standard deviation; NS = not significant; ANCOVA = analysis of covariants.

verse effects. Nineteen children dropped out in week 1 (15 on PL, 4 on MPH), 13 in week 2 (PL = 8, MPH = 5) and one in week 3 (PL). Analyses comparing the baseline characteristics of completers and non-completers indicated no significant differences.

ADHD behavior

On the SWAN, the MPH and PL groups did not differ significantly in parent or teacher ratings of total ADHD or inattention, or parent ratings of hyperactivity/impulsivity, with scores improving in both groups from pre to post. However, teacher ratings of hyperactivity/impulsivity indicated a trend ($p = 0.08$; ES = 0.27) in favor of the MPH group.

Social behavior

Children's social competence and social skills, based on parent ratings on the SCS and SSRS, respectively, did not differ significantly between the groups. A significant treatment effect ($p < 0.03$; ES = 0.39) was found in teacher ratings on the SCS, with preschoolers treated with medication improving in their social competence scores, whereas those on placebo showing no change from pre to post.

Parental stress

There was no significant difference in the PSI ratings of parents of children in the MPH and PL groups, with the mean Total scores decreasing in both groups from pre to post.

Mood

Compared to preschoolers treated with PL, children in the MPH group had significantly higher mood scores on the parent rated ECI Major Depressive Disorder ($p < 0.02$) and Dysthymic scales ($p < 0.001$). The group difference reflected an increase in mood symptoms from pre- to posttreatment with MPH in contrast to a decrease over time with PL (see Table 2). Subsequent item analyses of the mood symptoms comprising these two ECI scales indicated that the item "Has become more sensitive or tearful than usual" was the only symptom that significantly differentiated MPH from PL ($p < 0.003$).

Severity of illness

Clinicians' global ratings of severity on the CGI-S at posttreatment were significantly lower for children in the MPH group compared to those on PL ($p < 0.0001$; ES = 0.73).

DISCUSSION

Contrary to expectations, the effects of MPH on functional outcomes in preschoolers did not parallel the functional improvements reported in elementary school-aged youngsters with ADHD treated with MPH. Rather, in the current study, medication effects varied as a function of informant and outcome measure. The absence of MPH effects was most evident on parent measures. Preschoolers' social skills and social competence, as well as their level of ADHD behaviors on the SWAN, did not improve differentially with medication on the basis of parent ratings. Similarly, self-ratings of parental stress were not significantly different in parents of children treated with MPH or PL. Moreover, parents' ratings of their children's mood symptoms indicated a worsening of symptoms with medication. In contrast, positive medication effects were detected in clinicians' global severity ratings and in teachers' ratings of improved social competence in children on MPH. However, like parents, teachers' ratings of ADHD behaviors on the SWAN were not differentially related to the children's medication status.

A variety of factors need to be considered in interpreting the study outcomes. Forty five percent of the children in the PL group dropped out before the end of the 4-week treatment phase because of behavioral deterioration, compared to 15% of children receiving MPH. At dropout, efforts to obtain outcome measures, which were intended to serve as LOCF data, were not always successful. Consequently, the power to detect treatment differences was decreased because of the reduced sample size available for analysis.

The lack of terminal data on all dropouts precludes an explication of the exact nature of the "behavioral deterioration" in these youngsters. In the PATS primary efficacy paper (Greenhill

et al. 2006), we reported that attrition during the parallel group double-blind phase "was significantly correlated with elevated SNAP scores ($p < 0.009$)" (p. 1291), indicating that children withdrawn from the study had an increase in ADHD symptoms. It is unknown if these dropouts also showed an increase in functional impairment. To the extent that they did, the results reported here may be underestimates of MPH effects on functional outcomes. However, it is important to emphasize that the association between ADHD symptom severity and degree of functional impairment has been reported to be relatively small, with symptom severity predicting less than 25% of the variance in impairment in four separate studies (Gordon et al. 2006).

An underestimation of MPH effects could have also occurred if the completers were less functionally impaired on placebo than those who dropped out of the PL group. Here too, the absence of terminal ratings precludes a direct test of this possibility. However, as an indirect test of this notion, we examined if the completers and dropouts had a differential response to placebo during the preceding double-blind titration phase. Independent *t*-tests indicated no significant differences (*p* values ranged from 0.32 to 0.82) in the subgroups' scores on the parent and teacher Connors, Loney, and Milich (CLAM) and Swanson, Kotkin, Atkins, M-Flynn, and Pelhan (SKAMP) ADHD rating scales during the titration week when each child was on placebo.

The higher-than-expected rate of premature treatment discontinuation may be related to the multistage, sequential design of PATS. Children participating in the placebo-controlled trial reported here had previously completed a within-subject titration showing superiority of MPH over placebo at the individual patient level. Parents' experience during the titration phase presumably heightened their awareness of the behavioral differences associated with active and placebo medication. Such knowledge, in conjunction with study guidelines that allowed parents to forego or discontinue participation in the double-blind, parallel-group phase and have their child move directly to open maintenance treatment with MPH, likely contributed to dropout decisions for some parents.

We considered the possibility that the dropouts in the PL group showed more improvement with medication during titration than did the completers in the PL group, increasing the likelihood of dropout. To this end, we compared these two subgroups' parent and teacher scores on the CLAM and SKAMP ADHD rating scales when they were on their optimal dose of MPH during titration. The PL dropouts and completers did not differ significantly on any of these measures.

The MPH doses in the double-blind parallel group study phase were relatively low ($M = 14.22 \pm 8.1$ mg/day), which may have limited functional improvements Findings from the PATS maintenance phase (Vitiello et al., this issue), provide some support for this notion. For example, the increase in children's MPH doses from the first to the tenth month of maintenance treatment ($M = 19.98 \pm 9.56$ mg/day) was associated with improvements in children's social skills as rated by parents. These results must be tempered because of the absence of an untreated group as a temporal control. However, future studies might explore the possibility that children's social functioning is facilitated with higher doses.

Although MPH resulted in a significant increase in scores on the Major Depressive Disorder and Dysthymic Disorder scales on the ECI compared to PL, the scores were not in the clinical range. The higher score in the medication group on the item "Has become more sensitive or tearful than usual" likely reflects the significant increase in emotional outbursts/crying with MPH compared to PL reported in the initial titration phase of the study (Wigal et al. 2006). Notably, the frequency of emotional outbursts/crying decreased significantly during the 10-month maintenance period, even though the mean MPH total daily dose increased during this period (Wigal et al. 2006). A similar pattern of findings has been reported in 7- to 9-year-old children with ADHD, who showed initial increases in their Children's Depression Inventory scores after 5 weeks of MPH treatment, followed by a significant decrease in CDI scores after 6 months of treatment with MPH (Hechtman et al. 2004).

Teachers, unlike parents, reported gains in social competence with MPH. Poor concor-

dance rates for parent and teacher ratings of ADHD symptoms in the PATS sample has been reported by Murray et al. (this issue). The lack of agreement between parent and teacher ratings of children's behavior is well established, and, in children with ADHD, it is considered to reflect the variability of children's behaviors across situations (McDermott et al. 2005). Relatedly, contextual factors could have facilitated teachers' ability to detect medication related changes in social competence, because they had more opportunities than parents to see children in social situations. These informant differences illustrate the importance of collecting and analyzing information from key individuals regarding preschool children's functioning to obtain a more complete picture of treatment outcome.

Stimulant medication in children with ADHD has been reported to have positive effects on some, but not all aspects of parenting. Improved parent–child interactions, decreased negative parenting practices, and improved ratings of parental effectiveness often occur with MPH treatment (Stein et al. 1996; Hechtman et al. 2004). In contrast, medication has not been shown to increase positive parenting practices (Hechtman et al. 2004) or positive changes in parent functioning, such as improved mood and ability to complete tasks (Chronis et al. 2003). In the current study, parental stress was not differentially reduced in parents whose children were treated with MPH relative to those on PL. The reasons for this are not clear. It is likely that children showed symptomatic improvement throughout much of the day. However, parental difficulties in managing their children in the morning, before medication effects were observable, or later in the day, when medication effects dissipated, conceivably continued to be salient, stressful events that influenced parents' judgments and self-ratings of stress levels.

Clinicians' global impressions of illness severity were significantly reduced in children treated with MPH compared to those on PL, yielding an ES of 0.73, the largest obtained on any outcome measure. CGI-S ratings, which take into account the youngster's overall functioning, have been reported to be influenced by a variety of factors, including severity of ADHD symptoms, peer relationship problems, oppositional defiant disorder (ODD), conduct disorder (CD), and internalizing symptoms (Coghill et al. 2006). Consequently, the degree to which clinicians' CGI-S ratings were influenced by functional improvements and/or reductions in children's ADHD symptoms is unknown. However, the absence of treatment effects in teacher and parent SWAN ratings of ADHD symptoms, with children in both groups improving over time, suggests that clinicians' judgments reflected, at least in part, improvements in non-ADHD-related areas of functioning.

Limitations

The present study has some limitations. First, as described above, the differential attrition rates in the two groups limited power to detect treatment differences and may have resulted in an underestimation of MPH effects on functional outcomes. Second, missing data, especially from teachers, precluded analyses of teacher ratings on the SSRS and ECI. As a result, it is unknown whether broader aspects of children's social skills, beyond those associated with social competence, improved in the school setting with MPH. Similarly, it is unknown whether the increase in sensitivity and tearfulness with MPH reported by parents occurred in school as well. Third, little is known about the psychometric properties of the CGI-S in preschool-aged children. The absence of reliability and validity information in this age group needs to be considered in interpreting the findings on the CGI-S. Fourth, in an effort to minimize treating preschoolers with medication unnecessarily, the PATS study design incorporated several features, including a 10-week parenting program, which preceded the study's medication phases, and a conservative set of diagnostic and inclusion criteria to minimize false positive diagnoses. These criteria included elevated scores on both the teacher and parent Conners Rating scales and an impairment score on the C-GAS $\leq$55. The resulting study sample had a mean C-GAS score of 47, which is considerably lower than the typical C-GAS score of 65 for children with ADHD seen in clinic settings. Consequently, the generaliz-

ability of the findings reported here to preschoolers with less severe levels of ADHD and impairment is uncertain.

Finally, although 4 weeks is typically sufficient to detect improvements in ADHD symptoms, a longer treatment period may be needed for functional changes to occur. However, because of design features of the PATS trial, it was not deemed ethical or clinically viable to keep children on placebo for more than 4 weeks. Specifically, the participants in the parallel-group phase had all participated in the previous within-subject titration phase and had demonstrated benefit with MPH treatment. In light of their prior experience with MPH, there was concern about the length of time individuals would tolerate treatment with PL, which led to the decision to limit the randomized, parallel-group phase to four weeks. Even with this design, the dropout rate was quite high in the PL group. It is likely that attrition in the PL group would have been even higher with an extended randomized, parallel-group phase. However, a parallel-group design that included randomization to MPH or PL for a longer treatment period, such as 8 weeks, might be viable in preschoolers without any prior exposure to MPH. Such an extended treatment period would provide greater opportunity for any functional improvements that occur to consolidate and be detected.

CONCLUSION

Preschoolers with ADHD treated with MPH for 4 weeks show some improvements in functioning, although not as extensive as those found in their elementary school-aged counterparts. We cannot rule out the possibility that these different outcome patterns are an artifact of the study design and uneven attrition rates in the MPH and PL groups. Nonetheless, it may be that additional functional improvements in preschoolers with ADHD require a longer treatment period, higher doses than those used in the current study, and/or the use of intensive behavioral treatment in combination with medication. Although there is a scarcity of evidence-based psychosocial interventions for preschool children with ADHD, the inclusion of "established" parenting programs [e.g., New Forest Parenting Program (Sonuga-Barke et al. 2001); Parent-Child Interaction Therapy (Eyberg et al. 1995)], perhaps in conjunction with school-based behavioral approaches, might lead to additional improvements in children's social functioning and in parent stress levels beyond those reported here. Systematic, randomized controlled trials are needed to address this issue.

DISCLOSURES

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