J Child Adolesc Psychopharmacol Vol. 14(4):542-554 (2004)
ISSN: (print 1044-5463) (online 1557-8992)
doi:10.1089/cap.2004.14.542


# A Double-Blind, Placebo-Controlled Withdrawal Trial of Dexmethylphenidate Hydrochloride in Children with Attention Deficit Hyperactivity Disorder

**L. Eugene Arnold, M.Ed., M.D., Ohio State University, Columbus, Ohio., Ronald L. Lindsay, M.D., Children's Health Center of St. Joseph's Hospital and Medical Center, Arizona Child Study Center, Developmental and Behavioral Pediatrics, Phoenix, Arizona., C. Keith Conners, Ph.D., Duke University Medical Center, Department of Psychiatry and Behavioral Sciences, Durham, North Carolina., Sharon B. Wigal, Ph.D., University of California—Irvine, Department of Pediatrics, Irvine, California., Alan J. Levine, M.D., Denver Center for Medical Research, Denver, Colorado., Diane E. Johnson, Ph.D., Duke University Medical Center, Department of Psychiatry, Durham, North Carolina., Scott A. West, M.D., CNS Healthcare, Orlando, Florida., R. Bart Sangal, M.D., Attention Disorders Institute, Troy, Michigan., Timothy P. Bohan, M.D., Texas Children's Hospital, Baylor University, Houston, Texas., Jerome B. Zeldis, M.D., Ph.D. Celgene Corporation, Warren, New Jersey.**

Objectives:

*d,l*-threo-methylphenidate HCl (*d,l*-MPH) is the most common treatment of attention deficit hyperactivity disorder (ADHD). A previous report showed placebo-controlled efficacy for the purified d-isomer (dexmethylphenidate hydrochloride, *d*-MPH, Focalin™) with a 2:1 potency compared to *dl*, and suggested a 6-hour duration of action. This study complements that report by studying the effect of placebo-controlled discontinuation and retesting the duration of action.

Methods:

A 6-week, open-label titration of *d*-MPH (2.5–10 mg twice-a-day) was followed by a double-blind, placebo-controlled, 2-week withdrawal study of responders.

Results:

In the open titration, 82% of the 89 enrolled patients achieved a Clinical Global Impression—Improvement (CGI-I) rating of much or very much improved. Only 5 patients discontinued for adverse events. Seventy-five patients continued into the placebo-controlled discontinuation. For the randomly assigned *d*-MPH ($n$ = 35) and placebo ($n$ = 40) groups, mean ages, respectively, were 10.1 ± 2.9 and 9.9 ± 2.7 years, 86% and 78% were male, and 70.6% and 80.0% took the ceiling dose of 10 mg twice-daily, respectively. Each group had 80% combined-type ADHD and 20% inattentive type. By the end of the 2-week, placebo-masked withdrawal, significantly more placebo patients (24 of 39) than *d*-MPH continuers (6 of 35) relapsed (61.5% versus 17.1%, $p$ = 0.001). Compared to *d*-MPH continuers, placebo patients deteriorated significantly more in the 2-week period on teacher ratings of the 18 ADHD symptoms rated 0–3 ($p$ = 0.028), the 3 p.m. and 6 p.m. parent ADHD symptom ratings ($p$ = 0.0026 and $p$ = 0.0381,

respectively), and clinic (2–3 p.m.) and home (6 p.m.) Math Tests ($p = 0.024$ and $p < 0.0001$, respectively). The 6 p.m. scores replicated the significant effect at 6 hours reported in the previous study.

*Conclusions:*

*d*-MPH is safe, tolerable, and effective, with a 6-hour duration of effect suggested by the significant difference from placebo at 6 hours on a double-blind discontinuation.

## Introduction

Attention deficit hyperactivity disorder (ADHD) is a common neurobehavioral syndrome affecting approximately 3%–5% of school-aged children in the United States (American Psychiatric Association 1994; Jadad et al. 1999; National Institutes of Health 1998). With persistent core symptoms of developmentally inappropriate overactivity, distractibility, inattention, and impulsivity, it impairs social, academic, and occupational functioning (American Psychiatric Association 1994). Stimulant medications (methylphenidate and amphetamine) are first-line pharmacotherapy for ADHD (American Academy of Pediatrics 2001; Dulcan 1997; Jadad et al. 1999), producing rapid improvement in behavior and attentiveness, generally followed by improved academic performance (Elia et al. 1999; Goldman et al. 1998; National Institutes of Health 1998). For decades, the most widely prescribed stimulant has been racemic *threo*-methylphenidate (*d,l*- MPH). Methylphenidate (MPH) is stereoisomeric in two ways: it has *threo* and *erythro* enantiomers, each of which has a *dextro* and *levo* enantiomer, making 4 possible stereoisomers. Racemic (*d,l) threo*-methylphenidate has been available for over 45 years in the United States and is considered one of the pharmacologic treatments of choice for ADHD. The racemic mixture of *d-threo* and *l-threo* enantiomers undergoes enantioselective metabolism without racemization after oral dosing in humans (Kimko et al. 1999; Srinivas et al. 1992). Both the pharmacological properties (Patrick et al. 1987) and the clinical efficacy of *d,l-threo*-MPH reside in the *d-threo* enantiomer, with improvement in sustained attention attributed to treatment with equimolar doses of *d*-MPH and *d,l*-MPH, but not with *l*-MPH (Srinivas et al. 1992).

*d*-MPH (Focalin™) is a chirally pure refinement of *d,l*-MPH. Because *d*-MPH does not racemize after oral administration (Srinivas et al. 1992), administration of doses lower than currently used for the racemate may be possible without reducing efficacy or increasing adverse events (AEs). In another phase III trial (Wigal et al. 2004), *d*-MPH was significantly more effective than placebo in treating ADHD symptoms. Compared to *d,l*-MPH doses containing the same amount of *d*-MPH, *d*-MPH showed similar efficacy and a nominally longer duration of action: at 6 hours postdose, *d*-MPH but not *d,l*-MPH was still significantly better than placebo on parent-rated ADHD symptoms and on a timed arithmetic test (Wigal et al. 2004). No AEs unique to chirally pure *d*-MPH were reported.

This study was intended to complement the above study. The primary aim of this study was to determine the placebo-controlled efficacy of twice-daily dosing with *d*-MPH in sustaining a reduction of ADHD symptoms through the 7th and 8th week in children who were responding to *d*-MPH. A secondary aim was to confirm the 6-hour duration of efficacy found in the placebo-controlled comparison to *d,l*-MPH (Wigal et al. in press).

## Methods

### *Subjects*

Subjects were children and adolescents 6–17 years of age enrolled in school (minimum, Grade 1) who met the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) for any of the three ADHD subtypes (predominantly inattentive,

predominantly hyperactive/impulsive, or combined) (American Psychiatric Association 1994). Diagnosis was confirmed by the Diagnostic Interview Schedule for Children version IV (DISC-IV) administered to parents (Shaffer et al. 2000). Concurrent treatment with other psychoactive medication was not allowed, and patients were withdrawn from other ADHD medications during screening and for 48 hours before baseline. Patients needed to be within 30% of normal body weight and able to participate for the full 8 weeks.

Exclusion criteria included history or evidence of cardiovascular, renal, respiratory (other than asthma/allergy), endocrine, or immune system disease; history of substance abuse; hypersensitivity to *d,l*-MPH or other stimulants; treatment with any investigational drug within 30 days of screening; other significant central nervous system disorders; and treatment with antidepressants, neuroleptics/antipsychotics, mood stabilizers, anticonvulsants, beta blockers, $alpha_2$ agonists, other stimulants, thyroid medications, chronic oral steroids, or sedatives/hypnotics.

Informed consent was obtained from the parent/guardian, and verbal or written assent was obtained from the participant. The protocol was approved by each center's institutional review board and carried out according to the Declaration of Helsinki.

Subjects were prematurely terminated if AEs or classroom behavior became intolerable. In addition, if therapeutic response, defined as Clinical Global Impression—Improvement (CGI-I) of 1 or 2, was not evident with *d*-MPH at 20 mg daily during the initial 6-week, open-label phase, the participant was considered a therapeutic failure and discontinued**.**

### *Study Design*

This 7-center U.S. study (Table 1) consisted of a 6-week, open-label, dose-titration phase (Part A) and a 2-week, double-blind, randomized, placebo-controlled withdrawal (Part B). An open-label extension of up to 44 weeks (Part C) will be pooled with two other open-label studies for analysis and reporting.

After an initial screening (Visit 1), which included a medical history, physical examination, clinical laboratory studies, and recording of concomitant medications, eligible children entered a 6-week, open-label, dose-titration phase. Baseline evaluations were completed and *d*-MPH titration was initiated at Visit 2, after all other medications for ADHD were discontinued for at least 48 hours. *d*-MPH was initiated in doses ranging from 2.5 to 10 mg twice-daily, depending on individual subjects' prior medication experience. Children who had received *d,l*-MPH began with half their total daily *d,l*-MPH dose administered as *d*-MPH, but not more than 20 mg/day; those who had not previously received *d,l*-MPH started *d*-MPH at 2.5 mg twice daily.

During the first 4 weeks, *d*-MPH was titrated to one of three benchmarks: 1) a maximum of 20 mg/day, 2) dose-limiting AEs, or 3) achievement of a CGI-I score of 1 or 2: "very much improved" or "much improved." Even if a CGI-I of 1 or 2 was not achieved by the 4th week, subjects continued on the dose administered in week 4 for the remainder of Part A to stabilize the response.

Subjects were seen weekly for efficacy assessments (Table 1); physical examinations relevant to any complaint; and review of concomitant medications, concurrent illness, and other AEs.

In the interval between visits, teachers rated children's symptoms of ADHD twice a week in the afternoon using the Swanson, Nolan, and Pelham (SNAP)-ADHD Rating Scale (Swanson et al. 2001). On Saturdays and Sundays, parents rated their child's ADHD symptoms on the SNAP-ADHD twice-daily, at 3 p.m. (approximately 3 hours after the second *d*-MPH dose) for

the day and at 6 p.m. for the previous 2 hours. During the final 2 weeks of Part A, a timed Math Test was also administered at home on Saturday and Sunday approximately 6 hours after the second daily *d*-MPH dose, as was done at the afternoon clinic visit.

For the 2-week, double-blind withdrawal phase (Part B), subjects having a CGI-I of 1 or 2 at the end of Part A were randomized to either continue on *d*-MPH at the same dose as during the final 2 weeks of Part A or to receive placebo. (Those who had not achieved a CGI-I of 1 or 2 were dropped from the study and treated clinically.) At weekly visits, the CGI-I and Math Tests were administered, along with a physical examination and review of concomitant medications, concurrent illness, and AEs. Between visits, the Teacher and Parent SNAP-ADHD ratings and weekend 6 p.m. Math Test were completed, as in Part A.

| *Duration* | *2-14 days* | *6 weeks* | | | | | | | *2 weeks* | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | *Part A: Open-label dose-titration phase* | | | | | | | *Part B: Double-blind withdrawal phase* | |
| *Phase of study* | *Screening period* | *Titrate* | | | | *Optimal dose* | | | | |
| Visit* | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8[†] | 9 | 10[‡] |
| Begin Study Week | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | |
| Weeks on Treatment | | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| CGI-S | | ◆ | | | | | | ◆ | | |
| CGI-I | | | ◆ | ◆ | ◆ | ◆ | ◆ | ◆ | ◆ | ◆ |
| Math Test (Home) 6 p.m. | | | | | | | ◆ | ◆ | ◆ | ◆ |
| Math Test (Clinic) 3 p.m. | | | | | | | ◆ | ◆ | ◆ | ◆ |
| Teacher SNAP-ADHD[§] | | | ◆ | ◆ | ◆ | ◆ | ◆ | ◆ | ◆ | ◆ |
| Parent SNAP-ADHD[‖] | | | ◆ | ◆ | ◆ | ◆ | ◆ | ◆ | ◆ | ◆ |

**Table 1.**Study design and schedule of outcome measures

Results of a 7-center, 8-week study consisting of a 6-week open-label, dose-titration phase (Part A) and a 2-week, double-blind, randomized, placebo-controlled withdrawal (Part B).

CGI-S, Clinical Global Impression—Severity of Illness Scale; CGI-I, Clinical Global Impression—Improvement Scale; SNAP-ADHD, Swanson, Nolan, and Pelham—Attention Deficit Hyperactivity Disorder symptom scale.

*Visits were to occur within 0.5–3 hours of the child ingesting the study medication. The interval between Visits 1 and 2 was preferably 4–7 days; however, it could be 2–14 days. All other visits were ±2 days when weekly.

[†]Randomization occurred at the end of Visit 8.

[‡]The end of Part B was Visit 10, or Visit 9 if patient stopped study after Visit 9.

[§]To be recorded twice weekly by the teacher at school in the afternoon during the week preceding the listed clinic visit.

[‖]To be recorded twice by the parent on the weekend preceding the listed clinic visit.

### *Efficacy Measures*

The primary efficacy variable was the percentage of treatment failures at the end of Part B, defined as a CGI-I score of 6 or 7 (“much worse” or “very much worse”) relative to Visit 8 (week 6, the end of the initial open treatment). The primary duration-of-effect variable was the objective 6 p.m. Math Test, the only measure specific to 6 p.m. It is more relevant than the parent ratings made at the same time both because it is more objective and because it is more specific to the exact time: Parent ratings were influenced by behavior over the preceding 2 hours. Secondary efficacy variables included the change from baseline (end of titration) to the end of Part B in the Teacher and Parent SNAP ratings and mid-afternoon, clinic-based Math Test scores.

The CGI-I, completed by the investigator, uses a 7-point scale as an index of change in the child's behavioral symptoms, ranging from "very much improved" (1) to "very much worse" (7). CGI-I scores were based on scores from at least one Teacher SNAP-ADHD, one Parent 3 p.m. SNAP-ADHD, and an interview with the parent and child, which, during Part A, were compared to the same data from the original baseline and, during Part B, were compared to the same data from the end of Part A, after the child had been on the effective dose for at least 2 weeks. The CGI—Severity (CGI-S) was administered twice during Part A, initially to verify that the patient's illness severity warranted pharmacological treatment. The CGI-S is a 7-point scale, ranging from "normal, not at all [ill]" (1) to "among the most severely ill patients" (7) (Guy 1976).

The SNAP-ADHD rating scale consists of 18 questions similar in wording to the diagnostic symptoms for ADHD in the DSM-IV (Gaub and Carlson 1997; www.adhd.net). Parents and teachers completed evaluation forms. For each question, the teacher or parent indicated whether the symptom described the child "not at all" (0) to "very much" (3). Weekly scores were computed as the average per item, averaged separately for the Teacher and Parent SNAP-ADHD.

The Math Test consisted of 300 problems (60 problems at each grade level, 1 through 5). Patients had 10 minutes to complete the test (without encouragement), which was designed so that all children could solve at least some problems and no one was likely to finish all. The score was the number of correct answers. Baseline scores were derived from an average of scores on Visits 7 and 8 (last 2 weeks of the initial Part A open treatment). Treatment scores were averages of Visits 9 and 10 (double-blind weeks) or just Visit 9 if the patient discontinued. Results were interpreted as the ability to focus and perform academic seat work, and not mathematical aptitude (see Swanson et al. 1998 for use of the math test [PERMP, or permanent product] as an objective measure of time-course effects).

### *Safety assessments*

The safety of *d*-MPH was assessed by monitoring AEs and changes from baseline in vital signs, physical examination, and clinical laboratory parameters throughout the study. Also recorded were the number of children who discontinued because of AEs, the incidence and severity of each AE, action taken, and relationship to study drug.

Laboratory evaluations included complete blood count with hemoglobin and hematocrit; serum chemistries, including liver function tests, glucose, electrolytes, albumin, total protein, total bilirubin, uric acid, and alkaline phosphatase; and urinalysis, including ketones, bilirubin, glucose, and protein. A urine pregnancy test was administered at the final study visit to females who reached menarche.

### *Study drug*

To maintain blinding, *d*-MPH was available in tablet strengths of 2.5, 5, and 10 mg, each identical in appearance to a matching placebo. Patients received a total *d*-MPH dose ranging from 2.5 to 10 mg twice daily.

Study drug (or placebo) was dispensed in bottles containing a weekly supply, labeled for use at "Home" and "School," with the strength designated "A," "B," or "C." The initial dose was 2.5 mg twice-daily for treatment-naïve patients and one half the *d,l*-MPH dose (5 or 10 mg) twice-daily for previously treated patients. In Part B, patients/guardians and medical personnel were blinded to the drug. Parents/ guardians were instructed to administer a single tablet between 7 a.m. and 8 a.m. and a single tablet between 11:30 a.m. and 12 p.m.

### *Statistical methods*

Analysis of efficacy parameters used the intent- to-treat sample: Patients who received *d*-MPH and had a Part B baseline efficacy evaluation and at least one postbaseline assessment. Except for the Math Test, low values indicated greatest therapeutic benefit. Analysis of variance (ANOVA) blocked by site was used for between-group comparisons of continuous efficacy variables and baseline demographics. Categorical and/or ordinal efficacy variables and demographic baseline variables between groups were assessed with Cochran Mantel Haenszel tests stratified by site. Categorical variables, assumed *a priori* to have very small counts in some cells, were evaluated by a Fisher's Exact test.

Safety evaluations included all patients who received at least 1 *d*-MPH dose. Analyses of AEs, laboratory values, and vital signs used descriptive rather than inferential statistics.

## Results

### *Patients*

Of 116 patients screened for enrollment, 89 patients (76.7%) passed all screening, qualified at baseline, and entered Part A (72 boys [80.9%] and 17 girls [19.1%]). ADHD Combined Type was the most common (80%), with 71.9% of patients treatment-naïve. CGI-S scores at baseline showed significant impairment: 1 patient was borderline, approximately half (51.7%) were moderate, and the others were markedly (29.2%) or severely (18.0%) ill.

Thirteen of 89 patients discontinued treatment during Part A because of therapeutic failure (4 patients), AEs (4), lost to follow-up (3), withdrawal of consent (1), or protocol violation (1). Because nonresponders dropped out in the first 6 weeks, the 76 subjects who successfully completed Part Aappeared to make an 85.3% response rate, but because of missing data, only 73 responders had CGI-I ratings of 1 or 2, making for a technical response rate of 82%. Of these 76 responders, 75 entered Part B; the other patient discontinued before Part B because of AEs (headache, insomnia, and rash). Two patients (1 patient per treatment group) did not complete Part B; 1 patient switched to open-label *d*-MPH after 1 week because of poor behavior and 1 patient received only one assessment during 9 days of double-blind treatment.

Demographic and baseline clinical characteristics of patients entering Part B are listed in Table 2. Treatment groups were similar in age, gender, ethnicity, and ADHD type. There were slightly more treatment-naïve patients receiving *d*-MPH than placebo. By Part B (i.e., following 6 weeks of open treatment with *d*-MPH), most patients demonstrated mild-to-no ADHD behavioral symptoms (88.6% of patients subsequently randomized to *d*-MPH; 87.5% of patients subsequently randomized to placebo). Part B baseline scores on outcome measures were similar between groups. Part B baseline use of concomitant medications (antihistamines, nonsteroidal anti-inflammatory agents, multivitamins, nasal decongestants, or other analgesics or antipyretics) was also similar, with use in 34.3% of *d*-MPH patients and 40.0% of placebo patients.

| *Characteristic* | d-*MPH* n = *35* | *Placebo* n = *40* |
|---|---|---|
| Age, years | | |
| Mean ± SD | 10.1 ± 2.9 | 9.9 ± 2.7 |
| Range | 6-16 | 6-16 |
| Gender, *n* (%) | | |
| Male | 30 (85.7) | 31 (77.5) |
| Female | 5 (14.3) | 9 (22.5) |
| Ethnicity, *n* (%) | | |

| | | |
|---|---|---|
| Caucasian | 28 (80.0) | 30 (75.0) |
| African-American | 5 (14.3) | 5 (12.5) |
| Hispanic | 2 (5.7) | 5 (12.5) |
| ADHD type, *n* (%) | | |
| Inattentive | 7 (20.0) | 8 (20.0) |
| Combined (Inattentive + Hyperactive/Impulsive) | 28 (80.0) | 32 (80.0) |
| Stimulant naïve, *n* (%) | 29 (82.9) | 25 (62.5) |
| CGI-S, *n* (%) | | |
| Normal, not at all ill | 8 (23.5) | 5 (12.5) |
| Borderline mentally ill | 15 (44.1) | 15 (37.5) |
| Mildly ill | 8(23.5) | 15 (37.5) |
| Moderately ill | 3 (8.8) | 4 (10.0) |
| Markedly ill | 0 | 1 (2.5) |
| Severely ill | 0 | 0 |
| Extremely ill | 0 | 0 |
| Teacher SNAP-ADHD, Mean ± SD* | 0.7 ± 0.7 | 0.7 ± 0.7 |
| Parent SNAP-ADHD, Mean ± SD* | | |
| 3 p.m. (average) | 0.6 ± -0.4 | 0.4 ± 0.3 |
| 6 p.m. (average) | 0.7 ± 0.6 | 0.7 ± 0.6 |
| 3 p.m. Office Math Test, Mean Correct ± SD* | 122.9 ± 57.7 | 120.1 ± 59.5 |
| 6 p.m. Home Math Test, Mean Correct ± SD* | 121.2 ± 55.4 | 120.8 ± 64.4 |
| Patients taking 10 mg d-MPH b.i.d., n (%) | 24 (70.6) | 32 (80.0) |

**Table 2.** Baseline (Visit 8, end of part A, beginning of double-blind placebo discontinuation) Demographic and clinical characteristics of subjects randomized in part B

Demographic and baseline clinical characteristics for the 2-week, double-blind, randomized, placebo-controlled withdrawal group (Part B). By this point (i.e., following 6 weeks of open treatment with *d*-MPH), most patients demonstrated mild to no ADHD behavioral symptoms (88.6% of patients subsequently randomized to *d*-MPH; 87.5% of patients subsequently randomized to placebo).

*d*-MPH, *d*-methylphenidate; SD, standard deviation; ADHD, attention deficit hyperactivity disorder; CGI-S, Clinical Global Impression—Severity of Illness Scale; SNAP-ADHD, Swanson, Nolan, and Pelham—Attention Deficit Hyperactivity Disorder symptom scale.

*Ns varied according to outcome measure.

### *Doses*

Most patients (86.5%) started *d*-MPH at 2.5 mg twice-daily. With weekly dose escalation, 83.9% of patients took 5 mg twice-daily after 1 week and 70.2% of patients took 10 mg twice-daily after the 2nd week. Most patients were maintained on 10 mg twice-daily for the remainder of Part A. At the baseline visit of the withdrawal phase (Part B), 70.6% and 80.0% of *d*-MPH and placebo patients, respectively, were dispensed doses of 10 mg twice-daily. At the last visit of Part B, 68.6% of *d*-MPH continuers and 79.5% of placebo patients were ostensibly receiving 10 mg twice-daily.

### *Efficacy*

Results for primary and secondary efficacy variables are listed in Table 3. There were significantly more treatment failures (CGI-I of 6 or 7, much worse or very much worse) at the end of Part B in the placebo group than in the *d*-MPH group (61.5% versus 17.1%; $p = 0.001$). Even if treatment failure were redefined to include the score of 5 (slightly worse) on the CGI-I, there were still significantly more treatment failures (CGI-I of 5, 6, or 7) in the placebo group than in the *d*-MPH group (71.8% versus 45.8%; $p = 0.0235$). Baseline illness severity was not predictive of medication response. There was also significantly more deterioration in the 6 p.m.

Math Test for placebo patients (mean of 17.2 fewer correct answers, compared to 1.2 fewer for *d*-MPH patients, $p < 0.0001$), demonstrating a 6-hour duration of significant benefit.

| *Endpoint measure** | d-*MPH* | *Placebo* | P *value* |
|---|---|---|---|
| *CGI-I Scores of 6 or 7* | | | |
| End of 1 week of Part B, *n* (%) | 5/35 (14.3) | 22/40 (55.0) | __ |
| Treatment failure** (end of 2 weeks), *n* (%) | 6/35 (17.1) | 24/39 (61.5) | 0.0010 |
| *Teacher SNAP-ADHD* | | | |
| Baseline (Visit 8,end of Part A), Mean ± SD | 0.7 ± 0.7 | 0.7 ± 0.7 | __ |
| End of withdrawal phase (Visit 10), Mean ± SD | 0.7 ± 0.7 | 1.4 ± 0.9 | __ |
| Change from baseline, Mean ± SD† | 0 ± 0.7 | 0.7 ± 0.8 | 0.028 |
| *Parent SNAP-ADHD, 3 p.m.* | | | |
| Baseline (Visit 8, end of Part A), Mean ± SD | 0.6 ± 0.4 | 0.4 ± 0.3 | __ |
| End of withdrawal phase (Visit 10), Mean ± SD | 0.8 ± 0.7 | 1.3 ± 0.9 | __ |
| Change from baseline, Mean ± SD† | 0.2 ± 0.6 | 0.8 ± 0.8 | 0.0026 |
| *Parent SNAP-ADHD, 6 p.m.* | | | |
| Baseline (Visit 8, end of Part A), Mean ± SD | 0.7 ± 0.6 | 0.7 ± 0.6 | __ |
| End of withdrawal phase (Visit 10), Mean ± SD | 0.9 ± 0.7 | 1.4 ± 1.0 | __ |
| Change from baseline, Mean ± SD† | 0.1 ± 0.5 | 0.6 ± 0.8 | 0.0381 |
| *Deterioration on Math Test, Mean ± SD‡* | | | |
| Office-based 2-3 p.m. | 0.9 ± 16.9 | -11.7 ± 22.0 | 0.024 |
| Home-based 6 p.m. | -1.2 ± 17.5 | -17.2 ± 35.6 | <0.0001 |

**Table 3.** Results from double-blind withdrawal phase (part B)

Results for efficacy variables. Overall, the placebo group experienced significantly more treatment failures than the *d*-MPH group at the end of Part B, including deterioration in the 6 p.m. Math Test and the Teacher SNAP-ADHD and both the 3 p.m. and 6 p.m. Parent SNAP-ADHD scores.

*d*-MPH, *d*-methylphenidate; SNAP-ADHD, Swanson, Nolan, and Pelham–Attention Deficit Hyperactivity Disorder symptom scale; SD, standard deviation.

*Ns varied according to outcome measure.

†Mean change from baseline (Visit 8) to the end of the double-blind phase (Visit 10).

‡Mean change from average Visits 7 and 8 compared with average Visits 9 and 10.

** Treatment failure = Clinical Global Impression—Improvement Scale (CGI-I) of 6 or 7 at end of 2-week withdrawal phase compared to end of 6 weeks of open treatment.

During Part B, placebo patients showed a significant deterioration from baseline in performance versus *d*-MPH patients on all secondary efficacy variables, including the Teacher SNAP-ADHD ($p = 0.028$) and both the 3 p.m. and 6 p.m. Parent SNAP-ADHD scores (Fig. 1; $p = 0.0026$ and $p = 0.0381$, respectively).

On the clinic-based 2 p.m.–3 p.m. Math Test, placebo patients demonstrated a mean of 11.7 fewer correct answers than at baseline versus a mean of 0.9 more correct answers by *d*-MPH patients ($p = 0.024$). For all efficacy variables, *d*-MPH patients continued to demonstrate the stable benefit obtained during the open-label titration phase, and the magnitude of the effect at 6 hours after the noon dose was similar to the effect at 3 hours (Table 3 and Fig. 1).

In reference to additional efficacy variables, of 74 patients who had CGI ratings at the final open-label titration phase Part A visit, 73 patients (98.6%) were classified as responders based on a CGI-I score of “very much improved” or “much improved.” Significant improvement

in CGI-S score distribution was noted at the end of Part A, with 89.2% of patients judged normal to mildly ill versus 1.1% at baseline ($p < 0.001$). Mean Teacher SNAP-ADHD scores improved from 1.4 at baseline to 0.7 at Visit 8, while both 3- and 6-hour post-dose Parent SNAP-ADHD baseline scores (1.5 and 1.6, respectively) showed a steady improvement during *d*-MPH titration (to 0.6 and 0.8, respectively).

### *Safety of* d-*MPH*

No deaths and no serious treatment-related AEs occurred during the study. The only serious AE was a baseball injury unrelated to treatment. Seventy-seven of 89 patients (86.5%) experienced one or more AE during Part A (Table 4), although no conclusions can be made regarding their relationship to treatment. Two patients in Part A experienced AEs considered both severe and treatment-related (rambling speech and tremor in 1 patient and labile mood in the other), and both discontinued the study. Two additional patients discontinued because of AEs during this phase (1 patient for moderate headaches and another patient for sleep terrors with sleepwalking). Dosage reductions were made in 8 patients as a result of tremor and anergy, gastrointestinal distress, headache and insomnia, unusual sensory experience, nausea, irritability, hypertension (believed to be the result of a discontinuation of verapamil), and emesis and diarrhea. Following dose reduction, AEs resolved for the patients experiencing gastrointestinal distress, unusual sensory experience, nausea, irritability, and emesis and diarrhea. Headaches, but not insomnia, resolved following dose reduction in the patient experiencing those AEs.

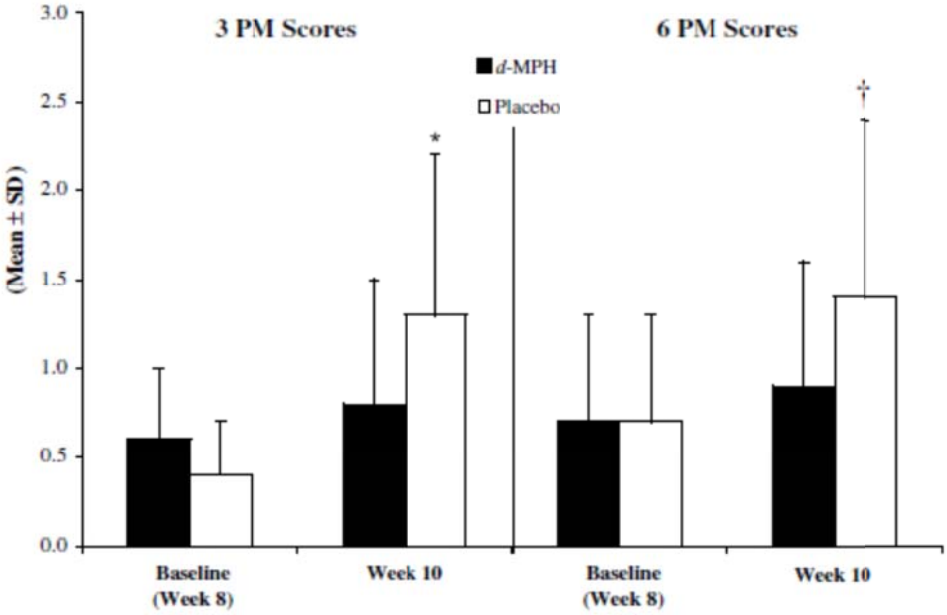


**FIG. 1.** Parent SNAP-ADHD scores (mean ± SD) for *d*-MPH and placebo patients: Part B. Both 3- and 6-hour post-dose Parent SNAP-ADHD baseline scores (1.5 and 1.6, respectively) showed a steady improvement during *d*-MPH titration (to 0.6 and 0.8, respectively). Double-blind parent ratings worsened for both placebo and active *d*-MPH at both 3 p.m. and 6 p.m., possibly the result of parental knowledge that treatment was withdrawn. *d*-MPH, *d*-methylphenidate; SNAP-ADHD, Swanson, Nolan, and Pelham–Attention Deficit Hyperactivity Disorder symptom scale; SD, standard deviation. *$p = 0.0026$ versus *d*-MPH for mean change from baseline (Visit 8) to the end of Part B (Visit 10) for 3 p.m. scores. †$p = 0.0381$ versus *d*-MPH for mean change from baseline (Visit 8) to the end of Part B (Visit 10) for 6 p.m. scores.

In Part B, approximately 46% of *d*-MPH patients and 38% of placebo patients experienced at least one AE, which were generally mild. Abdominal pain and headache were the most common. Insomnia, known to be associated with stimulant use, was reported only in patients receiving placebo; headache incidence also was greater in placebo patients. No patient experienced an AE judged both severe and treatment-related. No patient discontinued the study because of an AE during this phase, and no dosage reductions were required for AEs. Abrupt *d*-MPH discontinuation at the start of the randomized withdrawal phase was *not* associated with drug-related rebound or withdrawal symptoms.

| | | *Part B: Double-Blind withdrawal* | |
|---|---|---|---|
| *AE. n (%)* | *Part A: open-label titration n = 89* | *d-MPH n = 35* | *Placebo n = 40* |
| Headache | 24 (27.0) | 2 (5.7) | 3 (7.5) |
| Viral infection | 18 (20.2) | 0 | 0 |
| Anorexia | 16 (18.0) | 0 | 0 |
| Insomnia | 16 (18.0) | 0 | 2 (5.0) |
| Abdominal pain | 15 (16.9) | 3 (8.6) | 0 |
| Accidental injury | 10 (11.2) | 0 | 0 |
| Pharyngitis | 10 (11.2) | 0 | 0 |
| Asthenia | 7 (7.9) | 0 | 0 |
| Fever | 7 (7.9) | 0 | 0 |
| Nausea | 7 (7.9) | 0 | 0 |
| Cough increased | 7 (7.9) | 2 (5.7) | 0 |
| Dyspepsia | 6 (6.7) | 0 | 0 |
| Rash | 6 (6.7) | 0 | 0 |
| Rhinitis | 5 (5.6) | 0 | 2 (5.0) |
| Pain | 3 (3.4) | 0 | 2 (5.0) |
| Vomiting | 3 (3.4) | 0 | 0 |
| Weight loss | 3 (3.4) | 0 | 0 |
| Chest pain | 0 | 2 (5.7) | 0 |
| Gastroenteritis | 0 | 0 | 0 |
| Sinusitis | 0 | 0 | 0 |
| Otitis media | 0 | 0 | 0 |

**Table 4.** Adverse events that occurred in at least 5% of patients in any one treatment group: Study phases A and B

Adverse events that occurred during treatment. Although 77 of the 89 patients (86.5%) experienced one or more AE during Part A, no deaths or serious treatment-related AEs occurred. Dosage reductions resolved most AEs. AE, adverse event; *d*-MPH, *d*-methylphenidate.

Clinically trivial mean increases in pulse rate (PR) and blood pressure (BP) were noted in both treatment groups in relation to baseline. A few PR and BP changes met technical criteria for clinically significant change, but most of these were *lower* and benign (exceptions noted below).

- During Part A, mean systolic BP (SBP) rose 2.6 ± 10.8 mm Hg, diastolic BP (DBP) rose 0.86 ± 0.8 mm Hg, and PR rose 3.7 ± 12.7 bpm, as would be expected with stimulant treatment. Three patients had transient hypertension and 2 patients had transient increases of PR to 120 bpm.

- During Part B, the BP rise from original baseline was nominally lower in *d*-MPH versus placebo patients (SBP 2.6 ± 11.6 versus 3.1 ± 9.5; DBP 0.0 ± 7.1 versus 0.2 ± 6.8). PR increase from original baseline was 5.4 ± 12.2 (versus 1.9 ± 10.7 in the placebo group).

There was no evidence of clinically significant treatment-related changes in hematologic or blood-chemistry parameters.

**Discussion**

This study evaluated the safety, efficacy, and duration of effect of *d*-MPH in maintaining improvement in ADHD in children who respond to this agent. Efficacy data are based on 75 patients randomized to *d*-MPH or placebo during Part B.

Patients receiving *d*-MPH in doses of 5–20 mg/day in Part A showed substantial improvement from baseline. The parent and teacher SNAP-ADHD mean ratings of 0.6–0.8 are essentially normal. These mean item ratings are between "no symptom at all" and "just a little." The National Institute of Mental Health (NIMH) Multimodal Treatment Study of Children with ADHD (MTA) used a SNAP item mean of 1.0 or less as a measure of normalization (Swanson et al. 2001). The CGI-S ratings at 6 weeks were consistent with the parent and teacher ratings: 89.2% of patients were mildly ill, borderline ill, or normal, compared to only 1.1% at baseline.

During Part B, the proportion of treatment failures in the placebo group (61.5%) was 3.6 times as great as in the *d*-MPH group (17.1%; $p = 0.001$). Behavioral scores based on the Teacher and Parent SNAP-ADHD also deteriorated significantly in placebo-treated, but not *d*-MPH–treated, patients during this phase. In fact, patients maintained on *d*-MPH throughout Part B had no or mild behavioral symptoms on Parent and Teacher SNAP-ADHD tests measured both 3 and 6 hours after taking *d*-MPH. CGI scores in this group also remained generally stable, maintaining the improvement from original baseline noted at the start of Part B. A dramatic clinical improvement in the placebo-treated patients was observed following the resumption of *d*-MPH treatment in the open extension.

Of considerable interest is *d*-MPH's duration of action of at least 6 hours, supported by differences between the treatment and placebo groups (favoring *d*-MPH) in the 6-hour post-dose weekend Math Test and the 6-hour postdose Parent SNAP-ADHD scores. The behavioral scores based on the Teacher and Parent SNAP-ADHD were consistent with children having no or negligible symptoms (SNAP score, <1.0) when measured at both 3 hours (0.7 and 0.8) and 6 hours (0.85) after taking *d*-MPH. In contrast, the comparable scores for the placebo group were 1.2–1.3 and 1.4. The latter scores replicate other reports of placebo-controlled natural deterioration in ADHD behavior in the late afternoon (e.g., Wigal et al. 2004).

AEs were consistent with those of other stimulant medications. No serious AEs were considered treatment-related (one serious AE—an accidental injury—occurred during Part B and was considered unrelated to treatment). Data from this study are consistent with the results of the earlier randomized, placebo-controlled phase III trial comparing efficacy of *d*-MPH and *d,l*-MPH over 4 weeks in children with ADHD (Wigal et al. 2004). In that study, the Teacher SNAP-ADHD score, the primary efficacy variable, was significantly improved by both active treatments versus placebo. Both active drugs also improved the secondary measures of CGI-I, Parent 3 p.m. SNAP-ADHD, and 3 p.m. Math Test versus placebo. However, only *d*-MPH improved Parent SNAP-ADHD and Math Test scores at 6 hours postdosing, demonstrating a nominally longer duration of efficacy than *d,l*-MPH, which showed a nonsignificant tendency in the same direction, compared to placebo. The data from this study confirm a duration of efficacy of at least 6 hours for *d*-MPH after the 2nd daily dose.

The randomized withdrawal approach used in this study is especially suitable for drugs such as *d*-MPH that can suppress symptoms or signs of a chronic illness (U.S. Department of Health and Human Services 2001). The withdrawal study becomes, in effect, a relapse-prevention trial. This design is appropriate for ADHD, in which long-term, placebo-controlled trials would be especially difficult for patient and caregiver. When used with an early-escape endpoint, the period of exposure to placebo with poor response is minimized. Prompt monitoring of study endpoints ensures that treatment failures are rapidly identified.

This study design has some potential limitations. Patients could develop withdrawal signs or symptoms, although none were noted. There is a scientific risk that the expected deterioration on placebo may not occur, at least not as quickly as anticipated. Although it is widely accepted that withdrawal of stimulant in ADHD precipitates prompt relapse, the published documentation is less abundant than the belief, and some reports actually suggest the contrary (e.g., Gillberg et al. 1997; Abikoff and Gittelman 1985). More importantly, treatment effects in such trials may be larger than those seen in unselected populations, because the randomized withdrawal phase preselected responders to the drug from the open-label titration phase (U.S. Department of Health and Human Services 2001). The result is similar to, but the mechanism different from, the increase in evident placebo-controlled responders after a placebo washout. In both cases, the difference between placebo and active treatment is enhanced: With a placebo washout, placebo responders are eliminated, reducing the number of placebo responders in the randomized sample; in contrast, with a discontinuation study of responders, nonresponders are eliminated before randomization. Those who were randomized in Part B included placebo responders and true responders, but not nonresponders. On the other hand, the tendency for placebo discontinuation studies to inflate the responder rate may be neutralized, to some extent, by "negative placebo effect," in which parent and teacher ratings of a child continuing active treatment may deteriorate from the knowledge that the child might be having helpful treatment withdrawn. This phenomenon is illustrated in Fig. 1, showing that the double-blind parent ratings worsened for both placebo and active *d*-MPH at both 3 p.m. and 6 p.m., although significantly less for *d*-MPH. Note that the same phenomenon is not nearly as apparent in the more objective Math Tests (Table 3).

Another possible limitation is the duration of the discontinuation (2 weeks). Abikoff and Gittelman (1985) noted in a placebo discontinuation after 16 weeks of *d,l*-MPH treatment that it took over 2 weeks, on average, for patients to deteriorate enough on placebo to need remedication. Conceivably, the proportion of relapses on placebo might have been greater if the discontinuation had been extended for another week. However, comparison of the proportion of relapsers in weeks 1 and 2 of this study suggests that a plateau had been reached by week 2.

A possible criticism of the statistical analyses is that the Bonferroni correction for multiple tests was not used. One might argue that with 6 outcome tests for Part B, the required significance level should be divided by 6. A more realistic argument would be that each domain with multiple measures should have such correction: behavior ratings (3 measures) divided by 3 and objective Math Test (2 measures) divided by 2. However, with the two critical outcome measures significant at 0.001 (percent treatment failure) and <0.0001 (6 p.m. Math Test), and with all measures showing a large effect size, the issue seems moot.

## Conclusions

In summary, this study confirms earlier observations that the *d*-enantiomer of *d,l*-MPH is effective in the treatment of childhood ADHD, and that there is no need to compensate for the loss of *l*-enantiomer "activity." This observation contrasts with amphetamine, in which both

enantiomers are approximately equipotent for behavioral benefit (Arnold et al. 1972; Arnold et al. 1976).

More importantly for clinicians, this study demonstrates a duration of effect of at least 6 hours. This effect allows for an additional option besides the usually quoted 4-hour duration of immediate-release *d,l*-MPH and the long-acting bead or osmotic tablet preparations.

## Acknowledgements

The study was supported by the Celgene Corporation. Drs. Arnold, Wigal, and Bohan received research funding from Celgene for the study reported; Dr. Wigal and Dr. West are on the Advisory Panel and Speakers Bureau for Novartis; Dr. Arnold and Dr. Bohan are on the Speakers Bureau for Novartis; Dr. Zeldis is Chief Medical Officer and Vice President for Medical Affairs at the Celgene Corporation.

## References

Abikoff H, Gittelman R: Hyperactive children treated with stimulants. Is cognitive training a useful adjunct? Arch Gen Psychiatry 42:953–961, 1985.

American Academy of Pediatrics: Clinical Practice Guideline: Treatment of the school-aged child with attention deficit hyperactivity disorder. Pediatrics 108:1033–1044, 2001.

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV). Washington (DC), American Psychiatric Association, 1994, pp. 78–85.

Arnold LE, Huestis RD, Smeltzer DJ, Scheib J, Wemmer D, Colner G: Levoamphetamine versus dextroamphetamine in minimal brain dysfunction. Replication, time response, and differential effect by diagnostic group and family rating. Arch Gen Psychiatry 33:292–301, 1976.

Arnold LE, Wender PH, McCloskey K, Snyder SH: Levoamphetamine and dextroamphetamine: Comparative efficacy in the hyperkinetic syndrome. Assessment by target symptom. Arch Gen Psychiatry 27:816–822, 1972.

Dulcan M: Practice parameters for the assessment and treatment of children, adolescents, and adults with attention deficit hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 36(Suppl 10):85S–121S, 1997.

Elia J, Ambrosini PJ, Rapoport JL: Treatment of attention deficit hyperactivity disorder. N Engl J Med 340:780–788, 1999.

Gaub M, Carlson CL: Behavioral characteristics of DSM-IV ADHD subtypes in a school-based population. J Abnorm Child Psychol 25:103–111, 1997.

Gillberg C, Melander H, von Knorring A-L, Janols L-O, Thernlund G, Hagglof B, Eidevall-Wallin L, Gustafsson P, Kopp S: Long-term stimulant treatment of children with attention deficit hyperactivity disorder symptoms. A randomized, double-blind, placebo-controlled trial. Arch Gen Psychiatry 54:857–864, 1997.

Goldman LS, Genel M, Bezman RJ, Slanetz PJ: Diagnosis and treatment of attention deficit hyperactivity disorder in children and adolescents. JAMA 279:1100–1107, 1998.

Guy W: Assessment Manual for Psychopharmacology (revised). Rockville (Maryland), U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institutes of Mental Health, Pharmacology Branch, 1976.

Jadad AR, Boyle M, Cunningham C, Kim M, Schachar R: Treatment of attention deficit hyperactivity disorder. Evidence Report/Technology Assessment No. 11. AHRQ Publication No. 00-E005. Rockville (Maryland), U.S. Department of Health and Human Services, Agency for Healthcare Research and Quality, 1999.

Kimko HC, Cross JT, Abernethy DR: Pharmacokinetics and clinical effectiveness of methylphenidate. Clin Pharmacokinet 37:457–470, 1999.

National Institutes of Health: Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder (ADHD). NIH Consensus Statement. Bethesda (Maryland), National Institutes of Health, 1998.

Patrick KS, Caldwell RW, Ferris RM, Breese GR: Pharmacology of the enantiomers of threo-methylphenidate. J Pharmacol Exp Ther 241: 152–158, 1987.

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 39: 28–38, 2000.

Srinivas NR, Hubbard JW, Quinn D, Midha KK: Enantioselective pharmacokinetics and pharmacodynamics of dl-threo-methylphenidate in children with attention deficit hyperactivity disorder. Clin Pharmacol Ther 52:561–568, 1992.

Swanson JM, Kraemer HC, Hinshaw SP, Arnold LE, Conners CK, Abikoff HB, Clevenger W, Davies M, Elliott GR, Greenhill LL, Hechtman L, Hoza B, Jensen PS, March JS, Newcorn JH, Owens EB, Pelham WE, Schiller E, Severe JB, Simpson S, Vitiello B, Wells K, Wigal T, Wu M: Clinical relevance of the primary findings of the MTA: Success rates based on severity of ADHD and ODD symptoms at the end of treatment. J Am Acad Child Adolesc Psychiatry 40:168–179, 2001.

Swanson JM, Wigal S, Greenhill LL, Browne R, Waslik B, Lerner M, Williams L, Flynn D, Agler D, Crowley K, Fineberg E, Baren M, Cantwell DP: Analog classroom assessment of adderall in children with ADHD. J Am Acad Child Adolesc Psychiatry 37:519–526, 1998.

U.S. Department of Health and Human Services: Guidance for Industry E 10. Choice of Control Group and Related Issues in Clinical Trials. Rockville (Maryland), U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, 2001, Available at: http://www.fda.gov/ cder/guidance/index.htm. Accessed July 2001.

Wigal S, Swanson JM, Feifel D, Sangal RB, Elia J, Casat CD, Zeldis JB, Conners CK: Adouble-blind, placebo-controlled trial of dexmethylphenidate hydrochloride and d,l-threo-methylphenidate hydrochloride in children with attention deficit hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 43:1406–1414, 2004.