A Dose-Response Study of OROS Methylphenidate in Children With Attention-Deficit/Hyperactivity Disorder

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ABSTRACT. Objective. OROS methylphenidate HCL (MPH) is a recently developed long-acting stimulant medication used to treat attention-deficit/hyperactivity disorder (ADHD). This study was conducted to examine dosage effects on ADHD symptoms and stimulant side effects and to explore potential moderating effects of ADHD subtype.

Methods. Children with ADHD combined type (ADHD-CT) or predominantly inattentive type (ADHD-PI; n = 47), ages 5 to 16 years, underwent a placebo-controlled, crossover trial using forced titration with weekly switches at 3 dosage levels. Parent and teacher ratings of ADHD symptoms were used to evaluate efficacy. In addition, vital signs and standardized measures of stimulant side effects were obtained weekly.

Results. Parent ratings were more sensitive to treatment effects than teacher ratings. ADHD symptoms and Clinical Global Impressions Severity Index ratings at each dose condition differed significantly from placebo and baseline ratings, which did not differ from one another. For those with ADHD-CT, there was a clear linear dose-response relationship, with clinically significant reductions in ADHD Rating Scale-IV scores occurring in two thirds to three fourths of the subjects during either 36- or 54-mg dose conditions. Children with ADHD-PI, conversely, were more likely to respond optimally to lower doses and derived less benefit from higher doses, with 60% displaying significant improvement on the ADHD Rating Scale-IV at 36 mg or lower. Mild stimulant side effects were reported during placebo and at all dosage levels. With the exception of insomnia and decreased appetite, which were more common at higher doses, parent report of side effects was not related to dose. In addition, younger and smaller children were more likely to display sleep difficulties and decreased appetite at the higher dose levels although pulse rate increased slightly with increasing dose, there were no dose effects on blood pressure.

Conclusions. In children with ADHD-CT, the most common subtype of ADHD, increasing doses of stimulant medication were associated with increased improvement of inattention and hyperactivity symptoms. In children with ADHD-PI, symptom improvement occurred at lower doses and less benefit was derived from higher doses. In both ADHD subtypes, higher doses were associated with parent ratings of increased insomnia and decreased appetite. Pediatrics 2003;112:e404–e413. URL: http://www.pediatrics.org/cgi/content/full/112/5/e404; attention-deficit/hyperactivity disorder, methylphenidate, pharmacologic treatment.

ABBREVIATIONS. ADHD, attention-deficit/hyperactivity disorder; MPH, methylphenidate; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; ADHD-PI, attention-deficit/hyperactivity disorder predominantly inattentive type; ADD, attention-deficit disorder; ADHD-CT, attention-deficit/hyperactivity disorder combined type; ODD, oppositional defiant disorder; ADHD RS-IV, ADHD Rating Scale-IV; Home Edition; CGI, Clinical Global Impressions Severity Index; SERS, Side Effect Rating Scale; ACTeRS, ADD-H Comprehensive Teachers Rating Scale; SD, standard deviation; RCI, reliable change index.

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurobehavioral disorders of childhood and represents a significant public health problem because of its prevalence, persistence, associated psychiatric comorbidity, and impairments in adaptive functioning. Both the American Academy of Pediatrics and the American Academy of Child and Adolescent Psychiatry have recently developed clinical practice guidelines for this disorder. Stimulant medications, such as methylphenidate (MPH), have been evaluated extensively in hundreds of empirical studies and are the most common medical treatment for ADHD. According to a recent review, “Stimulants are among the most effective psychotropic medications in clinical use today.”

Currently, the most commonly prescribed medication for ADHD is OROS MPH, a long-acting stimulant designed to release gradually increasing concentrations of methylphenidate over 10 to 12 hours. The effectiveness of OROS MPH is supported by 2 studies conducted in laboratory settings and a multisite efficacy study. In these studies, OROS MPH was shown generally to mimic the efficacy and side-effect profile of three times a day (TID) MPH in treating childhood ADHD. Recently, a 1-year open follow-up study indicated that OROS MPH is well tolerated with few clinically significant adverse effects. Dosage varied from 18 to 54 mg in these studies, with the most common dose being 36 mg. However, none of
Conducted before DSM-IV, Barkley et al.18 examined the relationship between OROS MPH dose and behavioral and cognitive symptoms of ADHD. As defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV),10 ADHD is a heterogeneous disorder with considerable variation within individuals in their degree of cognitive (ie, inattention) and behavioral (ie, hyperactivity) symptoms.11 Studying interindividual differences within and across different domains of functioning can increase our understanding of the pathophysiology of the disorder and facilitate understanding of pharmacotherapy.12 Stimulant medications are usually titrated until there is optimal symptom reduction or significant stimulant side effects occur. Mild side effects are commonly reported in children who take stimulant medications, and changes in timing and dosage often result in improvement. The two most frequent untoward effects of immediate-release stimulant medications are sleep disturbance and decreased appetite; slightly less common side effects include negative mood changes (eg, irritability, sadness, anxiety), headaches, tics, and stomachaches.13 Stimulant side effects are often presumed to be dose related, with higher doses yielding more severe side effects. However, with the exception of decreased appetite, this has not been demonstrated within the mild to moderate dose ranges (ie, 0.3–0.5 mg/kg/dose) in studies of short-acting stimulants with school-age children.14,15 The relationship between dose and stimulant side effects has not been evaluated systematically using long-acting stimulants.

In 1937, Bradley16 first noted that children vary significantly in their response to stimulant medication and stressed the importance of identifying correlates of treatment response to further our understanding and improve clinical decision making. Moderators, or subgroups defined by baseline characteristics, may respond differentially to stimulant treatment. For example, the landmark MTA study examined several potential moderators, such as previous medication use, demographic characteristics, and comorbidity.17 However, one of the most common ADHD subgroups, individuals with ADHD predominantly inattentive type (ADHD-PI), were not included in the MTA sample. Thus, it is unclear whether stimulant medication response is moderated by ADHD subtype. In an earlier study conducted before DSM-IV, Barkley et al.18 examined the efficacy of 5, 10, and 15 mg of MPH administered twice per day, in children with DSM-III-defined attention-deficit disorder (ADD) with and without hyperactivity. The subgroup of children with ADD without hyperactivity responded to lower dosages relative to children with ADD with hyperactivity. Extrapolating to DSM-IV, we hypothesized that ADHD subtype will moderate dose-response relationships to OROS MPH.

Thus, the goal of the present study was to examine the relationship between OROS MPH dose and ADHD symptoms, impairment, and side effects. A secondary goal was to evaluate the potential moderating effects of ADHD subtype.

Subjects
Forty-seven children who were ages 5 year 11 months to 16 years who referred to the Hyperactivity, Attention and Learning Problems Clinic at Children’s National Medical Center (CNMC) served as subjects. Yths with mental retardation, severe mood disorders (requiring antidepressant or concurrent psychotropic medications), Tourette syndrome, seizure disorders, or other medical disorders associated with symptoms that may mimic ADHD (eg, thyroid disorder) were excluded, as were children who were taking systemic medications.

All subjects completed a semi-structured diagnostic interview conducted with the parents and the child by a child and adolescent psychiatrist or psychologist. As part of the interview, parents were asked to provide information about specific DSM-IV symptoms for common childhood psychiatric disorders (disruptive behavior, anxiety, mood, and pervasive developmental disorders) and impairment. All subjects met DSM-IV criteria for ADHD.10 Evaluation of ADHD and other psychiatric disorders was based on a “best-estimate” diagnosis, after reviewing interview and all available data, including behavioral observations during cognitive testing with the Wechsler Intelligence Scale for Children, Third Edition,19 and Wechsler Individual Achievement Test, Second Edition,20 the Test of Variables of Attention,21 Child Behavior Check List,22 and Conner’s Teacher Rating Scale.23 These measures were part of the standard diagnostic test battery that was administered to school-aged children who were referred to the multidisciplinary Hyperactivity, Attention, and Learning Problems Clinic, which includes pediatricians, psychologists, neurologists, and child and adolescent psychiatrists. Thirty-two (68%) subjects received a diagnosis of ADHD-Combined type (ADHD-CT), 15 (32%) received a diagnosis of ADHD-I. In addition, 17.0% met criteria for oppositional defiant disorder (ODD), 10.6% displayed enuresis/encopresis, and 21% displayed tic disorders. Thirty-three (70%) children were stimulant naïve, and 14 (30%) had taken stimulant medications in the past. As in most clinic-ascertained studies of ADHD, there was a strong male preponderance: 70.2% (33) were male and 29.8% (14) were female. In addition, 89.4% (42) of the subjects were white, 4.3% (2) were black, 2.1% (1) were Hispanic, and 4.3% (2) reported other ethnicities.

Procedures
Once children met inclusion criteria, parents and children were given a detailed description of the project and each subject’s parent(s) or guardian(s) were required to give signed informed consent; subjects aged 7 years or older were also required to give written assent. The consent and assent forms, study protocol, and any advertisements for subjects were reviewed and approved by the Institutional Review Board of Children’s National Medical Center.

Experimental Design
The 47 subjects were evaluated in a placebo-controlled, crossover study with 3 dose conditions of OROS MPH. Children who previously took stimulant medications completed a 2-week washout period before beginning the study. During the trial, patients received their usual school-based educational interventions and were not allowed to begin additional family-based or new psychosocial treatments until the medication trial was completed. The research pharmacist prepared weekly blister packs for each subject, each containing a 7-day supply of study drug for each week. Blister packs contained either a commercially available placebo capsule slightly larger than the OROS MPH preparations1 or 18

1 Unfortunately, it was not possible to ensure identical appearance of placebo and the active drug, due to the proprietary nature of OROS MPH and the fact that the manufacture did not supply placebos for this study. We conducted several analyses to investigate the impact of these differences in appearance on the findings of our study. Deleting the placebo condition from the repeated-measures analyses had almost no impact on the results, as the magnitude of the dose-response effects and the ADHD subtype differences therein were virtually identical to those in which the placebo also was included. The magnitude of the dose-response effects also was very similar when the highest dosage level (54 mg) was deleted from analyses, although the magnitude of the ADHD subtype difference was diminished.
mg, 36 mg, or 54 mg (18 + 36 mg) of OROS MPH. Dosing schedules were assigned from a randomly ordered list of all dosing schedules with the exception that no child could start with the 54-mg dose. In addition, 1 child who weighed <40 kg did not receive the 54-mg dose to minimize potential side effects in smaller children.

**Weekly Procedures and Measures**

During the initial visit and each weekly visit, children and their parents met with the clinical staff to discuss medication effects and to complete rating scales and questionnaires. Each week the following measures were completed:

- **ADHD Rating Scale-IV: Home Version (ADHD RS-IV)**: The ADHS RS-IV consists of 18 items that assess DSM-IV criteria for inattention and hyperactivity. The rating scale includes inattention and hyperactivity–impulsivity subscales as well as a total symptom score.
- **Clinical Global Impression-Severity (CGI)**: The CGI is a single-item clinician rating of the clinician’s assessment of the severity of ADHD symptoms. Severity of impairment is rated on a 7-point scale (1 = not at all ill, 7 = maximal, profound impairment).
- **Side Effect Rating Scale (SERS)**: The SERS is a 17-item scale composed of a variety of central nervous system stimulant side effects. The severity of each symptom is rated by parents on a 10-point (0–9) scale ranging from absent to serious. This scale has been used to measure the prevalence and severity of stimulant side effects in several treatment studies.
- **Vital signs**: Children’s weight, height, blood pressure, pulse, and temperature were obtained weekly.

In addition to parent and child ratings, teachers were queried weekly to assess medication response in school. Before medication (baseline) and during each subsequent week of the trial, teachers completed the ADD-H Comprehensive Teachers Rating Scale (ACTeRS). The ACTeRS consists of 24 items with 5 to 7 items assessing each of 4 categories of behavior: attention, hyperactivity, social skills, and oppositional behaviors.

**Statistical Plan**

Frequency data were evaluated using χ². Repeated measures analyses of variance or multivariate analyses of variance were used to evaluate treatment effectiveness. Trend analyses were conducted to test for hypothesized linear and higher-order dose-response curves. All follow-up analyses were completed using Bonferroni correction for multiple comparisons. A paired t test was used to evaluate differences between the ADHD subtypes at baseline and to test the significance of change from baseline to follow-up visits on vital signs. Effect sizes were calculated by dividing the difference of the mean scores by the standard deviation (SD) for the placebo phase or were provided by the statistical package (viz, SPSS for Windows, v.11) as the percentage of variance accounted for.

Three procedures were used to determine the clinical significance of OROS MPH treatment:

1. Examining rates of improvement through commonly used cutoffs on the ADHS RS-IV that approximate those used in the MTA optimal responder analyses.
2. Determining global changes in severity via the CGI.
3. Calculating clinically significant change using a reliable change index (RCI).

The guidelines established by Jacobson and Truax, clinically significant change was defined as when the posttreatment level of functioning results in a subject rated closer to the mean of the functional population than to the mean of the dysfunctional population. Clinical improvement was calculated separately for inattention and hyperactivity symptoms using the ADHS RS-IV. A t score of 30, the population mean, was used to define the mean of the functional population. To evaluate whether the change was statistically reliable, we also calculated RCI scores.

**RESULTS**

**Diagnostic and Descriptive Information**

With the exception of 1 child who tested in the borderline range for verbal and full-scale IQ, all children had scores within the average or above-average range on the Wechsler Intelligence Scale for Children, Third Edition (mean IQ: 105). However, 31.9% of the children received a diagnosis of a learning disability on the basis of a significant discrepancy between Wechsler Individual Achievement Test scores and IQ. Consistent with an ADHD diagnosis, the highest mean Child Behavior Check List scores were on the Attention Problems Scale. Similarly, on the Conner’s Teacher Rating Scale, the highest mean score was on the Hyperactivity Index (Table 1).

**Child Behavior Check List Attention and Hyperactivity**

**Table 1. Demographic and Descriptive Characteristics of Sample (n = 47)**

<table>
<thead>
<tr>
<th>Item</th>
<th>Total (n = 47; mean [SD])</th>
<th>Inattentive Type Only (n = 15; mean [SD])</th>
<th>Combined Type Only (n = 32; mean [SD])</th>
<th>t Score</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>9.0 (2.5)</td>
<td>10.1 (3.0)</td>
<td>8.5 (2.1)</td>
<td>2.1</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>WISC-III (standardized scores)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full-Scale IQ</td>
<td>106.8 (16.5)</td>
<td>108.1 (17.3)</td>
<td>106.1 (16.4)</td>
<td>0.38</td>
<td>NS</td>
</tr>
<tr>
<td>WIAT (standardized scores)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basic Reading</td>
<td>105.4 (14.5)</td>
<td>105.2 (17.8)</td>
<td>105.5 (13.1)</td>
<td>0.06</td>
<td>NS</td>
</tr>
<tr>
<td>Mathematics Reasoning</td>
<td>105.8 (11.4)</td>
<td>103.4 (14.0)</td>
<td>106.9 (10.0)</td>
<td>0.91</td>
<td>NS</td>
</tr>
<tr>
<td>Written Expression</td>
<td>100.0 (11.2)</td>
<td>98.0 (11.7)</td>
<td>101.2 (11.1)</td>
<td>0.67</td>
<td>NS</td>
</tr>
<tr>
<td>CBCL (t scores)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>60.0 (9.0)</td>
<td>55.1 (8.0)</td>
<td>62.4 (8.6)</td>
<td>2.8</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Internal</td>
<td>54.7 (12.8)</td>
<td>49.3 (14.4)</td>
<td>57.4 (11.1)</td>
<td>2.1</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>External</td>
<td>56.7 (9.7)</td>
<td>50.3 (9.1)</td>
<td>59.9 (8.4)</td>
<td>3.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Thought Problems</td>
<td>59.0 (7.4)</td>
<td>56.1 (6.9)</td>
<td>60.5 (7.3)</td>
<td>1.9</td>
<td>.06</td>
</tr>
<tr>
<td>Attention Problems</td>
<td>67.1 (8.8)</td>
<td>64.7 (8.0)</td>
<td>68.4 (9.1)</td>
<td>1.3</td>
<td>NS</td>
</tr>
<tr>
<td>Aggression Behavior</td>
<td>57.9 (7.5)</td>
<td>53.3 (9.9)</td>
<td>60.3 (7.7)</td>
<td>3.3</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>ADHD Parent Rating Scale (t scores)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Attention</td>
<td>75.7 (10.5)</td>
<td>76.1 (10.9)</td>
<td>75.6 (10.5)</td>
<td>0.15</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>69.4 (13.2)</td>
<td>62.7 (15.3)</td>
<td>72.5 (11.0)</td>
<td>2.5</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>CGI</td>
<td>4.4 (.93)</td>
<td>4.2 (.98)</td>
<td>4.4 (.91)</td>
<td>0.75</td>
<td>NS</td>
</tr>
<tr>
<td>Conner’s Teacher Rating Scale (t scores)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperactivity Index</td>
<td>70.7 (12.0)</td>
<td>70.7 (25.3)</td>
<td>70.7 (9.1)</td>
<td>0.00</td>
<td>NS</td>
</tr>
<tr>
<td>ACTeRS (t score)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention</td>
<td>63.8 (8.7)</td>
<td>63.6 (7.2)</td>
<td>64.0 (9.5)</td>
<td>0.14</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>56.8 (12.0)</td>
<td>54.4 (7.9)</td>
<td>58.0 (13.6)</td>
<td>0.93</td>
<td>NS</td>
</tr>
</tbody>
</table>

WISC-III indicates Wechsler Intelligence Scale for Children, Third Edition; WIAT, Wechsler Individual Achievement Test; CBCL, Child Behavior Check List; NS, not significant.
Changes in ADHD Symptoms and Impairment

Changes in inattentive and hyperactive ADHD symptoms as a function of OROS MPH dosage were assessed using the ADHD RS-IV and the ACTeRS. As OROS MPH dose increased from 0 to 54 mg, parent-rated ADHD symptoms decreased in a linear manner \((F[1,38] = 96.71, P < .001, \text{partial } \eta^2 = 0.72)\), similarly for inattentive and hyperactive-impulsive symptoms \((F[1,38] = 89.55, P < .001, \text{partial } \eta^2 = 0.70; F[1,38] = 81.28, P < .001, \text{partial } \eta^2 = 0.68, \text{respectively})\).

We also examined the differential sensitivity of parent and teacher ratings of ADHD symptoms to treatment. Although similar linear decreases with increased OROS MPH dosage were noted for teacher ratings of inattentive and hyperactive-impulsive symptoms, effect sizes for these decreases were more moderate in magnitude \((F[1,23] = 21.87, P < .001, \text{partial } \eta^2 = 0.49; F[1,23] = 8.55, P = .008, \text{partial } \eta^2 = 0.27, \text{respectively})\), suggesting that parent ratings are slightly more sensitive than teacher ratings in detecting OROS MPH effects.

The effects of OROS MPH on impairment were examined by modeling changes in CGI as a function of dosage level. Overall impairment decreased with increasing OROS MPH dose \((F[1,38] = 57.49, P < .001, \text{partial } \eta^2 = 0.60)\).

ADHD Subtype Differences in Treatment Response and the Effects of Comorbid ODD and Learning Disability

There were no subtype differences in severity of CGI measured impairment as a function of increasing OROS MPH dose \((F[1,37] = 0.31, P = .578, \text{partial } \eta^2 < 0.01)\), and these results did not differ when comorbid ODD and learning disability were taken into account. In contrast, there were significant differences in parent-rated hyperactive-impulsive and inattentive symptoms between the ADHD-CT and ADHD-PI subtype groups. As shown in Figs 1 and 2, there was a trend for the difference between the ADHD-CT and ADHD-PI groups in the reduction of hyperactive-impulsive symptoms with increasing OROS MPH dose \((\text{quadratic trend } F[1,37] = 3.55, P = .067, \text{partial } \eta^2 = 0.09)\). This subtype difference in reduction of hyperactive-impulsive symptoms was enhanced when comorbid ODD was controlled \((F[1,36] = 5.68, P = .023, \text{partial } \eta^2 = 0.14)\) and remained when comorbid learning disability and ODD both were controlled \((F[1,34] = 4.49, P = .041, \text{partial } \eta^2 = 0.12)\). The nature of this subtype difference in the quadratic trend for reduction of hyperactive-impulsive symptoms was that the ADHD-PI showed greater treatment response at lower OROS MPH doses, whereas the ADHD-CT group showed greater treatment response at higher doses. Specifically, in the ADHD-CT group, there was a greater decrease in hyperactive-impulsive symptoms from the 36-mg condition to the 54-mg condition \((P = .002)\) than from the 18-mg to the 36-mg condition \((P = .296)\) or the placebo to the 18-mg condition \((P = .034; \text{Fig 2})\), whereas in the ADHD-PI group, there was a greater decrease from baseline and placebo to the 18-mg condition \((P = .010 \text{ and } .123, \text{respectively})\) than from 18-mg to 36-mg or from 36-mg to 54-mg dose \((P = .109 \text{ and } .807, \text{respectively})\).

A similar subtype difference in treatment response...
was found for inattentive symptoms, which are elevated in both subtypes. Specifically, there was a trend for the ADHD-CT and ADHD-PI groups to differ in the reduction of inattentive symptoms with increasing OROS MPH dose (quadratic trend \( F[1,37] = 3.13, P = .085, \text{partial } \eta^2 = 0.08 \)). This subtype difference in reduction of inattentive symptoms was enhanced when comorbid ODD was controlled (\( F[1,36] = 4.72, P = .037, \text{partial } \eta^2 = 0.12 \)) as well as when comorbid learning disability and ODD both were controlled (\( F[1,34] = 4.48, P = .042, \text{partial } \eta^2 = 0.12 \)). The nature of this significant subtype difference in the quadratic trend for reduction of inattentive symptoms was that the ADHD-PI group showed greater treatment response at lower OROS MPH doses, whereas the ADHD-CT group showed greater treatment response at higher doses. Specifically, in the ADHD-CT group, there was a greater decrease in hyperactive-impulsive symptoms from 36- to 54-mg conditions (\( P = .003 \)) than from the 18-mg to 36-mg dose (\( P = .141 \)) or the placebo to the 18-mg dose (\( P = .059 \)). Whereas in the ADHD-PI group, there was a greater decrease from baseline and placebo to the 18-mg condition (\( P = .005 \) and .085, respectively) than from the 18-mg to 36-mg or the 36-mg to the 54-mg dose (\( P = .973 \) and .107, respectively). This pattern also was borne out in the \( t \) scores for inattentive symptoms in that clinically significant declines were seen for the ADHD-CT group from the 36-mg to the 54-mg dose (mean \( t \) scores: 61 vs 55, respectively; a decrease \( >0.5 \) SD), whereas for the ADHD-PI group, the most substantial decline was seen from the baseline to the 18-mg dose (mean \( t \) scores: 76 vs 59, respectively; a decrease \( >1 \) SD) with very slight declines from the 18-mg to the 36-mg dose and from the 36-mg to the 54-mg dose (mean \( t \) scores: 59, 58, and 56, respectively; decreases \(<0.10 \) and 0.25 SD, respectively). These results suggest that the subtype differences in reduction of ADHD symptoms with increasing OROS MPH dose were similar in magnitude for the hyperactive-impulsive and inattentive symptoms of ADHD.

### Clinical Improvement/Return to Normalcy

Three procedures were used to examine the clinical significance of changes in ADHD symptom. First, common cutoffs for the ADHD RS-IV were used to estimate clinically significant improvement. A score of 9 or less (\( T \leq 60 \)) on the inattentive scale indicated “normalization” for the ADHD-PI subgroup, and a score of 18 (\( T \leq 60 \)) or less on the total score was used to indicate “normalization” for the ADHD-CT subgroup. Thirty-three percent of the ADHD-PI subjects met this criterion during the placebo phase: 43% at 18 mg, 60% at 36 mg, and 50% at 54 mg (Table 2). There were no dose-related differences in the proportion of subjects whose scores were “normalized” in this group (\( \chi^2(2) = .86 \); not significant).

Within the ADHD-CT group, however, the proportion of normalized subjects was 14%, 32%, 40%, and 66% at placebo, 18 mg, 36 mg, and 54 mg of OROS MPH, respectively. Within this group, there were few placebo responders and greater improvement was reported at higher doses of OROS MPH (\( \chi^2(2) = 7.2, P < .05 \)).

Clinically significant improvement was also assessed using the CGI. Severity of impairment for more than two thirds (\( \geq 67\% \)) of subjects in the ADHD-PI group diminished to subclinical levels (eg, CGI \( \leq 3 \)) at 36 mg and 54 mg of OROS MPH (Table 2). Within this group, 43% displayed an excellent response as indicated by “no or mild impairment” (CGI \( \leq 2 \)) at 36 mg, and 58% showed “no or mild impairment” at 54 mg of OROS MPH. For the ADHD-CT group, CGI severity decreased to subclinical levels for 65% of subjects at 36 mg and for 72% of subjects at 54 mg of OROS MPH. Forty-five percent of ADHD-CT subjects at 36 mg and 52% of subjects at 54 mg had no or mild impairment (Table 2).

Following Jacobson and Truax’s procedures, subjects were classified as “normalized” when they achieved clinical improvement and a significant RCI indicating reliable symptom improvement. As shown in Table 3, the proportion of subjects in the
inattentive subgroup who met criteria for normalization of inattention symptoms was approximately half at all 3 doses of OROS MPH. Thus, with the use of this method, the inattentive subtype did not seem to experience incremental treatment benefits with higher doses of OROS MPH over the 18-mg dose. Within the ADHD-CT group, the proportion of subjects who met criteria for normalization on attention symptoms ranged from more than one third at 18 mg of OROS MPH to more than two thirds at 54 mg. ADHD-CT subject normalization on hyperactivity symptoms increased from one fourth at 18 mg of OROS MPH to two thirds at 54 mg of OROS MPH.

**Premature Discontinuation and Compliance**

Any child who could not complete a treatment phase was classified as a premature discontinuation. Their data were included for all phases that were completed. One (2%) child dropped out during placebo, 2 (4%) children did not complete the 36-mg condition, and 5 (10%) did not complete the 54-mg level condition. Reasons for discontinuation (not mutually exclusive) included irritability and negative mood (n = 4), decreased appetite (n = 3), insomnia (n = 2), staring (n = 2), somatic complaints (n = 1), tics/nervous movements (n = 1), drowsiness (n = 1), and euphoria (n = 1). There was a marginally significant trend indicating that premature discontinuation was more likely to occur during the 54-mg condition ($\chi^2(3) = 7.3, P = .06$).

Compliance was assessed weekly by querying parents on missed doses. Compliance was adequate, with 92% of all study medications given.

**Side Effects**

To examine effects of OROS MPH dose on perceptions of untoward or stimulant side effects, we compared scores from the parent-completed SERS at placebo and each dose. OROS MPH dose did not have a significant effect on SERS total score ($F[3,123] = 1.78$; not significant. Although stimulant side effects were reported at all dose levels, these were generally mild.

Following the recommendations of Barkley et al,26 ratings of 7 and higher were taken as an indication of a serious or severe side effect (Table 4). In addition, regression analyses were used to explore the rela-
TABLE 4. Frequency of Presence of Any Side Effect and Any Severe Side Effects at Each Dose of OROS MPH

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>% Present</th>
<th>% Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia or trouble sleeping</td>
<td></td>
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<tr>
<td>Nightmares</td>
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<tr>
<td>Stares a lot or daydreams</td>
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<tr>
<td>Talks less with others</td>
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<tr>
<td>Uninterested in others</td>
<td></td>
<td></td>
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<tr>
<td>Decreased appetite</td>
<td></td>
<td></td>
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<tr>
<td>Irritable</td>
<td></td>
<td></td>
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<tr>
<td>Stomachaches</td>
<td></td>
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<tr>
<td>Headaches</td>
<td></td>
<td></td>
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<tr>
<td>Drowsiness</td>
<td></td>
<td></td>
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<tr>
<td>Sad/unhappy</td>
<td></td>
<td></td>
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<tr>
<td>Prone to crying</td>
<td></td>
<td></td>
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<tr>
<td>Anxious</td>
<td></td>
<td></td>
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<tr>
<td>Bites fingernails</td>
<td></td>
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<tr>
<td>Euphoric/unusually happy</td>
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<td></td>
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<tr>
<td>Dizziness</td>
<td></td>
<td></td>
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<tr>
<td>Tics or nervous movements</td>
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</tbody>
</table>

Effects of OROS MPH Dose on Vital Signs

To determine whether OROS MPH had an effect on blood pressure, we compared the proportion of subjects beyond the 95th percentile for their age and sex at placebo and each dose of OROS MPH with baseline values. OROS MPH dose was not related to changes in either systolic or diastolic blood pressure ($\chi^2$ = 0.00; not significant). Neither age nor weight was related to complaints of irritability on 36 mg or 54 mg of OROS MPH ($F < 1.26$, $P > .2$).

DISCUSSION

The primary purpose of this study was to determine dosage effects of OROS MPH on ADHD symptoms, impairments, and side effects. Similar to studies with short-acting stimulants, OROS MPH significantly reduced the frequency and severity of ADHD symptoms. Normalization occurred on at least 1 dose in half to two thirds of subjects. Consistent with previous studies with hyperactive or ADHD-CT samples, treatment response followed an inverse linear dose-response curve with ADHD.
symptoms and impairment declining with increasing dose up to 54 mg. Although only slight improvements occurred relative to baseline when receiving placebo or 18 mg of OROS MPH, clinically significant improvement occurred in one half to two thirds of youths with ADHD at 36- and 54-mg dose levels. This is consistent with the intermediate-term, open-label follow-up study of OROS MPH treatment reported by Willens et al.9

ADHD subtype moderated the dose-response relationship. In contrast to children with ADHD-CT, children with ADHD-PI and receiving 18 mg of OROS MPH displayed little additional benefit at the 2 higher dosage levels. Our findings, although based on a relatively small sample of children with ADHD-PI, are consistent with the report of Barkley et al.18 that children with ADD without hyperactivity are more likely to do well on lower MPH dosages, whereas children with ADD with hyperactivity are likely to require higher dosages for clinical management. Their findings and those in the present study both suggest improvement in inattentive symptoms at lower stimulant doses relative to doses effective for treating children with both hyperactivity and impulsivity symptoms.

The finding of differential response based on ADHD subtype are reminiscent of Sprague and Sleuror's widely reported study of differential dose effects of immediate-release MPH in hyperactive children.34 In that study, a lower dose of MPH (0.3 mg/kg) produced the most improvement on a cognitive task, but performance worsened at higher doses associated with optimal improvement in ratings of hyperactivity. This differential dose-response pattern has not been replicated consistently. Rather, several dose-response studies using mild to moderate doses of immediate-release MPH typically report a linear dose-response pattern on behavioral and cognitive measures (14,31–33). The present findings highlight the importance of assessing, within each subtype, effects of dose on multiple domains of cognitive functioning and attention in children with ADHD.

In contrast to previous studies of short-acting stimulants (eg, 35), parent ratings were more sensitive to medication effects than teacher ratings. This may reflect the longer duration of action of OROS MPH and consequently increased opportunity for parents to observe medication effects directly. This finding has practical implications in situations in which teacher ratings are unavailable, because parent ratings alone were sensitive to medication effects. Nonetheless, we agree with the American Academy of Pediatrics practice guidelines that call for a multimodal assessment battery to monitor treatment effects, including teachers and other adults in the child's environment, as differences in perspectives are clinically important for eliciting a comprehensive profile of ADHD symptoms, associated problems, and impairments to guide treatment.36

Considerable controversy exists on defining "optimal" response to stimulant medication. Studies of community treatment of ADHD, such as the MTA study, suggest that "undertreatment" in terms of dose and duration of active treatment is common.37 Even in the MTA medication management condition, which set the standard for careful titration and which offered coverage of 10 to 12 hours of active treatment, approximately half of the subjects displayed symptoms ratings that were considered "normalized."38 We used 3 different procedures to calculate clinical improvement, and all resulted in similar estimates of clinical significance: normalization occurred on at least 1 dose in half to two thirds of subjects. It should be noted that the highest dosage used in this study was 54 mg, and some youths with ADHD may require higher dosages for optimal responding.39 Given the significant morbidity associated with partially treated ADHD as suggested by the community treatment condition in the MTA and other studies (eg, 17,40), perhaps clinicians should pursue a higher standard of effectiveness than mere ADHD symptom reduction and titrate until there is normalization, little room for improvement, or clinically significant or persistent side effects.

Although stimulant side effects are often presumed to be dose related, it should be noted that side effects often associated with stimulants are frequently reported in children with ADHD even when they are taking a placebo.26 Previous studies using side effects rating scales and short-acting stimulants indicated few differences in side effects between children who were receiving low to moderate doses (ie, 0.3–0.8 mg/kg dose) of MPH.14,15,26 It is interesting that Rapport and Moffitt41 found that somatic complaints, which are often seen as side effects associated with stimulant use, improved with increasing MPH dose in a linear manner, whereas insomnia and decreased appetite severity were associated with increasing dose. In the present study, mild side effects were common during all dosing conditions, and the total number of side effects did not increase significantly with increasing dose. However, when examined individually, severe insomnia and decreased appetite seemed to worsen in proportion to dose. These side effects were reported for >20% of those who were taking 54 mg of OROS MPH. In addition, younger children and those who weighed less seemed to be more prone to these side effects, despite excluding the smallest children from the highest dose level. Consequently, clinicians should be alert to greater risk of stimulant side effects in younger children with lower body mass.

The forced titration procedure deserves some comment. The advantage of this procedure is the increased potential to determine optimal response. However, this procedure is likely to result in increased reports of stimulant side effects compared with a more gradual titration procedure. In addition, direct inquiry about potential side effects is more likely to elicit reports of side effects than more open-ended questioning and spontaneous reporting.

In interpreting the results, several limitations should be kept in mind. First, potential expectancy biases or placebo effects need to be considered because each medication differed in appearance, size, color, and, in the case of the 54-mg condition, number of capsules. Although parents were not told...
which dose condition their child was receiving each week, it is possible that some parents or patients may have assumed that the larger OROS MPH capsules or that 2 capsules represented higher dosages. We attempted to examine the potential impact of expectancy or placebo effects using analyses previously mentioned in footnote 1. In addition, we presume that expectancy or placebo effects were minimal, because measures of ADHD symptoms obtained during the placebo phase, during which the largest capsule was taken, were almost identical to baseline scores. Moreover, children with ADHD-PI did not display greater improvement with the larger capsules or higher doses. In theory, this may be attributable either to the true effects of dosage level or to the different appearance of the 54-mg dose. In our opinion, the former is more plausible, given that the different appearance of the 54-mg dose did not affect dose-response effects on ADHD symptoms disregarding ADHD subtype and that children in the ADHD-PI subtype group did not experience any additional improvement with the 54-mg dose over and above that experienced with the lower doses (18 and 36 mg). Indeed, differential response of the ADHD-CT and ADHD-PI groups to both the 54-mg and the 18-mg doses seemed to account for the majority of the subtype difference in treatment response in this study. Nonetheless, the unavailability of identical placebo and drug conditions for the present study tempers our conclusions.

Other limitations include the short-term nature of the study, the relatively small number of subjects with ADHD-PI, and the measures of ADHD symptoms used that were rating scales rather than behavioral observations or laboratory measures of attention. Additional studies that use more direct and specific measures of cognitive and behavioral symptoms of ADHD and side effects are needed to examine intermediate- and long-term dose-response effects of long-acting stimulants.

The present study sample seems to have less comorbidity overall than other clinical samples, such as the MTA, which did not include children with ADHD-PI. This may partially explain the higher response rate relative to the MTA study. Differences in inclusion and exclusion criteria, ascertainment methods, and referral characteristics may have contributed to differences between samples. In terms of referral characteristics, almost two thirds of the sample was stimulant naive. This may reflect the predominately mid- to upper socioeconomic status referral base of the clinic and that approximately one third of the sample had ADHD-PI. Consistent with previous studies of ADHD-PI, individuals with this subtype displayed lower rates of disruptive behavior disorders and increased learning difficulties and educational impairments. In the present study, the moderating effects of ADHD subtype on stimulant response were not attributable to comorbid ODD or learning disorder. Nonetheless, additional study is needed with other clinic samples, such as samples that contain children with mood or tic disorders, who were excluded from the present study.

The present study has several clinical implications. First, it is clear that long-acting stimulants, such as OROS MPH, are similar to short-acting stimulants in their remarkable efficacy in quickly reducing ADHD symptoms and impairment. Significant beneficial effects were evident within 1 week, and parent ratings were highly sensitive medication effects. Second, for children with ADHD-CT, there is generally a linear dose-response relationship for attention and hyperactivity symptoms within the low to moderate dosage range used in the study. Third, additional study is needed to determine whether greater efficacy occurs above 54 mg of OROS MPH, which is currently the upper dose limit. Fourth, for children with ADHD-PI, clinicians should expect attention problems to improve at lower dosages than for youths with hyperactivity and impulsivity symptoms. A caveat is that there is often wide individual variation in response. Finally, for both ADHD subtypes, it is recommended that practitioners continue to titrate to obtain optimal response or normalization by systematically monitoring ADHD symptoms throughout the child’s day, as well as key functional outcomes related to impairment, such as family and social adaptive functioning.

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REFERENCES


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DOI: 10.1542/peds.112.5.e404

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