

A Comparison of Ritalin and Adderall: Efficacy and Time-course in Children With Attention-deficit/Hyperactivity Disorder

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ABSTRACT. *Objective.* Very little research has focused on the efficacy of Adderall (Shire-Richwood Inc, Florence, KY) in the treatment of children with attention-deficit/hyperactivity disorder (ADHD), and no studies have compared it with standardized doses of Ritalin (Novartis Pharmaceuticals, East Hanover, NJ). It is thought that Adderall has a longer half-life than Ritalin and might minimize the loss of efficacy that occurs 4 or 5 hours after Ritalin ingestion. We compared two doses of Ritalin and Adderall in the treatment of ADHD in children in an acute study and assessed the medications' time courses.

Design. Within-subject, double-blind, placebo-controlled, crossover design lasting 6 weeks. As in our previous work, medication changes occurred on a daily basis in random order over days.

Setting. Eight-week, weekday (9 hours daily) summer treatment program at the State University of New York at Buffalo, using an intensive behavioral treatment program including a point system and parent training.

Study Participants. Twenty-five children (21 boys and 4 girls) diagnosed as ADHD using standardized structured interview and rating scales, mean age 9.6 years, 88% Caucasian, of average intelligence, with no medical conditions that would preclude a trial of stimulant medication. Thirteen were comorbid for oppositional-defiant disorder and another 8 for conduct disorder.

Interventions. Children received 10 mg of Ritalin, 17.5 mg of Ritalin, 7.5 mg of Adderall, 12.5 mg of Adderall, or placebo, twice a day (7:45 AM and 12:15 PM), in random order with conditions changing daily for 24 days.

Outcome Measures. Daily rates of behaviors in recreational and classroom settings, and standardized ratings from counselors, teachers, and parents, were averaged across days within condition within child and compared. Within-subject relative sizes of the medication effects were computed by taking the placebo-minus-drug mean difference divided by the placebo standard deviation for each child, and were compared hourly between first daily ingestion (7:45 AM) and 5:00 PM to assess the time course of the two drugs. Measures were taken at 12:00 PM (recess rule violations) and at 5:00 PM (parent behavior ratings) to determine whether Adderall was still effective at times when the effects of Ritalin should have worn off. Parent

ratings were also made for evening behavior to assess possible rebound, and side effects ratings were obtained from parents, counselors, and teachers. Parents, counselors, and teachers also rated their perceptions of medication status and whether they recommended the continued use of the medication given that day. Finally, a clinical team made recommendations for treatment taking into account each child's individual response.

Results. Both drugs were routinely superior to placebo and produced dramatic improvements in rates of negative behavior, academic productivity, and staff/parent ratings of behavior. The doses of Adderall that were assessed produced greater improvement than did the assessed doses of Ritalin, particularly the lower dose of Ritalin, on numerous but not all measures. This result suggests that the doses of Adderall used were functionally more potent than those for Ritalin. Adderall was generally superior to the low dose of Ritalin when the effects of Ritalin were wearing off at midday and late afternoon/early evening. The lower dose of Adderall produced effects comparable to those of the higher dose of Ritalin. Both drugs produced low and comparable levels of clinically significant side effects. Staff clinical recommendations for continued medication favored Adderall three to one. Almost 25% of the study participants were judged to be nonresponders by the clinical team, presumably because of their large beneficial response to the concurrent behavioral intervention and minimal incremental benefit from medication.

Conclusions. This is the first investigation to assess comparable doses of Adderall and Ritalin directly. Results showed that Adderall is at least as effective as Ritalin in improving acutely the behavior and academic productivity of children with ADHD. These results show clearly that Adderall should be added to the armamentarium of effective treatment for ADHD, particularly for children in whom the effects of Ritalin dissipate rapidly and a longer acting medication is desired. Measures taken at times of the day when Ritalin is expected to have worn off—4 to 5 hours after ingestion—generally showed that Adderall was more effective than Ritalin at these times. The 7.5-mg twice-a-day dose of Adderall and the 17.5-mg twice-a-day dose of Ritalin produced equivalent behavioral changes. This indicates that a 5-mg dose of Adderall (or slightly less) is equivalent to a 10-mg dose of Ritalin, indicating that Adderall is twice as potent; this potency ratio is similar to the well-known 1:2 ratio between d-amphetamine and methylphenidate. A higher dose of Adderall did not produce incremental improvement beyond that of the 7.5-mg dose, and parents were less likely to desire the continuation of the higher Adderall dose than the other medication conditions. Three-quarters of the responders to medication were recommended the lower rather than higher of the doses

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Received for publication Apr 6, 1998; accepted Nov 17, 1998.

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assessed. These findings are similar to our previous reports that there is a diminishing incremental value with stimulant medications beyond low to moderate doses, particularly when a behavioral intervention is concurrently implemented. Time-course results indicated that the afternoon dose of medication seemed to have a larger effect than the morning dose, raising the possibility that afternoon doses of stimulant medication may be able to be reduced relative to the morning dose without a corresponding reduction in efficacy. Although this practice is commonly used with some cases in clinical settings, it is almost never used in empirical investigations and no studies have systematically investigated the practice. Our results suggest that systematic studies of a reduced mid-day dose are indicated. Further studies of dose equivalence and dose-response, including mg/kg dosing rather than absolute dosing, are necessary to firmly establish the Adderall:Ritalin dosing ratio and guidelines for clinical practice. Studies comparing Adderall to d-amphetamine should be conducted to determine whether the compound is superior to d-amphetamine alone. Further examinations of time-course are necessary to determine the length of action of Adderall—for example, whether a single morning dose will be sufficient to provide coverage throughout the school day. *Pediatrics* 1999;103(4). URL: <http://www.pediatrics.org/cgi/content/full/103/4/e43>; attention-deficit/hyperactivity disorder, methylphenidate, Ritalin, Adderall.

ABBREVIATIONS. ADHD, attention-deficit/hyperactivity disorder; SD, standard deviation; STP, summer treatment program; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed; ANOVA, analysis of variance; DRC, daily report card; ES, effect size; MPH, generic methylphenidate.

Attention-deficit/hyperactivity disorder (ADHD) accounts for more referrals to mental health counselors, special education placement for behavior problems, and behavioral referrals for pediatric services than any other childhood disorder.¹ From an early age, children with ADHD exhibit difficulties in attention, impulse control, and activity level modulation that lead to severe impairment in daily life functioning, including problems in school functioning and relationships with parents, teachers, and peers. Using current diagnostic criteria, including symptom duration, degree of impairment, and presence in multiple settings, prevalence estimates in elementary-aged children range from 1% to 7%.²

Central nervous system stimulant medications (d-amphetamine, methylphenidate, pemoline) are the most widely used treatments for ADHD, having been used successfully for the past 30 years. Short-term beneficial effects of stimulants on cognitive and behavioral measures are among the most well-documented effects in the field of treatments for childhood mental health disorders, having been studied in thousands of children in hundreds of studies. Stimulant effects have been shown on laboratory cognitive measures, classroom measures of disruption and academic completion, teacher ratings, parent-child interactions, and peer relationships.³⁻⁷

For the past 20 years, methylphenidate (Ritalin, Novartis Pharmaceuticals, East Hanover, NJ) has been the primary stimulant used in the treatment of

children with ADHD. In 1994, it was estimated that ~80% of all diagnosed cases of ADHD were treated with Ritalin.⁸ Although it is the most commonly prescribed medication for ADHD, Ritalin has several limitations. For example, it has a short behavioral half-life. After oral administration, the drug is rapidly absorbed; its clinical effects appear within 1 hour and last ~4 hours. The serum blood level and the primary behavioral effect of Ritalin have a similar time course: both reach a maximum between 1 and 2 hours after oral administration and have a half-life of ~3 hours.^{9,10} Thus, multiple doses per day are required. In clinical practice and in research studies, both twice daily and three-times-per-day dosing schedules have been used. In both of these regimens a dose must be given at school, an event that some ADHD children and some school personnel actively avoid.¹¹ Many schools have policies that prohibit school personnel from administering psychoactive medication.¹² Some ADHD children must therefore take Ritalin to school in their lunch boxes and remember themselves to take their midday pill. This is likely to contribute to the poor compliance that has characterized stimulant treatment of ADHD.¹³

In addition to its short half-life, some children do not respond positively to Ritalin. Among the 30% to 40% of nonresponders, many may respond to other stimulant medications.^{10,14} These limitations of Ritalin emphasize the need to use other stimulants with ADHD children, particularly those with a longer effective duration of action. A sustained release form of Ritalin has been developed (Ritalin SR), but it is considered to be less effective than the immediate-release form, and thus has not been widely adopted for clinical use. This may be attributable to problems of efficacy.^{10,15} Dexedrine Spansule (Smith-Kline Beecham, King of Prussia, PA), although effective,¹⁰ has not received widespread use, presumably because of early reports¹⁶ that Dexedrine had a higher side effect profile than other stimulants. Finally, pemoline is an effective long-acting stimulant,^{10,17} but recent concerns about side effects have resulted in reduced confidence in its utility as a first-line treatment.¹⁸

Adderall (Shire-Richwood Inc, Florence, KY) is a racemic mixture of d- and l-amphetamine that seems to be effective in treating ADHD. The different isomers have different properties, and may have complementary effects in combination. For example, Arnold and colleagues,¹⁹⁻²² in a series of studies, compared the two different isomers in both animals and children. They found that many children showed differential response to the two isomers, some showing improvement with d-isomer and others with the l-isomer.

The first empirical studies to be performed using Adderall^{23,24} have suggested that Adderall has a longer half-life than Ritalin and that it may enable the use of a single dose to cover most of a child's school day, which is the goal of long-acting stimulants. Swanson et al^{23,24} studied four different doses of Adderall (5, 10, 15, and 20 mg) in comparison with children's typical doses of Ritalin in a laboratory school setting, and showed that the average peak

time for Adderall occurred 45 minutes to more than 1 hour later than the peak time for Ritalin, depending on Adderall dose (with higher doses producing later peak times). In addition, they found that higher doses of Adderall resulted in longer duration of action than did Ritalin and that the effects of higher doses lasted up to twice as long as those of Ritalin—as long as 6 hours for the highest dose. These results are quite promising, and suggest that Adderall should be considered as an effective treatment for children with ADHD.

However, Swanson et al^{23,24} did not control for the dose of Ritalin given. Children received their current clinical dosing regimen which varied from 5 mg to 20 mg per dose; therefore, further study of direct dosage comparisons between Adderall and Ritalin remains necessary. With the exception of Swanson et al's study,^{23,24} no empirical studies have been conducted of the effects of Adderall, and direct comparisons with comparable doses of Ritalin have not been performed. There have been a small number of comparative studies of Ritalin and amphetamine compounds. In a review, Arnold²⁵ has argued that existing controlled crossover studies in humans have typically shown general, although nonsignificant, superiority for amphetamine. However, we are aware of only one dose-response study of amphetamine in comparison with Ritalin.¹⁴ Further study is needed to address issues such as whether there are linear increases in response to increasing doses, and whether dose-response curves vary for the different forms of amphetamine.

In summary, Adderall was recently approved by the Food and Drug Administration for the treatment of ADHD based on historical efficacy data. Well-controlled, parametric evaluations of the dose and time course of effects produced by Adderall, particularly as compared with standard short-acting Ritalin and other stimulants, are required to guide

physicians in the optimal use of the drug.²⁶ The current study was designed to evaluate more completely the profile of effects produced by Adderall in children with ADHD. Daily frequency counts of social behavior and classroom academic performance were measured. We examined two doses of Adderall in comparison with equivalent doses of Ritalin to compare the dose-response properties of each medication. In addition, we sought to more thoroughly investigate the time course properties of Adderall, to determine if its effects last somewhat longer than standard Ritalin.

METHODS

Participants

Participants were 25 children, aged 5.8 to 12.7 years (mean = 9.6 years, standard deviation [SD] = 1.6), who were enrolled in the 1997 summer treatment (STP) program for children with ADHD conducted through the psychology department at the State University of New York at Buffalo. One additional child was enrolled in the study, but because of uncontrollable behavior on placebo days that was not ameliorated by any medication condition, he was removed from the protocol. The parents of all the children agreed to participate in a clinical medication assessment for their child, and all children met criteria for a *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) diagnosis of ADHD as defined by a structured parent interview and parent and teacher rating scales. Thirteen children also met DSM-IV criteria for oppositional-defiant disorder, and another 8 met criteria for conduct disorder. Twenty-one of the participants (84%) were boys and 4 were girls. Eighty-eight percent of the participants were white. The median family income was ~\$40 000, with incomes ranging widely (from <\$10 000 per year to >\$100 000 per year). Table 1 summarizes descriptive information and standardized rating scale scores for the participants, gathered on enrollment to the STP. Participants and their parents gave informed consent to the procedures before participating in the project.

Procedures

Design

The study included a within-subject, placebo-controlled, crossover design of two doses of Ritalin (10 mg and 17.5 mg) given

TABLE 1. Means and Standard Deviations for Participant Characteristics at Enrollment

Item	Mean	Standard Deviation
Age in years	9.6	1.6
WISC vocabulary scaled score	12.3	5.7
WISC block design scaled score	11.2	4.9
WIAT spelling scaled score	95.7	16.2
WIAT reading scaled score	101.6	18.5
WIAT math scaled score	105.7	13.3
DSM ADHD items endorsed in a parent structured interview	10.8	2.7
DSM ODD items endorsed in a parent structured interview	5.3	3.1
DSM CD items endorsed in a parent structured interview	1.8	2.3
Abbreviated Conners Rating Scale—parent ²⁷	22.6	5.3
Abbreviated Conners Rating Scale—teacher ²⁷	19.6	6.0
Iowa Conners Teacher Rating Scale inattention-overactivity ^{28,29}	11.8	2.3
Iowa Conners Teacher Rating Scale oppositional-defiant ^{28,29}	9.6	4.7
Disruptive behavior disorders parent rating scale ³⁰		
ADHD	1.5	0.5
Oppositional/defiant	1.7	0.5
Conduct disorder	1.8	0.5
Disruptive behavior disorders teacher rating scale ³⁰		
ADHD	2.4	1.0
Oppositional/defiant	2.5	0.8

Abbreviations: WISC, Wechsler Intelligence Scale for Children; WIAT, Wechsler Individual Achievement Test; DSM, *Diagnostic and Statistical Manual of Mental Disorders*; ADHD, attention-deficit/hyperactivity disorder; ODD, oppositional-defiant disorder; CD, conduct disorder.

twice daily and two doses of Adderall (7.5 mg and 12.5 mg) given twice daily. One boy's doses were reduced, because of his small size, to 6.25 mg of Ritalin, 12.5 mg of Ritalin, 5 mg of Adderall, and 10 mg of Adderall. The doses of Ritalin and Adderall were estimated to be equivalent based on Swanson et al.^{23,24} who compared a range of fixed doses of Adderall to the current doses of Ritalin children were receiving clinically. The Adderall and Ritalin means in Swanson's study were compared to select the ratio of Adderall:Ritalin (ratio, 3:4) that we used.

All participants received medication twice daily, at approximately 7:45 AM and 12:15 PM, each Monday through Thursday for a period of 6 weeks for a 24-day clinical medication assessment. Active medication and placebo were disguised in opaque gelatin capsules and were dispensed in daily pill reminders. Each condition occurred once within each rolling 5-day period (eg, Thursday, Monday-Thursday), with the order of the conditions randomized on a daily basis. Thus, it was planned that each child would have ~5 days of data in each of the five drug conditions, with absences accounting for reductions from the planned number of days per condition. Data were averaged across days within conditions for each child, so that all children had complete data for each condition. The average number of days for each condition (and SD) were: 4.2 (0.9) for placebo; 4.3 (0.6) for 10 mg of Ritalin; 4.2 (0.7) for 17.5 mg of Ritalin; 4.3 (0.8) for 7.5 mg of Adderall; and 4.4 (0.8) for 12.5 mg of Adderall. Daily activities were scheduled such that recreational activities and academic seatwork were completed during peak medication hours. Our medication assessment procedure has been described in detail elsewhere.^{10,31-33}

STP Overview

Children attended the STP from 8:00 AM until 5:00 PM, Monday through Friday, and participated in the following activities: an academic class and an art class, each staffed by a special education teacher and an aide; three outdoor recreational activities (softball, soccer, basketball); swimming; lunch; and recess. For all activities except the academic classes and recess, a lead counselor supervisor and four undergraduate counselors supervised 12 children grouped by age. The children in this study were distributed across three groups. A behavioral point system was in effect throughout the day, in which children earned points for appropriate behavior and lost points for inappropriate behavior. Staff members gave behavioral feedback continually, and children exchanged points earned for backup reinforcers including privileges (eg, field trips) and honors. The first 2 weeks of the program served as a period of baseline observation and adaptation for the children and staff members, and medication assessments were conducted during the last 6 weeks of the program. Children participated in special activities on Fridays, which were therefore not included in the medication assessment. More extensive descriptions of the STP are available elsewhere.³⁴⁻³⁶ Staff members who worked with the children were kept blind to medication conditions.

Classroom Procedures

A behavior modification system consisting of rewards and response/cost was used in the classroom.^{33,37} Each child received points at the beginning of each class period, and lost points any time he or she violated a classroom rule (eg, talking without raising hand). The academic classroom period was divided into three segments: seatwork, peer tutoring, and computers. During the seatwork period, children completed individualized assignments for 30 minutes.^{33,37} Children earned points for assignment completion and for accuracy. During the peer tutoring segment, children worked in pairs to develop reading skills, using the Peabody Classwide Peer Tutoring methods (L. Fuchs and D. Fuchs, Vanderbilt University). During the computer segment, children completed individualized assignments using integrated instructional software (Advanced Learning System; American Education Corporation, Oklahoma City, OK).

Each day, children were observed for the seatwork and peer tutoring segments of the classroom period by trained observers. The observation system was adapted from the Classroom Observations of Conduct and Attention Deficit Disorders Observation Scheme³⁸ and is described in detail elsewhere.³³ Observers recorded disruptive behavior and on-task behavior for each child. Classroom staff members and observers were blind to medication conditions.

Daily Report Cards (DRCs)

Each day, the children received feedback regarding individualized target behaviors via a DRC. Staff members developed individualized target behaviors depending on a child's presenting symptoms determined at intake and by his behavior and performance in the STP. Report cards were reviewed with parents at the end of the day, and parents provided positive consequences at home when children reached their daily goals.^{34,39} The percentage of positive marks on each child's report card was used as an individualized measure of medication response.

Recess

After the lunch period, children had a 15-minute recess period. Children who had met their individualized DRC goals during the morning activities were given the opportunity to engage in free-play activities, and children who had not met their goals participated in group problem-solving discussions with the counselors during the recess period. The discussions focused on the specific reasons that children did not meet their behavioral criteria and on what the children could do differently in the future to meet their daily goals.

Dependent Measures

Point System

Throughout the day, counselors recorded the frequencies with which the children exhibited the behaviors targeted by the point system,³⁴⁻³⁶ and these frequency counts were summed throughout the day to yield measures of behavior. The following point system categories were used as dependent measures: a) percentage following activity rules; b) percentage attention questions answered correctly; c) noncompliance; d) interrupting; e) complaining; f) positive peer behaviors (the sum of helping, sharing, and ignoring provocation); g) conduct problems (the sum of lying, stealing, destruction of property, and aggression); and h) negative verbalizations (the sum of verbal abuse to staff, teasing peers, and swearing). These measures have been shown to be reliable and sensitive to medication effects in our previous studies.^{10,31,39-41}

Classroom Measures

Information from the classroom response-cost system provided a measure of following rules for each of the three classroom segments. The percentages of points that children kept served as a daily measure of classroom rule-following behavior. In addition, productivity (percentage of assigned seatwork completed) and accuracy (percentage correct) in the seatwork tasks served as dependent measures.

The percentages of intervals during which children displayed on-task behavior and disruptive behavior during the seatwork period, obtained from the observation procedure, also served as dependent measures. Reliability observations were conducted weekly by having the two observers watching the same children; average κ values for on-task behavior and disruptive behavior, respectively, were 0.80 and 0.82. These measures have been shown to be sensitive to drug effects in our previous studies.^{10,33,37}

DRCs

The percentage of behavioral targets that each child met during the day was used as an individualized measure of medication response. This measure has been shown to be sensitive to drug effects in our previous studies.^{10,39,41}

Recess Rule Violations

For all children, the number of rule violations exhibited during the 15-minute recess period were recorded each day, either by the counselors leading the group problem-solving discussions or by the recess monitors. Because the recess period occurred directly before the administration of afternoon medication, the measure of following rules was used to detect whether there were any remaining effects of Ritalin versus Adderall at ~4.5 hours after ingestion, a time when Ritalin has typically worn off.

Counselor and Teacher Ratings

At the end of each day, counselors rated each child on the Iowa Conners Rating Scale.^{28,29} The inattention/overactivity and oppo-

sitional/defiant subscale scores were averaged across counselors and were used as standardized measures of children's daily behavior. Teachers also completed Iowa Conners Rating Scales after the classroom period each day. Teachers and counselors completed daily ratings of side effects as a safety measure, using a checklist of the most common stimulants' side effects and rating their presence on a scale of "not present," "mild," "moderate," or "severe."^{3,36} Finally, teachers and counselors completed two items assessing: 1) whether they thought the child had received medication or placebo that day; and 2) if they thought the child was medicated, whether they thought the child should continue to receive the dose given that day as part of his or her continued treatment. These items were asked to obtain a global impression of the effectiveness of each dose of medication.

Parent Ratings

Each day, parents completed a questionnaire that incorporates items from several standardized behavior rating scales, including the Iowa Conners Rating Scale. Parents were instructed to rate their child's behavior between the hour of 5:00 PM and 6:00 PM only, to detect differences between drug conditions at a time when the afternoon dose of medication would have typically worn off. Parents also completed a second rating using the Iowa Conners and the side effects checklist described above that summarized their impressions of their child's behavior throughout the entire evening; these ratings were examined for evidence of rebound effect and for possible adverse side effects of medication. Parents also completed the two items listed above that assessed their perceptions of the child's medication status and whether the dose given that day should be continued.

Data Analysis

Data were evaluated in six major parts: 1) total daily medication effects on the point system, classroom, DRC, and counselor/teacher rating measures described above; 2) time course measures of medication effects on disruptive behavior for each period of the day; 3) midday recess rule violations; 4) end-of-day parent ratings of children's behavior; 5) parent, teacher, and counselor evaluations of side effects; and 6) clinical medication recommendations made at the end of the medication assessments for each child.

To examine total daily effects, daily totals were computed for each of the point system and academic measures described above. These totals, as well as the counselor and teacher ratings and DRCs, were averaged across days in each drug condition and were compared with each other and to placebo.

To examine the time course effects of each of the two stimulants, data were collected for each of the eight periods of the treatment day, using the procedures described above. Because of the need to use measures from different settings throughout the day, we combined the measures for each hour into an overall measure of disruptive behavior. For the recreational activities, disruptive behavior was measured by counselor-recorded rule violations, interruptions, and negative verbalizations. For the

classroom activities, teacher-recorded rule violations were used to measure disruptive behavior. Because a slightly different point system was used in the classroom, behaviors that would be classified as negative verbalizations and interruption in the recreational activities were recorded as rule violations in the classroom setting; thus, these measures are comparable across all activities. The data points were then converted to a standard unit of measure for each period to enable comparisons across different activities. The unit of measurement used was within-subject effect size (ES), a z score measuring change for each medication relative to placebo. Individual ESs were computed for each child, for each drug condition. Individual ESs were calculated for each measure by subtracting each child's treatment mean from the placebo mean, and dividing the result by that child's SD on placebo days.^{33,42} Because means were expected to decrease with treatment, a positive ES indicates a beneficial response to treatment.

To examine midday effects of medication, children's rule violations during the daily recess period were examined. This period was used because it falls at a time when the effects of Ritalin are expected to have dissipated whereas those of Adderall are expected to continue to be present. Frequencies of rule violations were averaged across days within each medication condition. To examine end-of-day effects of medication, parent ratings completed for the period between 5:00–6:00 PM were evaluated. Similar to the recess period, this period falls during a time after the midday dosing when Ritalin is typically no longer active but Adderall is expected to be. Parent ratings were averaged across days within medication conditions.

RESULTS

Daily Frequencies

Point System

The point system data were first analyzed in a five-way (medication: placebo, low dose of Ritalin, high dose of Ritalin, low dose of Adderall, high dose of Adderall) multivariate analysis of variance (BMDP 4V, BMDP Statistical Software, Inc, Los Angeles, CA) to determine if there were differences between placebo and medication, with follow-up contrasts between each dose and placebo. The analysis indicated that there was a significant effect of medication, $F(32, 329.81) = 4.6, P < .0001$, with significant univariate effects for all measures except for positive peer behaviors and attention questions. Table 2 presents means, SD, and analysis of variance (ANOVA) results for each of the dependent measures. Follow-up contrasts between each drug condition and placebo showed that all four medication

TABLE 2. Means, Standard Deviations, and Analysis of Variance Results for Point System Measures*

Measure	Placebo	Ritalin		Adderall		Ritalin versus Adderall Comparisons†		
		10 mg	17.5 mg	7.5 mg	12.5 mg	Drug	Dose	Drug × Dose
Following rules	50.5 (21.9)	71.4 (16.2)	74.5 (16.2)	75.4 (11.8)	79.9 (10.2)	10.38§	18.49#	0.46
Attention	62.9 (14.9)	64.0 (15.7)	64.3 (15.4)	68.2 (13.0)	68.2 (13.1)	5.47§	0.00	0.01
Noncompliance	13.8 (17.4)	2.2 (3.7)	0.8 (1.5)	0.9 (1.6)	1.2 (2.5)	5.65§	5.56§	2.16
Interruption	38.0 (43.5)	10.6 (9.6)	6.7 (6.6)	6.2 (5.4)	6.8 (6.9)	7.48	15.33#	7.67
Complaining/whining	17.1 (23.1)	4.1 (5.6)	2.6 (2.8)	2.9 (3.4)	2.0 (2.0)	4.12‡	6.12§	0.31
Positive peer behaviors	8.2 (3.9)	8.8 (5.5)	8.8 (4.2)	8.1 (4.0)	7.8 (3.5)	1.82	0.06	0.08
Conduct problems	19.6 (41.8)	1.4 (2.8)	0.1 (0.3)	0.4 (1.2)	0.2 (0.5)	5.17§	3.91‡	4.54§
Negative verbalizations	37.1 (57.0)	6.1 (9.2)	2.2 (3.0)	2.0 (2.9)	2.2 (0.1)	7.89¶	5.15§	6.10§

* All drug conditions were significantly different from placebo in an overall multivariate analysis of variance with the exception of the measures of attention and positive peer behaviors.

† $F(1, 24)$.

‡ $P < .10$.

§ $P < .05$.

|| $P < .025$.

¶ $P < .01$.

$P < .001$.

conditions were significantly different from placebo: $F(8, 17) = 8.25, P < .001$ for 10 mg of Ritalin; $F(8, 17) = 8.22, P < .001$ for 17.5 mg of Ritalin; $F(8, 17) = 10.24, P < .0001$ for 7.5 mg of Adderall; $F(8, 17) = 13.89, P < .0001$ for 12.5 mg of Adderall.

To determine differences between Ritalin and Adderall, a series of 2 (drug: Ritalin, Adderall) \times 2 (dose: low, high) planned ANOVA were then performed. The effect of drug was significant for seven of the eight variables. Dose effects were significant for five of the measures, and the interaction was significant for the three measures of interruption, conduct problems, and negative verbalizations. Examination of the means shown in Table 2 illustrate that, in general, rates of behavior were improved on Adderall relative to Ritalin and for higher as opposed to lower doses. The two-way interactions were followed-up by examining the simple effects of dose for each drug. Follow-up tests showed that the effect of dose was significant for Ritalin on all three measures but was nonsignificant for Adderall. As the means indicate, 10 mg of Ritalin did not produce as large an effect as 7.5 mg of Adderall.

As the results in Table 2 indicate, there was a great deal of variability in the data, and several variables were skewed; therefore, we transformed the variables by taking the fourth root of the average for each drug condition and reanalyzed the data. Results did not differ from the untransformed data.

Classroom Measures

The same analyses that were performed for the point system measures were repeated for the classroom measures and the children's DRC percentages. Table 3 illustrates the results of each medication condition for the classroom measures. The overall analysis showed a significant effect of medication, $F(32, 3329.81) = 4.86, P < .0001$, with significant univariate tests for all measures except for seatwork accuracy. The contrasts showed that each of the four drug conditions was significantly different from placebo:

$F(8, 17) = 9.47, P < .0001$ for 10 mg of Ritalin; $F(8, 17) = 13.11, P < .0001$ for 17.5 mg of Ritalin; $F(8, 17) = 9.07, P < .0001$ for 7.5 mg of Adderall; $F(8, 17) = 10.92, P < .0001$ for 12.5 mg of Adderall.

The drug times dose ANOVAs for the classroom and DRC measures showed no main effects of drug or dose, or the interaction, with the exception of the DRC measure, although there were trends toward significance for the rule-following measures. The DRC results showed a main effect of drug and an interaction, which showed that children earned positive marks on their report cards more often on the higher dose of Ritalin than on the lower dose, whereas the percentages were superior to Ritalin but approximately equivalent between the two doses of Adderall. These results parallel those found for the point system measures and show that on the behaviors deemed most clinically significant for each child, the low dose of Adderall seemed to have a greater effect than the low dose of Ritalin.

Recess

To assess midday effects, the number of rule violations during the recess period was first examined in an ANOVA with five levels of drug, as with the point system and daily measures. The analysis was significant, $F(1, 24) = 11.47, P < .0001$, with children exhibiting fewer rule violations on all medication conditions than on placebo (see Table 3). The drug times dose analysis for the recess measure showed that the effect of dose was significant, $F(1, 24) = 5.76, P < .05$, with children exhibiting fewer violations on the higher doses than the lower doses, but that the effect of drug was a trend only and the interaction was not significant.

Counselor and Teacher Ratings

Counselor and teacher ratings on the Iowa Conners were examined using a similar set of analyses. The overall analysis showed a significant effect of drug, $F(16, 284.76) = 7.40, P < .0001$. The drug times

TABLE 3. Means, Standard Deviations, and Analysis of Variance Results for Classroom Measures, Daily Report Cards, and Recess Rule Violations*

Measure	Ritalin			Adderall		Ritalin versus Adderall Comparison [†]		
	Placebo	10 mg	17.5 mg	7.5 mg	12.5 mg	Drug	Dose	Drug \times Dose
Classroom variables								
Rule-following								
Seatwork	64.8 (27.7)	84.3 (18.2)	87.8 (15.1)	89.7 (14.4)	90.7 (13.8)	4.06 [†]	1.94	0.55
Peer tutoring	69.8 (24.9)	91.4 (8.1)	94.8 (7.3)	95.1 (7.1)	95.0 (6.5)	3.71 [†]	3.13 [†]	2.44
Computer	61.6 (28.9)	87.3 (16.0)	92.6 (9.1)	91.1 (11.4)	94.4 (5.7)	2.80	3.63 [†]	0.51
Seatwork completion	58.0 (25.8)	69.5 (15.4)	69.2 (19.5)	71.6 (16.1)	67.1 (18.6)	0.00	1.12	0.50
Seatwork accuracy	89.0 (9.6)	87.9 (9.8)	87.1 (12.4)	87.6 (9.4)	87.3 (8.3)	0.00	0.18	0.04
Observational measures								
On-task behavior	78.9 (15.4)	89.2 (10.5)	89.6 (8.6)	89.0 (10.5)	89.9 (12.7)	0.00	0.17	0.07
Disruptive behavior	13.8 (13.1)	6.9 (7.7)	6.2 (7.6)	6.4 (6.0)	6.4 (9.6)	0.15	0.11	0.13
Daily report card	50.5 (20.7)	76.4 (9.7)	81.7 (12.3)	83.8 (8.1)	82.8 (7.6)	6.63 [§]	2.50	6.84
Recess rule violations	3.3 (4.0)	1.3 (2.0)	0.7 (1.5)	1.0 (2.0)	0.4 (0.8)	3.21 [†]	5.76 [§]	0.00

* All drug conditions were significantly different from placebo in an overall multivariate analysis of variance with the exception of the measure of seatwork accuracy.

[†] $F(1, 24)$.

[‡] $P < .10$.

[§] $P < .05$.

^{||} $P < .025$.

TABLE 4. Means, Standard Deviations and Analysis of Variance Results for Parent, Teacher, and Counselor Iowa Conners Ratings*

Measure	Ritalin			Adderall		Ritalin versus Adderall Comparison†		
	Placebo	10 mg	17.5 mg	7.5 mg	12.5 mg	Drug	Dose	Drug × Dose
Counselor ratings:								
I/O	5.6 (2.9)	3.4 (1.8)	2.6 (1.4)	2.4 (1.3)	2.2 (1.3)	14.3**	10.71#	3.09§
O/D	5.2 (4.2)	2.3 (2.4)	1.1 (1.1)	1.0 (0.9)	0.8 (0.9)	13.85#	10.4#	4.68
Teacher ratings:								
I/O	3.7 (2.6)	1.8 (1.4)	1.1 (1.2)	1.2 (1.7)	1.2 (1.5)	0.72	2.15	2.13
O/D	2.6 (2.6)	1.3 (1.7)	0.6 (1.0)	0.7 (1.4)	0.4 (0.9)	3.22§	4.04§	1.11
5:00–6:00 parent ratings:‡								
I/O	3.0 (2.9)	1.5 (1.4)	1.0 (1.1)	0.9 (0.8)	0.5 (0.6)	5.25	9.66#	0.03
O/D	5.2 (4.8)	1.2 (1.1)	1.1 (1.1)	0.8 (1.1)	0.6 (0.8)	4.09§	0.99	0.01
All evening parent ratings:								
I/O	3.0 (2.7)	2.6 (1.9)	1.7 (1.5)	1.5 (1.5)	1.4 (1.1)	3.33§	6.75¶	3.46§
O/D	2.5 (2.1)	2.4 (1.5)	1.2 (1.4)	1.9 (1.6)	1.2 (1.4)	0.71	12.17#	1.24

* Abbreviations: I/O, inattention/overactivity; O/D, oppositional/defiant. All drug conditions were significantly different from placebo in an overall multivariate analysis of variance.

† $F(1, 24)$.

‡ $n = 23$; 2 subjects' parents did not complete ratings.

§ $P < .10$.

|| $P < .05$.

¶ $P < .025$.

$P < .01$.

** $P < .001$.

dose analyses showed a significant main effect of drug only for the counselor ratings, a significant effect of dose for the counselor ratings, and a significant drug times dose interaction for the counselor oppositional/defiant rating. Table 4 illustrates the means, SD, and ANOVA results.

Parent Ratings

The parent ratings were analyzed in two ways. First, because parents completed two identical ratings of their child's behavior, one for behavior between 5:00 PM and 6:00 PM and one for the entire evening, we needed to establish that the parents were able to discriminate between their ratings. Therefore, a 5 (drug) × 2 (time: 5:00–6:00 PM, entire evening) multivariate analysis of variance was performed for the parent Iowa Conners rating scores. The analysis showed a significant effect of drug, $F(8, 174) = 7.24, P < .0001$, indicating that parents discriminated between drug conditions, and a significant time effect, $F(2, 21) = 6.54, P < .01$, indicating that the parents' ratings from 5:00 PM to 6:00 PM were different from those completed overall. A significant drug times time interaction was also found, $F(8, 174) = 6.40, P < .0001$, which indicates that the parents did indeed complete distinct ratings based on different time periods.

Therefore, a series of drug times dose analyses

similar to those performed on the other daily measures was conducted for both sets of parent ratings to assess whether the different medications were differentially affecting the child's behavior during the period from 5:00 to 6:00 PM and throughout the evening. Results are summarized in Table 4. For the 5:00 to 6:00 PM ratings, the parents' ratings of inattention/overactivity showed significant effects of both drug and dose. Parents ratings were higher (ie, more deviant) on Ritalin than on Adderall; they were higher on low doses than on high doses. The interaction was not significant. For ratings covering the entire evening, drug did not significantly affect the parents' ratings but there were significant effects of dose, indicating that ratings were lower when the children were on higher doses of medication.

Medication Ratings

Counselors, teachers, and parents rated every day whether they thought each child was medicated or received placebo that day, and if medicated, whether the dose received that day should be part of continued treatment. A similar series of analyses were conducted on these two questions as for the other ratings. Table 5 illustrates the means and SDs for each condition.

TABLE 5. Counselor, Teacher, and Parent Reports of Perceived Medication Status*

	Counselor		Teacher		Parent	
	Medicated?	Continue?	Medicated?	Continue?	Medicated?	Continue?
Placebo	36 (28)	26 (24)	48 (22)	45 (21)	46 (36)	46 (39)
10-mg Ritalin	75 (17)	60 (21)	76 (24)	73 (25)	69 (22)	66 (35)
17.5-mg Ritalin	88 (8)	73 (15)	85 (18)	83 (23)	83 (22)	81 (26)
7.5-mg Adderall	84 (12)	71 (18)	84 (21)	80 (21)	84 (23)	74 (25)
12.5-mg Adderall	87 (10)	71 (16)	84 (19)	80 (21)	93 (15)	62 (38)

* Mean (standard deviation) percentages of respondents who rated children as being medicated each day and who replied that the child should continue to receive that dose are reported.

Counselor Ratings

A drug times dose comparison revealed a significant effect of dose, $F(1, 24) = 12.3, P < .01$, and a significant interaction, $F(1, 24) = 4.58, P < .05$. As the means show, this interaction was similar to those reported above and indicated that counselors were more likely to report that children were medicated on the higher dose than the lower dose of Ritalin, but that their reports were approximately equivalent for the two Adderall conditions. When they were asked about continuing the day's dose, the same pattern of results emerged, with a main effect of dose, $F(1, 24) = 5.87, P < .05$, and an interaction, $F(1, 24) = 5.07, P < .05$. Again, counselors thought that the higher dose of Ritalin should be continued more often than the lower dose, but perceived no difference between the two doses of Adderall.

Teacher Ratings

The drug times dose analysis for the medication question revealed only a trend toward significance for the two-way interaction, $F(1, 24) = 3.89, P = .060$. Again, the same pattern of means emerged with no difference between the Adderall doses but with a higher percentage for the 17.5-mg dose of Ritalin than for the 10-mg dose. There were no significant effects for the continuation question asked of the teachers, which agrees with the relative lack of differences found between drugs and doses for the classroom measures.

Parent Ratings

For the parent medication question, the drug times dose analysis revealed significant main effects of drug, $F(1, 24) = 9.45, P < .01$, and dose, $F(1, 24) = 10.6, P < .01$, and no interaction. Parents were more likely to think their children were medicated on Adderall than on Ritalin, and on higher doses compared with lower doses. For the continuation question, a significant two-way interaction was found, $F(1, 24) = 7.44, P < .025$. This interaction showed that, whereas parents preferred the higher dose of Ritalin compared with the lower dose, they preferred the lower dose of Adderall to the higher dose. It is especially interesting that, although parents believed their children were medicated 93% of the time on the 12.5-mg dose of Adderall, they only endorsed the continuation of that dose 62% of the time, the lowest of all four drug conditions. This may correspond to the relative increase in the side effects of appetite loss and difficulty sleeping that parents reported on the higher dose of Adderall.

Time Course

To examine the time course of each drug and dose, the standard ESs that were computed for each period were analyzed in a 2 (drug) \times 2 (dose) \times 8 (period) analysis of variance. In addition to significant main effects of drug, $F(1, 24) = 15.90, P < .001$, and dose, $F(1, 24) = 40.06, P < .0001$, there was also a significant effect of period, $F(7, 168) = 2.93, P < .01$. There were no interactions. Figure 1 illustrates the time course for each drug and dose condition. As Fig 1

shows, a dip in ES occurred for the low doses of both drugs at midday, and ES steadily increased as the afternoon progressed. Figure 1 shows that Adderall consistently resulted in higher ES than Ritalin and that higher doses consistently resulted in higher ES than lower doses.

To further examine our expected differences between the two drugs at midday and the end of the day, follow-up tests of the simple effects of dose and of drug (BMDP 4V) were computed at each time period. These comparisons showed significant ($P < .05$) effects of dose for each period beginning with the third period, which began ~3 hours after ingestion. Significant effects of drug were found only at midday (periods 4 and 5) and at the end of the day (period 8), which was in line with our expectations.

As is illustrated in Fig 1, the smallest effect sizes were produced by the low dose of Ritalin, and the largest by the higher dose of Adderall. The time course lines for the higher dose of Ritalin and the lower dose of Adderall were virtually identical throughout the course of the day.

Side Effects

Each day during the assessment, counselors, teachers, and parents rated common stimulant-related side effects as a safety measure. One boy was eliminated from the protocol early because his parents were concerned that the stimulants were exacerbating preexisting motor tics; however, his data up to the point of termination are included herein. No other participants were judged to have adverse side effects of either Ritalin or Adderall that would preclude recommending medication, although recommendations were made for lower doses for some children based on concerns about possible side effects of higher dosages. Table 6 summarizes the percentages of children rated as showing moderate to severe side effects by counselors and parents on any day during the assessment, and Table 7 summarizes the percentages of children rated on the average as showing moderate or severe side effects (teachers did not endorse moderate or severe side effects for any of the children).

Counselor ratings showed that picking/nail biting, dull/tired/listless, stomachaches, and loss of appetite were reported differentially more for either a lower or a higher dose of Adderall than for Ritalin on at least 1 day, typically the first day the drug was administered. On parent ratings, headaches, stomachaches, tearful/sad, trouble sleeping, and loss of appetite were reported differentially more for either a lower or a higher dose of Adderall than for Ritalin on at least 1 day. However, averaged across all medication days, differential side effects were apparent only for loss of appetite and trouble sleeping for the high dose of Adderall. No other side effects were experienced by a substantial percentage of the children.

Clinical Medication Recommendations

At the end of the STP, a team of medical, research, and clinical staff members discussed each child's data and response to medication on the dependent

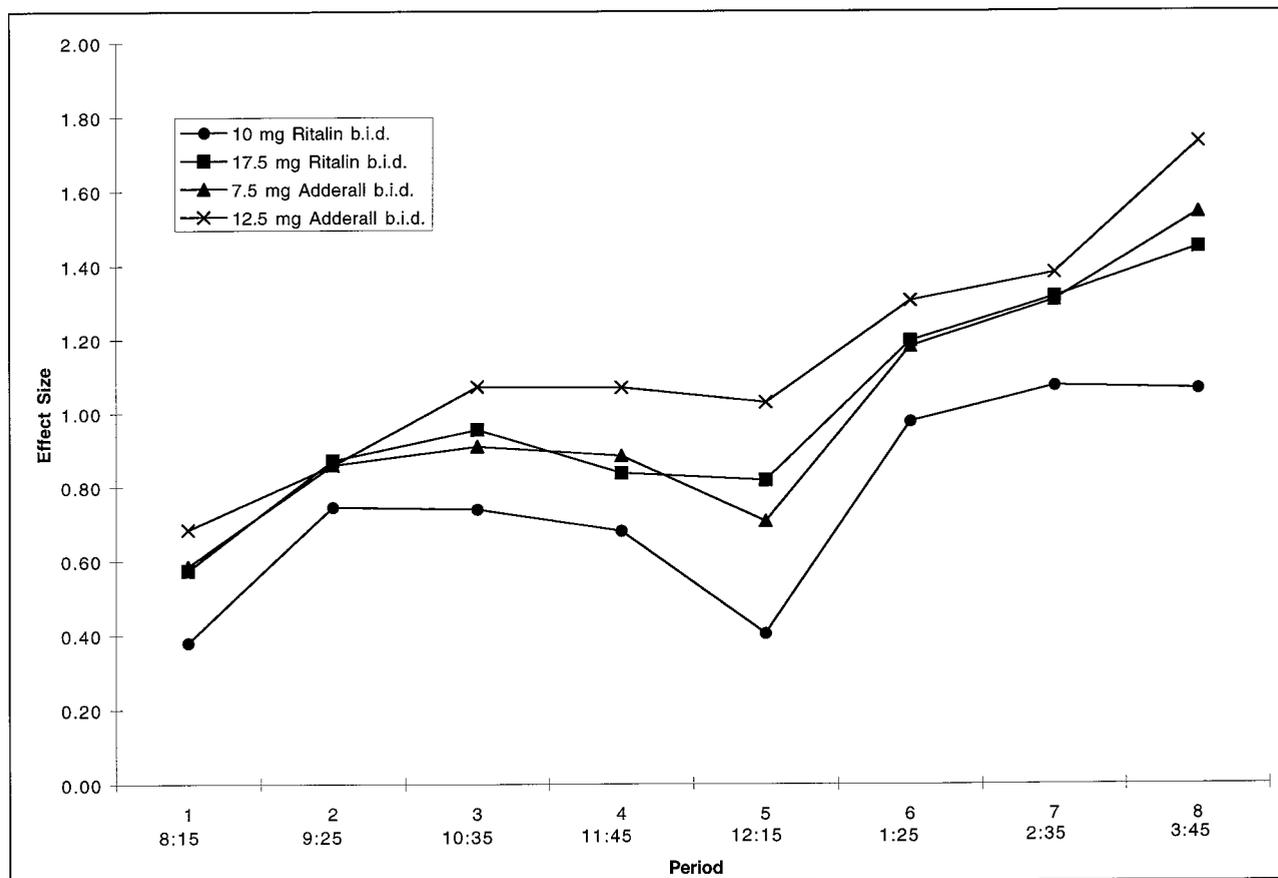


Fig 1. Average effect sizes for disruptive behavior as a function of time and drug condition. Beginning times are listed for each period; all periods were 60 minutes in length except for #4 which was 30 minutes in length. The first dose was administered between 7:30 and 8:00 AM; the second dose was administered at 12:15 PM.

TABLE 6. Percentages of Children for Whom Side Effects Were Reported as Moderate or Severe on at Least 1 Day by Parents and Counselors*

	Counselors					Parents				
	P	LR	HR	LA	HA	P	LR	HR	LA	HA
Motor tics	0	8	4	8	8	8	4	0	4	8
Buccal-lingual movements	0	12	4	0	8	4	0	4	0	8
Picking, nail-biting, etc.	4	4	8	8	16	4	0	0	0	0
Worried/anxious	8	8	8	12	12	4	4	4	4	16
Dull, tired, listless	8	0	20	16	36	28	8	12	28	40
Headaches	4	8	8	12	12	4	12	16	12	20
Stomachache	12	8	28	16	32	0	4	8	12	36
Crabby, irritable	32	4	8	8	4	32	24	16	32	36
Tearful, sad, depressed	8	16	24	12	32	8	20	16	20	28
Socially withdrawn	0	8	16	16	16	12	0	8	16	20
Hallucinations	0	0	0	0	0	0	0	0	0	0
Trouble sleeping	—	—	—	—	—	12	32	24	48	64
Loss of appetite	60	60	68	76	80	8	8	20	40	72

* Abbreviations: P, placebo; LR, 10 mg of Ritalin; HR, 17.5 mg of Ritalin; LA, 7.5 mg of Adderall; HA, 12.5 mg of Adderall. Children were counted if they were rated on any day as exhibiting the side effect.

measures that were most clinically important for that child. The team made recommendations for post-STP treatment based on those meetings. Consistent with the data reported for the group effects, the team recommended of the lower dose of Adderall for 11 (44%) of the children, which was by far the largest group of recommendations made. Recommendations were made for 3 children (12%) to receive either the low dose of Ritalin or the low dose of Adderall (that is, the two were judged to be equivalent), for 4 (16%)

to receive the higher dose of Ritalin, and for 2 (8%) to receive the higher dose of Adderall. Four children showed such a positive response to the intensive behavioral treatment that no dose of medication showed a substantial incremental improvement over behavioral treatment alone. For these children, continued behavioral treatment was recommended with the possible addition of medication at a later date if deterioration occurred in a less-structured setting. Medication was not recommended for the 1 boy who

TABLE 7. Percentages of Participants Rated by Counselors and Parents as Showing an Average of Moderate to Severe Side Effects

	Counselors					Parents				
	P	LR	HR	LA	HA	P	LR	HR	LA	HA
Motor tics	0	0	0	0	4	0	0	0	0	4
Buccal-lingual movements	0	0	4	0	4	0	0	0	0	4
Picking, nail-biting, etc.	0	0	0	0	0	0	0	0	0	0
Worried/anxious	0	0	0	0	4	0	4	0	0	0
Dull, tired, listless	0	0	0	0	0	0	0	0	0	0
Headaches	0	0	0	0	0	0	0	0	0	0
Stomachache	0	0	0	0	0	0	0	0	0	4
Crabby, irritable	4	0	0	0	0	4	4	0	0	4
Tearful, sad, depressed	0	0	0	0	0	4	0	0	0	4
Socially withdrawn	0	0	0	4	0	0	0	0	0	0
Hallucinations	0	0	0	0	0	0	0	0	0	0
Trouble sleeping	—	—	—	—	—	4	8	4	4	12
Loss of appetite*	4	4	12	4	24	0	0	4	8	24

Abbreviations: P, placebo; LR, 10 mg of Ritalin; HR, 17.5 mg of Ritalin; LA, 7.5 mg of Adderall; HA, 12.5 mg of Adderall.

* For counselor ratings, children were counted if they were reported as eating one-quarter or less of their lunch; for parents, a rating of moderate or severe appetite loss was used.

ended the protocol early because of parent reports of adverse side effects.

The clinical team was not blind to medication condition when making their recommendations. Therefore, as a reliability check of the clinical team's recommendations, one of the authors (J.W.) who was not involved in the clinical team meetings made independent recommendations based on the same data given to the clinical team. This rater was blind to drug condition except placebo. Where discrepancies occurred, one of the members of the clinical team discussed the reasons for the discrepancies with the independent rater; in two cases the independent rater changed his rating to agree with the team. The resulting recommendations agreed 80% of the time. In two of the five cases in which disagreement occurred, the second rater judged side effects to be more clinically relevant than did the clinical team. In a third case, the independent rater judged that the effects of 7.5-mg of Adderall and 17.5-mg of Ritalin were equivalent and chose the lower dose (Adderall) whereas the team chose the Ritalin dose. In only one case was there disagreement regarding which dose/drug had the consistently better effects.

DISCUSSION

The purpose of this investigation was to evaluate the efficacy of Adderall in comparison with Ritalin in a well-controlled study with multiple dependent measures. Time course and dose-response information was also investigated. This study added to Swanson et al's^{23,24} findings by directly comparing Adderall with Ritalin, and it yielded several important findings: 1) Adderall is at least as effective as Ritalin in improving acutely the behavior and academic performance of children with ADHD. 2) Adderall produced no more clinically significant side effects than did Ritalin, and side effects were minimal, as is typical with low to moderate doses of stimulants. 3) The time course investigation showed that the shape of the response curve was similar for Adderall and Ritalin, increasing throughout the day, but that the two doses of Adderall produced consistently higher effect sizes than the two doses of Ritalin, particularly at midday and at the end of the

day, and that the effects of all doses were greatest at the end of the program day (5:00 PM). 4) Measures taken at times of the day when Ritalin is expected to have worn off—4 to 5 hours after ingestion—generally showed that Adderall was more effective than Ritalin at these times. 5) Clinical recommendations made by both open and blind clinical staff at the end of the assessment were more likely to favor Adderall than Ritalin.

Foremost, both doses of Ritalin and both doses of Adderall produced substantial and significant improvements in the social behavior of ADHD children in recreational group settings. On all measures taken except positive peer interactions and attention, significant drug effects were found, and all four doses were significantly different from placebo. As Table 2 illustrates, the magnitude of these effects were substantial, moving children from unacceptable levels of disruptive and antisocial behavior (see placebo column) to levels that approached (but did not reach) normative levels.³⁶ For every category in Table 2 except complaining and positive peer behaviors, Adderall produced significantly more improvement than did Ritalin. For several key measures, including several categories of negative behaviors and the children's individualized DRC, a drug times dose interaction was found. As Table 2 shows, the interaction was because of the following pattern: for most measures, the low and high doses of Ritalin differed, whereas the low dose and high dose of Adderall produced equivalent levels of behavior. The effect of 7.5-mg of Adderall twice daily was equivalent to the effect of 17.5-mg of Ritalin, and the higher dose of Adderall did not produce incremental benefit. The general effects on social behavior, as well as this pattern of interactions, were obtained also on the ratings completed by the counselors who interacted with the children during the recreational settings (see Table 4).

These effects on social behavior—both objective measures and ratings—are quite similar to those that we have reported previously in studies conducted in the same STP setting^{10,40,41,43} and that others have reported in similar settings,^{44,45} and show that psychostimulants improve disruptive and aggressive be-

havior in ADHD children and adolescents in social settings. These results also support our contention that most of the effect of stimulant medication on social behaviors is produced by relatively low doses and that relatively little incremental improvement is brought by higher doses.⁴⁶ Our results extend all these previous findings with Ritalin to show that Adderall has similar effects. A similar result indicating diminishing returns of higher doses has been reported for teacher ratings on Adderall using a dose range comparable to ours.²³

For the classroom measures, all four drug conditions showed improvement relative to placebo on all measures except seatwork accuracy, which showed an expected ceiling effect. However, there were no dose effects and no differences between the two medications. As with the measures of behavior in recreational settings, the teacher ratings reflected the same pattern of results as did the objective classroom measures (see Table 4). These stimulant effects on measures of classroom functioning replicate many previous studies showing that stimulants produce beneficial changes on daily academic performance, on-task behavior, and classroom disruption, and they extend these findings beyond previous studies demonstrating the effects for Ritalin,^{10,33,37,42,47–49} Dexedrine,¹⁰ and pemoline¹⁷ to include Adderall. As is the case with measures of social behavior, however, there were no incremental effects of the higher doses of either Ritalin or Adderall, again demonstrating diminishing returns with higher dosages of stimulants.⁵⁰ Swanson et al²³ reported the same finding using similar academic tasks with Adderall doses between 10 and 20 mg.

The side effect reports from counselors and parents revealed relatively few side effects and yielded rates for Adderall that are comparable to those reported in other studies with Ritalin, pemoline, and d-amphetamine.^{10,17,51,52} Tables 6 and 7 separate side effects into those that were considered moderate or severe and appeared once versus the averages obtained throughout the entire trial. As Table 6 shows, a higher percentage of children were reported by counselors or parents to have side effects at least once in response to the 12.5-mg dose of Adderall than to any other drug condition (dull, stomachache, tearful, trouble sleeping, and loss of appetite). These effects are comparable to the relative increase in side effects reported in a recent comparison of d-amphetamine and Ritalin.⁵² Side effects were typically obtained on the child's initial dose. As Table 7 demonstrates, when examined across all days per condition, side effects rapidly dissipated, such that only appetite suppression showed differential effects for the high dose of Adderall. This effect is likely a function of the time course of Adderall (see below). Only 1 child had side effects (motor tics on all drug conditions) of sufficient concern (in this case to the parents) that neither medication was indicated. This child's parents discontinued the trial before it was completed, but because he had at least two data points for each condition, his efficacy and side effect data are included in this report.

The time course results (see Fig 1) showed that all

four conditions had some efficacy at 1 hour after ingestion of the morning pill and reached peak efficacy between 2 and 3 hours after ingestion. Interestingly, all four doses continued to show some effect even in the putative valley period at midday, although the effect of the lower dose of Ritalin was clearly wearing off. A question of interest was whether the relative time course of Adderall was longer than for Ritalin, an effect recently reported by Swanson et al.²³ We predicted, based on Swanson et al's report, that Adderall would continue to be effective in the fifth hour after ingestion both at midday and in the evening. Figure 1 shows that Adderall had significantly greater effects than Ritalin both at midday and during the last hour of the day program. In addition, the parent ratings revealed differential effects for Adderall compared with Ritalin between the hours of 5 and 6 PM, the fifth and sixth hour after ingestion of the midday dose of medication.

These time course effects are similar to those reported by Swanson et al,²³ who reported a peak effect of Adderall between 1.5 to 3 hours, depending on dose. Swanson et al also demonstrated that the effects of a single 20-mg dose of Adderall continued to have a beneficial effect on teacher ratings and arithmetic tasks for more than 6 hours after ingestion and possibly for 7.5 hours, with shorter spans of action for lower doses (3.5, 4.8, and 5.4 hours for 5, 10, and 15 mg, respectively). Also of interest is that the pattern of effects in our study was different for the afternoon dose in comparison to the morning dose. As Fig 1 shows, the individual ES increased throughout the day, with all four doses showing greater ES in the afternoon compared with the morning. While the low dose of Ritalin seemed to be reaching a plateau at period 8, the other three conditions—particularly Adderall—continued to improve during the fourth hour after the midday dose, when the expectation would be that they would have already reached their peak effectiveness. Combined with Swanson et al's^{23,24} data and other earlier studies,⁹ these results suggest that some of the morning dose of stimulant may still have been active in the afternoon, combining additively with the midday dose to yield a greater effect in the afternoon.

If these results are replicated in other settings, they have implications for clinical practice with Adderall or with higher doses of Ritalin and presumably other stimulants: the midday dose of stimulants that must be administered twice daily may not need to be as high as the morning dose to yield the same behavioral effect as the morning dose. Given that low total lifetime dose is a goal with psychoactive medications, routinely reducing the midday dose of stimulants may be a beneficial strategy for ADHD children.

The fact that Adderall lasts for an hour or more beyond Ritalin in all likelihood accounts for the differential appetite suppressing effects discussed above for the higher Adderall dose. To minimize a negative impact of appetite suppression on growth, parents could increase children's appetite at the dinner hour by giving Adderall doses earlier in the morning than we did (eg, at 7 AM), and could either

delay dinner time or give late evening snacks to the child.

As a final and perhaps most noteworthy measure of treatment response, consider the clinical recommendations that our staff made for the children's subsequent medication treatment. Fifty-two percent of the children were judged to show such a differentially positive response to Adderall that it was recommended, with 85% of those recommendations being for the 7.5-mg dose (or a 5-mg dose) administered twice a day. Only 12% of the children had Ritalin differentially recommended, and 16% were responsive to both medications. Twenty-three percent of the children were adverse responders ($n = 1$), nonresponders ($n = 4$), or insufficient responders ($n = 1$) to the two medications. These figures are interesting for several reasons. First, Adderall was clearly preferred over Ritalin by the study team. Even although the 7.5-mg dose of Adderall and the 17.5-mg dose of Ritalin were found to have equivalent behavioral effects, 7.5 mg of Adderall was recommended almost three times as often as 17.5 mg of Ritalin. Similarly, the time courses shown in Fig 1 were identical for the 7.5-mg dose of Adderall and the higher dose of Ritalin, so differences in time course are unlikely to account for the effect. One is left to speculate whether there is something in the active pharmacologic agents in Adderall (a racemic mixture of d- and l-amphetamine)—or of Dexedrine, which was not included in this study—are more effective than Ritalin. Although we are not aware of any putative neurochemical basis for such a conclusion, others have speculated concerning its nature.²⁵ Whatever the reason for these results, it is clear that Adderall is effective and should be added to the clinical armamentarium for ADHD.

At the same time, it is interesting to note that 23% of the children did not have medication recommended. Some authors¹⁴ have argued that more than 90% of ADHD patients will respond to a stimulant, if multiple doses and drugs are used in a trial. This is the second time that we have conducted such a trial, the first including standard Ritalin, pemoline, Dexedrine Spansule, and Slow Release Ritalin, and our response rate in that trial was similar to what we found herein. We believe that the estimate that more than 90% of ADHD children are responders to and should therefore be prescribed stimulants is a gross overestimate. Part of the reason for this outcome may be that we conduct our trials, as this one, in the context of a behavioral treatment program. We are thus evaluating the incremental benefit of medication beyond that of a psychosocial treatment. The 4 children for whom we could not find evidence of drug effects may have been so responsive to the behavioral intervention that no further improvement could be gained with medication. The 77% response rate herein is comparable to our previous report that 78% of the children in one of our STP studies showed incremental improvement in classroom functioning when Ritalin was added to a behavioral intervention.³³

Additional dose-response studies are needed to determine the dose equivalency of Adderall in com-

parison to Ritalin. The results of this study suggest that a 7.5-mg dose of Adderall is behaviorally equivalent to a 17.5-mg dose of Ritalin. A 12.5-mg dose of Adderall would thus be expected to be behaviorally equivalent to a 30-mg dose of Ritalin—considerably higher than we used for our highest Ritalin dose. We consider these unnecessarily high doses of stimulant. The high dose of Adderall used herein offered no incremental benefit beyond the lower dose of Adderall, and was least often endorsed by parents as a desired dose. We had selected what we thought would be comparable doses of the two medications based on the only existing study of Adderall,^{23,24} which used fixed doses of Adderall and compared them to the dose of Ritalin each child was currently prescribed by his or her physician. Swanson et al^{23,24} then extrapolated means to suggest the ratio of Adderall:Ritalin that we selected. Based on our present results, we suggest that a dose of 5 mg (or slightly less) of Adderall is comparable to a 10-mg benchmark dose of Ritalin. If replicated, this suggestion makes Adderall very slightly more potent than d-amphetamine, which produces equivalent effects to Ritalin at a 1:2 dose ratio.

It should be noted that the children in our sample varied widely in terms of weight (range = 22–67 kg) such that mg/kg equivalents for the two doses varied from 0.15 to 0.46 for the low dose of Ritalin, from 0.26 to 0.80 for the high dose of Ritalin, from 0.11 to 0.34 for low dose of Adderall, and from 0.19 to 0.57 for the high dose of Adderall. The decision to use absolute dosing in the study was made because most prescribing physicians use absolute dosing. However, we would suggest that future stimulant-comparative studies with children should use mg/kg dosing to provide more precise information regarding dosing equivalency between the two drugs.

We emphasize that this study was conducted in the context of an intensive behavioral treatment. Given that such behavioral treatments have demonstrated efficacy,^{34,53} when in place they may affect the shape of the dose-response curve for stimulants.³⁷ It is possible that this fact differentially influenced the dose-response functions obtained if the Adderall doses were functionally higher than the Ritalin doses. It is also possible that the behavioral intervention may play a role in the increasing effect sizes seen throughout the day. The behavioral treatment may have combined with the morning medication to yield positive outcomes that motivated the children to behave even more positively as the day wore on—in other words, success may have bred success.⁴¹

Given our results, when would it be appropriate for a primary care physician to use Adderall rather than, for example, generic methylphenidate (MPH), which costs less? The time course data suggest that if MPH loses its effects for a child relatively quickly at midday or in the late afternoon and issues such as feasibility and noncompliance make it difficult to increase the frequency of MPH dosing, Adderall (or possibly d-amphetamine—see below) could be tried. In our clinic, we routinely compare multiple doses and/or types of stimulants in school-based clinical

assessments such as the one used herein⁵⁴ so that we can directly answer for each patient questions of which stimulant or dose is best for the child. Finally, we compared only Adderall and Ritalin. It is possible that Dexedrine would have produced similar results to those of Adderall. Future research should compare Adderall with Dexedrine to evaluate their relative effects.

ACKNOWLEDGMENTS

This study was supported by a grant from the Shire Richwood Pharmaceutical Company, manufacturer of Adderall. During this research, Dr Pelham was also supported by grants from the National Institute of Mental Health (Grants MH53554, MH45576, and MH50467).

This study was conducted during the 1997 Summer Treatment Program conducted by the ADHD Program at the Psychology Department, SUNY at Buffalo.

We thank the Psychology Department and the Psychological Services Center for their support, as well as the staff of the Summer Treatment Program. We also thank Kenton Crowley, PharmD, at the Child Development Center, University of California at Irvine; the pharmacy staff of the Children's Hospital of Buffalo for helpful cooperation; and L. Eugene Arnold, MD, for his instructive comments on the manuscript.

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DOI: 10.1542/peds.103.4.e43

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