Efficacy and Duration of Effect of Extended-Release Dexmethylphenidate Versus Placebo in Schoolchildren With Attention-Deficit/Hyperactivity Disorder

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ABSTRACT

Objective: The aim of this study was to assess changes in symptomatology of attention-deficit/hyperactivity disorder (ADHD) with extended-release dexmethylphenidate (d-MPH-ER) versus placebo in a laboratory classroom setting.

Methods: This double-blind, placebo-controlled, crossover study randomized 54 children 6–12 years of age, stabilized on methylphenidate 20–40 mg/day. Patients participated in a practice day, then received 5 days of treatment with d-MPH-ER 20 mg/day or placebo. After a 1-day wash-out, they returned to the classroom and received 1 dose of their assigned treatment. Evaluations occurred predose and at postdose hours 1, 2, 4, 6, 8, 9, 10, 11, and 12. Children were then crossed over to the alternate treatment, using identical protocol. Primary efficacy variable was the Swanson, Kotkin, Agler, M-Flynn, and Pelham rating scale (SKAMP)-Combined scores, and primary analysis time point was 1 hour postdose; secondary efficacy variables over 12 hours included SKAMP-Attention and -Deportment scores and written math test results. Safety was assessed by adverse event (AE) recording following each period. Vital signs were recorded at each visit; laboratory tests were conducted at screening and final visit.

Results: D-MPH-ER 20 mg/day showed a significant advantage over placebo as early as 1 hour postdose on SKAMP-Combined scores \( p < 0.001 \). When analyzing the entire sample of 54 children, d-MPH-ER maintained significant superiority over placebo from hours 1 through 12 \( p \)-values ranged from < 0.001 to 0.046). D-MPH-ER was well tolerated, with no severe AEs reported.

Conclusions: D-MPH-ER is safe and effective and improves classroom attention, deportment, and performance in children with ADHD.
INTRODUCTION

ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER (ADHD) is diagnosed in approximately 5% to 6% of school-age children (4–17 years of age) in the United States (Guevara et al. 2002; Lesesne et al. 2003). The presence of ADHD is more frequently diagnosed in boys than in girls, with ratios ranging from 4:1 to 9:1 (Diagnostic and Statistical Manual of Mental Disorders, Fourth edition, text revision (DSM-IV-TR; American Psychiatric Association 2000)). The disorder is characterized by persistent, developmentally inappropriate inattention, hyperactivity/impulsivity, and non–goal-directed behavior. Some patients, however, predominantly exhibit inattention, whereas others exhibit predominantly hyperactivity or impulsivity. These symptoms lead to difficulties in cognitive and behavioral areas, family and social relationships, and self-esteem (DSM-IV-TR 2000; Biederman et al. 1996). Typically first identified during the elementary school years (Goldman et al. 1998), ADHD can persist into adolescence and adulthood. If poorly treated or left untreated, ADHD can increase the risk for failure at school or work, delinquent behavior, drug abuse, and the development of antisocial personality disorder (Barkley 2002; Biederman et al. 1996; Dulcan 1997; Wilens et al. 2004).

The etiology of ADHD remains unknown. The broad spectrum of cognitive, behavioral, and emotional symptoms seen with the disorder, however, suggests the involvement of multiple genetic and psychosocial factors (Faraone 2004). Structural and functional neuroimaging research indicate that disruption of the frontal neostriatal dopaminergic system, as well as cerebellar dysfunction, are central to the executive function deficits and motor abnormalities that characterize ADHD (Roth and Saykin 2004; Seidman et al. 2004).

Psychostimulants are the pharmacologic treatment of choice for ADHD. The American Academy of Child and Adolescent Psychiatry (AACAP) has drafted practice parameters for the use of stimulant medication (Greenhill et al. 2002). Currently, the most widely prescribed choices are immediate-release and extended-release formulations of racemic methylphenidate (MPH; a 50/50 mixture of the d-threo- and l-threo-enantiomers) (NIH 1998). Developed in 1955, this agent has been shown to be both efficacious and safe (Barkley 1977; Goldman et al. 1998; Kavale 1982; Spencer et al. 1996; Wilens and Biederman 1992). Some studies indicate that the clinical efficacy of d,l-MPH may be mediated by the d-enantiomer (Patrick et al. 1987; Srinivas et al. 1992). In one study, improvement in sustained attention was seen with equimolar doses of dexmethylphenidate (d-MPH) and d,l-MPH, but not with l-MPH (Srinivas et al. 1992).

Dexmethylphenidate hydrochloride (d-MPH; Focalin™; Novartis Pharmaceuticals, East Hanover, NJ) is the chirally pure d-isomer of d,l-MPH. Like d,l-MPH, this agent is approved for twice-daily administration for the treatment of ADHD. Because it does not racemize after oral administration (Srinivas et al. 1992), doses of d-MPH at one half those for the racemic mixture can produce comparable levels of efficacy and tolerability (Swanson et al. 2004; Wigal et al. 2004). In a phase III trial (Wigal et al. 2004), d-MPH was significantly more effective than placebo in relieving ADHD symptoms, yielding a level of efficacy for ADHD symptoms comparable to that seen with d,l-MPH doses containing the same amount of d-MPH. The same study suggests longer duration of therapeutic effects with d-MPH than with racemic d,l-MPH; at 6 hours postdose, parent-rated ADHD symptoms improved significantly with d-MPH, but not with d,l-MPH, when compared with placebo (Wigal et al. 2004). In a prospective, open-label study of d-MPH administered once-daily, parents observed improvements that lasted 7.5 hours and teachers observed improvements that lasted 6.2 hours postdose (Silva et al. 2004).

Whereas sound clinical findings substantiate the efficacy of d-MPH and other MPH-containing compounds, the need for 2 doses daily, with 1 dose typically given at mid-day, presents certain challenges. Long-term compliance with such a regimen can be problematic, and concern about potential noncompliance in the school setting has been raised. Moreover, the daily need to receive a mid-day dose from the school nurse may further erode the already compromised social functioning and self-
esteem of children with ADHD. In response to these issues, a once-daily extended-release formulation of d-MPH (d-MPH-ER) has been developed using proprietary spheroidal oral drug absorption system (SODAS) technology. This formulation, which provides an initial release of medication immediately after dosing—with a second release approximately 4 hours later—is intended to mimic the pharmacokinetic profile of immediate-release d-MPH given twice-daily. If proven safe and effective, once-daily d-MPH-ER may offer substantial advantages over some currently available ADHD preparations by improving long-term patient compliance and by minimizing the risk for drug diversion and for the social stigma associated with mid-day drug administration during the school day.

The aim of this study was to evaluate efficacy, in terms of the onset and duration of effect, as well as the safety and tolerability of d-MPH-ER 20 mg/day versus placebo in pediatric patients with ADHD over 12 hours in a laboratory classroom setting. Used in previous studies of various MPH formulations for ADHD in school-age children (Lawrence et al. 2004; Swanson et al. 2004), the laboratory classroom setting allows trained observers to assess children’s attention, deportment, and cognitive performance and to define the time course of treatment effects based on repeated assessments throughout the day. Assessments in this trial were based on change from pre-dose on the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale (Swanson et al. 1998) and on performance on a pencil-and-paper math test.

METHODS

Study design

This study employed a double-blind, placebo-controlled, within-subjects, crossover design; this allowed each child to be exposed to both treatments (6 days each of d-MPH-ER 20 mg/day and placebo) and act as his or her own control. Patients were randomly assigned to receive d-MPH-ER-placebo (sequence A) or placebo–d-MPH-ER (sequence B) (Fig. 1). Following a practice day, efficacy of each treatment was assessed during 12 hours in a laboratory classroom on 2 consecutive Saturdays (Table 1).

Study population

Boys and girls 6–12 years of age who had been diagnosed with ADHD were eligible for enrollment at 1 of 3 centers in the United States participating in this study. Patients were recruited from the investigators’ private practices, child neurology clinics, school referrals, pediatricians’ offices, and general psychiatry offices. Patients eligible for inclusion were required to fulfill the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV; American Psychiatric Association 1994) criteria for ADHD of any type, as established by the Computerized Diagnostic Interview Schedule for Children (C-DISC-4). Patients must also have been stabilized on 20–40 mg/day of MPH for at least 1 month prior to screening. Only those patients whose parents and/or guardians provided written, informed consent were enrolled. Assent was also obtained from all children (documented by signature of those older than 9 years). Girls were required to be premenarchal, sexually abstinent, or using a reliable contraceptive method. Sexually active girls were required to show negative results on a urine pregnancy test.

At screening (days −14 to −7), all prospective patients underwent a physical examination, an electrocardiogram (ECG), blood and urine sampling for routine laboratory tests, urine drug screening, and, for girls, a urine pregnancy test. Informed consent was also documented. A complete medical and psychiatric history was obtained, and the C-DISC-4 was conducted to confirm ADHD diagnosis. Children were excluded if the investigator deemed the child’s IQ was below average or if there was evidence of an IQ below 80, or if they were home schooled, were diagnosed with Tourette syndrome or a tic disorder, had a concurrent or history of a significant medical or psychiatric illness (schizophrenia, bipolar disorder, or autism) or substance abuse disorder, or if they or their parents or guardians
were unable to understand or follow instructions necessary to participate in the study. Patients taking antidepressants, those who had initiated psychotherapy within 3 months preceding screening, and those with a positive urine drug screen, were also ineligible. Children with poor response or intolerance to MPH, currently taking other medications for ADHD, taking or planning to take another investigational drug within 30 days of study start, or who had previously participated in d-MPH-ER studies were also excluded.

Treatment schedule

All eligible patients completed four visits: A screening day (7–14 days before study initiation), a practice day (day 0), a Period 1 classroom day (day 7), and a Period 2 classroom day (day 14). The latter three visits occurred on three consecutive Saturdays at a participating center. Patients were randomized by computerized random number assignment to a treatment sequence and, 1–2 weeks following screening, participated in a practice visit to become familiar with the laboratory classroom and study evaluations (Table 1). Children were given a placement math test and assigned a difficulty level, based on the number of problems answered correctly. Patients were instructed to take their last dose of regularly prescribed medication on the Thursday prior to the practice day.

Upon completion of the practice visit, the first assigned treatment was dispensed to parents; study medication comprised either 1 bottle of 5 capsules of blinded study medication or 1 bottle of 5 matching placebo capsules, according to randomization sequence. Parents were instructed to dispense the first dose (1 capsule) in the morning on the following day (Sunday, day 1). Once-daily morning dosing

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**FIG. 1.** Flow chart. This diagram illustrates this study’s progression and the number of children included in each sequence.
was to continue for the next 4 days, with no capsules administered on Friday to prevent any behavioral carryover effect associated with the active treatment arm. On the morning of their Period 1 visit (day 7), the same blinded study treatment from days 1 through 5 was dispensed to the children by study personnel. Upon completion of testing on day 7, treatment was switched and dispensed to parents. The same dosing schedule was repeated for the second treatment period, with the Period 2 classroom visit occurring on day 14.

**SKAMP and math test assessments**

The SKAMP rating scale comprises 13 items intended to measure target classroom manifestations of ADHD (Swanson et al. 1998; Swanson et al. 2003). The ratings are based on the frequency and quality of behaviors, as observed by raters. Three independent, blinded raters were trained on SKAMP rating instruments by an instructor not involved in the study. These trained raters completed SKAMP ratings for all participants at specified intervals throughout the 12-hour testing period. The primary efficacy variable was the SKAMP—Combined score, with a primary analysis time point of 1-hour postdose. The SKAMP Deportment and Attention subscales were among the secondary efficacy measures obtained over 12 hours postdose.

Secondary measures of academic productivity were derived from a paper-and-pencil math test, the Permanent Product Measure of Performance (PERMP), conducted at specified intervals during the day (Swanson et al. 1998). PERMP measures a child’s ability to pay atten-
tion and stay on task, correlated with an increase in the number of correctly completed problems. The test consisted of 400 math problems at the difficulty level assessed for each child on the practice day. The children were instructed to work through as many problems as possible in 10 minutes. Measures obtained from these tests include the number of problems attempted (Math—Attempted) and the number of problems answered correctly (Math—Correct). The responses are reviewed by comparing them to an answer template, and they are triple-checked for accuracy.

Safety assessment and adverse events

Safety assessments included the monitoring of vital signs at each visit and the recording of adverse events (AEs) at the end of each treatment period, which were obtained through observation of the subject on the assessment day, spontaneous reporting by the subject, and reports from parents during the preceding week. Laboratory parameters (including hematology, blood chemistry, and urinalysis) were also assessed for any abnormalities at the screening and final visits. ECGs were conducted at the screening visit and reviewed by a physician and a pediatric cardiologist at each site.

Statistical methods

The safety population consisted of all patients who received at least 1 dose of study medication. The efficacy population comprised all randomized patients who provided valid efficacy measurements for both treatment periods. Descriptive statistics for all patients were obtained for background and demographic variables at screening (Table 2).

The primary efficacy outcome measure was defined as the change from predose in the SKAMP—Combined score at 1 hour postdose. This change was calculated by subtracting the predose value from the postdose value; therefore, negative values indicate improvement in ADHD symptoms. This variable was compared between treatments, using an analysis of covariance (ANCOVA) model that included the fixed effects of center, sequence, treatment, period, and baseline (hour 0 predose value) and the random effects of patients within sequences and within-patient errors. The effects of center and sequence were tested, using the patients within sequences as the error term. Overall treatment and period effects were tested at the 0.05 level of significance, using the mean square error from the ANCOVA model. A t test with a two-sided alternative was performed at the 0.05 level of significance to establish superiority.

Secondary efficacy variables included change from predose in SKAMP—Combined, SKAMP—Attention, SKAMP—Deportment, Math—Attempted, and Math—Correct scores at postdose hours 1, 2, 4, 6, 8, 9, 10, 11, and 12. The same methods used to calculate and analyze the primary efficacy variable were used to analyze the secondary efficacy variables. Unlike the SKAMP scores, however, positive change from predose values for math test performance indicates improvement. To control for Type I error for multiple comparisons over time for each secondary efficacy variable, the null hypotheses of equal treatment effect were tested at the 0.05 level at each time point, starting at 1 hour postdose for each efficacy variable. Testing proceeded to the next time point only if the treatment difference at the previous time point was significant ($p \leq 0.05$).

### Table 2. Demographic and Baseline Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (N = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>38 (70.4)</td>
</tr>
<tr>
<td>Female</td>
<td>16 (29.6)</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>9.4 (1.6)</td>
</tr>
<tr>
<td>Mean height, cm (SD)</td>
<td>138.6 (10.3)</td>
</tr>
<tr>
<td>Mean weight, kg (SD)</td>
<td>36.0 (11.5)</td>
</tr>
<tr>
<td>DSM-IV ADHD Type, n (%)</td>
<td></td>
</tr>
<tr>
<td>Inattentive</td>
<td>5 (9.3)</td>
</tr>
<tr>
<td>Hyperactive/impulsive</td>
<td>0</td>
</tr>
<tr>
<td>Combined</td>
<td>49 (90.7)</td>
</tr>
<tr>
<td>ADHD mean duration, years (SD)</td>
<td>4.6 (1.6)</td>
</tr>
</tbody>
</table>

Note: Information shown in this table reflects baseline data from all randomized patients. SD = standard deviation; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; ADHD = attention-deficit/hyperactivity disorder.
Duration of therapeutic effect was estimated using change from predose values for the SKAMP—Combined score observed across postdose hours 1, 2, 4, 6, 8, 9, 10, 11, and 12. Duration of effect was defined as the difference between offset and onset in hours (offset–onset). Treatment onset was defined as the time point halfway between the last time at which no effect was observed and the first time point at which an effect was observed; treatment offset was defined as the time point halfway between the last time an effect was observed and the first time that no effect was observed.

Equality of paired predose values were examined, using paired differences formed by subtracting Period 1 predose values from Period 2 predose values. These paired differences were analyzed, using an analysis of variance (ANOVA) model, including sequence effect, to test for unequal carryover effects (i.e., whether the paired differences in predose values were different between treatment sequences) (Hwang 1993). If the results were statistically significant, a post hoc analysis was performed, based on Period 1 data.

It was estimated that 54 patients were required to detect a 0.05-level treatment difference at 90% power. The sample-size calculation was performed using PASS 2000 (NCSS, Kaysville, Utah), with the assumptions that the treatment difference and standard deviation were 0.5 and 0.8 (on a per-item basis), respectively.

RESULTS

Patient population and disposition

Randomized patients (N = 54) in both treatment sequences had similar DSM-IV ADHD subtype, demographic, and background characteristics. Patients were predominantly Caucasian boys with a 4-year history of the combined inattentive/hyperactive form of ADHD (Table 2). Of the 54 randomized patients, 53 completed the study (sequence A [d-MPH-ER–placebo], n = 27; sequence B [placebo–d-MPH-ER], n = 26). One patient receiving sequence B discontinued because of nausea during the first study period while receiving placebo. Exposure to study medication in both treatment sequences was approximately 6.0 days.

Primary efficacy results

Analyses of the data revealed no sequence or order effects at any of the measured time points for each of the SKAMP ratings. The analysis for site by treatment interaction was also not significant. The predose value for SKAMP—Combined score in the d-MPH-ER group was 25.7 ± 11.14; in the placebo group, 21.6 ± 11.97 (see Fig. 2A). The adjusted mean change in SKAMP—Combined score from predose to 1-hour postdose was significantly greater with d-MPH-ER 20 mg (−10.014) than with placebo (0.878; p < 0.001); effect size was 1.33. Mean percent changes from predose were −42.7 with d-MPH-ER versus 8.8 with placebo.

Duration of effect

SKAMP—Combined scores at all time points showed significantly superior outcomes with d-MPH-ER than with placebo (p < 0.001); effect size at 12 hours was 0.67. Based on these results, the estimated duration of effect of d-MPH-ER is 1.0–12 hours postdose. Mean change from predose in SKAMP—Combined scores is shown in Figure 2B.

Predose values for SKAMP—Attention and SKAMP—Deportment scores were 12.3 ± 4.8 and 13.4 ± 7.88, respectively, with d-MPH-ER and 9.4 ± 4.7 and 12.2 ± 8.63 with placebo. Changes from predose in SKAMP—Attention and SKAMP—Deportment scores (largest p = 0.046, effect size at 12 hour = 0.40; largest p = 0.001, effect size at 12 hour = 0.69, respectively) were significantly better at all time points with d-MPH-ER than with placebo. Figures 2C and 2D show mean changes from predose in these variables.

Predose values for Math—Attempted and Math—Correct scores were 65.83 ± 35.97 and 62.53 ± 36.87, respectively, with d-MPH-ER and 86.38 ± 41.6 and 79.89 ± 41.94 with placebo. Changes from predose indicate that d-MPH-ER
was significantly more effective than placebo at all time points (Math—Attempted, largest $p < 0.001$, effect size at 12 hour = 0.88; Math—Correct, largest $p < 0.001$, effect size at 12 hour = 0.84). Mean changes from baseline in Math—Attempted and Math—Correct scores are shown in Figure 3A and 3B.

At 2 hours postdose with d-MPH-ER, a time point that corresponds approximately with peak improvements in SKAMP scores, children attempted an average of 123 math problems and correctly answered an average of 117 problems. This contrasts sharply with scores from the same patients during the placebo phase, when an average of 83 problems were attempted and 79 were answered correctly.

Tests for imbalanced predose values were statistically significant for SKAMP—Combined ($p = 0.001$), SKAMP—Attention ($p < 0.001$), Math—Attempted ($p < 0.001$), and Math—Correct scores ($p < 0.001$), meaning that significant differences in predose values emerged between treatment sequences for these variables. For the SKAMP—Combined, this finding was largely attributable to higher predose values in patients given d-MPH-ER during Period 1. Mean predose SKAMP—Combined scores for patients in the d-MPH-ER group were 27.7 in Period 1 and 21.6 in Period 2. Supportive analyses on Period 1 data showed that treatment-by-predose interactions were not statistically significant, indicating greater effects with d-MPH-ER than with placebo across the range of predose values.

Post hoc analysis of SKAMP—Combined scores in Period 1 ($n = 27$) showed significant
differences between d-MPH-ER and placebo from hours 1 through 10 (p < 0.015), but not at hours 11 (p = 0.062) and 12 (p = 0.199) (Fig. 4).

SKAMP—Attention scores in Period 1 showed significant differences between treatments at hours 1, 2, 4, 6 and 9 (p ≤ 0.015) but not at hours 8 (p = 0.099), 10 (p = 0.303), 11 (p = 0.086), and 12 (p = 0.486). Because SKAMP—Deportment scores did not show differences in pre-dose values, post hoc analysis of Period 1 data was unnecessary.

Post hoc analysis of Math—Attempted scores in Period 1 showed significant differences between treatments at hours 1, 2, 4, 6, and 8 (p ≤ 0.015) but not at hours 9 (p = 0.313), 10 (p = 0.191), 11 (p = 0.127) or 12 (p = 0.523).

Post hoc analysis of Math—Correct scores in Period 1 showed significant differences between treatments at

FIG. 3. (A) Math–Attempted scores. Mean change from predose (N = 54) in the number of problems attempted on math tests at postdose hours 1 through 12. (B) Math–Correct scores. Mean change from predose (N = 54) in math questions answered correctly at postdose hours 1 through 12.

FIG. 4. Period 1 SKAMP–Combined scores. Mean change from predose (N = 27) in SKAMP–Combined scores at postdose hours 1 through 12, Period 1 only.
between treatments at hours 1, 2, 4, 6, and 8 ($p \leq 0.022$) but not at hours 9 ($p = 0.418$), 10 ($p = 0.146$), 11 ($p = 0.109$) or 12 ($p = 0.419$).

Safety

AEs were attributed to the treatment received at the time of AE onset. Reported AEs were mild or moderate in intensity, with no unexpected, serious, or severe AEs occurring; there was also no evidence of toxicity to any organ. The percentage of patients experiencing AEs was comparable between d-MPH-ER (28.3%) and placebo (22.2%). In line with AEs typically associated with psychostimulant medications, AEs that occurred more frequently with d-MPH-ER than with placebo and were considered possibly related to study drug included decreased appetite (9.4% vs. 0%), anorexia (7.5% vs. 0%), upper abdominal pain (5.7% vs. 1.9%), fatigue (3.8% vs. 0%), and insomnia (3.8% vs. 0%). Other AEs reported in 2% or more of patients included headache (1.9% vs. 5.6%) and irritability (0% vs. 5.6%). Few clinically notable laboratory or vital sign abnormalities occurred. Specifically, 2 patients each had a pulse rate of 68 while on d-MPH-ER, as compared to 1 patient on placebo, with the same pulse rate. There were no clinically notable systolic or diastolic blood pressure changes associated with either d-MPH-ER or placebo during this trial. During placebo treatment, 1 patient discontinued the study because of nausea. There were no discontinuations attributable to laboratory abnormalities.

DISCUSSION

The aim of this study was to assess the efficacy, safety, tolerability, and duration of effect of d-MPH-ER 20 mg/day versus placebo observed in children over 12 hours in a laboratory classroom setting. D-MPH-ER effectively improved a broad range of ADHD symptoms. Improvements in attention, deportment, and math test performance occurred rapidly (within 1 hour postdose) and were maintained for periods up to 12 hours postdose. D-MPH-ER was safe and well tolerated, with no severe AEs reported; only 1 patient, who was receiving placebo, withdrew because of an AE.

The behavioral improvements observed with d-MPH-ER emerged rapidly, showing significant advantages over placebo as early as 1 hour postdose in all efficacy variables. When examining the entire sample of 54 subjects, the improvements were maintained throughout the 12-hour evaluation period (Figs. 2 and 3). The primary efficacy end point, change in predose SKAMP—Combined score at 1 hour postdose, was significantly better with d-MPH-ER than with placebo. Similar changes were observed in SKAMP—Attention, SKAMP—Deportment, Math—Attempted, and Math—Correct scores. Effect onset was first detected at hour 1.0 postdose but may have occurred earlier. Future studies should investigate differences earlier than 1.0 hour following medication administration. D-MPH-ER also demonstrated a significantly superior effect on the primary and secondary end points, compared with placebo at all other times assessed; duration of effect of d-MPH-ER was estimated to be 12 hours when the data for the entire sample were analyzed. This duration of action is in line with two previous reports of longer-lasting therapeutic effects observed with twice-daily dosing of immediate-release d-MPH than with traditional, racemic, immediate-release d,l-MPH (Quinn et al. 2004; Wigal et al. 2004). In each study, the authors found significantly greater improvements with d-MPH than with placebo at 6 hours postdose (Quinn et al. 2004; Wigal et al. 2004) and, in one of these studies, no significant effect of d,l-MPH persisted at 6 hours postdose (Wigal et al. 2004). A recent open-label study of d-MPH in school-age children yielded similar findings (Silva et al. 2004). The difference in duration of effect between racemic d,l-MPH and d-MPH does not appear to be attributable to the pharmacokinetic profile of d-MPH; Quinn et al. found that, at 6 hours after oral administration, serum levels of d-MPH were similar for both agents. Our findings in this study provide further evidence of the extended duration of action of d-MPH-ER.

D-MPH-ER was well tolerated by the patient population in this study; reported AEs were consistent with those seen for other psycho-
stimulants. The most frequently reported AEs were decreased appetite and anorexia, both of which were considered at least possibly related to study drug by raters and were anticipated side effects of d-MPH-ER. No serious or severe AEs were observed during this study, and the few clinically notable findings reported for vital sign measures and clinical laboratory values were considered to be not related to study drug. However, in a study such as ours, the inclusion of individuals that are currently stabilized on a similar stimulant medication tends to impact by decreasing the number and severity of AEs reported by subjects. Larger-scale, placebo-controlled studies of patients that include treatment naïve subjects are better suited for identifying the array of AEs associated with an active agent.

Although studies of different designs cannot be directly compared, two trials of other ADHD medications in similar patient populations—with similar duration of drug exposure—suggest that d-MPH-ER may have a different tolerability profile. In our study, for example, the placebo-subtracted rates of decreased appetite or anorexia totaled 16.9% with d-MPH-ER 20 mg, whereas in other studies the comparable rate of decreased appetite was 29.7% to 45.4% with OROS-methylphenidate 18–54 mg (Concerta®, ALZA Corporation; Mountain View, CA) and that of anorexia was 4.7% to 32.7% with extended-release mixed amphetamine salts 10–30 mg (Adderall XR®, Shire U.S., Inc.; Wayne, PA) (McCracken et al. 2003; Stein et al. 2003). Similarly, the placebo-subtracted frequency of insomnia was considerably lower with d-MPH-ER (3.8%) than with OROS-methylphenidate (19.7% to 27.2%) (Stein et al. 2003). The comparable rates of abdominal pain were 5.7% with d-MPH-ER, 15.9% to 25.1% with OROS-methylphenidate, and 4.7% to 11.5% with extended-release mixed amphetamine salts (McCracken et al. 2003; Stein et al. 2003). The somewhat higher AE rates reported with OROS-methylphenidate may be partly a reflection of the subjects’ previous experience with stimulant medications. In this study of d-MPH-ER, all patients had been previously stabilized on MPH; hence, they were likely to tolerate this drug class well. Similarly, 92% of patients in the extended-release mixed amphetamine salts study had a history of positive response to stimulants. In contrast, only 30% of children in the OROS-methylphenidate study had prior experience with stimulants (McCracken et al. 2003; Stein et al. 2003). From this review of the literature, it seems that d-MPH-ER did no worse and might have done better. Ultimately, a head-to-head comparison is needed to make any reasonable statement of difference.

In this study, the issues of imbalanced predose values dictated a post hoc analysis, which had diminished power owing to the reduced number of subjects. This constraint may have contributed to the lack of significant differences between placebo and d-MPH-ER at the later hour ratings. It should be noted that the power analysis done prior to study commencement specified that the full sample size (N = 54) would be required to demonstrate significant differences between the treatment arms. Although this difference may have been the result of reduced power, it is also possible that they reflect the true situation. Future studies should be undertaken to replicate our findings. A larger sample, without issues of imbalanced predose values, would help confirm the duration of action of this agent.

Limitations

As with any study, there are always limitations. One of the inclusion criteria in this study was patients who were known to be currently stable on another methylphenidate preparation. As a result, information related to onset of action and duration of effect were limited to populations that responded to a methylphenidate agent. In terms of AEs, we listed all side effects irrespective of whether they were identified by a parent or child. These were gathered both during the week preceding the laboratory observation days and during the laboratory classroom day. This may have posed certain limitations in assessing side effects and the type of side effects most complained about by individuals taking the medication. Another limitation was that we did not systematically analyze compliance data during the week preceding the laboratory
classroom; it should be noted that there was 100% compliance with study medication on all laboratory classroom sessions. Finally, crossover designs are subject to carryover effects and order effects. There were no order effects in this study. However, the predose effect seen in this study may be considered a form of carryover effect by some. The randomization created two different groups that had significantly different predose values. However, even with this discrepancy, there were no treatment-by-group interactions.

CONCLUSIONS

In this study, once-daily d-MPH-ER 20 mg was a safe and effective treatment for ADHD symptoms in pediatric patients. The onset of effect was relatively rapid (1.0 hour), and the duration of effect was relatively long (up to 12 hours), as demonstrated by improvements in attention, deportment, and math test performance over a 12-hour testing period. These findings indicate that d-MPH-ER is a safe and effective once-daily treatment for pediatric ADHD. This agent adds to the current options for long-acting stimulants for the treatment of ADHD.

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