Efficacy and Safety of Dexmethylphenidate Extended-Release Capsules in Adults with Attention-Deficit/Hyperactivity Disorder

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Background: This multicenter, randomized, fixed-dose, double-blind, placebo-controlled study evaluated efficacy of extended-release dexmethylphenidate (d-MPH-ER) in adults with attention-deficit/hyperactivity disorder (ADHD).

Methods: Randomized adults with ADHD (n = 221) received once-daily d-MPH-ER 20 mg, 30 mg, or 40 mg or placebo for 5 weeks. The primary efficacy variable was change from baseline to final visit in DSM-IV ADHD Rating Scale (ADHD-RS) total score. Secondary efficacy parameters included the proportion of patients with improvement >30% in ADHD-RS total score and final scores on Clinical Global Impressions-Improvement (CGI-I) scale.

Results: Of 218 evaluable patients, 184 completed the study. All d-MPH-ER doses were significantly superior to placebo in improving ADHD-RS total scores. Placebo scores improved by 7.9; d-MPH-ER, 20 mg, improved by 13.7 ($p = .006$); d-MPH-ER, 30 mg, improved by 13.4 ($p = .012$); and d-MPH-ER, 40 mg, improved by 16.9 ($p < .001$). Overall distribution of CGI-I ratings at final visit was significantly better with each d-MPH-ER dosage than with placebo. There were no unexpected safety or tolerability concerns, based on experience with racemic methylphenidate (MPH) in adults and dexmethylphenidate (d-MPH) in children.

Conclusions: Once-daily d-MPH-ER at 20 mg, 30 mg, or 40 mg is a safe and effective treatment for adults with ADHD.

Key Words: ADHD, adults, capsules, d-MPH-ER, efficacy, safety

Follow-up studies of childhood attention-deficit/hyperactivity disorder (ADHD) indicate that 10% to 60% of cases persist into adulthood (Weiss et al. 1985; Mannuzza et al. 1993). A review of the literature supports the validity of this diagnosis in adults (Faraone et al. 2000; Wilens et al. 2004) and indicates a prevalence of approximately 4% (Kessler et al. 2006; Wilens et al. 2004). Untreated adult ADHD is associated with antisocial behavior, substance abuse, and poor functioning in educational, occupational, and socioeconomic domains (Kessler et al. 2006; Spencer et al. 1994). Despite these profound role impairments, adult ADHD is often unrecognized.

Racemic methylphenidate (MPH), while approved for the treatment of ADHD in children (Spencer et al. 1995; Wender et al. 1985), is not yet approved by the Food and Drug Administration for use in adults. A double-blind study of MPH in 146 adults with ADHD found significant differences between MPH and placebo, emerging as early as 2 weeks in patients, with a 44% decrease in ADHD symptoms by 6 weeks (Spencer et al. 2005). Among initial responders, treatment continued to relieve symptoms for 6 months. A recent meta-analysis of six double-blind, placebo-controlled studies also concluded that MPH is effective for treating adult ADHD (Faraone et al. 2004).

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Received November 16,2005; revised July 6,2006; accepted July 13,2006.

The pathophysiology of ADHD is thought to lie in the dysregulation of catecholamine neurotransmitters in the frontal or fronto-striatal networks (Biederman 1998). Binding and imaging studies suggest its therapeutic effects are mediated primarily by blocking the presynaptic dopamine transporter, thereby raising levels of dopamine in the synaptic cleft. Inhibition of dopamine reuptake is accomplished almost exclusively by the d-threo enantiomer of MPH (Ding et al. 1997), now available as the chirally pure isomer dexmethylphenidate (d-MPH). In preclinical studies, d-MPH raised extracellular levels of dopamine more than sixfold while 1-threo MPH (1-MPH) had no effect (Ding et al. 1997). Furthermore, d-MPH binds specifically to dopamine transporters primarily in the basal ganglia, whereas 1-MPH binding is largely nonspecific (Ding et al. 1997). In animal models of ADHD, the d-isomer is more than twice as potent as the 1-isomer (Davids et al. 2002).

In a controlled trial in children with ADHD, the safety and efficacy of d-MPH were similar to those of racemic MPH but at half the dose. A single daily 10-mg dose of d-MPH significantly and consistently improved academic performance and behavior for at least 6 hours (Quinn et al. 2004). In other research, morning and midday doses of d-MPH yielded effective behavioral control for at least 10 hours in children aged 6 to 17 years (Celgene Corporation, Summit, New Jersey, unpublished data, 2005).

Immediate-release d-MPH, available in tablet form, has a plasma elimination half-life of approximately 2.2 hours. To extend its therapeutic effect, a long-acting formulation has been developed (d-MPH-ER) using proprietary SODAS technology (Elan Pharmaceuticals, Inc., Dublin, Ireland) to provide an initial release of medication immediately after oral administration, followed by a second release approximately 4 hours later, mimicking the twice-daily dosing of immediate-release d-MPH.

This report summarizes results of a controlled, multicenter trial of d-MPH-ER 20 mg/d, 30 mg/d, or 40 mg/d in adults with ADHD.

0006-3223/07/$32.00
doi:10.1016/j.biopsych.2006.07.032

Methods and Materials

This randomized, double-blind, parallel-group, placebo-controlled, fixed-dose study was conducted at 18 U.S. centers. Patients provided written, informed consent for all study procedures, approved by each center's institutional review board. Participants eligible for inclusion were aged 18 to 60 years, diagnosed with DSM-IV ADHD (any subtype) with childhood onset of symptoms. They had to have a DSM-IV ADHD Rating Scale (ADHD-RS) total score of at least 24 at screening and baseline. This cutoff was selected to be consistent with previous studies of ADHD in adults and to ensure that the study would be able to detect an effect of treatment (Spencer et al. 1995, 1998). In addition, they were required to display functional impairment, defined as a Global Assessment of Functioning (GAF) score of 60 or less. Patients with a history of alcohol or substance abuse within the last 6 months were excluded, as were patients with any psychiatric or medical comorbidity that may have interfered with study participation or assessments or for which MPH treatment may have posed a risk. Patients were also excluded if the investigator judged that they had a history of poor response or intolerance to stimulants (e.g., MPH, d-MPH, amphetamine salts, or dextroamphetamine salts). No patient had previously used d-MPH-ER. Women were excluded if they were pregnant, nursing, or not using acceptable methods of contraception. The screening visit took place 1 week before the baseline visit. Patients were required to discontinue all psychotropic drugs within 1 to 4 weeks prior to the screening visit.

After screening and baseline visits, patients were equally randomized to one of four treatments (d-MPH-ER 20 mg, 30 mg, or 40 mg, or placebo), administered once daily for 5 weeks, with weekly visits scheduled during this double-blind phase (Figure 1). To minimize adverse events (AEs), all patients were started on 10 mg/d, titrated in increments of 10 mg/wk to randomly assigned fixed dosages, and then maintained at that dosage for at least 2 weeks. Compliance was assessed based on patient reports and counting of unused capsules.

The primary efficacy variable was change from baseline to final visit in DSM-IV ADHD-RS total scores during the double-blind phase. The instrument consists of 18 items adapted directly from the DSM-IV ADHD symptom list, modified slightly for use in adults.

ADHD-RS Validity/Reliablity

The ADHD Rating Scale (DuPaul et al. 1998), shown to be sensitive to drug effects in pediatric (Barkley 1990) and adult (Spencer et al. 1995, 1998) populations, assesses each of the 18 individual criteria symptoms of ADHD in DSM-IV-R on a severity grid (0 = not present; 3 = severe; overall minimum score = 0; maximum score = 54). Five raters independently reviewed audiotaped interviews of five subjects. An intraclass correlation of .99 was obtained for interrater reliability of the ADHD symptom checklist. Pre hoc secondary efficacy variables included the following: proportion of patients with at least 30% improvement in DSM-IV ADHD-RS total scores; change in DSM-IV ADHD-RS subscale scores for inattention and hyperactivity/impulsivity; proportion of patients at each level of the clinician-rated Clinical Global Impressions-Improvement Scale (CGI-I) at final visit; proportion of patients with improvement on the CGI-I scale, defined as a final visit score of 1 (very much improved) or 2 (much improved); proportion of patients with improvement on the clinician-rated Clinical Global Impressions-Severity Scale (CGI-S); change in total score on the self-report and observer scales (short versions) of Conners' Adult ADHD Rating Scale (CAARS); change in clinician-rated Global Assessment of Functioning scores; and change in patient-rated Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) total score (Endicott et al. 1993). The validity of the Q-LES-Q as a measure of quality of life was established in adults with ADHD (Mick et al. 2006).

The CGI-I scale comprises seven ratings ranging from 1 (very much improved) to 7 (very much worse), while the CGI-S scale comprises seven ratings ranging from 1 (not at all ill) to 7 (among most extremely ill patients) (Guy 1976). The CAARS instrument measures ADHD symptoms and behaviors based on patient self-reports and reports by close observers, e.g., a family member, friend, or coworker. The short self-report (CAARS-S:S) and observer (CAARS-O:S) forms use four-point scales ranging from 0 (not at all) to 3 (very much; frequently) on each of 26 items

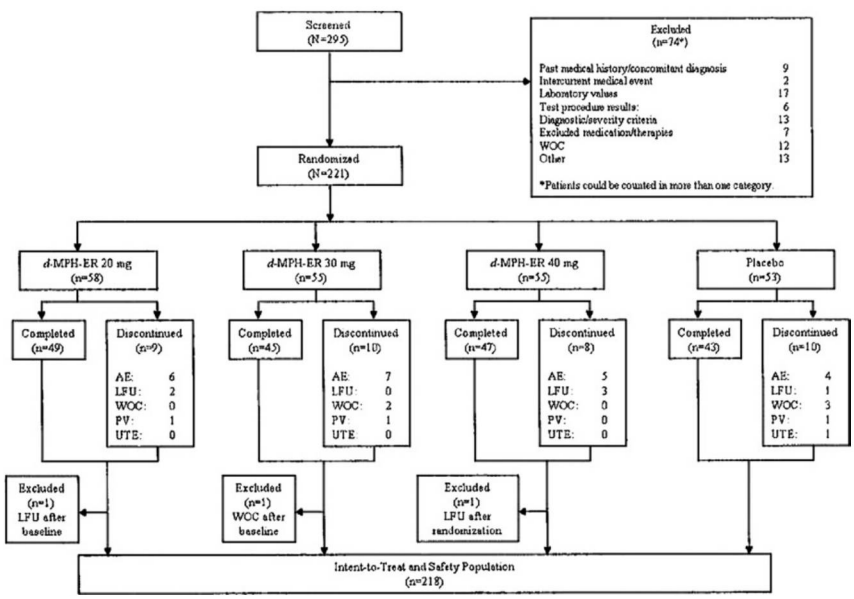

Figure 1. Schematic of study design from baseline. WOC, withdrawal of consent; AE, adverse event; LFU, lost to follow-up; PV, protocol violation; UTE, unsatisfactory therapeutic effect.

(total score for each scale: 0 to 78 points) (Conners et al. 1999)- The GAF is a 100-point, single-item instrument that evaluates overall functioning (psychological, social, and occupational) on a scale of 1 (most impaired) to 100 (healthiest). The Q-LES-Q is the sum of scores ranging from 1 to 5 on 14 items that comprise social relationships, leisure activities, and work (American Psychiatric Association 2000).

Adverse events were collected and recorded throughout the study after patients started treatment. Heart rate and blood pressure (BP) were recorded at baseline and at each weekly visit. Body weight, hematology, blood chemistry, electrocardiograms (ECGs), urine pregnancy tests, and physical examinations were recorded at screening and final visits. Urine drug tests were performed at screening.

Demographic, baseline, efficacy, and safety results were summarized by treatment group (and by visit, where applicable). The primary efficacy variable was change from baseline to final visit in DSM-IV ADHD-RS total scores. There were two primary comparisons, d-MPH-ER 30 mg versus placebo and d-MPH-ER 40 mg versus placebo. Hochberg's procedure was used to adjust for multiplicity (Hochberg 1988). A secondary comparison between d-MPH-ER 20 mg and placebo was made at the two-sided type I error level of 5%.

The maintenance dosage of once-daily 20 mg to 40 mg d-MPH-ER was based on results from previous studies of immediate-release d-MPH and racemic MPH that suggested an effective, well-tolerated dose of d-MPH in adults would be approximately .5 mg/kg/d, or 35 mg/d for a 70-kg adult. For d-MPH-ER, the optimal dose was predicted to be between 30 mg/d and 40 mg/d. Comparisons of d-MPH-ER 30 mg/d and 40 mg/d versus placebo were therefore designated as primary efficacy objectives. The study was not designed or powered for direct comparisons between doses.

For the primary efficacy variable, treatment groups were compared using least square means derived from an analysis of covariance (ANCOVA) model, with treatment group, center, and baseline DSM-IV ADHD-RS total scores as factor variables. The analysis was performed on the last observation carried forward (LOCF) data set of the intent-to-treat (ITT) population, which included all randomized patients who received at least one dose of study drug and had at least one prerandomization and one postrandomization assessment for the primary efficacy variable. The LOCF technique was used to impute missing values for all final-visit analyses. Effect size was calculated for the primary efficacy variable.

Secondary efficacy variables were analyzed, without adjustment for multiplicity, using the LOCF data set of the ITT population. The proportion of patients with at least 30% improvement in DSM-IV ADHD-RS total scores was analyzed using a logistic regression model with treatment, center, and baseline scores as factor variables. Changes from baseline to final visit in DSM-IV ADHD-RS subscale scores, CAARS total and subscale scores, GAF scores, and Q-LES-Q total scores were analyzed by ANCOVA models similar to that of the primary efficacy variable (because GAF data were not normally distributed, a nonparametric analysis based on the Mann-Whitney-Wilcoxon test became the main analysis). The proportion of patients with improvement on the CGI-I and CGI-S scales was analyzed using logistic regression models, with treatment and center as factor variables. The CGI-I rating at final visit was analyzed by an extended Cochran-Mantel-Haenszel (CMH) test, stratified by center.

The safety population comprised all patients who received at least one dose of study drug and had at least one safety measurement after baseline. Safety was assessed based on the incidence of AEs and the number of laboratory values falling outside prespecified ranges. Other safety data, such as vital signs and ECGs, were considered as appropriate.

Results

Of 221 patients randomized (127 men; 94 women; mean age 38.7 years), 218 were included in both the ITT and safety populations and 184 completed the double-blind phase. The d-MPH-ER group (m = 168; mean age 38.8 years; mean weight 85.6 kg) included 100 men and 68 women, while the placebo group (m = 53; mean age 38.1 years; mean weight 87.5 kg) comprised 27 men and 26 women. Baseline characteristics are shown in Table 1. Treatment groups were well matched. For all randomized patients, the mean baseline DSM-IV ADHD-RS total score (37.0 on a scale of 0 to 54) indicated moderate to marked severity of ADHD symptomatology. Their mean baseline GAF score (54.6 on a scale of 0 to 100) signified moderate difficulty in social, occupational, or work/school functioning.

Efficacy

For the primary efficacy variable, all dosages of d-MPH-ER were significantly superior to placebo (Figure 2). Mean improvement (decrease) from baseline in DSM-IV ADHD-RS total score was 7.9 for placebo (from 37.5 to 29.6), 13.7 for d-MPH-ER 20 mg (from 36.8 to 23.1; t = 2.77, df= 108, p = .006), 13.4 for 30 mg

Table 1. Baseline Characteristics of All Randomized Patients

Baseline Variable	Placebo (n = 53)	D-MPH-ER 20 mg (n = 58)	D-MPH-ER 30 mg (n = 55)	D-MPH-ER 40 mg (n = 55)
ADHD Subtype, n (%)				
Inattentive	12(22.6)	17 (29.3)	14(25.5)	16(29.1)
Hyperactive/Impulsive	1 (1.9)	2 (3.4)	3 (5.5)	1 (1.8)
Combined	40 (75.5)	39 (67.2)	38(69.1)	38(69.1)
Duration of ADHD symptoms (Years)	31.1	32.9	33.5	31.9
Prior ADHD medications, n (%)	26(49.1)	20 (34.5)	12 (21.8)	22 (40.0)
MPH/d-MPH	19(35.8)	18(31.6)	9(16.7)	15 (27.8)
Non-MPH stimulants	7(13.2)	8(14.0)	4 (7.4)	10 (18.5)
Nonstimulants	9(17.0)	3 (5.3)	5 (9.3)	8 (14.8)
Baseline DSM-IV ADHD Rating Scale, Total Score	37.5	36.9	36.9	36.7
Mean Baseline Global Assessment of Functioning Score	54.8	53.9	54.2	55.8

D-MPH-ER, extended-release dexmethylphenidate; ADHD, attention-deficit/hyperactivity disorder; MPH, methyl phenidate; d-MPH, dexmethylphenidate.

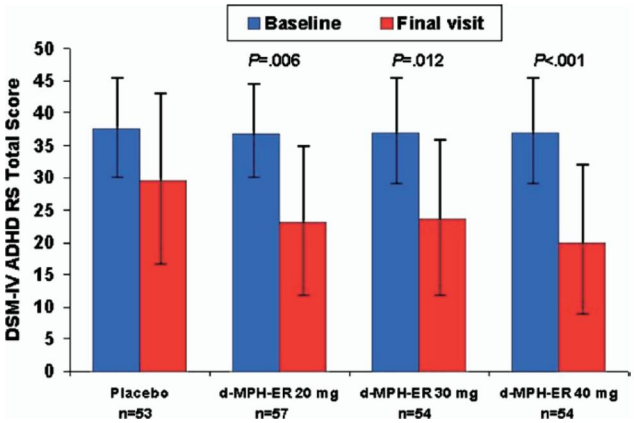

Figure 2. Mean DSM-IV ADHD-RS total scores at baseline and final visit (last observation carried forward, intent-to-treat population). All p values refer to comparison versus placebo. Vertical bars represent standard deviation (SD). ADHD-RS, ADHD Rating Scale; ADHD, attention-deficit/hyperactivity disorder.

(from 36.9 to 23.5; t = 2.53, df= 105, p = .012), and 16.9 for 40 mg (from 36.9 to 20.0; t = 4.28, df= 105, p = .001). Effect sizes for this variable were .53 for 20 mg, .49 for 30 mg, and .83 for 40 mg.

Neither gender nor age influenced treatment response. Change from baseline in DSM-IV ADHD-RS total scores was comparable for men and women within each treatment group. Differences between d-MPH-ER and placebo were significant for patients both older and younger than 40 years. No statistically significant treatment-by-center interactions were found.

Within each treatment group, percent changes from baseline in DSM-IV ADHD-RS total scores were generally similar in patients with the combined subtype of ADHD and the inattentive subtype. Among combined subtype patients, mean percent changes from baseline in ADHD-RS total score were 37.7% for d-MPH-ER 20 mg, 36.1% for 30 mg, 43.4% for 40 mg, and 24.2% for placebo. Respective percent changes among inattentive subtype patients were 34.2%, 40.1%, 47.9%, and 15.0%. There were too few inattentive subtype patients to permit inferential statistical analysis of the differences.

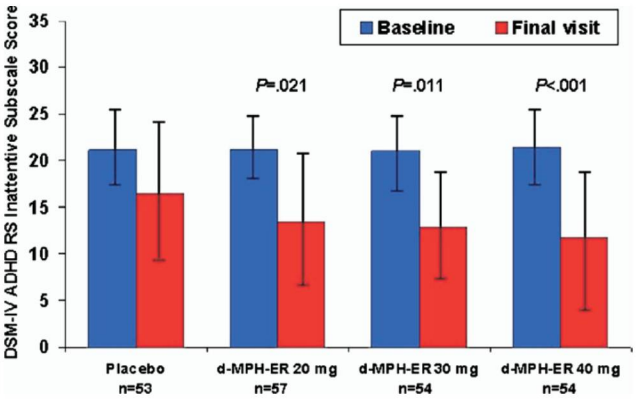

Figure 3. Mean DSM-IV ADHD Rating Scale inattentive subscale scores at baseline and final visit (last observation carried forward, intent-to-treat population). All p values refer to comparison versus placebo. Vertical bars represent standard deviation (SD). ADHD, attention-deficit/hyperactivity disorder.

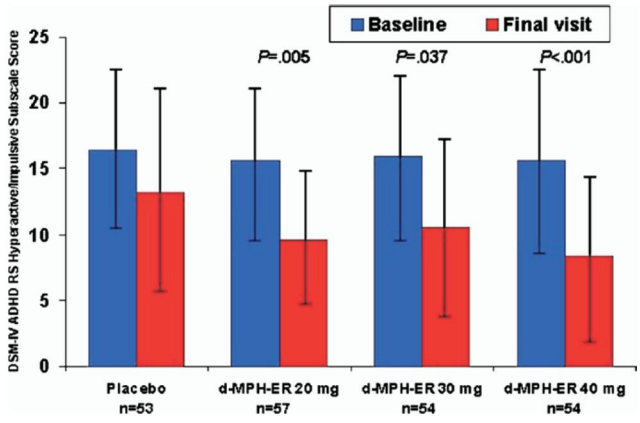

Figure 4. Mean DSM-IV ADHD Rating Scale hyperactive/impulsive subscale scores at baseline and final visit (last observation carried forward, intent-to-treat population). All p values refer to comparison versus placebo. Vertical bars represent standard deviation (SD). ADHD, attention-deficit/hyperactivity disorder.

When all patient subtypes were analyzed together, all dosages of d-MPH-ER were significantly superior to placebo on both the DSM-IV ADHD-RS inattentive and hyperactive-impulsive subscales (Figures 3 and 4). The percentage of patients with an improvement of 30% or greater in the total score was 34.0% with placebo, 57.9% with d-MPH-ER 20 mg (df= 1, chi-square = 5.75, p = .017), 53.7% with 30 mg (df = 1, chi-square = 3.71, p = .054), and 61.1% with 40 mg (.df = 1, chi-square = 7.33, p = .007).

Significant differences were observed between the d-MPH-ER and placebo groups in the overall distribution of CGI-I ratings at final visit (CMH = 8.20, p = .004 for d-MPH-ER 20 mg; CMH = 5.34, p = .021 for 30 mg; CMH = 11.01, p < .001 for 40 mg) (Figure 5). The percentage of responders (those deemed "very much improved" or "much improved" at final visit) was 26.4% with placebo, 47.4% with d-MPH-ER 20 mg (df= 1, chi-square = 4.90, p = .027), 37.0% with 30 mg (p = NS), and 55.6% with 40 mg (df = 1, chi-square = 9.07, p = .003) (all p values versus placebo). At last visit, the percentage of patients showing improvement was numerically greater with each dose of d-MPH-ER than with placebo.

Decrease in illness severity, manifested as a decline in CGI-S score at final visit, was observed in 41.5% of the placebo group, 68.4% of the d-MPH-ER 20-mg group (df= 1, chi-square = 6.75,

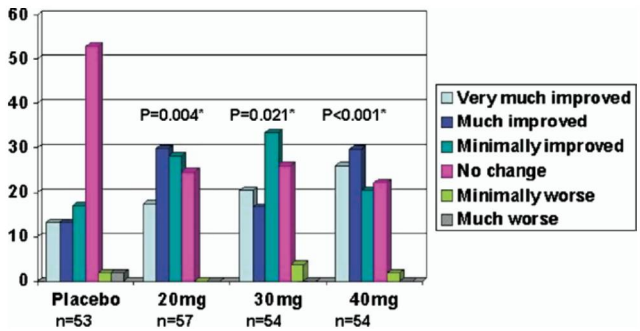

Figure 5. Percentage of patients with each Clinical Global Impression-Improvement rating at final visit (last observation carried forward, intent-to-treat population). "Statistically significant. All p values refer to comparison versus placebo.

p = .009), 61.1% of the 30-mg group (p = NS), and 64.8% of the 40-mg group (.df = 1, chi-square = 4.63, p = .031) (all p values versus placebo). The proportion of patients with two-point improvement on the CGI-S was 15.1% for the placebo group, 24.6% for the 20-mg group (NS), 33.3% for the 30-mg group (NS), and 40.7% for the 40-mg group (df = 1, chi-squre = 7.74, p = ■ 005) (p value is versus placebo).

All doses of d-MPH-ER were significantly superior to placebo in CAARS-S:S and CAARS-O:S total scores. Mean decrease (improvement) from baseline to final visit in the CAARS-O:S score was 3.1 with placebo, 10.0 with d-MPH-ER 20 mg (f = 2.88, df= 80, p = .005), 12.8 with 30 mg (f = 2.95, df= &), p = .004), and 9.6 with 40 mg (f = 3.37, df= 81, p < .001). Mean change in the CAARS-S:S score was 7.2 with placebo, 16.0 with d-MPH-ER 20 mg (t = 2.99, df = 101, p = .003), 12.7 with 30 mg (t = 2.02, df = 101, p = .045), and 15.6 with 40 mg (f = 3.53, df = 99, p < .001).

Improvements (increases) from baseline in GAF scores were significantly greater with d-MPH-ER than with placebo. Mean changes were 5.4 with placebo, 11.1 with d-MPH-ER 20 mg (z = —3.714, p < .001), 8.7 with 30 mg C? = —2.864, p = .004), and 11.3 with 40 mg (ar = —2.957, p = .003).

There were no significant differences between placebo and d-MPH-ER in mean change from baseline to final visit in Q-LES-Q score and no group showed marked improvements. Increases from baseline were placebo, 1.9; d-MPH-ER 20 mg, 2.2; 30 mg, 2.5; and 40 mg, 3.2.

Safety and Tolerability

Safety and tolerability were as expected, based on experience with MPH products in adults and with immediate-release d-MPH in children (Keating and Figgitt 2002). Only dry mouth and jitteriness were significantly more common with d-MPH-ER than with placebo (p < .05). Most AEs were numerically more common with the higher doses of d-MPH-ER than with the lower dose (Table 2). Most AEs in the d-MPH-ER group were mild (33.3%) or moderate (45.5%) in severity. Respective rates with placebo were 22.6% and 39-6%. Rates of severe AEs were 8.5% with d-MPH-ER and 5.7% with placebo, including two patients with severely decreased appetite and two with severe insomnia, all in the d-MPH-ER group; all other severe AEs in the d-MPH-ER group occurred in one patient each. The severity of AEs was similar across dosage groups.

Among AEs considered to be treatment related, the most common were headache (23.0% with d-MPH-ER and 11.3% with placebo), decreased appetite (18.2% and 11.3%, respectively), and dry mouth (15.8% and 3.8%, respectively). With d-MPH-ER, 6.7% of treatment-related AEs were severe versus 1.9% with placebo. Two patients receiving d-MPH-ER 40 mg experienced serious AEs requiring hospitalization; neither event was considered treatment related. The first patient had ulcerative colitis and hypovolemic shock (with a long history of colitis), and the second had a high fever and loss of consciousness. Both patients recovered and completed the double-blind phase.

Overall laboratory findings and ECGs showed no clinically significant differences between treatment groups; no clinically important changes from baseline were observed in any group. Changes in blood pressure were minimal across all groups (mean changes of <2.5 mm Hg). Patients receiving d-MPH-ER showed a small increase in mean pulse (4.4 ± 11.0; p = .0007), whereas those receiving placebo showed a slight decrease (-1.4 ± 9-3). There were no significant differences between d-MPH-ER and placebo in changes in systolic (d-MPH-ER, -.5 ± 11.5; placebo, — 1.7 ± 11.3) or diastolic (d-MPH-ER, 1.0 ± 8.4; placebo, .3 ± 7.8) blood pressure, and changes did not appear to be dose related (although this was not analyzed statistically). However, pulse increases demonstrated an apparent trend toward a dose relationship: 3.1 beats per minute (bpm) for d-MPH-ER 20 mg (p = .0269), 4.3 bpm for 30 mg (p = .0068), and 6.0 bpm for 40 mg (p = .0002) (all p values versus placebo).

Two patients (3.8%) in the placebo group experienced new, clinically notable low blood pressure values, but no clinically notable changes occurred in the d-MPH-ER groups.

Drug-related cardiac AEs occurring at low frequencies in the combined d-MPH-ER group included increased heart rate (m = 4, 2.4%), palpitations (m = 4, 2.4%), and tachycardia (m = 2, 1.2%). All were mild to moderate, but many were accompanied by anxiety, jitteriness, and sweaty palms. One patient who experienced tachycardia also experienced palpitations, and one patient with tachycardia had a 10-year history of hyperthyroidism. Changes in pulse were described as “tachycardia” or “increased heart rate” according to investigator’s judgment. These findings were not associated with ECG abnormalities. The incidence of palpitations did not appear to be dose related (20 mg, 0%; 30 mg, 5.6%; 40 mg, 1.9%).

Mean weight loss was slightly greater with d-MPH-ER than with placebo (1.4 kg versus .1 kg), consistent with reports of decreased appetite in the d-MPH-ER groups. The difference was not statistically significant. Weight loss did not appear dose related (20 mg, 1.4 kg; 30 mg, 1.2 kg; 40 mg, 1.7 kg). Baseline body mass index (BMI) was 28.3 kg/m^2 for the consolidated d-MPH-ER group and 29.0 kg/m^2 for the placebo group, somewhat overweight compared with recommended ideal BMIs. Six patients (3.6%) in the consolidated d-MPH-ER group and one

Table 2. Incidence of Most Frequent Adverse Events

Adverse Event	20-mg D-MPH-ER Group (n = 57)	30-mg D-MPH-ER Group (n = 54)	40-mg D-MPH-ER Group (n = 54)	Consolidated D-MPH-ER Group (n = 165)	Placebo Group (n = 53)
Total Events, n (%)“	48 (84.2)	51 (94.4)	46 (85.2)	145 (87.9)	36 (67.9)
Most Common Events, n (%)					
Headache	15 (26.3)	16(29.6)	21 (38.9)	52 (31.5)	10(18.9)
Decreased Appetite	11 (19.3)	9(16.7)	10 (18.5)	30(18.2)	6(11.3)
Insomnia	10 (17.5)	7(13.0)	10 (18.5)	27 (16.4)	6(11.3)
Dry Mouth[6]	4 (7.0)	11 (20.4)	11 (20.4)	26(15.8)	2 (3.8)
Jitteriness[6]	5 (8.8)	10 (18.5)	5 (9.3)	20(12.1)	1 (1.9)
Events Considered to be Drug Related, n (%)"	38 (66.7)	43 (79.6)	42 (77.8)	123 (74.5)	30 (56.6)

D-MPH-ER, extended-release dexmethylphenidate.

"Incidence significantly higher in consolidated d-MPH-ER group than in placebo group (p < .05, Fisher's exact test).

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patient (1.9%) in the placebo group experienced clinically notable weight loss (decrease of a 7% from baseline). One patient (1.9%) in the placebo group experienced a clinically notable weight gain (increase of a 7% from baseline).

The overall proportion of patients who discontinued from the study was slightly higher in the placebo group (18.9%) than in the consolidated d-MPH-ER group (16.1%). Discontinuation rates attributable to AEs were 7.5% with placebo and 10.9% with d-MPH-ER. In the 20-mg, 30-mg, and 40-mg d-MPH-ER groups, respective discontinuation rates attributable to AEs were 10.5%, 13.0%, and 9-3%, with insomnia and jitteriness the most common reasons (d-MPH-ER group, 1.8% each; placebo group, 1.9% for insomnia, 0% for jitteriness). No patients withdrew because of laboratory abnormalities or serious AEs.

Discussion

The results of this study demonstrate that d-MPH-ER, taken once daily at doses of 20 mg, 30 mg, or 40 mg, is safe and effective for treating ADHD symptoms in adults. Improvements were consistently observed by investigators, patients themselves, and observers such as family members.

For the primary efficacy variable (change from baseline in DSM-IV ADHD-RS total score), all dosages of d-MPH-ER were significantly superior to placebo. Additionally, 20-mg and 40-mg dosages were significantly more effective than placebo in all eight clinician-rated secondary efficacy variables. The 30-mg dosage was significantly superior to placebo in five of those eight variables and numerically superior in the remaining three. For the CAARS:S-S and CAARS:O-S total scores, all three dosages were significantly superior to placebo. There has been some concern that adults with ADHD may underestimate improvements in their condition, but efficacy observed with self-ratings in this study was equivalent to or even slightly greater than that with observer ratings.

On the CGI-I scale, response rates with 20 mg and 40 mg were significantly greater than with placebo, despite a relatively high placebo response rate (26.4%). The placebo response rate is comparable to what has previously been reported in adults but greater than what has previously been reported in children (Faraone et al. 2004).

Global Assessment of Functioning scores improved significantly more with each dosage of d-MPH-ER than with placebo, and mean improvements were comparable across all three dosages (about 10 points for d-MPH-ER groups and 5 points for placebo). Dose-related differences in functional improvement may not be detectable in a short-term study of this type, particularly because patients in the highest dosage groups received their target dose for only 2 or 3 weeks, due to the titration schedule. However, an improvement of 10 points on this scale is dramatic, and the average patient's score at study end point rose to above 60, a range that does not generally indicate a need for clinical treatment.

Quality of life as measured by the Q-LES-Q showed little change from baseline with d-MPH-ER or placebo. However, the trial may not have been long enough to demonstrate measurable enhancements in quality of life, especially for patients who received their target dose for only 2 or 3 weeks.

Effect sizes for the primary efficacy variable in this study would be characterized as medium or large compared with other behavioral therapeutic agents (Faraone 2003; Faraone et al. 2004). Given the generally higher effect size in single-site trials, results reported here are consistent with those in the literature.

As noted, this study was not designed or powered for direct comparisons between dosages. Nevertheless, for most efficacy variables, activity was numerically greater with d-MPH-ER 40 mg than with 20 mg and 30 mg, although all three dosages were significantly superior to placebo. In addition, the incidence of AEs was numerically somewhat greater with the higher dosages than with the lowest. This apparent trend toward a dose-response pattern was observed in some previous studies of ADHD medications (Stein et al. 2003; Swanson et al. 1998) and documented in a recent meta-analysis of adult treatment studies (Faraone et al. 2004). However, the relationship is highly variable among patients, so the dose must always be individualized for optimal efficacy and tolerability (Kimko et al. 1999).

Although a possible dose-response relationship was observed, improvements with the 30-mg dose were not greater than those with the 20-mg dose for most efficacy variables, as might have been expected. In fact, improvements on the CGI-I and CGI-S scales were numerically greater with d-MPH-ER 20 mg and 40 mg than with 30 mg. The 30-mg dose also produced numerically smaller changes than the 20-mg and 40-mg doses on the investigator-rated DSM-IV ADHD-RS total score and the patient-rated CAARS-S:S score. However, mean improvement in the CAARS-O:S score was numerically somewhat greater with 30 mg than with 20 mg or 40 mg. Compared with placebo, the 30-mg dose was more effective overall but was not significantly more effective on all scales and subscales analyzed.

The treatment arms did not differ markedly in baseline body weight (85.2 kg for the 20-mg group, 87.6 kg for the 30-mg group, 83-9 kg for the 40-mg group, and 87.5 kg for the placebo group), hence body weight is unlikely to account for the apparent response differences among d-MPH-ER dosage groups.

There were no unexpected safety concerns related to this class of medications. Observed AEs were consistent with those previously reported with MPH and d-MPH in the treatment of ADHD (Gualtieri et al. 1985; Spencer et al. 1995). Overall rates of AEs were somewhat higher with d-MPH-ER than with placebo, but there was no evidence of toxicity to any organ system.

Although most AEs were reported more frequently with the higher d-MPH-ER dosages than with the lowest dosage, many were most common in the 30-mg group, so dose-relationship trends were rarely linear. Discontinuations attributable to AEs showed a similar pattern. Dry mouth, headache, and anxiety showed apparent trends toward dose relationships. Severity of AEs and mean weight loss were not dose related, nor were many common AEs, such as decreased appetite, insomnia, and jitteriness. Jitteriness has not typically been among the most common AEs in clinical studies of MPH or extended-release mixed amphetamine salts in adults (Goodman et al. 2004; Spencer et al. 2005), although "nervousness" was fairly common in a long-term study of the latter compound (Biederman et al. 2004). Changes in systolic and diastolic blood pressure were not dose related, but pulse increases demonstrated a trend toward dose relationship. In clinical practice, dosages should be titrated to optimal efficacy and tolerability based on individual response.

Study Design Limitations

There are a number of possible limitations to the design of this study. Study length may not have optimally characterized improvements in psychosocial function, and the study was not adequately powered to determine a true dose-response relationship. Also, random assignment of patients to fixed dosages

does not reflect clinical practice, in which patients are titrated to optimal dosages. Although randomization is an essential tool in clinical research, efficacy may be underestimated because some patients are randomized to suboptimal doses. Conversely, adverse effect rates may be overestimated because some patients are randomized to doses that exceed their ideal. This is particularly true with stimulants, which have a wide interindividual variability in dose response. Lastly, although this was a relatively large study with weekly AE reports that supported the tolerability and safety of these d-MPH-ER dosages, it cannot predict the possibility of a rare AE in this population.

Since patients with significant comorbidities or a recent history of substance abuse were excluded from the study, the findings may not be broadly generalizable. Although comorbidities were ruled out by clinical interview, structured diagnostic instruments were not used.

Conclusions

This adequately powered, well-controlled study demonstrates that d-MPH-ER is an effective treatment for adults with ADHD. Efficacy was consistently noted by clinicians, observers, and patients themselves. Using a fixed-dose study design, all three d-MPH-ER dosages (20 mg/d, 30 mg/d, 40 mg/d) showed significantly superior efficacy versus placebo. The 40-mg dose showed a trend toward being the most efficacious. This evidence indicates that extended-release d-MPH will be a useful addition to the therapeutic arsenal for adult ADHD, offering patients the advantage of therapeutic efficacy at lower doses than racemic MPH and the convenience of once-daily dosing.

In this study, d-MPH was safe and well tolerated. The incidence of premature discontinuations because of AEs was similar across all doses of d-MPH-ER and placebo. The most commonly reported treatment-related AEs (headache, decreased appetite, dry mouth, insomnia, and jitteriness) were consistent with the known AE profile of racemic MPH and d-MPH. Changes in vital signs and body weight were minimal and were not considered clinically significant; modest increases in heart rate and BP are consistent with the known AE profile of stimulants. No clinically meaningful changes in ECG or laboratory parameters occurred. (Mick et al, unpublished data, 2006).

Funding for this study was provided by Novartis Pharmaceuticals Corporation.

We thank the Adult ADHD Research Group for their contributions to this study.

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