Methylphenidate Versus Dexamphetamine in Children With Attention Deficit Hyperactivity Disorder: A Double-blind, Crossover Trial

Daryl Efron, FRACP; Frederick Jarman, FRACP; and Melinda Barker, Grad Dip Ed Psych

ABSTRACT. Objective. To compare methylphenidate (MPH) and dexamphetamine (DEX) in a sample of children with attention deficit hyperactivity disorder (ADHD).

Method. A total of 125 children with ADHD received both MPH (0.3 mg/kg twice daily) and DEX (0.15 mg/kg twice daily) for 2 weeks a double-blind, crossover study. Outcome measures were Conners’ Parent Rating Scale–Revised, Conners’ Teacher Rating Scale–Revised, a Parent Global Perceptions questionnaire, the Continuous Performance Test, and the Barkley Side Effects Rating Scale.

Results. There were significant group mean improvements from baseline score on all measures for both stimulants. On the Conners’ Teacher Rating Scale–Revised, response was greater on MPH than DEX on the conduct problems and hyperactivity factors, as well as on the hyperactivity index. On the Conners’ Parent Rating Scale–Revised, anxiety was the only factor to differ significantly, in favor of MPH. Parents rated 73% of subjects as globally improved on MPH and 69% improved on DEX, compared with baseline. Overall, 46% of parents chose MPH as the preferred drug, compared with 37% who chose DEX. On the Continuous Performance Test, there was no difference in the number of correct responses or errors between the two drugs.

Conclusions. Most children with ADHD improve significantly on both MPH and DEX. There was a slight advantage to MPH on most measures. Pediatrics 1997;100(6). URL: http://www.pediatrics.org/cgi/content/full/100/6/e6; attention deficit hyperactivity disorder, stimulant medication, methylphenidate, dexamphetamine.

ABBREVIATIONS. ADHD, attention deficit hyperactivity disorder; MPH, methylphenidate; DEX, dexamphetamine; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th ed; CBCL, Child Behavior Checklist; TRF, Teacher Report Form; CPRS–R, Conners’ Parent Rating Scale–Revised; CTRS–R, Conners’ Teacher Rating Scale–Revised; CPT, Continuous Performance Test; SERS, side effect rating scale.

Stimulant medication is the most effective treatment for children with attention deficit hyperactivity disorder (ADHD).1,2 Stimulants have been shown to induce short-term enhancement of behavioral, academic, and social functioning. Many well-designed, placebo-controlled studies have demonstrated beyond doubt the benefits of stimulants in the vast majority of children with ADHD.2–4 In a review of 110 studies on the effects of stimulant drugs on more than 4200 children with ADHD, Barkley5 found that ~75% of subjects were regarded as improved on stimulants. The mean placebo response was 39%.

Methylphenidate (MPH) and dexamphetamine (DEX) are the two stimulants prescribed most frequently and have been shown to have similar types of positive effects in children with ADHD. However, it is not known whether one is more efficacious than the other in terms of probability of producing a positive response, magnitude of response, quality of improved performance, or side-effect profile. Some authors suggest that the two stimulants are equally effective6 or that “there is little to choose between them,”6 whereas a number of clinicians have the impression that MPH is the more efficacious of the two and has fewer associated adverse effects. MPH is often designated the drug of first choice in psychopharmacology texts, despite the absence of supporting evidence.7

Clinical experience suggests that although most children respond equally well to one of these stimulants, a subgroup of children seem to respond better to one than the other. However, there has been surprising little research published examining the question of relative efficacy and toxicity of the two most commonly used drugs in childhood behavior disturbance. No advantage to either drug has been demonstrated to date in the sparse literature directly comparing MPH with DEX. Hence, the choice of drug is often made on the basis of previous anecdotal experience, trial and error, and/or cost. In the present study, we set out to compare systematically MPH and DEX in a sample of children with ADHD.

METHODS

Subjects

Subjects were selected from ambulatory patients referred to the Royal Children’s Hospital, Melbourne, Australia, for an assessment for possible ADHD. Referral sources included pediatricians, family practitioners, school nurses, and psychologists. In addition, many parents self-referred by calling the hospital, usually at the suggestion of a relative, friend, the child’s teacher, or the state ADHD parent support group.

Criteria for enrollment in the trial were 1) age between 5 and 15 years; 2) satisfy Diagnostic and Statistical Manual of Mental Disorders, 4th ed (DSM–IV) criteria for ADHD.5 The DuPaul ADHD

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rating scale\textsuperscript{9} was used in which each DSM–IV ADHD symptom was marked on a four-point scale: “never or rarely,” “sometimes,” “often,” or “very often”; only symptoms rated often or very often were considered present and counted toward the diagnosis; 3) T score of at least 1.5 SD units above the mean on the attention problems scale of the Child Behavior Checklist (CBCL)\textsuperscript{10} or Teacher Report Form (TRF)\textsuperscript{11}; 4) no history of intellectual disability, gross neurologic abnormality, or Tourette’s syndrome; and 5) decision made to undertake stimulant medication trial on clinical grounds.

Procedure

This study used a double-blind, crossover design. Subjects were randomized to receive either DEX or MPH for the first 2 weeks of the study. After a 24-hour washout period, they were crossed over to receive the other stimulant for the 3rd and 4th weeks. Each drug was administered twice a day, after breakfast and after lunch, at a standardized dose. The dose was 0.15 mg/kg/dose for DEX and 0.3 mg/kg/dose for MPH, rounded off to the nearest capsule size. Both drugs were presented in identical form, as a crushed powder in opaque gelatin capsules (2.5 mg for DEX and 5 mg for MPH). The investigators, families, subjects, and teachers were blind to the randomization order throughout the study period. The study protocol was approved by the Ethics in Human Research Committee of the Royal Children’s Hospital, and written informed consent was obtained from parents.

Measures

The following four principle measures of response to stimulant medication were used in this study.

Conners’ Parent Rating Scale–Revised (CPRS–R)\textsuperscript{12}3

This 48-item questionnaire yields five factors: conduct problems, learning problems, psychosomatic, impulsive–hyperactive, and anxiety. In addition, a composite hyperactivity index has been derived from the 10 items with the highest loading from the factor scales. Each item is rated on a four-point scale (not at all = 0, just a little = 1, pretty much = 2, and very much = 3). Raw scores for each factor are transformed by age and sex into T scores, with a mean of 50 and an SD of 10. The CPRS–R was completed by parents at baseline and at the completion of each trial period.

Conners’ Teacher Rating Scale–Revised (CTRS–R)\textsuperscript{12}

This 28-item questionnaire complements the CPRS–R, and scoring is identical. It was completed at the same time as the CPRS–R. The CTRS–R has the following three factors: conduct problem, hyperactivity, and inattentive–passive. A hyperactivity index has again been derived from the 10 highest loading.

Parental Global Perceptions Questionnaire

Parents of study subjects were asked to rate their child in comparison with his/her usual self at the completion of each medication cycle. Two attributes, activity and concentration, as well as overall perceptions each were rated on a five-point scale. At the completion of both study cycles (before unblinding), parents were asked which medication they thought was the most helpful, taking everything into account.

Continuous Performance Test (CPT)\textsuperscript{13}

The CPT is a computerized test of sustained attention and impulsivity. In this study, we used the A–X paradigm. This is a successive discrimination task, in which the subject responds to a designated target only when it occurs after a specified warning signal. The target stimulus was an “X,” and the warning signal was an “A.” Single letters were randomly displayed in the center of a monitor for 500 msec, with an interstimulus interval of 1500 msec. A 10-minute task was used, during which there were 60 targets within 300 presentations. The number of omission errors (missed targets) is thought to be a measure of inattention, and the number of commission errors (false alarms) is thought to reflect the degree of impulsivity.

Subjects attempted the CPT at baseline and again on the final day of each medication cycle, 1 to 2 hours after ingestion of their morning dose (ie, at a time coinciding with peak behavioral effects).

Side effects were evaluated using the Barkley Side Effects Rating Scale (SERS). This questionnaire assesses the frequency and severity of 17 common side effects of stimulants, rated on a scale from 0 (absent) to 9 (severe). Because children with ADHD often display some of these apparent side effects before receiving medication, this questionnaire was also administered at baseline, so that true medication effects were able to be measured.

A short form of the Wechsler Intelligence Scale for Children, 3rd ed.,\textsuperscript{14} comprising two verbal (similarities and vocabulary) and two performance (block design and object assembly) scale subtests.

Data Analysis

The methods used to analyze the CPRS–R and CTRS–R were identical. Data were analyzed by factor. The principal measure used was the difference in T score from baseline to the end of the treatment period (ie, baseline T score–treatment T score).

Initially within-subject analysis of variance (ANOVA) for repeated measures was computed for the means of all factors (ie, comparison of scores at three trial conditions: baseline, DEX, and MPH). Because all F values were significant, planned comparisons were conducted to define differences, using paired-samples t tests (Table 1). The change in T score for each factor was then submitted to the Hills and Armitage analysis for data from crossover trials.\textsuperscript{15} Data were first tested for period effects and treatment-by-period interaction effects, and finally the magnitudes of the effects of the two interventions were compared.

Subjects were then classified into responders and nonresponders to each stimulant. This enabled a categorical analysis of response, using the same three scores. On the CPRS–R and CTRS–R, subjects were grouped according to the change in hyperactivity index T score from the baseline score. The cutoff point was chosen so as to classify response in a meaningful way, both clinically and statistically. Subjects whose T score decreased by ≥10 points (1 SD) were classified as responders. All others were classified as nonresponders. On the Parent Global Perceptions questionnaire, subjects rated “better” or “much better” at the completion of a cycle were classified as responders to that medication, and those rated “about the same,” “worse,” or “much worse” were classified as nonresponders.

A number of child and family variables were analyzed for their hypothesized association with response to each stimulant. The dependent variable was change from baseline in CPRS–R and CTRS–R factor T scores on each stimulant used as the outcome measures for evaluation of predictors. Pearson product moment correlations were calculated to examine the following continuous variables: age, gender, deviation IQ, self-perception, parent-rated behavior (CBCL), teacher-rated behavior (TRF), socioeconomic status, family functioning, and maternal mental health. The following categorical variables were examined as predictors using independent samples t tests: aggressive–delinquent behavior (CBCL T score ≥67 on both aggressive behavior and delinquent behavior syndrome scales), anxiety–depression (CBCL T score ≥67 on anxious/depressed syndrome scale), learning disability (reading), and DSM–IV category. Because multiple analyses were conducted, a variable was not considered a predictor unless the P value of the correlation coefficient or t test score was <.01.

RESULTS

Sample Characteristic

A total of 125 subjects (114 boys and 11 girls) met the inclusion criteria and were enrolled in the trial between April 1995 and August 1996. Age ranged from 60 months to 179 months, with a mean age overall of 104.8 months (SD = 27.6 months). Mean age for boys was 105 months, and for girls 102.4 months.

All subjects satisfied DSM–IV diagnostic criteria
TABLE 1. Comparisons of T scores on CPRS-R and CTRS-R Factors at Three Conditions: Baseline, DEX, and MPH

<table>
<thead>
<tr>
<th>Mean T Score (SD)</th>
<th>ANOVA</th>
<th>Paired t Tests</th>
<th>Parent Global Perceptions Questionnaire</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>DEX</td>
<td>MPH</td>
</tr>
<tr>
<td>CPRS-R Conduct problems</td>
<td>74.12 (16.91)</td>
<td>62.39 (16.80)</td>
<td>60.66 (14.93)</td>
</tr>
<tr>
<td>Learning problems</td>
<td>89.09 (10.28)</td>
<td>69.16 (15.65)</td>
<td>68.79 (15.09)</td>
</tr>
<tr>
<td>Psychosomatic</td>
<td>61.19 (19.31)</td>
<td>55.94 (16.01)</td>
<td>53.86 (15.33)</td>
</tr>
<tr>
<td>Impulsive–hyperactive</td>
<td>73.46 (9.85)</td>
<td>57.33 (11.22)</td>
<td>57.39 (10.53)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>55.56 (12.6)</td>
<td>48.67 (10.08)</td>
<td>47.77 (9.59)</td>
</tr>
<tr>
<td>Hyperactivity index</td>
<td>84.63 (10.19)</td>
<td>64.89 (13.74)</td>
<td>64.28 (13.46)</td>
</tr>
<tr>
<td>CTRS-R Conduct problems</td>
<td>69.31 (16.43)</td>
<td>58.39 (13.69)</td>
<td>55.16 (11.99)</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>71.26 (13.24)</td>
<td>58.88 (11.08)</td>
<td>56.20 (11.02)</td>
</tr>
<tr>
<td>Inattentive–passive</td>
<td>71.46 (8.80)</td>
<td>55.69 (8.90)</td>
<td>54.09 (7.61)</td>
</tr>
<tr>
<td>Hyperactivity index</td>
<td>71.46 (11.45)</td>
<td>58.76 (10.57)</td>
<td>56.14 (10.17)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.

for ADHD. Of the subjects, 101 (80.8%) were ADHD–mixed type, 22 (17.6%) ADHD–predominantly inattentive, and 2 (1.6%) ADHD–predominantly hyperactive/impulsive, according to the diagnostic criteria for ADHD. Mean IQ was estimated to be 98.9 (SD = 13.8).

Highest group mean [SD] T scores on the CBCL were the attention problems (75.9 [8.4]), aggressive behavior (73.4 [11.2]), and total problems (72.0 [6.8]) scores. A similar pattern was seen on the TRF (attention problems 75.9 [8.4]), aggressive 67.4 [10.5], and total problems 67.0 [7.4]).

Response to Stimulant Medication

The CPRS–R and CTRS–R are considered together, followed by the Parental Global Perceptions questionnaire.

CPRS–R and CTRS–R

Mean T scores for every factor of the CPRS–R and CTRS–R were significantly lower on each drug, compared with scores at baseline (Table 1). Largest effects were found for the learning problems and impulsive–hyperactive factors of the CPRS–R and the hyperactivity and inattentive–passive factors of the CTRS–R for both drugs.

The results of the Hills and Armitage analysis of each factor of the CPRS–R and CTRS–R are presented in Table 2. There was a systematic trend toward MPH having a larger treatment effect than DEX. Differences were of small magnitude on the CPRS–R, with the anxiety factor being the only one with a P value <.05. On the CTRS–R, however, T scores were improved to a significantly greater degree on MPH than on DEX on all three factors, as well as on the hyperactivity index. Parent Global Perceptions Questionnaire

The five-point scales were dichotomized to represent positive or negative responses in that domain. Parental perceptions of their children’s reduced activity (DEX, 41.6%; MPH, 37.9%; P = .57) and improved concentration (DEX, 70.4%; MPH, 74.2%; P = .59) did not differ between the two drugs (McNemar’s modified χ² test). The parents of 68.8% of subjects rated them as “better” or “much better” overall (responders) during the period in which they took DEX, compared with 72.6% during the MPH period. There was no significant difference in the proportion of responders to the two drugs (McNemar’s test, χ² = .27; P = .60).

Parents’ Comparison of the Two Trial Periods

The parents of 104 (83.2%) of the 125 study subjects indicated that one trial period was clearly superior to the other for their child. The parents of 46 subjects (36.8%) specified the period in which their child was taking DEX as the preferred period, compared with 72.6% during the MPH period. There was no significant difference in the proportion of responders to the two drugs (McNemar’s test, χ² = 1.38; P > .1).

Responders Versus Nonresponders

Table 3 classifies the sample by combinations of response and nonresponse to the two stimulants, by the criteria described above, on each of the main outcome measures. There was only one nonresponder to both stimulants by all three measures. In Table 4, these data are presented in a slightly different way to address the important clinical question: If a child does not respond to one stimulant, what is the likelihood of response to the alternative stimulant?
Continuous Performance Test

Subjects achieved a higher number of correct responses on DEX compared with baseline score ($P = .01$), with a similar trend during the MPH phase ($P = .06$). Compared with the baseline score, subjects made fewer commission errors and omission errors on both DEX and MPH ($P < .001$). There was no significant difference between DEX and MPH on any of these measures.

Side Effects

The data concerning the relative side effects of these two drugs from the present study has been reported previously. There were two main findings: 1) Many symptoms commonly considered to be side effects of stimulant medication were present at baseline and, in fact, diminished with medication treatment; and 2) DEX was associated with a significantly greater severity of side effects than MPH, particularly negative emotional side effects (eg, irritability, tearfulness, anxiety).

Predictors of Response

The severity of baseline parental behavior rating (CBCL), severity of baseline teacher behavior rating (TRF), and aggressive–delinquent behavior predicted a greater response to both stimulants. Subjects with the DSM–IV category ADHD–combined type responded to a greater degree than those with predominantly inattentive type. Compared with subjects with an IQ $85$, those with IQ $<85$ had a significantly less marked response to DEX, but not to MPH. Response to the two drugs was then compared directly for the subgroup with IQ $<85$ ($n = 16$), but no differences were found.

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**TABLE 2.** Comparison of the Effects of DEX and MPH, by Conners’ Rating Scales Factors (Change in T Scores From Baseline)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Period Effect (Period A–Period B)</th>
<th>Treatment-by-Period Interaction</th>
<th>Difference in Treatment Effect (MPH Effect–DEX Effect)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPRS-R Conduct problems</td>
<td>$-0.98$ (.50) $(-3.81,1.85)$</td>
<td>$0.06$</td>
<td>$2.18$ ($-6.5,5.01)$</td>
</tr>
<tr>
<td>CPRS-R Learning problems</td>
<td>$-3.46$ (.03) $(-6.58,3.33)$</td>
<td>$0.54$</td>
<td>$-0.79$ $(-2.34,3.91)$</td>
</tr>
<tr>
<td>CPRS-R Psychosomatic</td>
<td>$-3.94$ (.01) $(-6.96,-0.92)$</td>
<td>$0.04$</td>
<td>$-2.12$ $(-9.0,5.14)$</td>
</tr>
<tr>
<td>CPRS-R Impulsive–hyperactive</td>
<td>$-1.83$ (.13) $(-4.23,5.55)$</td>
<td>$0.43$</td>
<td>$-0.21$ $(-2.18,2.61)$</td>
</tr>
<tr>
<td>CPRS-R Anxiety</td>
<td>$-0.97$ (.06) $(-1.98,0.04)$</td>
<td>$0.83$</td>
<td>$1.20$ $(-1.92,2.20)$</td>
</tr>
<tr>
<td>CTRS-R Conduct problems</td>
<td>$-2.58$ (.10) $(-5.64,4.99)$</td>
<td>$0.90$</td>
<td>$1.03$ $(-2.03,4.10)$</td>
</tr>
<tr>
<td>CTRS-R Hyperactivity</td>
<td>$-1.73$ (.10) $(-3.81,3.55)$</td>
<td>$0.93$</td>
<td>$2.78$ $(1.11,5.50)$</td>
</tr>
<tr>
<td>CTRS-R Inattentive–passive</td>
<td>$-1.2$ (.07) $(-2.52,1.11)$</td>
<td>$0.94$</td>
<td>$1.61$ $(0.29,4.92)$</td>
</tr>
<tr>
<td>CTRS-R Hyperactivity index</td>
<td>$-2.13$ (.03) $(-4.04,-22)$</td>
<td>$0.58$</td>
<td>$2.60$ $(0.69,4.51)$</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.

**TABLE 3.** Number (%) of Responders and Nonresponders to DEX and MPH, by Parent Global Perceptions, CPRS-R, and CTRS-R

<table>
<thead>
<tr>
<th>Measure</th>
<th>Responders to Both</th>
<th>Responders to DEX but not to MPH</th>
<th>Responders to MPH but not to DEX</th>
<th>Nonresponders to Both</th>
<th>$P$ Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent Global Perceptions</td>
<td>58 (46.4)</td>
<td>72 (57.6)</td>
<td>16 (12.8)</td>
<td>27 (82)</td>
<td>41 (32.8)</td>
</tr>
<tr>
<td>CPRS-R†</td>
<td>29 (23.2)</td>
<td>25 (20)</td>
<td>16 (27.3)</td>
<td>16 (67.7)</td>
<td>0.21</td>
</tr>
<tr>
<td>CTRS-R†</td>
<td>39 (31.2)</td>
<td>32 (82)</td>
<td>34 (27.2)</td>
<td>27 (79.4)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

* Hyperactivity index.

**TABLE 4.** Proportion of Nonresponders to One Stimulant Who Responded to the Alternative Stimulant

<table>
<thead>
<tr>
<th>Measure</th>
<th>Nonresponders to DEX (%) Total</th>
<th>No. (%) of DEX Nonresponders Who Responded to MPH</th>
<th>Nonresponders to MPH (%) Total</th>
<th>No. (%) of MPH Nonresponders Who Responded to DEX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent Global Perceptions</td>
<td>39 (31.2)</td>
<td>32 (82)</td>
<td>34 (27.2)</td>
<td>27 (79.4)</td>
</tr>
<tr>
<td>CPRS-R†</td>
<td>29 (23.2)</td>
<td>19 (65.5)</td>
<td>31 (24.8)</td>
<td>21 (67.7)</td>
</tr>
<tr>
<td>CTRS-R†</td>
<td>50 (40)</td>
<td>25 (100)</td>
<td>41 (32.8)</td>
<td>16 (39)</td>
</tr>
</tbody>
</table>

* Hyperactivity index.
Age, gender, socioeconomic status, and anxiety–depression were not predictive of a greater or lesser response to either drug.

DISCUSSION

Reviews of separate trials of individual drugs (ie, MPH studies and DEX studies) were published in 196717 and 1977.4 However, only seven published studies have compared these two drugs directly (Table 5). As part of a recent review, Richters et al12 tallied the subjects from such comparative studies of the two major stimulants. Of a total of 141 subjects, 50 were rated globally as better on DEX, 37 responded preferentially to MPH, and most of the remainder did well on both. No advantage to either drug has been demonstrated to date.

This study is the first to report differential efficacy between the two stimulants MPH and DEX. Differences were most marked by teacher report (CTRS–R). The degree of response as measured by the CTRS–R was greater for MPH than for DEX. Mean improvement on the hyperactivity index was 2.6 T score points greater with MPH than with DEX. Thus, the differences were not only statistically significant but clinically important as well. Categorical analysis of these data demonstrated that almost 8% more subjects were rated as responders to MPH than to DEX by CTRS–R.

By parental rating (CPRS–R), the differences in efficacy between the two stimulants were in the same direction as with teacher report (ie, greater benefit from MPH than from DEX), although not as marked. In addition, almost 10% more parents said they preferred MPH to DEX (46.4% vs 36.8%), all things considered. It is important to note that these findings were seen with a twice-daily dosing regimen. Parents would possibly have reported greater differences had an after-school dose been used. This was not given because it was felt that an afternoon dose of DEX would have caused a great deal of sleep disturbance.

Approximately 60% of subjects were rated by their parents as “the same” or “more than usual” for activity for both drugs. This may have reflected variation in parents’ interpretation of the question. Increased activity may be seen as a positive reaction, ie, more productive.18 This may be particularly so for those subjects with ADHD–predominantly inattentive type, in which overactivity was not a presenting problem. Parents felt that the child’s concentration was improved in 70.4% of subjects while taking DEX, and in 74.2% with MPH. These figures are remarkably similar to the proportions seen by parents as improved overall, suggesting that impaired concentration was the primary symptom in the eyes of parents.

The categorical analysis of nonresponders demonstrated that if a child with ADHD does not do well on one stimulant, he has a good chance of responding to the alternative. Depending on the measure examined, between 50% and 82% of nonresponders to DEX responded to MPH, and between 39% and 79.4% of nonresponders to MPH responded to DEX. By trying both drugs and using a range of outcome measures, 124 of 125 subjects were rated as responders on at least one measure. This is consistent with earlier work. Winsberg et al19 conducted a random-order intrasubject comparative study of MPH, DEX, and placebo, and found that equal proportions (60%) of subjects responded to either drug, but that a small number of children responded selectively to one or the other. More recently, Elia et al20 measured the response of 48 boys with ADHD to DEX and MPH in a well-designed and comprehensive study. A total of 79% of subjects responded to MPH and 88% to DEX, and all but 2 responded to one or the other stimulant by global rating. Overall, 47 of 48 boys were considered to have responded to one or the other stimulant and were discharged on that drug (22 on MPH, 25 on DEX). Vyborova et a121 reported a higher proportion of subjects to be responsive to DEX, although the mean magnitude of effect was greater with MPH. Unfortunately the same dose was used for both DEX and MPH in this single-blind, crossover study. The finding of similar efficacy between long-acting forms of MPH and DEX21 has limited applicability to the use of the standard DEX preparation.

On the CPT, subjects made more correct responses and fewer errors on both DEX and MPH relative to baseline performance. These results are consistent with the improvement in CPT performance found previously with stimulant medication.22,23 No differences between the two stimulants were seen on these primary CPT measures.

The main finding from analysis of predictors of response was that the magnitude of response was related to the severity of baseline symptoms. This phenomenon has been reported previously24,25 and may be considered a true clinically useful predictive factor. However, regression to the mean artifact may partly account for this; that is, subjects with the most statistically deviant scores at baseline tend to display the greatest change in score with treatment. The finding of a greater response among aggressive subjects may be another expression of the phenomenon of more severe children improving by a greater margin. ADHD subjects with comorbid aggressive–delinquent behavior may be considered a more severe group and, therefore, have the most room to move toward the normal range. The data from this study suggest that children with ADHD–combined type may show a greater degree of response than those with ADHD–predominantly inattentive type. This finding may reflect the problem of adequately measuring change in children with ADHD–predominantly inattentive type. In children without hyperactivity, short-term change may be harder to discern, and multiple measures or repeated measures over longer intervals may be needed to demonstrate equivalent benefits from medication. Because the subgroup of girls studied was small, the power to detect gender differences was limited.

Several authors have discussed the lack of reliable predictor variables,12,24 and their identification remains one of the most elusive aspects of stimulant drug research. There are a number of possible reasons why specific predictors of response were not defined in this study. First, the number of subjects...
<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Experimental Design</th>
<th>Dosage</th>
<th>n (Boys)</th>
<th>Age (Mean)</th>
<th>Outcome Measures</th>
<th>Primary Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weiss et al (1971)</td>
<td>Results of two separate parallel group, double-blind, placebo-controlled studies of DEX and MPH</td>
<td>Individualized to maximum of DEX 20 mg qid, MPH 50 mg qid</td>
<td>DEX, 38 (32) MPH, 51 (44)</td>
<td>6–12 (8.1)</td>
<td>Mothers' global judgment, various cognitive measures</td>
<td>Both stimulants superior to placebo, and roughly equivalent</td>
</tr>
<tr>
<td>Conners (1972)</td>
<td>Parallel group, double-blind study</td>
<td>Individualized to DEX 15 mg bid, MPH 30 mg bid</td>
<td>75 (70)</td>
<td>6–13 (9.3)</td>
<td>Various psychometric tests, CPT</td>
<td>Similar overall efficacy</td>
</tr>
<tr>
<td>Winsberg et al (1974)</td>
<td>Placebo-controlled double-blind crossover study</td>
<td>Individualized to DEX 20 mg bid, MPH 30 mg bid</td>
<td>18 (15)</td>
<td>5–11 (8.5)</td>
<td>CTRS</td>
<td>Both drugs superior to placebo; equal proportions of subjects responded to each</td>
</tr>
<tr>
<td>Arnold et al (1978)</td>
<td>Placebo-controlled double-blind crossover study</td>
<td>Individualized to DEX 5–30 mg/d, MPH 10–60 mg/d</td>
<td>29 (22)</td>
<td>5–12 (8)</td>
<td>Various parent-, teacher-, and psychiatrist-completed ratings scales</td>
<td>Both more effective than placebo; no significant differences; 89% responded well to one or other</td>
</tr>
<tr>
<td>Vyborova et al (1984)</td>
<td>Single-blind crossover</td>
<td>Mean 38 mg/d for both DEX and MPH</td>
<td>28 (25)</td>
<td>6–14 (NA)</td>
<td>Cerny scale</td>
<td>63% responded to DEX, 53% to MPH; mean improvement greater with MPH</td>
</tr>
<tr>
<td>Pelham et al (1990)</td>
<td>Placebo-controlled, double-blind, crossover study comparing sustained-release DEX (DS), sustained-release MPH (SR-20), and standard MPH</td>
<td>DS 10 mg mane, SR-20 20 mg mane, MPH 10 mg bid</td>
<td>22 (22)</td>
<td>8–13 (10.4)</td>
<td>Frequencies of certain behaviors, ACTRS, academic productivity and accuracy, daily report card, CPT</td>
<td>No significant group differences between the three drug conditions, all of which were superior to placebo</td>
</tr>
<tr>
<td>Elia et al (1991)</td>
<td>Placebo-controlled, double-blind, crossover study</td>
<td>Based on body weight; increased weekly to DEX 1.3 mg/kg/d, MPH 2.5 mg/kg/d</td>
<td>48 (48)</td>
<td>6–12 (8.6)</td>
<td>ACTRS, CTRS, CPRS, CPT, PAL, truncal activity monitor</td>
<td>Both drugs superior to placebo; no significant group differences; 98% responded well to one or other stimulant</td>
</tr>
</tbody>
</table>

ACTRS indicates Abbreviated Conners’ Teacher Rating Scale; PAL, paired associate learning task.
may not have been sufficient to determine predictive utility. The second possible explanation is that the relevant or important influences on response to stimulant medication were not examined. Finally, there may not actually be any factors that inform the clinician of which children are likely to respond favorably to stimulant medication. In ADHD, there are so many interrelated influences on the child’s presentation and response to therapy that it may be impossible to anticipate response to stimulant medication based on any one attribute or feature of the case. The short-term trial, which is used by practitioners in everyday clinical practice, may ultimately be the best mean of determining the suitability of stimulant drug treatment for an individual child.

Children with ADHD with comorbid anxiety disorders have been reported to respond less consistently and less dramatically to MPH than those without anxiety.26 In this study, however, subjects with or without anxiety responded equally well. It is unclear why this finding should contrast with earlier work.

The dose of 0.3 mg/kg twice daily for MPH used in this study has been commonly used in research studies, because this moderate dose has been shown to induce maximal improvements in distractibility and performance on memory tasks (speed and accuracy), with a relatively low risk of adverse effects.27 Less is known about the optimal dose of DEX, because there has been much less investigation into this drug than into MPH. The recommended dose of DEX is half that of MPH.28 However, there is wide variation in the individual dose required to achieve maximal effect,29,30 and a proportion of nonresponders would possibly have done better on a higher dose. The use of a varying dosage regimen in future studies might shed more light on the question of the optimal doses of these two stimulants.

This study provides strong evidence of a group mean superiority of MPH over DEX from the teachers’ point of view, and some evidence that parents also prefer MPH over DEX. This is the first research data to indicate that one of these stimulants may have a general advantage over the other. However, it needs to be emphasized that DEX was the preferred drug for more than one third of subjects. Because DEX is substantially less expensive and there appears to be no reliable predictors of which children will do better on which stimulant, it would seem reasonable to prescribe DEX as the first-line agent for children with ADHD in whom a trial of medication is considered clinically appropriate. If the child is not greatly improved or experiences unacceptable adverse effects with DEX, then MPH should be tried.

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REFERENCES

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