A Double-Blind, Placebo-Controlled Study of Modified-Release Methylphenidate in Children With Attention-Deficit/Hyperactivity Disorder

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ABSTRACT. *Objective.* **To compare the efficacy, safety, and tolerability of once-daily administration of modified-release methylphenidate (MPH MR) with placebo in children with attention-deficit/hyperactivity disorder (ADHD).**

Methods. **The study was a 3-week, double-blind, 32-site, randomized clinical trial comparing MPH MR with placebo. Children were 6 to 16 years of age, had a diagnosis of ADHD, and had not failed a previous trial of stimulant treatment for ADHD. After a 1-week, single-blind, placebo-washout period, participants received a once-daily dose of MPH MR or placebo, which was started with 1 capsule (20 mg) and individually titrated up to a maximum of 3 capsules (60 mg). The primary outcome measure was specified as a reduction in ADHD symptom severity from the teacher version of the 10-item Conners' Global Index. Investigators, teachers, and parents evaluated safety.**

Results. **The study randomized 321 children: 158 to MPH MR and 163 to placebo. Children in the MPH MR group were started on a dose of 20 mg/d and reached a mean dose of 40.7 mg/d (1.28 mg/kg/d) at endpoint. Compared with placebo, MPH MR significantly reduced ADHD symptoms ratings on the teacher version of the 10-item Conners' Global Index, on the parent version of the Conners' Global Index, on the parent assessment of global efficacy, and on investigator assessment of global improvement. The most common adverse events in the MPH MR group were headache, anorexia, abdominal pain, and insomnia. Only anorexia occurred at a rate that was significantly greater than placebo.**

Conclusion. **MPH MR administered once daily in the morning is effective and safe in controlling ADHD symptoms throughout the school day.** *Pediatrics* 2002; **109(3). URL: http://www.pediatrics.org/cgi/content/full/ 109/3/e39;** *methylphenidate, attention-deficit/hyperactivity disorder, psychopharmacology, stimulants, Conners' Global Index.*

ABBREVIATIONS. ADHD, attention-deficit/hyperactivity disorder; *DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition;* IR, immediate-release; MPH, methylphenidate; SR, sustained-release; MPH MR, methylphenidate modified-release; ER, extended-release; CGI, Clinical Global Impression; ANOVA, analysis of variance; SD, standard deviation.

Attention-deficit/hyperactivity disorder (ADHD), as defined by criteria in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*), affects 3% to 6% of school-aged children in the United States.[1–3] For more than 60 years, stimulant medications have been used to reduce ADHD symptoms.[4] Currently, several immediate-release (IR) stimulant formulations are available, including methylphenidate ([MPH]; Ritalin), pemoline (Cylert), dextroamphetamine (Dexedrine or Dextrostat), and a mixed salts of amphetamine (Adderall).[5] After oral administration of IR formulations, optimum behavioral effects occur within 1 to 2 hours, with a duration of 3 to 5 hours.[6–9] The relatively short duration of action mandates multiple daily doses for most children, with doses given during the school day. This raises a number of issues related to compliance, privacy, peer ridicule, controlled drug storage and accountability on the part of the school administration and nurses, and potential abuse.[5] Wax-matrix sustained-release MPH (Ritalin-SR) formulations of MPH, developed in the late 1970s to solve this problem, have not been adopted in clinical practice (2001 sales through July constitute <2% of market share), because of their delayed onset of action, insufficient duration of effect, and comparatively lower effectiveness.[10,11] For the 2001 year through July, stimulant sales were led by mixed salts of amphetamine and more modern long-duration methylphenidate products.

Modified-release methylphenidate (MPH MR [Metadate CD]) was developed and manufactured by Celltech Pharmaceuticals Inc (Rochester, NY). It was designed to produce a rapid onset of therapeutic effect but has a sufficient duration to eliminate the need for a midday dose at school. It utilizes a new dual-phase formulation that contains IR and extended-release (ER) forms of the drug in a 30:70 ratio by weight. Each 20-mg MPH MR capsule contains 2 types of coated bead-delivery systems in a 30:70 ratio by weight: IR beads (6 mg) and ER beads (14 mg). The capsules use Eurand's Diffucaps technology, a multiparticulate bead-delivery system with each bead acting as a drug reservoir. In pharmacokinetic

studies in children, peak serum drug levels were achieved at 1.5 hours after dosing, followed by a second peak of similar magnitude at 4.5 hours.[12]

The primary objective of this study was to compare the efficacy, safety, and tolerability of once-daily administration of MPH MR with placebo in children with ADHD. The secondary objective was to compare separately the morning and afternoon therapeutic responses of the MPH MR formulation with placebo. This would determine whether MPH MR's onset of action was rapid enough to secure good teacher ratings in the morning and its duration of action was long enough to yield good afternoon symptom control.

METHODS

Participants

Children recruited were 6 to 16 years of age and had a primary diagnosis of ADHD, combined subtype or the predominately hyperactive-impulsive subtype as defined in *DSM-IV* (diagnostic code 314.01).[13] The diagnosis of ADHD was based on a parent interview using the National Institute of Mental Health Diagnostic Interview Schedule for Children–Version 4.0.[14] Children had to be in a first-grade or higher school setting in which a single teacher could assess their behavior in the morning and afternoon on specified days. Blood pressure, heart rate, and oral temperature had to be within normal range.

Exclusion criteria included a comorbid psychiatric diagnosis; history of seizure or tic disorder or a family history of Tourette's syndrome; IQ below 80; inability to follow or understand study instructions; female who had undergone menarche; use of amphetamines, pemoline, or an investigational drug within 30 days of study entry; concomitant use of clonidine, anticonvulsant drugs, or medications known to affect blood pressure, heart rate, or central nervous system function; hyperthyroidism or glaucoma; or any concurrent chronic or acute illness (eg, allergic rhinitis, severe cold) or disability that could confound the study results. Also excluded were children who had failed a previous trial of stimulants for ADHD, had required a third daily dose in the afternoon or evening, had a documented allergy or intolerance to MPH, or were living with anyone who currently had substance abuse disorder (excluding dependency). Children provided signed assent, and their legal guardians signed an institutional review board-approved consent form before children could participate in the study.

Assignment and Blinding

Eligible children entered a single-blind, 1-week placebo-washout period. Responders to this phase were excluded to detect better those who had a stable, long-term positive response to this medication without the "noise" that might occur from a placebo response. After completion of the washout period, children were stratified on the basis of whether they had or had not received previous drug treatment for ADHD and then randomized in a 1:1 ratio to receive MPH MR or placebo once daily for 3 weeks.

Identically appearing MPH MR and placebo capsules were packaged in blister cards containing 30 capsules. Each card represented a 7-day supply plus 3 extra days in case the next study visit was delayed. Children were instructed by their parents to take 3 capsules (1 row of the blister card) in the morning before breakfast and to swallow the capsules whole without chewing. Data were not collected for the specific time of morning dose administration. For the first week of double-blind treatment, the blister card in the active treatment group consisted of 10 capsules of 20-mg MPH MR in the first column and placebo-containing 10 capsules in the remaining 2 columns. For subsequent weeks, 20-mg, 40-mg, or 60-mg blister cards were dispensed according to the individually titrated dosage. Blister cards containing all placebo capsules were dispensed in the washout period to all children and in the double-blind period to children who were assigned to the placebo group.

Study Design

This study was conducted at 32 centers in the United States in accordance with the principles of the Declaration of Helsinki and its amendments. At a screening visit, all medical tests were performed to ensure that children satisfied health-related inclusion criteria and did not meet exclusion criteria. The child's teacher and school were contacted by telephone to verify their willingness to participate in the study and to ensure confidentiality of the child's records. Study procedures were subsequently explained to the teacher, and training materials were forwarded. In addition, parents and teachers were given instructions regarding completion of the Conners' Global Index[15] and side-effect questionnaires. After all screening assessments were completed, the investigator rated the severity of disorder using the Clinical Global Impression (CGI) scale and then dispensed a placebo blister card for the 1-week washout period.[16] Children, parents, and teachers were blinded to the identity of treatment during this period. Parents were instructed to keep a medication diary and a diary of observations that noted their child's condition during the placebo-washout week.

At the end of the washout period, children and their parents returned to the study center for a baseline visit. Eligible subjects—who had a confirmed ADHD diagnosis, met study eligibility requirements, and had not responded to placebo with a reduction of ADHD symptoms—were then randomized to double-blind treatment and instructed to return weekly to the study center. A blister card containing either MPH MR 20 mg or placebo was dispensed for use during the first week of the treatment period. At the week 2 and week 3 visits, investigators assessed the adequacy of the dosage on the basis of clinical judgment and child and parent interviews, total scores on the previous week's parent and teacher versions of the Conners' Global Index and the side-effect questionnaire, and adverse event profile. Children were continued on the same dosage for the next week if they achieved a satisfactory treatment response and tolerated treatment. However, if the child had tolerated treatment but still had room for improvement, then the study drug (either MPH MR or placebo) was titrated to the next-higher dose level (20 mg to 40 mg daily or 40 mg to 60 mg daily).

Outcome Measures

The primary efficacy measure used in this study was the teacher version of the 10-item Conners' Teacher Global Index. This was completed by telephone interview during the morning (around 10 AM) and afternoon (around 2 PM) of 3 alternating days of each treatment week. The Conners' Teacher Global Index contains 10 items that measure disruptive behavior (including inattention and hyperactivity/impulsivity), with each item scored on a scale from 0 (not true at all; never; seldom) to 3 (very much true; very often; very frequent) for a maximum total score of 30 points.

Secondary efficacy measures included the 10-item Conners' Parent Global Index that was completed on 1 day of each weekend during the morning, afternoon, and evening. In addition, the parents completed a parent global assessment at the final visit. Parents were asked to review the diary they had kept during the washout period and then rate their child's condition at the final visit compared with baseline using a 7-point categorical scale ranging from 7 (much improved) to 1 (much worse).

The clinician-rated CGI was used to evaluate the child's symptom severity of disorder at baseline (CGI-S) on a 7-point scale ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill). In addition, investigators used the CGI for improvement (CGI-I) to assess the child's global change each week relative to the condition observed at baseline on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse).

The safety and tolerability of treatment were evaluated at each visit using reported and observed adverse events, and vital signs were collected at baseline and weekly thereafter. Laboratory testing was performed at baseline and at the end of double-blind treatment and included hematology, biochemistry, and urinalysis. Parents completed the Pittsburgh 11-item side-effect questionnaire—the same adverse event questionnaire used in the National Institute of Mental Health's Multimodal Treatment Study of Attention-Deficit/Hyperactivity Disorder (MTA Study)—after the child went to bed on the same day that they completed the Conners' Global Index. Teachers completed a similar side-effect questionnaire—identical to the parent version except for exclusion

of an item related to sleep—3 times per week near the end of the school day, on the same days they filled out the Conners' Global Index.

Statistical Analysis

All statistical summaries and analyses were conducted for the intention-to-treat population using the last-observation-carried-forward approach for children who withdrew prematurely. All comparisons between treatment groups were performed using 2-sided tests with a significance level of .05. The null hypothesis for all analyses was based on no difference between treatments.

Demographic characteristics of the 2 treatment arms were compared using a 2-sample t test for age and weight and χ^2 test for gender and race. ADHD characteristics were compared at baseline using a 2-sample t test for CGI severity of disorder and teacher and parent Conners' Global Index. The baseline value of the teacher and parent Conners' Global Index was derived by averaging all of the scores during the placebo-washout period.

The primary efficacy endpoint was defined a priori as the change from baseline in the average score of the teacher Conners' Global Index. The average was calculated from all individual morning and afternoon evaluations made on the 3 observation days of the last week. Differences between treatment arms were assessed using an analysis of variance (ANOVA) model, with treatment as the only fixed factor.

Secondary efficacy endpoints included separate analyses of the morning and afternoon average scores on the teacher version of the Conners' Global Index during the last week of treatment, average scores of the teacher Conners' Global Index at each week, and average scores of the parent Conners' Global Index at each week and during the last week. The changes from baseline in each of these secondary endpoints were analyzed using the same ANOVA model as that used for the primary endpoint. Ratings that were much improved or very much improved on the efficacy index of the CGI scale were equated with clinical response.

The effect size for MPH MR was assessed using the mean scores from the teacher and parent versions of the Conners' Global Index during the last week of treatment. Effect size was calculated by subtracting the mean rating given for the MPHMR group from the mean rating given for the placebo group, divided by the standard deviation (SD) of the placebo group.

Adverse events were classified by preferred terms and body system and defined by the CoStart System.[17] Furthermore, each adverse event was rated by the investigator in terms of its intensity and probability that it was related to the drug being taken. Differences between treatments in the percentage of children with at least 1 adverse event (primary safety endpoint) were compared using the χ^2 test for categorical data analysis. Similar analyses between treatments were made for all adverse events that occurred in at least 5% of children in either group.

RESULTS

Participants

Of the 507 children who were screened for the trial, 186 were disqualified during the screening period before and during the 1-week single-blind placebo-washout phase (Table 1). These children never entered the 3-week double-blind phase and were not included in any of the safety or efficacy analyses. A total of 321 children were randomized to double-blind treatment: 158 to MPH MR and 163 to placebo. Five children (3 MPH MR, 2 placebo) were excluded from the safety analyses, 4 because they received no study medication and 1 because of lack of safety data. Seven children (3 MPH MR, 4 placebo) were excluded from the efficacy analysis, 3 because of lack of minimal requisite efficacy data and 4 because of lack of adequate dosing records. Consequently, 316 children were included in the safety population, and 314 children were included in the intention-to-treat efficacy population. Twenty-eight children (17%) who received placebo withdrew from the 3-week

TABLE 1. Children Disqualified by Screening

Total number of children screened	507
Reasons for screen failure	
Did not satisfy inclusion criteria/met exclusion criteria	58
Placebo responder	45
Withdrew consent (child/guardian decision)	41
Protocol noncompliance	19
Reason not given	5
Intercurrent illness	4
Lost to follow-up	4
Teacher noncompliance with Conners' Global Index	4
Investigator decision	3
Other	3
Total number of children who were disqualified by screening	186

trial, whereas only 17 children (11%) who were assigned to MPH MR withdrew. Reasons for withdrawal were similar for both treatment groups. Patients' time of withdrawal varied substantially, with no clear pattern.

Demographic characteristics and baseline ADHD severity did not differ between children in the 2 treatment groups (Table 2). Stratification based on previous treatment before randomization ensured equal distribution across the 2 treatment groups. Although none of the patients had failed a trial of stimulants, only 64% of children in both MPH MR and placebo groups had been treated previously with medications for ADHD. The most frequently used previous medications were Ritalin (46% of all children), generic MPH (17%), Adderall (9%), Ritalin-SR (6%), and Dexedrine (5%). Data were not collected on special accommodations for ADHD made by the schools for these children.

TABLE 2. Demographics and Baseline ADHD Severity of the Intention-to-Treat Population

	MPH MR (n = 155)	Placebo (n = 159)	P Value
Age (y)			
Mean*	9 ± 2.0	9 ± 1.8	.24
Range	6–15	5–14	
Gender			
Male	128 (83%)	129 (81%)	.74
Female	27 (17%)	30 (19%)	
Race			
White	113 (73%)	110 (69%)	.47
Black	21 (14%)	27 (17%)	
Hispanic	17 (11%)	15 (9%)	
Other	4 (3%)	7 (4%)	
Weight (kg)*	34 ± 11.7	34 ± 11.4	.92
Height (cm)*	134 ± 13.0	136 ± 13.1	.21
Previously treated for ADHD	99 (64%)	102 (64%)	.98
Conners' Global Index–Teacher†	12.7 ± 7.2	11.5 ± 7.3	.13
Conners' Global Index–Parent†	13.6 ± 6.6	12.9 ± 7.6	.42
CGI Severity of Disorder‡	4.5 ± 0.9	4.4 ± 0.9	.23

* Mean (± SD).
† Mean (± SD) total score of 10-item Conners' Global Index. Each item was rated on a scale ranging from 0 (not true at all; never; seldom) to 3 (very much true; very often; very frequent). The groups did not differ significantly.
‡ Mean (± SD) score on 7-point scale ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill children). The groups did not differ significantly.

Dose and Compliance

In the MPH-MR group, the mean total daily dose for week 1 was 20 mg/d (0.64 mg/kg/d); for week 2, the mean total daily dose was 32.3 mg/d (1.02 mg/kg/d); and for week 3, the mean dose was 40.7 mg/d (1.28 mg/kg/d). During the third week of the treatment period, the total daily dose of MPH MR was 20 mg in 38 (25%) of 155 children, 40 mg in 59 (38%) of 155 children, and 60 mg in 43 (28%) of 155 children. In comparison, children who were assigned to placebo started with a dose of 20 mg/d for the first week but were increased by their clinicians to doses of 36.8 mg/d and 51.6 mg/d in placebo equivalents, higher than those on active medications.

Compliance was based on weekly medication counts, which showed satisfactory adherence in both groups. Of the 155 children in the MPH MR group, 105 (68%) had no discrepancies in drug accountability, and 35 (23%) missed only 1 or 2 doses. The remaining 15 children (10%) returned fewer capsules than expected. In the placebo group, 117 (73%) of 161 children (73%) did not have any discrepancies in capsule accountability, 28 (17%) missed only 1 or 2 doses, 8 (5%) missed 3 or more doses, and 8 (5%) returned fewer capsules than expected.

Teacher's Conners' Ratings

MPH MR significantly reduced ADHD symptoms compared with placebo based on results from the teacher version of the 10-item Conners' Global Index. In the MPH MR group, the teacher Conners' Global Index was reduced from a baseline score (mean ± SD) of 12.7 ± 7.2 to a score of 4.9 ± 4.7 in the last week of the double-blind treatment period. The corresponding scores in the placebo group were 11.5 ± 7.3 at baseline and 10.3 ± 6.9 at the end of the double-blind period. In the ANOVA model, the least squares mean change between treatment groups differed significantly in favor of the MPH MR group (95% confidence interval: 5.26–8.09; 2-tailed Student t test, $t = 9.27$; $df = 311$; $P < .001$). From the teacher assessment, an effect size of 0.78 was calculated for the MPH MR treatment compared with placebo during the last week of treatment.

Differences between teacher's Conners' Global Index ratings between MPH MR and placebo were evident when the morning and afternoon scores on the teacher Conners' Global Index were evaluated separately (Table 3). Last week mean morning ratings (±SD) for children assigned to either the MPH MR or to placebo groups were 4.8 ± 4.6 and 9.9 ± 6.6, respectively. During the afternoon, mean scores for the MPH MR and placebo groups were 5.4 ± 5.2 and 10.6 ± 6.9, respectively. For both the morning and afternoon of the last week of treatment, a large effect size of 0.8 was calculated for the MPH MR treatment compared with placebo.

Parent Conners' Ratings

In the parent rating of the 10-item Conners' Global Index, MPH MR significantly reduced ADHD symptoms relative to placebo. In the MPH MR group, the baseline score (mean ± SD) of 13.6 ± 6.6 was reduced to a mean score of 7.4 ± 5.9 in week 3 of the double-blind treatment period. In comparison, the baseline and week 3 mean scores in the placebo group were 12.9 ± 7.6 and 10.1 ± 6.7, respectively. In the ANOVA model, the least squares mean change between treatment groups differed significantly in favor of the MPH MR group (95% confidence interval: 1.7–4.9; 2-tailed Student t test, $t = 3.97$; $df = 297$; $P < .001$; Fig 1). From the parent assessment, a moderate effect size of 0.4 was calculated for the MPH MR treatment compared with placebo during the last week of treatment.
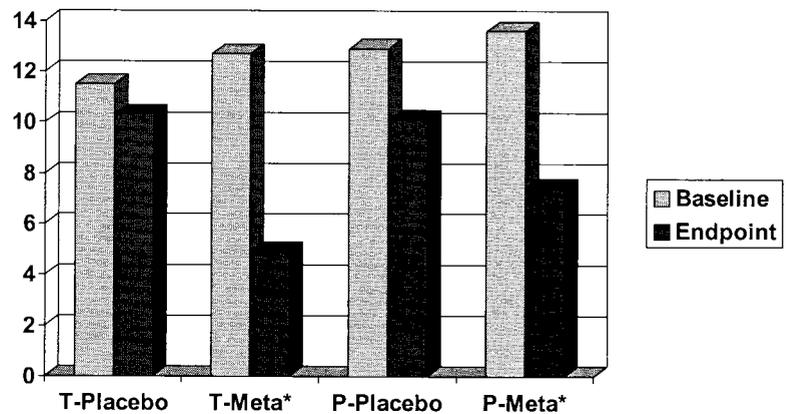
CGI Improvement Ratings

To determine the proportion of responders in the groups assigned to placebo or to MPH-MR, we counted all children as responders who had CGI Efficacy scores in the moderately improved range or better. Using this criterion, 64% (98 of 154) of the children who were treated with MPH MR were judged to be responders versus only 27% (41 of 156) in the placebo group.

Different results were obtained by examining the CGI Improvement scores, using the same criterion for responder status. Eighty-one percent (125 of 154) of those assigned to active drug versus 50% (78 of 156) of those assigned to placebo could be called responders on the basis of their CGI Improvement scores. The Mantel-Haenszel χ^2 test showed statisti-

TABLE 3. Conners' Global Index–Teacher: Weekly Morning and Afternoon Scores of the Intention-to-Treat Population

Time Point	Methylphenidate Mean (SD)	Placebo Mean (SD)	Analysis (t Value, df) (P Value)
Baseline	12.7 (7.24)	11.5 (7.35)	(1.51, 311) (0.1309)
Last week	4.9 (4.66)	10.3 (6.92)	(−10.67, 310) (0.0001)
Last week AM	4.6 (4.73)	9.9 (6.93)	(−10.04, 306) (0.0001)
Last week PM	5.1 (5.07)	10.6 (7.16)	(−10.33, 310) (0.0001)
Week 1	7.3 (4.93)	10.9 (6.56)	(−8.99, 310) (0.0001)
Week 2	5.8 (4.71)	10.4 (6.75)	(−9.42, 287) (0.0001)
Week 3	4.7 (4.77)	9.2 (6.30)	(−9.09, 265) (0.0001)
Week 1 AM	7.1 (5.00)	10.6 (6.52)	(−8.02, 305) (0.0001)
Week 1 PM	7.6 (5.36)	11.3 (6.88)	(−8.58, 310) (0.0001)
Week 2 AM	5.8 (4.87)	10.0 (6.81)	(−8.36, 280) (0.0001)
Week 2 PM	5.9 (5.04)	10.7 (6.87)	(−9.26, 286) (0.0001)
Week 3 AM	4.5 (4.85)	8.9 (6.33)	(−8.41, 257) (0.0001)
Week 3 PM	5.0 (5.21)	9.4 (6.54)	(−8.70, 265) (0.0001)

Fig 1. Conners' Global Index Scale: controlled ADHD symptom ratings. Asterisks indicate differences between baseline and endpoint and are significantly different ($P < .05$)

cally different ($P < .001$) CGI-I scores for the 2 treatment groups. The least squares mean CGI improvement score ($\pm$SE) in the MPH MR and placebo groups was 2.4 $\pm$ 0.1 and 3.5 $\pm$ 0.1, respectively ($P < .001$).

Adverse Events

During the treatment period, 80 (52%) of 155 children in the MPH MR group and 61 (38%) of 161 children in the placebo group spontaneously reported 1 or more adverse events irrespective of their relationship to study treatment ($P = .014$). The most common adverse events were headache, anorexia, abdominal pain, and insomnia (Table 4). Of these, only anorexia occurred at a rate significantly greater in children who were treated with MPH MR than with placebo (9.7% vs 2.5%; $P = .007$). Of the spontaneously reported adverse events for children who received MPH MR or placebo, 32.9% and 17.4%, respectively, were considered by the investigator to be related to study agent.

Only 2 children discontinued treatment because of adverse events. One child developed a pruritic, non-erythematous, periumbilical rash on the sixth day of treatment with MPH MR, whereas the other child developed a headache on the fourth day and dizziness and stomachache on the fifth day of treatment with MPH MR. There were no serious adverse events reported in either treatment group.

There were no significant differences between treatment groups in mean and median systolic or diastolic blood pressure, pulse rate, or oral temperature. No differences between treatments were found in the physical examinations performed at the end of the treatment period. In both treatment groups, laboratory testing did not find any consistent changes in hematology, biochemistry, or urinalysis. In the MPH MR and placebo groups, 48 and 63 children, respectively, had out-of-range laboratory values that were within range at baseline. These out-of-range values were most commonly seen in eosinophil and neutrophil counts.

DISCUSSION

Although there have been other studies of once-daily stimulant medications given once in the morning, this is the first study of a controlled-delivery methylphenidate preparation to compare morning and afternoon assessments in the child's own classroom. It is also the first to report a reduction of ADHD symptoms at both time points from a single morning dose.[18] These scores were collected by telephone during the time of scoring, ie, either morning or afternoon. Notably, within the MPH MR group, the mean Teacher's Conners' Global Index score was similar to the morning and afternoon scores when analyzed separately (Fig 1). Furthermore, the degree of improvement in the MPH MR group relative to placebo was consistent for both the morning and afternoon assessments. The reduction in both morning and afternoon scores on the teacher version of the 10-item Conners' Global Index scale indicates that a single morning dose of MPH MR is effective throughout the school day. The parent ratings demonstrated that MPH MR was superior to placebo in reducing ADHD symptoms at home, corroborating the findings on the teacher evaluation.

At endpoint, investigators rated 64% of children as moderately or markedly improved by MPH MR compared with 27% of children given placebo. These findings are consistent with the response rates seen with IR MPH in controlled clinical trials.[1,5,6]

A moderate effect size of 0.78 was determined for the teacher assessment on the Conners' Global Index during the last week of treatment and for the separate assessments during the morning and afternoon of the last week. From the parent assessment, a small to moderate effect size of 0.4 was calculated during the last week of treatment. These magnitudes of effect are consistent with the literature, in which twice-daily dosing typically produces a larger effect during the school day when the medication levels are higher than at home after school when the medication levels have dropped.

MPH MR was safe and well tolerated and did not produce any unexpected adverse events. There were no serious adverse events during this study. The most common adverse events in the MPH MR group were headache, anorexia, abdominal pain, and insomnia; of these, only anorexia occurred at a rate that was significantly greater than placebo.

There are several limitations to this study. First, the dose-titration design did not focus on obtaining each child's optimal dose before the study started.

TABLE 4. Spontaneous Adverse Events That Occurred at an Incidence ≥5% in Either Treatment Group

Adverse Event	MPH MR (n = 155)	Placebo (n = 161)	χ^2 P Value
Any event	80 (51.6%)	61 (37.9%)	.014
Headache	23 (14.8%)	17 (10.6%)	.253
Anorexia	15 (9.7%)	4 (2.5%)	.007
Abdominal pain	15 (9.7%)	8 (5.0%)	.107
Insomnia	11 (7.1%)	4 (2.5%)	.054

Because no dose-response curves were collected on the children in the study, as had been collected on the children in the MTA Study, we could not determine whether the effects of MPH MR were dose related.

Even so, the study results suggest that reaching an effective level may be achieved in a relatively rapid manner with MPH MR. In comparison, IR formulations of MPH are often initiated at doses of 5 mg to 20 mg given 1 to 3 times daily, so management formulations must involve adjustments of both dose level and timing of dose. This means that establishing the child's optimal dose of an IR formulation might take longer than a preparation that is given only once daily.

Second, the study's inclusion and exclusion criteria selected for milder cases of ADHD. For example, our admission criteria excluded children with ADHD that required a third dose. Teacher's Conners' scores averaged 12 and the parent's Conners' scores average 13 of 30. This is lower than the average scores in the MTA Study at admission, which recruited children with ADHD of at least moderate severity. The lower scores in this trial mean that the findings may not be as generalizable and are a limitation.

Third, the 3-week duration of the trial did not allow the investigators to determine whether the dual-phase effects of MPH MR persist with long-term treatment. Also, the long-term safety issues that concern parents of children who take psychotropic medications could not be assessed in this short-term clinical trial.

Fourth, the study's design limited generalizability of the results because it excluded acute placebo responders and those who had failed to respond to any MPH treatment before the study. Within the context of a research protocol intended to assess the relative efficacy of MPH MR versus placebo, the exclusion of MPH nonresponders, like the exclusion of placebo responders, runs the risk of a type 1 error because it could magnify the relative efficacy of MPH MR over placebo. Of the 186 children who were disqualified at the end of the placebo-washout week, 45 (24%) had responded to placebo (ie, had a reduction in ADHD symptoms) and subsequently were excluded from the study. If they had entered the study without a placebo washout, then those who were randomized to placebo in the study might have responded, reducing placebo-active drug differences. Of course, there is an equal chance that any child entering the study could have been randomly assigned the MPH MR group.

Placebo response rates in trials of stimulants for children with ADHD run between 4% and 20%. For example, 13% of the children in the MTA study showed a placebo response. However, 29 of these 32 children later required full treatment with methylphenidate during the MTA open maintenance phase. More than 90% of children who had ADHD and had a placebo response in the MTA study relapsed within 15 to 60 days. Therefore, it would be difficult to predict what proportion of the placebo responders in this trial would have relapsed in the study reported here by the end of study measure and whether it would have changed the outcome of the study.

Fifth, we excluded children who had failed to respond to MPH in the past. In a clinical setting, this is easily justifiable. It is more ethical not to expose children who have done very poorly on a treatment to the same drug a second time. In a research study, however, excluding these children may make the study less representative by amplifying the magnitude of the difference in treatment between MPH MR and placebo.

Sixth, there could have been a bias because the parents were aware that the researchers had the option of stepping up the "dose" of placebo each week, based on the reported response to the previous week's treatment. Families who think that the increased dose meant that their children were getting more active medicine might expect and find im-

TABLE 5. Teacher and Parent Side-Effect Questionnaires in the Last Week of Treatment

Side Effect	Teacher Scores		Parent Scores	
	MPH MR (n = 155)	Placebo (n = 161)	MPH MR (n = 155)	Placebo (n = 161)
Appetite loss	42 (27%)	17 (11%)	73 (47%)	33 (20%)
Dull, tired, listless	47 (30%)	45 (28%)	48 (31%)	41 (26%)
Crabby, irritable	34 (22%)	48 (30%)	70 (45%)	79 (49%)
Tearful, sad, depressed	28 (18%)	33 (20%)	44 (28%)	37 (23%)
Worried, anxious	41 (26%)	43 (27%)	36 (23%)	39 (24%)
Motor tics	20 (13%)	26 (16%)	11 (7%)	8 (5%)
Buccal-lingual movements	17 (11%)	22 (14%)	9 (6%)	7 (4%)
Picking at fingers or skin, nail-biting, lip or cheek-chewing	32 (21%)	34 (21%)	37 (24%)	38 (24%)
Stomachaches	19 (12%)	8 (5%)	36 (23%)	25 (16%)
Headaches	18 (12%)	7 (4%)	33 (21%)	29 (18%)
Trouble sleeping	NE	NE	50 (32%)	38 (24%)

NE indicates not evaluated.

provement. However, the double-blind nature of the study's design prevented this from biasing the overall study results.

CONCLUSION

MPH MR administered once daily in the morning was well tolerated and significantly more effective than a double-blind comparison with placebo in controlling ADHD symptoms throughout the school day. Symptom control was achieved in the morning and afternoon. The total daily dose of MPH MR averaged 40.7 mg/d. This daily dose is slightly higher than the total dose reported in large clinical trials of IR MPH formulations.

Appendix

Members of the MPH MR ADHD Study Group: Jeffrey Apter, MD; Cheston Berlin, MD; Robert W. Block, MD; Jeffrey L. Blumer, PhD, MD; Samuel Boellner, MD; Daniel Brown, MD; Edward Cherlin, MD; C. Keith Conners, PhD; Daniel Coury, MD (with Philip Walson); Daniel J. Cox, MD (with Janet Carella); James Ferguson, MD; Robert L. Findling, MD; L. Matthew Frank, MD; Thomas Gaultieri, MD; Laurence Greenhill, MD; Saul Helfing, MD; James Hudziak, MD (with Scott Waterman, MD); Leighton Huey, MD; Archana Kumar, MD (with Jonathan Dowben, MD); Robert Lipetz, MD; Thomas W. Littlejohn, III, MD; Thomas C. Marbury, MD; Jeffrey Newcorn, MD; Donna Palumbo, PhD; Anil Patel, MD; Leon Rosenberg, MD; Murray Rosenthal, MD (with Simona Deacluc); Richard Rubin, MD; Howard I. Schwartz, MD; R. Bart Sangal, MD; Nathan Segall, MD; James Swanson, PhD (with Sharon Wigal, PhD, and Daniel Youpa, PhD); Denise Verones, PhD; and Daniel Wynn, MD.

REFERENCES

1. Swanson JM, Lerner M, Williams L. More frequent diagnosis of attention-deficit/hyperactivity disorder [letter]. *N Engl J Med*. 1995;333: 944
2. Safer DJ, Krager JM. A survey of medication treatment for hyperactive/inattentive students. *JAMA*. 1988;260:2256–2258
3. Barkley RA. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychol Bull*. 1997; 121:65–94
4. Bradley C. The behavior of children receiving benzedrine. *Am J Psychiatry*. 1937;94:577–585
5. Greenhill LL, Halperin JM, Abikoff H. Stimulant medications. *J Am Acad Child Adolesc Psychiatry*. 1999;38:503–512
6. Patrick KS, Mueller RA, Gualtieri GT, Breeze G. Pharmacokinetics and actions of methylphenidate. In: Meltzer HY, ed. *Psychopharmacology: A Third Generation of Progress*. New York, NY: Raven; 1987:1387–1395
7. Chan YM, Soldin SJ, Swanson JM, Deber CM, Thiessen JJ, Macleod S. Gas chromatographic/mass spectrometric analysis of methylphenidate (Ritalin) in serum. *Clin Biochem*. 1980;13:266–272
8. Chan YM, Swanson JM, Soldin SS, Thiessen JJ, Macleod SM, Logan W. Methylphenidate hydrochloride given with or before breakfast: II. Effects on plasma concentration of methylphenidate and ritalinic acid. *Pediatrics*. 1983;72:56–59
9. Shaywitz SE, Hunt RD, Jatlow P, et al. Psychopharmacology of attention deficit disorder: pharmacokinetic, neuroendocrine, and behavioral measures following acute and chronic treatment with methylphenidate. *Pediatrics*. 1982;69:688–694
10. Greenhill LL, Osman BB, eds. *Ritalin: Theory and Patient Management*. Larchmont, NY: Ann Liebert Inc; 1991
11. Pelham WE, Sturges J, Hoza J, et al. Sustained release and standard methylphenidate effects on cognitive and social behavior in children with attention deficit disorder. *Pediatrics*. 1987;80:491–501
12. Data on File. Protocol No. MAI 1001–02. Wayne, PA: Celltech Development
13. First MB, ed. *Diagnostic Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994
14. Shaffer D, Fisher P, Lucas CP, Dulcan MK, Schwab-Stone ME. NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): Description, differences from previous versions, and reliability of some common diagnoses. *J Am Acad Child Adolesc Psychiatry*. 2000;39: 28–38
15. Conners CK. *Conners' Global Index–Teacher*. North Tonawanda, NY: MultiHealth Systems Inc; 1997
16. Guy W, et al. *ECDEU Assessment Manual for Psychopharmacology, Revised*. Rockville, MD: National Institute of Mental Health, United States Department of Health, Education, and Welfare; 1976:217–222 (Publ. No. 76-338)
17. Department of Health and Human Services (DHHS). *COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms)*. 3rd ed. Rockville, MD: DHHS, FDA; 1989
18. Pelham WE, Gnagy EM, Chronis AM, et al. A comparison of morning-only and morning/late afternoon Adderall to morning-only, twice-daily, and three times-daily methylphenidate in children with attention-deficit/hyperactivity disorder. *Pediatrics*. 1999;104:1300–1311

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