

# Attention Deficit Disorder and Methylphenidate: Normalization Rates, Clinical Effectiveness, and Response Prediction in 76 Children

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## ABSTRACT

**Objective:** To evaluate the magnitude and clinical significance of methylphenidate (MPH) effects on the classroom behavior and academic performance of 76 children with attention deficit disorder/hyperactivity (ADHD). **Method:** A double-blind, placebo controlled, within-subject (crossover) experimental design was used to evaluate acute MPH effects at four dose levels (5 mg, 10 mg, 15 mg, and 20 mg) on children's attention, academic functioning, and behavior in regular classroom settings. Results were contrasted with a normal control sample. **Results:** Standard statistical analysis revealed MPH effects on classroom functioning that were primarily linear. Analysis of the clinical significance of effects indicated that large proportions of treated children exhibited significantly improved or normalized classroom functioning; however, a large subset of them failed to show improved academic functioning. Overall, children failing to respond at lower dose levels have a high probability of improving or becoming normalized as a function of increasing dose. **Conclusions:** For a majority of children with ADHD, MPH results in significantly improved or normalized attention and classroom behavior. A significant subset, however, fail to realize gains in their academic functioning and will require supplemental interventions. *J. Am. Acad. Child Adolesc. Psychiatry*, 1994, 33, 6:882-893. **Key Words:** attention deficit disorder, hyperactivity, methylphenidate, psychostimulants, academic functioning.

Few if any knowledgeable professionals question the short-term therapeutic efficacy of psychostimulants (particularly methylphenidate [MPH]) in treating children with attention-deficit hyperactivity disorder (ADHD). Its current status as a mainstay treatment and first-line defense for ADHD has evolved from an extensive body of scientific data demonstrating salutary effects across a broad range of behaviors and cognitive

abilities, including both in vivo and contrived situations and settings (see Barkley, 1990; Gadow, 1992; Henker and Whalen, 1989, for reviews).

The majority of treatment outcome research has emphasized three primary areas of inquiry: The effects of psychostimulants on (1) behaviors that are assumed to represent core components of the disorder itself such as attention, impulsivity, and overactivity; (2) interpersonal relationships or interaction styles; and (3) learning as it relates to classroom academic performance and achievement.

Findings representative of this latter area of inquiry have been equivocal and frequently debated over the past decade. The conundrum is embodied in the paradoxical findings that psychostimulants appear to enhance children's behavior on a short-term basis in both analog (Whalen et al., 1979) and natural classroom environments (Rapport et al., 1987), yet do not appear to translate into long-term gains related to academic achievement (Weiss and Hechtman, 1993). Conclusions drawn from long-term outcome studies have been

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criticized on methodological grounds and numerous explanations have been offered to account for the paradoxical findings (Pelham and Murphy, 1986). Chief among the concerns is the traditional practice of evaluating treatment response on the basis of parent and/or teacher reports. The practice has been questioned because of the inadequacy of such measures for establishing optimal dosage, especially with respect to cognitive and academic functioning (Rapport, 1990).

Questions concerning whether behavior and learning are affected at different dosage levels as proposed in the seminal study by Sprague and Sletor (1977) are also relevant to long-term outcome. Although most recent outcome studies have found similar dose-related effects on children's behavior and academic performance, their results have been limited by restricted dosage ranges (Douglas et al., 1986; Pelham et al., 1989) and/or derived from analog settings using contrived rather than actual classroom academic assignments (Douglas et al., 1988; Pelham et al., 1989). Conversely, Rapport and colleagues have conducted a series of dose-response studies in natural classroom settings using regular classroom academic assignments, but generalization of treatment effects have been restricted by the small to moderate size of their samples (see Rapport, 1990, for a review).

There is also relatively limited information available concerning the extent to which MPH-treated children approach normal levels of functioning. Previous outcome studies using standard statistical significance tests have reported enhanced attention (Loney et al., 1979; Whalen et al., 1979), reduced aggressiveness (Hinshaw et al., 1989), and improvements in some aspects of classroom behavior (Abikoff and Gittelman, 1985) sufficient to render MPH-treated children indistinguishable from normal control children. Standard analyses, however, do not allow specification of the extent to which individual MPH-treated children attain levels of functioning comparable to those of their normal peers, improve while remaining impaired, or deteriorate during treatment. A recent outcome study has addressed this issue directly (DuPaul and Rapport, 1993), but requires replication with a larger sample to facilitate the design of comprehensive treatment programs to maximize both overall and specific therapeutic gains.

Finally, limited empirical evidence exists concerning the prediction of psychostimulant response in children with ADHD (Loney, 1986). In particular, questions

concerning whether a child will respond favorably at higher doses given a lack of response at lower doses remain unanswered by past outcome studies.

The present study addresses the dose-response, clinical significance, and prediction issues raised above. It represents the largest double-blind, placebo-controlled, dose-response outcome study reported thus far concerning the effects of MPH on ADHD children's behavior and academic functioning in natural classroom environments.

## METHOD

### Subjects

Two groups of children participated in the study. The attention deficit disorder/hyperactivity (ADDH) group was selected from 134 children with chronic problems of inattention, impulsivity, and overactivity who were referred to the Children's Learning Clinic (CLC) by pediatricians, psychiatrists, and school system personnel over a 5-year time period. All referred children and their parents participated in a detailed, semistructured clinical interview with the senior author (M.D.R.) at the CLC; the interview was adapted from the Schedule for Affective Disorders and Schizophrenia for School-Age Children (Orvaschel et al., 1982) and reviewed each of the disorders usually first evident in infancy, childhood, or adolescence as described in the *DSM-III* (American Psychiatric Association, 1980). Seventy-six children met each of the following criteria and participated in the study: (1) an independent diagnosis by the child's referring physician and the CLC's directing clinical psychologist (M.D.R.) using *DSM-III* criteria for ADDH; (2) a maternal report of a developmental history consistent with ADDH and problems in at least 50% of the situations on Barkley's (1990) Home Situations Questionnaire; (3) a maternal rating of at least 2 standard deviations above the mean for the child's age on the Werry-Weiss-Peters Activity Scale (Routh et al., 1974); (4) a teacher rating of at least 2 standard deviations above the mean on the Abbreviated Conners Teacher Rating Scale (ACTRS) (Werry et al., 1975); and (5) absence of any gross neurological, sensory, or motor impairment as determined by pediatric examination.

Of the 58 nonparticipating children, 31 met diagnostic criteria and participated in an abbreviated placebo-controlled medication trial (5 to 15 mg of MPH) during the first year of the clinic's operation and are not reported herein. Insufficient data were collected for two subjects owing to school conflicts. One child moved out of state before completing the medication trials. The remaining 24 children scored within the established range for inclusion on the various rating scales, but their developmental histories were inconsistent with *DSM-III* criteria (i.e., onset of symptoms was not reported to occur before age 7 and/or duration was less than 6 months). Fourteen of these children met criteria for conduct disorder, seven showed distinct signs of anxiety according to structured interviews with parents (social phobia in one, and separation anxiety in six), two children were suspected of seizure disorder and referred for neurological evaluation, and one child met criteria for eating disorder.

Using the described inclusion criteria, a total of 76 children with ADDH (66 boys, 10 girls) between the ages of 6 and 11

years (mean = 8.51 years) participated in the study after informed consent was obtained from their parents. All children were Caucasian, of at least average intelligence (mean IQ = 102.17; SD = 10.87) as assessed by the Peabody Picture Vocabulary Test-Revised, Form L (Dunn and Dunn, 1981), and from families of low to middle socioeconomic status (Hollingshead, 1975). Eight children had experienced brief trials of psychostimulant within the past 4 years. All children were considered pervasively hyperactive according to the clinical interview and rating scale scores. Children who were comorbid for conduct disorder were purposefully excluded from the study. Comorbidity for oppositional disorder was not assessed owing to the controversial nature of the disorder at the time when the study was initiated. Many children experienced symptoms of but did not meet formal diagnostic criteria for anxiety and mood disorders.

The normal control group consisted of 25 children (20 boys, 5 girls) between the ages of 6 and 11 years (mean = 8.56, SD = 1.81) who were attending regular education classrooms in several public elementary schools in an urban district. These children were randomly selected from classroom rosters, did not evidence symptoms of ADDH or other problem behaviors according to parent and teacher report, and had never been referred for an evaluation of learning or behavior problems. The normal control children were of average or above-average intelligence based on standardized test results provided by each child's school and from families of low to middle socioeconomic status. Teacher ratings on the ACTRS for all members of this group were within 1.5 standard deviations of the mean for the child's age.

There were no significant differences between the ADDH and normal comparison groups with respect to age, IQ, and socioeconomic status. The presence of learning disability was not assessed in either group. All children were currently attending regular elementary school classrooms, although several of the ADDH children concurrently received special education services (usually in reading and processing skills).

### Experimental Design and Procedures

For children in the ADDH group, the dependent measures were collected on a weekly basis over the course of 6 consecutive weeks as part of an evaluation of their response to MPH. These same measures were obtained during a 1-week period for normal control subjects.

**Drug Administration.** A double-blind, placebo-controlled, within-subject (crossover) experimental design was used in which the ADDH children received each of the four MPH doses and an inert placebo after baseline assessment. Order of drug administration was counterbalanced and determined by random assignment such that an equal number of children received each dose during a given week of the study. MPH was prescribed by each child's physician in the following doses: placebo, 5 mg (range = 0.10 to 0.26 mg/kg), 10 mg (range = 0.20 to 0.52 mg/kg), 15 mg (range = 0.30 to 0.79 mg/kg), and 20 mg (range = 0.40 to 1.1 mg/kg). Fixed doses (versus milligrams per kilogram) were prescribed to reflect typical pediatric practice in the United States (*Physicians' Desk Reference*, 1993) and because children's response to MPH dosage manipulation has been shown to be independent of total body weight (Rapport et al., 1989; Swanson et al., 1991). All MPH and placebo doses were packaged in colored gelatin capsules by the clinic's pharmacist to avoid detection of dose and taste. Capsules were sealed in individual, daily dated envelopes to help control for accurate dose administration.

After baseline data collection (first week), parents were given 1 week's medication in predated envelopes at a single dose level (i.e., placebo, 5 mg, 10 mg, 15 mg, or 20 mg). This procedure continued until each child received every dose for 6 consecutive days. All weekly dose changes occurred on Sundays (i.e., no capsules were administered on Saturdays) to allow for "washout" and to control for possible rebound effects. Parents were instructed to give their child a capsule each morning, one-half hour before breakfast. Both used and unused envelopes were returned on a weekly basis to control for medication compliance. Medication was properly administered nearly 100% of the time, with "makeup" observation days scheduled after rare occasions when compliance was not obtained.

### Assessment: Classroom Measures

Children were observed in their regular classrooms for 20-minute intervals, 3 days per week across the 6-week (ADDH children) or 1-week (normal control group) evaluation period. No two children were in the same classroom. Observations were completed during the morning hours owing to the behavioral time-response course of MPH (Swanson et al., 1978) and began 1.5 to 2 hours after children with ADDH received their morning medication. Children in the normal control group were observed during the morning hours at a time that was held constant across all observation sessions. During each observation period, children completed their usual in-seat academic work assigned by the classroom teacher (e.g., mathematics or language arts worksheets).

**Teacher Ratings.** Classroom teachers completed the ACTRS each Friday throughout the study (i.e., 1 week for the normal control group and 6 consecutive weeks for the ADDH group). The outcome reflected the children's behavior during the morning hours (until 11:30 A.M.) only of that week. All teachers were blind as to when medication was administered and specific doses. The ACTRS was used owing to its sensitivity in detecting MPH effects and ease of administration.

**Attention.** Children were observed by trained undergraduate and graduate-level research assistants for 60 consecutive intervals during each observation period throughout the study. Each interval was divided into 15 seconds of observation followed by 5 seconds for recording. A child's behavior was categorized as either on-task or off-task in a manner identical with that used by Rapport et al. (1987). Off-task behavior was defined as visual inattention to one's materials for more than 2 consecutive seconds within each 15-second observation interval, unless the child was engaged in an alternative task-appropriate behavior (e.g., sharpening a pencil). Observers were situated in the classroom such that they avoided direct eye contact with and were distanced from the target child by approximately half the classroom size, while allowing for clear determination of task-related attention. Observers were blind to when medication was administered and specific doses for children in the ADDH group. For the normal control group, observers were blind to diagnosis and teacher ratings.

**Academic Efficiency.** Children's performance on regularly assigned academic work during scheduled observation periods was used as a dependent measure to preserve ecological validity yet maintain adequate experimental control. Classroom teachers assigned academic seat work consistent with the child's ability level, but with the stipulation that (1) the assignment be worked on during the optimal medication period (1.5 to 2 hours after medication), and (2) the assignment be gradable in terms of percentage completed and percentage accurate. Assignments were graded after class by either the teacher or primary observer. Daily performance was recorded for both the percentage of problems completed and the

percentage correct. The two scores were subsequently combined to calculate an academic efficiency score (AES), which represents the percentage of academic assignments completed correctly.

**Reliability.** Interobserver reliability checks of each child's on-task behavior were obtained on 33% of the observation days, and at least once per week for each participant in the study. Obtained and chance estimates were computed for occurrence, nonoccurrence, and overall agreement. Overall reliability was consistently above 85%, with a mean of 92.4% (range = 86.3 to 99.8) across children. A mean  $\kappa$  value of .84 was obtained across all observations. Overall reliability for AES data was consistently above 95%, with a mean of 97% and a  $\kappa$  coefficient of .96.

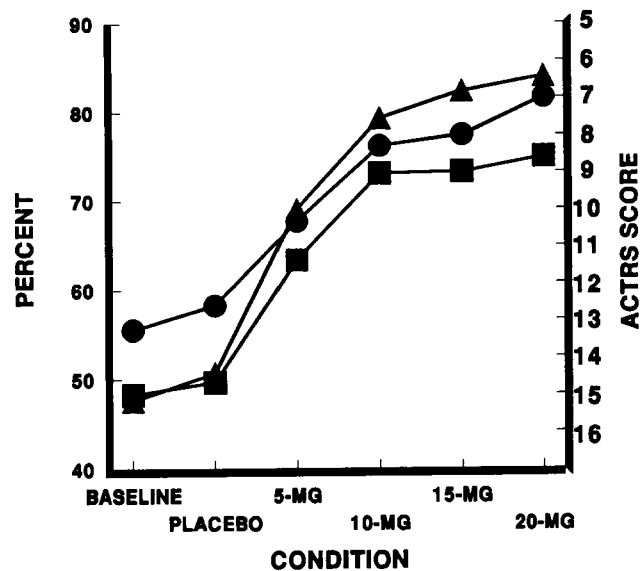
## RESULTS

MPH effects on children's attention (on-task), percentage of academic assignments completed correctly (AES), and weekly teacher ratings of classroom behavior (ACTRS) were subjected to a three-tier level of analysis to address the experimental questions posed in the study. The first series of analyses contains the overall, between-dose, and trend analysis for the ADDH group ( $n = 76$ ). In the second series, children with ADDH are compared with a normal control group to determine the degree to which different aspects of their classroom functioning fell within normal limits as a result of MPH treatment. Behavioral specificity of drug effects are assessed by analyzing the effects of dose on different domains of classroom functioning. The third series presents information relevant to the conditional probability of responding to increasingly higher doses of MPH for individual children given a lack of response at lower doses.

### Series I Analysis: Overall, Between-Dose Effects, and Trend Analysis

**Overall MPH Effects.** Children's attention (on-task), percentage of academic assignments completed correctly (AES), and weekly teacher ratings (ACTRS) under baseline, placebo, and the four active MPH conditions (5 mg, 10 mg, 15 mg, 20 mg) were analyzed using a 6 (dose condition)  $\times$  3 (classroom measures) multivariate analysis of variance. A significant main effect emerged for dose condition (Wilks'  $\lambda$  [5,71] = .185,  $p < .001$ ), indicating that scores on the composite of the three classroom measures changed reliably as a function of dose. Mean scores and dose-response curves for the three measures across experimental conditions are depicted in Figure 1.

Follow-up univariate analysis of variance (ANOVAs) with repeated measures across dose were performed to



**Fig. 1** Mean group dose-response curves for the three classroom measures: on-task (attention; ●), academic efficiency score (■), and the Abbreviated Conners Teacher Rating Scale (ACTRS; ▲). Upward movement on the y-axis indicates improvement.

examine the overall effects of MPH for each of the dependent variables. Significant main effects of dose emerged for children's attention ( $F[5,375] = 78.12$ ,  $p < .00001$ ), academic efficiency ( $F[5,375] = 43.46$ ,  $p < .00001$ ), and teacher ratings of classroom behavior ( $F[5,375] = 65.26$ ,  $p < .00001$ ). The two components of the academic efficiency measure were also analyzed to determine whether they were affected to a similar degree by MPH. Significant effects were observed for both the percent-complete ( $F[5,375] = 34.59$ ,  $p < .00001$ ) and percent-correct ( $F[5,375] = 14.66$ ,  $p < .00001$ ) components.

**Magnitude of Drug Effects.** Omega-squared values were calculated separately for the significant ANOVAs to determine the approximate percentage of variance of each dependent variable accounted for by MPH treatment. These values indicated that MPH accounted for a significant amount of variance for children's attention (46%), academic efficiency (32%), and teacher ratings (41%). A stronger relationship was found between dose and the percent-complete (27%) than the percent-correct (13%) component of the academic efficiency measure.

**Between-Dose Effects.** Post hoc comparisons, using the Dunn (Bonferroni) correction to control for experiment-wise error rates (Keppel, 1991), were conducted as a follow-up to all significant ANOVAs to elucidate

specific between-dose differences for each measure. Results are summarized in Table 1. Children's attention (on-task), academic efficiency (AES), and classroom behavior (ACTRS) were significantly enhanced under all active medication conditions relative to baseline and placebo ( $p < .00001$ ). Moreover, 10-mg, 15-mg, and 20-mg doses resulted in significant improvement for all three classroom measures compared with the 5-mg dose ( $p < .0001$ ). Children's attention was also significantly enhanced under the 20-mg dose compared with the 10-mg ( $p < .0001$ ) and 15-mg dose ( $p < .01$ ). No additional between-dose differences were significant.

Different patterns of between-dose differences emerged for the percent-complete and percent-correct components of academic efficiency. Children completed a significantly greater percentage of academic assignments under the 10-mg, 15-mg, and 20-mg MPH conditions compared with baseline, placebo, and 5 mg ( $p < .001$ ). In contrast, their accuracy was enhanced under all MPH conditions relative to baseline and placebo ( $p < .001$ ), but no other differences between active drug conditions were evident (see Table 1).

*Trend Analyses.* Analyses of trend were performed using placebo and active medication conditions to examine the shape of the relationships among dose and

children's attention, academic efficiency, and ACTRS scores. The proportion of treatment variance ( $R^2_{Trend}$ ) was computed for each trend component to elucidate the properties of the dose-response functions (Keppel, 1991). This analysis allows one to determine the relative contribution of each trend component (e.g., linear, quadratic, cubic) to a dose-response function when more than one component reaches statistical significance.

The shape of the relationships among dose and the three classroom measures was characterized by both significant linear and quadratic trends. Higher order trends (e.g., cubic) were not significant. The linear component accounted for the greatest percentage of explained variance for all three measures (see  $R^2_{Trend}$  in Table 2), indicating that classroom functioning improved primarily as a function of increasing dose with smaller increases in improvement rates evidenced as dose increased above 10 mg.

Series II Analyses: ADDH versus Normal Control

*Normalizing Effects of Dose.* Although statistically robust effects of MPH on ADDH children's classroom functioning were demonstrated in the preceding series of analyses, the clinical significance of these effects remains to be empirically established. Statistical methods described by Jacobson and Truax (1991), and modified by Speer (1992) to control for potential regression effects, were used to determine the degree to which the behavior of ADDH children under different doses of MPH resembled that of normal children.

Briefly, this approach assumes that deviation of initial scores (e.g., classroom measures) from the population mean are due in part to time-sampling error. Obtained scores are thus adjusted using a correction factor that is proportional to the test-retest reliability coefficient obtained for each dependent measure (i.e., on-task, AES, and ACTRS). A confidence interval whose width is equal to twice the standard error of measurement is then constructed on each side of the corrected score. This method allows for the derivation of statistically based categories describing different levels of clinical status. Children whose scores fall above the baseline (pretreatment) corrected score and outside the confidence interval as a function of treatment are considered reliably "improved"; cases falling within or below the interval are characterized as "unchanged" and "deteriorated," respectively; and those showing improvement

**TABLE 1**  
Summary of Between-Dose Comparisons

Measure	Dose			
	5 mg	10 mg	15 mg	20 mg
Attention (on-task)				
Baseline	†	†	†	†
Placebo	†	†	†	†
5 mg		†	†	†
10 mg				***
15 mg				*
Academic efficiency score				
Baseline	†	†	†	†
Placebo	†	†	†	†
5 mg		**	**	**
ACTRS scores				
Baseline	†	†	†	†
Placebo	†	†	†	†
5 mg		**	†	†

*Note:* All significant differences indicate that performance or behavior ratings under dose shown at the top of Table 1 were superior to those shown on the left side of the Table. ACTRS = Abbreviated Conners Teacher Rating Scale. There were no significant differences between placebo and active drug or baseline conditions for the three dependent measures.

\*  $p < .01$ ; \*\*  $p < .001$ ; \*\*\*  $p < .0001$ ; †  $p < .00001$ .

**TABLE 2**  
Summary of Trend Analysis

Measure	Trend	F	R <sup>2</sup> <sub>Trend</sub>	F <sub>tes</sub>
Attention (on-task)	Linear	182.02***	.92	6.76*
	Quadratic	22.63**	.07	1.99
Academic efficiency score	Linear	99.77***	.81	9.11*
	Quadratic	23.69***	.18	1.05
Teacher ratings (ACTRS)	Linear	132.92***	.84	11.01*
	Quadratic	28.78***	.15	<1

Note: R<sup>2</sup><sub>Trend</sub> = proportion of treatment variance attributable to corresponding trend; F<sub>tes</sub> = significance test determining whether treatment variance remaining after extraction of corresponding trend justifies extraction of next higher order trend; ACTRS = Abbreviated Conners Teacher Rating Scale.

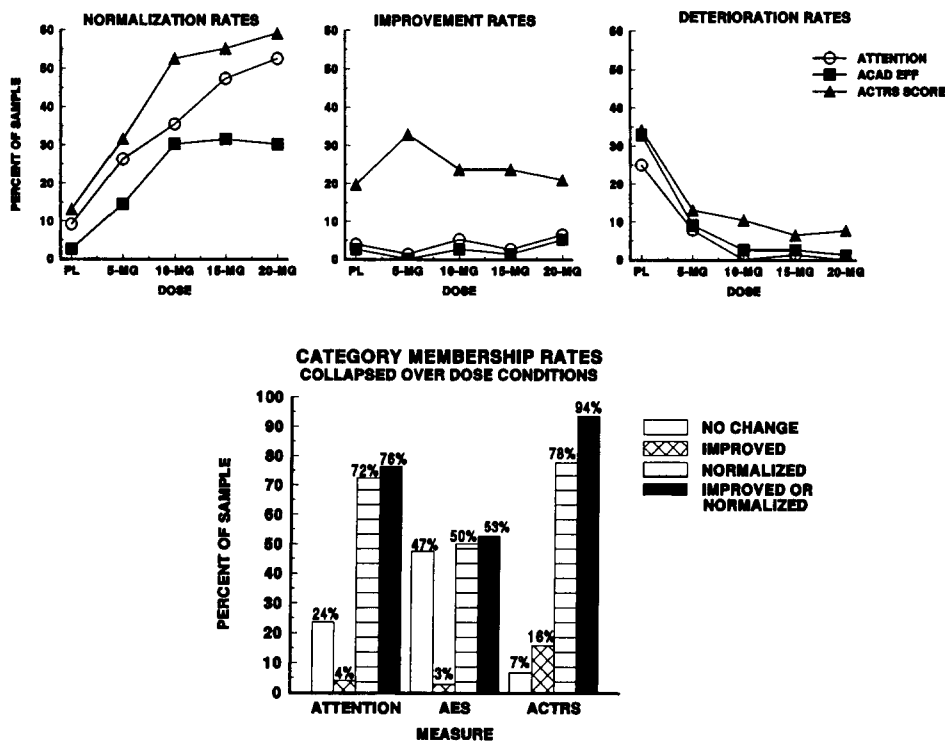
\* p < .001; \*\* p < .0001; \*\*\* p < .00001.

and whose scores exceed the cutoff score defining the normal population's range of functioning are considered "normalized." The cutoff score used herein was the adjusted midpoint between means for the ADDH and normal control children as discussed by Jacobson and Truax (1991).

The percentages of the ADDH sample falling in normalized, improved, and deteriorated categories are depicted in Figure 2 for each classroom measure (see top three graphs of Fig. 2). Inspection of the upper

left-hand graph reveals that relatively large proportions of children exhibited normalized attention and improvement in their classroom behavior as a function of increasing dose. Children's AESs, in contrast, showed an initially steep rise between placebo and 10-mg conditions, without further benefit thereafter.

Rates of significant improvement without normalization are depicted in the upper, center graph of Figure 2. Overall, relatively few children fell in this category with respect to their attention and academic efficiency



**Fig. 2** Upper three graphs: clinical status of group (n = 76) across methylphenidate and placebo (PL) dose conditions. Bottom graph: clinical status of the group collapsed across methylphenidate dose conditions for the three classroom measures. AES = academic efficiency score; ACTRS = Abbreviated Conners Teacher Rating Scale.

across dose conditions. In contrast, modest percentages of the sample showed improvement without normalization in classroom behavior as a function of MPH treatment, with the largest percentage occurring under the 5-mg dose.

Between 25% and 35% of the sample significantly deteriorated in their classroom functioning under the placebo condition as might be expected (upper, right-hand graph in Fig. 2). Deterioration rates declined subsequently with increasing dose. Approximately 10% of the ADHD children continued to evidence deterioration in their classroom behavior under at least one active medication condition, but these results appear to be due to inadequate levels of medication as opposed to behavioral toxicity (see below).

*Overall Normalizing Effects of MPH.* Responder-category membership rates collapsed across dose conditions are depicted in the bottom graph of Figure 2. Information contained in the figure addresses a more general, but practical clinical question: What is the likelihood that children will show normalized, significantly improved (but not normalized), or lack of change in different areas of their classroom functioning when prescribed a trial regimen of between 5 mg and 20 mg of MPH?

Category membership was assigned as follows: children falling within the normalized domain under any of the four active MPH doses were assigned to the "normalized" category; remaining cases falling within the improved-not normalized category under any MPH dose were assigned to the "improved" category; and remaining cases showing neither normalization nor significant improvement were assigned to the "no change" category.

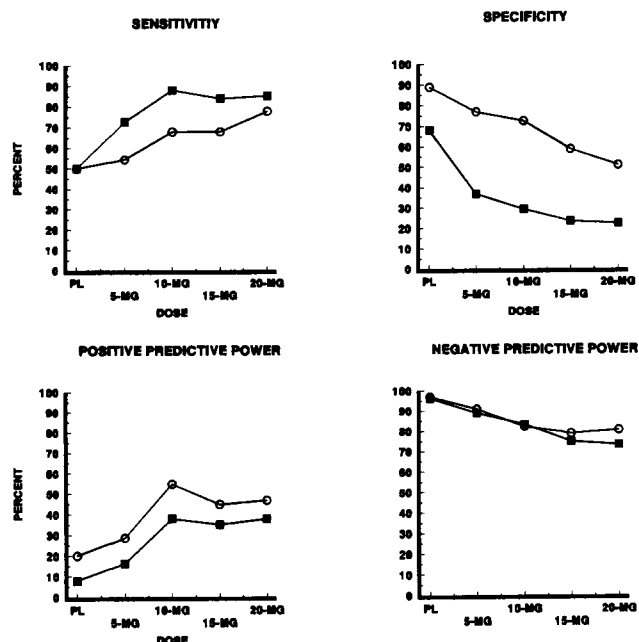
Inspection of Figure 2 reveals that nearly three fourths of the sample showed normalized attention in the classroom under at least one MPH dose, with 76% evidencing either normalized or significantly improved attention as a function of treatment. Teacher ratings of classroom behavior showed even higher rates of clinical response, with 94% of the children exhibiting either significantly improved or normalized function. In contrast, only 53% of the children evidenced significantly improved or normalized academic functioning with treatment.

*Behavioral Specificity of Classroom Measures.* Behavioral specificity, or the way in which a drug affects different aspects or domains of individual functioning,

was examined by calculating rates of sensitivity, specificity, positive predictive power (PPP), and negative predictive power (NPP). In calculating these rates, children's academic efficiency (AES) was selected as the "gold standard" because of its established relationship with educational achievement (DuPaul et al., 1991). The remaining two classroom measures (attention and behavior) were subsequently evaluated to determine the degree to which they reflected significantly improved and normalized academic functioning across dose conditions.

Sensitivity rates indicate the proportion of children showing concomitant improvement in attention and behavior (ACTRS) given significantly improved or normalized academic efficiency. Specificity rates indicate the proportion of children who fail to show significant change in their attention and behavior given a lack of change in their AESs. PPP rates reflect the proportion of children showing significantly improved or normalized academic efficiency given significant changes in their attention and classroom behavior. NPP rates represent the proportion of children who fail to show significant change in their academic efficiency given a lack of change in their attention and classroom behavior. Sensitivity, specificity, PPP, and NPP rates across dose conditions are depicted in Figure 3.

Large proportions of children showing academic improvement exhibited corresponding behavioral gains according to teacher ratings (ACTRS). Moreover, teacher ratings of classroom conduct paralleled their academic improvement more closely than did direct observations of attention to task (see "sensitivity," Fig. 3). The reverse held for specificity rates. For children who fail to show improved academic functioning, direct observations of their attention better reflect this state of affairs than do teacher ratings, with both measures showing decreasing specificity as dose increases. PPP rates indicate that when children show significant improvement or normalized attention and classroom behavior as a function of increasing dose, these measures tend not to reflect concomitant changes in academic functioning. Conversely, the NPP rates indicate that when children fail to show improved attention or behavior in the classroom with MPH treatment, they are also unlikely to exhibit improved academic functioning.



**Fig. 3** Sensitivity, specificity, positive and negative predictive power rates for children's attention (○) and classroom behavior (■; Abbreviated Conners Teacher Rating Scale) as indices of academic functioning. PL = placebo.

#### Series III Analyses: Conditional Probabilities of Drug-Related Improvement

In this final series of analyses, two complementary sets of data are presented. Both address specific clinical questions that are particularly relevant to physicians.

The first analysis presents a breakdown of children's clinical response as a function of incremental dose adjustments (Fig. 4). For example, of the 19 children showing significantly deteriorated attention under the placebo condition, 21.1% remained in this category when dose was increased to 5 mg. The remainder showed no change (63.2%) or a significant improvement without normalization (15.8%) (see "DET", "NC," and "IN" under placebo and 5 mg for the "attention" measure in Fig. 4). The four children who fell in the deteriorated category at the 5-mg dose showed no change at both 10-mg and 15-mg doses and attained normalized attention at the 20-mg dose. The outcome of all 76 children can be determined in this fashion from Figure 4.

Deterioration rates under active medication conditions across the three classroom measures are also of interest. It can be determined, for example, that 9%, 15%, and 16% of the total sample evidenced significant deterioration under at least one MPH condition for the domains of attention, academic efficiency, and

teacher-rated classroom behavior, respectively. The majority of these children eventually showed improved or normalized function in the attention and behavior domains at higher dose levels. This finding suggests that their deterioration under lower doses (primarily the 5-mg condition) in these domains was likely due to inadequate levels of medication. In the academic efficiency domain, however, 91% of those showing deterioration under at least one MPH dose failed to show significant improvement under any active medication condition.

In the second analysis, treatment response data were collated to determine the conditional probability of improved or normalized classroom functioning with incremental dose adjustments given a failure to respond at lower doses. For the attention measure, children failing to show significant change at lower doses were likely (65% to 74%) to improve after dose increments. In contrast, failure to show improvement in the academic and behavioral domains under lower doses predicted continued lack of response under higher dose conditions. Thus, increasing a child's MPH dose after a failure to respond at lower dose levels is likely to result in improved attention. Conversely, the law of diminishing returns appears to be operating in terms of children's academic efficiency and behavior beyond the 10-mg dose level.

#### DISCUSSION

It is a well-established fact that children with ADDH experience serious and chronic difficulties in school, including excessive levels of inappropriate (usually disruptive) behavior, more failing grades, grades failed, and higher dropout rates (Mannuzza et al., 1993; Weiss and Hechtman, 1993). Methodological shortcomings aside, it is also reasonably well established that the judicious application of potent treatments such as the psychostimulants appear not to affect the clinical course or outcome of the disorder (Barkley, 1990).

Two factors may have a direct bearing on these findings. The first is that nearly all of the outcome research, including both acute and long-term studies of psychostimulant effects, have relied upon *statistically* significant changes at the group level to infer *clinically* significant change in individual children. Comparisons with normal control children and alternative statistical computations are required to address this issue directly.



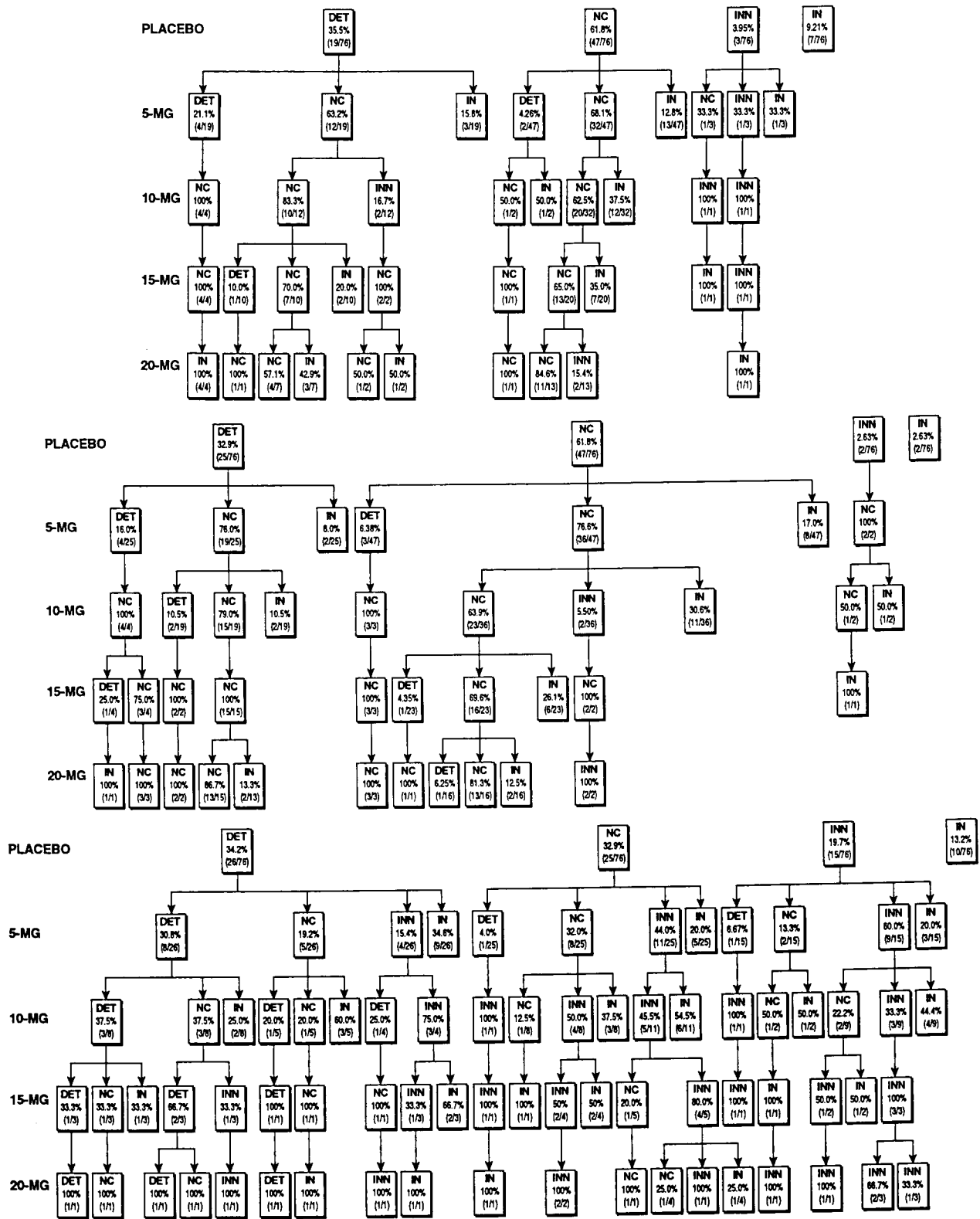


Fig. 4 Clinical status of total sample (n = 76) by drug condition. IN = significantly improved and normalized; INN = significantly improved but not normalized; NC = no significant change; DET = significantly deteriorated. All categories referenced against baseline level of functioning. Top: attention (on-task). Middle: academic efficiency score. Bottom: Abbreviated Conners Teacher Rating Scale.

In addition to or concomitant with the first factor is the possibility that in using traditional clinical titration methods we may be targeting the wrong behaviors for establishing optimal therapeutic dosage—especially if the academic functioning of ADDH children is of central concern.

In the present study we examined the dose-response effects of MPH on the behavior and academic performance of 76 children with ADDH in natural classroom settings and compared the outcome with the classroom functioning of a matched normal control group of children to address the two issues raised above. Before treatment, the ADDH children attended to and correctly completed their academic assignments at mean rates of 56% and 48%, respectively, which corresponded with severe (upper 5th percentile) levels of disruptive classroom behavior as judged by their teachers. As expected, these rates were significantly deviant compared with those obtained from the normal control group.

Standard statistical analyses revealed dose-response relationships similar to those reported in previous investigations—children's attention, academic efficiency, and behavior improved linearly as a function of increasing dose with similar patterns of between-dose differences (Douglas et al., 1988; Pelham et al., 1985; Rapport et al., 1988). One might reasonably conclude at this juncture that higher doses produce a better outcome than do lower doses and that all three domains of classroom functioning improve in a similar dose-related fashion. Results obtained from the second series of analyses, which examined the clinical significance of the findings by contrasting ADDH and normal control children, directly contradict this conclusion. The academic efficiency of children with ADDH showed a distinctly different dose-response pattern in terms of normalization response rates than did the attention and classroom behavior domains. Specifically, the overall percentage of children showing normalized functioning under any dose was proportionally lower for the academic efficiency domain compared with the attention and classroom behavior domains, and also stabilized at a lower dose (i.e., 10 mg). In contrast, proportionately greater percentages of children exhibited normalized attention and classroom behavior as dose was adjusted upward to 20 mg.

Improvement rates (without normalization) were also quite discrepant among the three classroom mea-

asures. For the attention and academic efficiency domains, 5% or fewer of the sample who failed to reach normalized levels of functioning evidenced significant clinical improvement under at least one of the four MPH doses. In contrast, 20% to 35% of the children who failed to exhibit normalized levels of classroom behavior evidenced significant improvement under at least one MPH dose. Overall, the evaluation of clinically significant treatment effects revealed that 76% and 94% of the group exhibited significantly improved or normalized attention and classroom behavior under at least one MPH dose, respectively, whereas only 53% of the group showed similar levels of improvement in academic functioning. Thus, both different dose-response patterns and rates of clinical improvement are associated with the behavioral domains of attention, academic functioning, and classroom deportment.

The sensitivity, specificity, PPP, and NPP analyses illuminate the above findings. For example, sensitivity rates for the sample address the question of whether the subset of children showing significant academic improvement as a function of MPH intervention show parallel benefits in the domains of attention and classroom behavior. Parallel dose-response patterns were obtained, indicating that improvement across all three domains are quite similar—a finding contrary to the low-dose learning, high-dose social behavior optimization hypothesis derived from Sprague and Sleator's (1977) seminal study.

Two key points are suggested by the specificity data. First, as dose increases specificity decreases for both attention and classroom behavior. That is, as dose increases, children who continue to show no evidence of academic improvement *do* exhibit improvement in their attention and classroom behavior. This finding supports Sprague and Sleator's (1977) argument concerning discordance among different behavioral domains except that it is predicated on first making a distinction between academic responders and nonresponders. The implication seems quite clear. There is a subset of children with ADDH whose pattern of MPH response varies across behavioral domains. The other key point derives from the observation that specificity is higher for attention than teacher ratings across the entire dose range. Among children failing to evidence academic benefit at any given dose, they are more likely to exhibit behavioral than attentional gains. This finding is in keeping with the results of

past attempts at predicting dose-response; namely, that attention is the key variable. The finding is also consistent with Sprague and Sleator's (1977) general predictions concerning behavioral specificity as long as the academic responder/nonresponder distinction is kept in mind. That is, there is a subset of children diagnosed with ADDH for whom MPH treatment will produce benefits in the behavioral but not the cognitive/academic domain.

The PPP data suggest that neither attention nor classroom behavior predicts academic functioning with more than moderate precision. In light of the preceding comments, this makes a fair amount of sense. The specificity data make clear that for the academic nonresponder subset of children, academic functioning is largely independent of attention and classroom behavior, keeping in mind that this particular subset of children represent a large percentage of the total sample depending upon which dose condition is under consideration. As such, low PPP rates would be expected.

The NPP rates were extremely high across the entire dose range and nearly identical for both the attention and classroom behavior domains. Thus, there is a subset of children whose attentional and behavioral functioning is largely unaffected by MPH, and the majority of these children also fail to evidence academic gains at any dose.

In summary, these results are consistent with the notion that subtyping of ADDH in terms of treatment response may yet have important clinical utility. For a substantial number of children, behavior, attentional, and academic functioning show a parallel response to MPH. For another substantial number of children, however, academic functioning appears unrelated to attentional and especially behavioral response to MPH. Among those children exhibiting the greatest response discordance among domains, attention to task is a better index of academic functioning than are teacher ratings across the entire dose range. Finally, there is a subset of children who are systematically different from the others; namely, those who do not evidence much treatment-related benefit in any domain.

Taken together, the data argue against the view that misbehavior always underlies poor academic functioning. From a conceptual point of view, it seems quite plausible to argue that disruptive behavior may be a primary cause of poor academic functioning in the absence of comorbid cognitive deficits, while serving

more as a contributory or mediating factor in their presence. Although the logic of correlation does not permit any firm conclusions, assessment of children's academic functioning both before and concomitant with pharmacological intervention should be considered the sine qua non of clinical titration. The influence of learning disabilities, mood and anxiety symptoms, or other mediating factors was not addressed herein but remains an important empirical question. It is worth noting, however, that the subset of ADDH children who did not evidence gains in academic achievement under MPH exhibited higher levels of academic functioning during baseline. This finding could not be explained by regression artifact and argues against a simple learning disabilities explanation.

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