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ARTICLES

Relative Efficacy of Long-Acting Stimulants on Children With Attention Deficit-Hyperactivity Disorder: A Comparison of Standard Methylphenidate, Sustained-Release Methylphenidate, Sustained-Release Dextroamphetamine, and Pemoline

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ABSTRACT. Twenty-two children with attention deficit-hyperactivity disorder underwent a double-blind, placebo-controlled, crossover evaluation of the efficacy of standard methylphenidate twice a day and comparable doses every morning of a sustained-release preparation of methylphenidate (SR-20 Ritalin), a sustained-release form of dextroamphetamine (Dexedrine Spansule), and pemoline. The children were participating in a summer treatment program in which they engaged in recreational and classroom activities. Dependent measures include evaluations of social behavior during group recreational activities, classroom performance, and performance on a continuous performance task. Results revealed generally equivalent and beneficial effects of all four medications. Dexedrine Spansule and pemoline tended to produce the most consistent effects and were recommended for 10 of the 15 children who were responders to medication. The continuous performance task results showed that all four medications had an effect within 2 hours of ingestion, and the effects lasted for 9 hours. The implications of these results for the use of long-acting stimulant medication in children with attention deficit-hyperactivity disorder are discussed. *Pediatrics* 1990;86:226–237; *attention deficit-hyperactivity disorder, long-acting stimulant medication, methylphenidate, dextroamphetamine, pemoline.*

ABBREVIATIONS. ADHD, attention deficit-hyperactivity disorder; b.i.d., twice a day; DS, Dexedrine Spansule; SR-20, Slow-Release Ritalin; q.a.m., every morning; CPT, continuous performance task; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, 3rd ed, revised.

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Medication with a central nervous system stimulant has been the most common treatment for children with attention deficit-hyperactivity disorder (ADHD) for 20 years. Numerous studies have demonstrated the short-term efficacy of central nervous system stimulants—usually methylphenidate—in the treatment of ADHD (for reviews, see References 1 and 2). These studies have shown that methylphenidate improves the classroom functioning of children with ADHD, as reflected in decreases in observed disruptive behavior, increases in academic productivity and accuracy, and improvement in teacher ratings.[3,4] Furthermore, methylphenidate improves the performance of children with ADHD on a variety of cognitive tasks, including measures of attention, learning, and memory.[5,6] Although considerably less research has been conducted with them, similar findings have been reported for dextroamphetamine and pemoline.[7–12] Thus, medication with a central nervous system stimulant—usually methylphenidate and far less often dextroamphetamine—has become the most common treatment for ADHD.

At the same time, pharmacotherapy with the standard preparations of stimulant has several limitations. For example, methylphenidate's brief half-life means that it must be administered at least twice daily—a morning and a noon dose—to ensure adequate treatment throughout a child's school day. Its rapid onset and its brief half-life mean that a child with ADHD on the standard twice a day (b.i.d.) dosing regimen will be maximally affected for only part of a typical school day. This lack of pharmacologic coverage throughout the school day may accou

to affect some key domains of functioning in children with ADHD. For example, it has been speculated that one reason why stimulant effects have not been found on measures of long-term achievement is that methylphenidate's narrow window of effect on cognitive performance (60 to 180 minutes after pill ingestion) often does not overlap with time when medicated children are performing academic tasks in school.[6,13,14] A child who takes a pill at 7:00 AM with breakfast and again at noon with lunch (a common regimen) may be in an active medication state that would facilitate performance on academic tasks only between 8:00 AM and 10:00 AM and between 1:00 PM and 3:00 PM. If school lasts from 8:45 until 2:45, a child medicated with standard methylphenidate may be effectively medicated for only 3.5 hours out of the 6-hour school day. A child receiving methylphenidate on this schedule would not be expected to benefit from a reading group or independent seatwork after 10:00 AM or during unstructured late-morning and midday activities, such as recess and lunch, which are often difficult for children with ADHD.

An additional difficulty associated with the standard methylphenidate regimen is that the child must be given a pill at school, an event that some children with ADHD and some school personnel actively avoid.[15] In our locality (metropolitan Pittsburgh), some schools have policies that prohibit school personnel from administering psychoactive medication. Some of the young children with ADHD in our outpatient clinic must, therefore, take methylphenidate to school in their lunch boxes and remember themselves to take their midday pill. This no doubt contributes to the poor compliance that has characterized stimulant treatment of ADHD.[16–18]

Dextroamphetamine has a longer half-life than methylphenidate,[19] and controlled studies have documented its effectiveness.[8–10] Despite these studies, dextroamphetamine has been widely thought to have a higher incidence of side effects than methylphenidate[20] and perhaps to be less effective.[21] It is, therefore, used far less often than methylphenidate—in only 5% of medicated children, compared with 90% for methylphenidate.[22] These limitations of methylphenidate and dextroamphetamine led to interest in stimulants with longer effective spans of action. Three such medications are available: Dexedrine Spansule (DS, a sustained-release form of dextroamphetamine), Slow-Release Ritalin (SR-20), and pemoline. There has been limited research with these long-acting preparations. Only two studies have examined the effectiveness of DS. Rapoport et al[23] examined the effects of 10 mg of DS on clinic playroom activity and teacher ratings in 19 hyperactive children and reported improvement on the playroom measures and on the hyperactivity factor of the Conners Teacher Rating Scale.[24] Brown et al[25] conducted a time course study of DS (0.5 mg/kg). The results showed that DS had a later peak plasma level that lasted longer than standard dextroamphetamine, but that "the significant [clinical] response appears to be shorter."[25(p234)] This is the only time course study of DS, and significant differences from placebo were reported only at 2 hours postingestion. The study has several limitations, however, including an N of only 9 and the fact that the dependent behavioral measures included only an activity monitor and the blood technician's ratings of the subjects' behavior during blood draws.

Pemoline has a much longer half-life than both methylphenidate and dextroamphetamine.[26] This longer half-life presumably enables it to be administered in a single morning dosage to cover an entire school day. Several direct comparisons of pemoline with methylphenidate or dextroamphetamine have shown it to be similar in its efficacy.[7,11] Furthermore, one acute study of the time of onset and time course of pemoline showed that pemoline exerts a clear behavioral effect within 2 hours of ingestion on the second consecutive day of administration and that its effects last for at least 6 hours.[27] However, it remains widely believed that pemoline is less effective than methylphenidate or dextroamphetamine[2] and that it takes weeks rather than hours or days before pemoline exerts an effect.[21] As a result, it is also used far less often than methylphenidate—in only 2% of medicated children, compared with 90% for methylphenidate.[22] Furthermore, although its longer half-life has been documented, the precise time course of the behavioral and cognitive effects of pemoline has not been clearly established.

Recently, a sustained-release preparation of methylphenidate, SR-20, has been developed. According to its manufacturer, SR-20 is currently being prescribed to 11% of the children younger than 10 years of age who are receiving Ritalin (personal communication, Timothy Horner, Ciba-Geigy, September 30, 1988). Although Ciba-Geigy advertises that the preparation is equivalent to a b.i.d. schedule of 10 mg of methylphenidate, the only published, controlled comparison of SR-20 and standard methylphenidate did not support this conclusion.[28] On most behavioral measures the two preparations had similar effects, but standard methylphenidate was more effective than SR-20 on several key measures of disruptive behavior. Although the time courses of the two medications were similar, SR-20 had a slower onset of action on a cognitive measure, and its effects wore off more quickly on a measure of social behavior. Further-

more, analyses of individual responsivity to medication favored the standard preparation. As in the studies of DS, this study also had a small N—13 for the first study and 9 for the analysis of time course.

Thus, although there are clear potential advantages to long-acting forms of central nervous system stimulants for treatment of ADHD, there have been few studies of the efficacy of the available preparations. Only one time course study is available for each medication, and these are not directly comparable, as each used different settings and dependent measures. Only one study each of behavioral effects is available for DS and SR-20, and only three are available for pemoline. Because there has never been a relative efficacy study of the long-acting medications, there are no guidelines for practicing physicians regarding which long-acting medication to prescribe when a long-acting drug would appear appropriate.

Perhaps as a result of this lack of information, the long-acting forms of stimulant are used with only a small percentage of the children with ADHD who are receiving medication. Given the potential utility of an effective long-acting stimulant preparation, there is a need for a comprehensive study of the relative efficacy of comparable doses of the three long-acting forms of stimulant—pemoline, DS, and SR-20—compared with the standard methylphenidate preparation. This investigation has that purpose. The paucity of information about long-acting stimulants means that an acute, short-term, crossover study appears more appropriate than a longer, between-group comparison. Thus, we designed a placebo-controlled, double-blind, within-subject study to compare 10 mg of methylphenidate b.i.d., SR-20 every morning (q.a.m.), 56.25 mg of pemoline q.a.m., and 10 mg of DS q.a.m., with midday placebos administered with the long-acting preparations and on placebo days. A wide range of dependent measures was used to expand on those that have been used in previous studies and to ensure a comprehensive assessment of effects. Furthermore, the most commonly used laboratory measure of stimulant response in children with ADHD, a continuous performance task (CPT), was administered repeatedly on 1 day of each medication condition to track the relative time courses of the drugs.

METHODS

Subjects

Twenty-two boys, aged 8.08 years to 13.17 years, participated in this study. Based on a structured parental interview, and parent and teacher rating scales, ADHD was diagnosed for all 22 subjects. Nine of the subjects also met the Diagnostic and Statistical Manual of Mental Disorders, 3rd ed, revised (DSM-III-R) criteria for a diagnosis of an oppositional/defiant disorder, and 4 others met DSM-III-R criteria for conduct disorder. Thirteen subjects had a discrepancy between their Wechsler Intelligence Scale for Children-Revised IQ and their Woodcock-Johnson Achievement scores of at least one full standard deviation in either reading, arithmetic, or written language, suggesting the presence of a learning disability. On the Swanson, Nolan, and Pelham Rating Scale (Pelham WE, Atkins MS, Murphy HA, and Swanson J, unpublished data, 1986), which lists the symptoms of attention deficit disorder presented in the DSM-III, teachers reported the presence of at least 8 symptoms in each of 15 subjects. Of the 7 children who did not meet this criterion 5 were medicated when the teacher ratings were gathered. Teacher ratings were also obtained on the Iowa Conners Teacher Rating Scale, resulting in 8 subjects' exceeding the cutoff score for the aggression factor.[29] No children had IQ scores below 80. One child had a concurrent seizure disorder for which he had received medication in the past, but he was not receiving medication at the time of the study. Means and standard deviations on several measures of subject characteristics are shown in Table 1.

TABLE 1. Subject Characteristics

Measure	Mean (SD)
Age, y	10.39 (1.38)
Wechsler Intelligence Scale for Children-Revised IQ score	105.68 (14.81)
Abbreviated Conners Rating Scale scores	
Teacher	15.50 (6.52)
Parent	19.32 (5.32)
Iowa Conners Teacher Rating Scale scores	
Inattention/Overactivity	9.59 (3.81)
Aggression	5.86 (4.45)
DSM-III-R Structured Interview for Parents*	
Attention deficit disorder items	11.36 (1.92)
Oppositional/defiant disorder items	5.36 (2.38)
Conduct disorder items	1.68 (1.73)
Woodcock-Johnson Achievement Test standard scores	
Reading	96.45 (14.89)
Mathematics	99.82 (17.21)
Language	99.00 (14.19)

* Number of symptoms endorsed by clinician. DSM-III-R, *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed, revised.

Setting

The boys in this protocol were participating in the 1988 Western Psychiatric Institute and Clinic Attention Deficit Disorder Program's Summer Treatment Program. Children attended the Summer Treatment Program from 8:00 AM until 5:00 PM on weekdays for 8 weeks. The children were divided into groups of 12 according to age. A broad-spectrum behavior modification intervention was the primary treatment modality. A day in the Summer Treatment Program was divided into the following activities: two academic classroom periods, each staffed by a special education teacher and an aide; an art class (The oldest two boys in the study were in a group that participated in a group discussion rather than an art class.); swimming; three supervised, group, outdoor recreational activities (eg, dodgeball); and lunch. For all activities except the academic classroom periods, five counselors supervised each group of 12 children and implemented the treatment programs. The 22 children receiving the drug protocol described herein were distributed across five different age groups. The first 1.5 weeks of the program served as a period of adaptation for the children and staff, and medication assessments were conducted during the last 6.5 weeks of the program.

Procedure

The clinical medication assessment procedure used in this study has been described in detail elsewhere.[28,30] It was a double-blind, placebo-controlled evaluation in which each child received, in random order for 3 to 6 days each, the following medications: placebo b.i.d., a standard regimen of 10 mg of methylphenidate b.i.d., and comparable doses of SR-20 q.a.m., 56.25 mg of pemoline q.a.m., and 10 mg of DS q.a.m. (The long-acting dosages were selected to be comparable with 10 mg of standard methylphenidate b.i.d. Empirical data have shown the comparability of this dose of pemoline and 10 mg of methylphenidate,[8,11] while dextroamphetamine is generally considered to be twice as potent as methylphenidate.[1]) Midday placebos were administered on long-acting medication days so that they could not be distinguished from standard methylphenidate days. Placebo, standard methylphenidate, SR-20, and DS were randomized over single days, and pemoline was randomized in triplets of days, with only the last 2 days of a triplet used for data. The average equivalent in milligrams per kilogram of body weight for a 10-mg dose of methylphenidate for these boys was 0.29. For 14 of the 22 boys, 10 mg was equivalent to 0.3 mg/kg, and the range for the other children was from 0.23 to 0.37 mg/kg. Active medication and placebo were disguised in gelatin capsules and prepackaged in individual daily pill reminders. Medication was administered either by parents with breakfast or by program staff on arrival at the program and by the program staff just before or just after lunch, depending on the child's treatment group's daily schedule. The time and location of pill administration remained constant for each child. Four to 6 days of data were gathered for placebo, standard methylphenidate, SR-20, and DS conditions, with the average number of days for each condition being 5.0, 5.1, 4.9, and 4.9, respectively. Three to 5 days (mean = 4.5) of data were gathered for the pemoline condition. The risks and benefits of psychostimulants were explained to all parents, and all parents signed treatment consents that described in detail the protocol and assessment procedures.

Dependent Measures

The reliabilities of all of the following dependent measures are acceptable and have been reported in detail in previous descriptions of our medication assessment.[3,28,30]

Daily Frequencies. As part of a behavior-modification point system in effect in all settings except the academic classrooms, counselors recorded the frequencies with which numerous appropriate and inappropriate behaviors occurred daily. The following five categories were derived: (1) following rules, (2) positive peer behaviors (eg, positive verbal statements to others), (3) noncompliance, (4) conduct problems (eg, aggression), and (5) negative verbalizations (eg, name-calling/teasing).

Classroom Measures. Teacher-recorded rates of rule-following behavior were derived from a response-cost procedure. Children lost points immediately upon the occurrence of a classroom rule violation. The percentages of points that each child kept were measures of medication effects on classroom rule-following behavior.

Each boy completed a 2-minute, timed, arithmetic drill and a 10-minute, timed, reading task, using materials selected as appropriate to his instructional level. The number of arithmetic problems and reading questions attempted and the percentage completed correctly within the allotted time served as the dependent measures. Other daily academic tasks were also individualized according to each child's needs (eg, language, spelling, additional reading, and arithmetic). Accuracy (percentage correct) and productivity (percentage of assigned seatwork completed) in these tasks were recorded daily.

Rating Scales. Teacher ratings on the Abbreviated Conners Teacher Rating Scale were obtained for each child two to four times in each medication condition. Counselor ratings, also using the Abbre-

viated Conners Teacher Rating Scale, were gathered two to four times per child per condition. Parent, teacher, and counselor side effects checklists were also gathered at least once per condition per child. If side effects were reported on that rating for a child, then side effect rating scales were repeated.

Daily Report Card. A number of each child's individual behavioral and academic goals (typically three to five targets) were included on daily report cards. Positive daily report cards were rewarded at home and monitored throughout weekly parent-training sessions. The percentage of days the child reached his daily report criterion was used as an individualized measure of drug response.

Continuous Performance Task. In addition to the measures from our standard medication assessment, the children in this protocol completed a CPT five times on 1 day of each medication condition to provide information about the behavioral time courses of the drugs. Each subject received a morning dose of medication and then a midday dose (for standard methylphenidate) or placebo (for long-acting medications) 4 hours after the morning dose. The task was administered at the following time intervals after morning medication ingestion: 1 hour, 2 hours, 4 hours, 6 hours, and 9 hours.

The CPT was the same as that used in a previous study,[28] with minor modifications. The rate of stimulus presentation was varied to control the level of difficulty and length of the task. Subjects performed the CPT in a group setting. All the computers were situated on desks that were placed around the perimeter of a classroom so that all the subjects were facing a wall. The task itself consisted of the repeated presentation of letters on a computer monitor (Lindgren S and Lyons D, unpublished data, 1985). The rate at which the letters were presented was predetermined by establishing a baseline when the subjects were unmedicated. To establish the baseline, the variable rate version of the task was used, in which the rate of stimulus presentation is varied as a function of the subject's error rate to achieve an optimal level of difficulty. A 20% to 40% error rate was selected to make this task comparable with other laboratory tasks that have been used to study stimulant effects.[11,31] The baseline task was administered on two different occasions and the average ending rate for stimulus presentation was calculated. Each subject was then assigned a presentation rate of either 0.3, 0.6, or 0.9 seconds, whichever was closest to his average rate during baseline. The task lasted for a total of 15 minutes regardless of the stimulus rate chosen, and the same rate was used for all subsequent administrations of the task for a given child.

The stimuli consisted of letters presented on a monitor with the target stimulus being the letter "H" followed by the letter "T." When this sequence occurred, the subject was instructed to respond by pressing the space bar. Errors of omission were recorded as the percentage of targets presented for which the subject failed to press the space bar. Errors of commission were recorded when the child responded to a nontarget stimulus. The percentage of errors of omission, along with the number of errors of commission, were the dependent measures for the task.

RESULTS

The results of the trial on the mean values of the dependent measures from the standard medication assessment protocol are shown in Table 2. A one-way (drug) MANOVA on these measures revealed a significant effect of drug, $F(60,260) = 2.47$, $P < .0001$. Follow-up analyses involved contrasting each drug with placebo for each dependent measure. Table 2 presents the means and the results of these follow-up contrasts. (The data from the timed arithmetic task were not analyzed and are not presented because inadequate randomization caused the problem difficulty level to be confounded with drug type and rendered the data uninterpretable.)

To assess the effects of drug on the consistency of children's responses to medication, a one-way MANOVA with drug as the factor was conducted on the average SDs across days within drug conditions for the dependent measures in the medication assessment. The SDs over days reflect the degree to which children's responses to the drugs varied across repeated administration. The effect of drug was significant, $F(60,260) = 2.42$, $P < .0001$, reflecting decreased variability with medication. Table 3 presents the average SDs over subjects by drug condition and the results of follow-up contrasts comparing each drug with placebo for each dependent measure.

Separate 5 (drug) × 5 (time) ANOVAs were conducted on the two dependent measures from the CPT—the percentage of omission errors out of presented targets and the number of commission errors to nontargets. There were no significant drug effects or interactions with drug on commission errors. For percentage omission errors, there were significant effects of drug, $F(4,20) = 14.2$, $P < .0001$, and time, $F(4,20) = 7.6$, $P < .0001$, and a significant drug × time interaction, $F(16,20) = 1.95$, $P < .025$. The significant drug × time interaction was investigated by comparing each drug with placebo at each hour. These results are presented in Table 4. Except for the lack of a difference between 10 mg of methylphenidate and placebo at the first hour

TABLE 2. Mean Scores for Medication Assessment Measures by Medication Condition*

Variable Measured	Medication Condition									
	Placebo		10 mg Methylphenidate b.i.d.		SR-20 Ritalin q.a.m.		56.25 mg Pemoline q.a.m.		10 mg Dexedrine Spansule q.a.m.	
Daily frequency measures										
Percentage following activity rules	75.2	(9.7)	80.9†	(4.2)	78.1‡	(7.7)	79.0‡	(6.2)	81.0§	(5.8)
Noncompliance	5.5	(5.7)	2.3†	(2.0)	2.3‖	(1.8)	2.0†	(1.8)	1.7§	(1.4)
Positive peer interactions	82.8	(31.9)	92.6¶	(42.8)	104.5‡	(55.0)	111.1§	(49.4)	100.0‡	(43.7)
Conduct problems	0.73	(1.29)	0.25¶	(0.25)	0.18‡	(0.27)	0.18‡	(0.23)	0.21‡	(0.36)
Negative verbalizations	5.4	(9.2)	1.6‡	(1.8)	2.0¶	(2.1)	1.6‡	(2.5)	1.4‡	(1.0)
Classroom measures										
Percentage following rules	84	(25)	92¶	(12)	94‡	(14)	95‡	(13)	95‡	(10)
Timed reading										
Number attempted	14.3	(8)	18.0‖	(8.3)	16.4	(7.3)	15.7	(6.3)	17.5†	(8.9)
Percentage correct	69	(18)	73	(18)	73	(13)	75	(14)	74	(16)
Seatwork										
Percentage completed	70	(24)	78‡	(17)	77‡	(18)	79¶	(13)	76	(16)
Percentage correct	84	(8)	84	(10)	87¶	(9)	87‡	(8)	86	(8)
Teacher rating (Abbreviated Conners TRS)	3.8	(4.6)	2.3	(2.0)	2.3	(2.1)	1.5‡	(1.5)	1.7‡	(1.4)
Counselor rating (Abbreviated Conners TRS)	6.3	(4.8)	4.8‡	(3.2)	5.0‡	(3.6)	5.1	(3.5)	4.5‡	(3.0)
Positive daily report: percentage of days received	51	(23)	63¶	(24)	64‖	(22)	71‖	(27)	67‡	(27)

* Values are given as mean (SD). Superscripts indicate the significance levels of post hoc contrasts between each drug and placebo for each dependent measure. b.i.d., twice a day; q.a.m., every morning; TRS, Teacher Rating Scale.
† $P < .005$.
‡ $P < .05$.
§ $P < .001$.
‖ $P < .01$.
¶ $P < .10$.

TABLE 3. Average Standard Deviations Over Days (Within-Subject Variability) by Medication Condition*

Variable Measured	Medication Condition									
	Placebo		10 mg Methylphenidate b.i.d.		SR-20 Ritalin q.a.m.		56.25 mg Pemoline q.a.m.		10 mg Dexedrine Spansule q.a.m.	
Daily frequency measures										
Percentage following activity rules	7.6	(4.5)	6.7	(3.5)	7.6	(6.3)	6.3	(4.7)	4.7†	(2.7)
Noncompliance	2.7	(1.8)	1.7†	(1.0)	1.7†	(1.0)	1.7‡	(1.3)	1.3‡	(0.7)
Positive peer interactions	26.3	(19.4)	32.0	(20.7)	42.4§	(34.2)	49.9‖	(40.0)	32.6	(16.3)
Conduct problems	0.73	(0.99)	0.42	(0.37)	0.21§	(0.30)	0.32¶	(0.38)	0.23‖	(0.33)
Negative verbalizations	3.9	(7.1)	1.5¶	(1.3)	1.7	(1.7)	1.7	(2.1)	1.3¶	(0.9)
Classroom measures										
Percentage following rules	15	(17)	10	(15)	8§	(15)	6‖	(12)	8‖	(12)
Timed reading										
Number attempted	7.2	(5.2)	8.8	(5.8)	6.7	(4.1)	5.3¶	(3.3)	5.4¶	(3.2)
Percentage correct	21	(11.2)	18	(10)	17	(8)	18	(1)	16¶	(9)
Seatwork										
Percentage completed	22	(14)	23	(13)	22	(14)	21	(14)	23	(13)
Percentage correct	15	(11)	12	(9)	8‖	(6)	10¶	(9)	11	(8)
Teacher rating (Abbreviated Conners TRS)	2.7	(2.4)	2.1	(1.6)	2.4	(2.3)	1.6¶	(1.5)	1.7	(1.4)
Counselor rating (Abbreviated Conners TRS)	2.2	(2.0)	1.8	(1.3)	1.5¶	(1.1)	2.3	(1.8)	1.4¶	(1.1)
Positive daily report: percentage of days received	49	(12)	42	(21)	43	(21)	31‡	(25)	36§	(23)

* Values are given as mean (SD). Abbreviations are expanded in the first footnote to Table 2.
† $P < .005$.
‡ $P < .0025$.
§ $P < .025$.
‖ $P < .01$.
¶ $P < .10$.

TABLE 4. Follow-up Contrasts of Each Drug vs Placebo by Testing Interval on the Percentage Errors of Omission on the Continuous Performance Task*

Hours After Pill Ingestion	Medication Condition				
	Placebo	10 mg Methylphenidate b.i.d.	SR-20 Ritalin q.a.m.	56.25 mg Pemoline q.a.m.	10 mg Dexedrine Spansule q.a.m.
1	43.0 (22.5)	38.0† (25.9)	31.2‡ (19.9)	28.5§ (19.4)	33.2‡ (22.5)
2	47.8 (23.0)	30.7‖ (21.6)	27.8¶ (17.8)	28.5‖ (21.8)	29.1§ (22.1)
4	42.1 (21.2)	29.3** (22.7)	24.0‖ (15.5)	22.6‖ (19.1)	23.7†† (18.5)
6	48.4 (21.2)	26.2‖ (22.1)	27.3‖ (18.3)	29.1‖ (18.8)	26.8‡‡ (20.1)
9	46.9 (19.4)	32.3** (22.1)	30.4†† (20.1)	30.9§ (21.6)	29.3¶ (20.2)

* Values are given as mean (SD). Abbreviations are expanded in the first footnote to Table 2.
† Not significant.
‡ $P < .025$.
§ $P < .0025$.
‖ $P < .0001$.
¶ $P < .001$.
** $P < .005$.
†† $P < .0005$.
‡‡ $P < .0002$.

after ingestion, all comparisons were significant. The time courses of the four medications and placebo on errors of omission are plotted in the Figure. As Table 4 and the Figure show, all three long-acting medications had detectable effects 1 hour after ingestion, and these effects remained 9 hours postingestion. Standard methylphenidate had a significant effect 2 hours postingestion and, with a second dose 4 hours after the first, had a time course similar to that of the long-acting medications thereafter.

Table 5 presents a summary of the side effects information for all subjects in the protocol. There are few clear differences between drugs. More subjects had side effects reported for DS than for other medications, but the differences were not great. All medications caused a loss of appetite relative to placebo, with the three long-acting forms having this reported for a larger percentage of children than standard methylphenidate. Considerably more difficulty falling asleep was reported for all long-acting drugs than for placebo and standard methylphenidate, with pemoline causing problems falling asleep for twice as many children as all other medications. One child had extreme difficulty falling asleep and also reported auditory and visual hallucinations in the evening of the first day he received pemoline. Pemoline was thus dropped as a condition for him. No other children had side effects sufficiently severe to terminate any medication conditions.

All of the information available on children was gathered at the end of the program and evaluated to make clinical recommendations for future treatment. The program staff examined each child's response on all measures to each medication. Considering (1) a child's presenting problems and areas

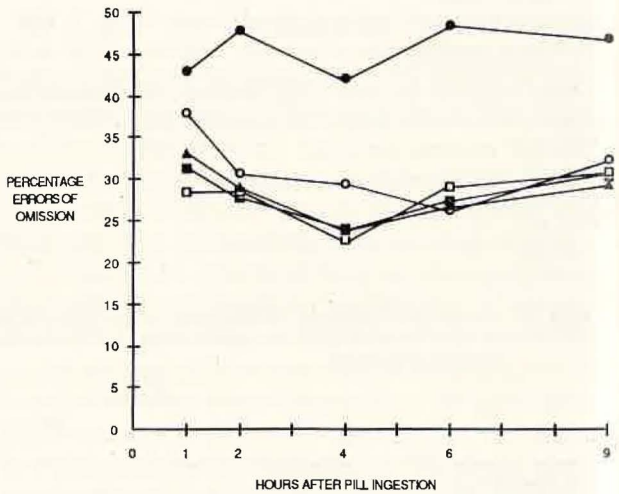

Figure. Percentage of target stimuli to which errors of omission occurred, presented by medication condition and hours after medication ingestion. Active long-acting medications were administered at time 0 with placebo at hour 4, 10 mg of methylphenidate was administered at time 0 and hour 4, and placebo was administered at time 0 and hour 4. ●, placebo; ○, methylphenidate; ■, SR-20 Ritalin; □, pemoline; ▲, Dexedrine Spansule.

of greatest need for improvement, (2) a child's final level of functioning on medication days, (3) the relative effects of the different medications on presenting problems and final level of functioning, and (4) side effects, clinical decisions about medication response and recommendations were made (see Reference 30 for a more detailed description of this procedure). The following numbers of subjects were recommended for continued treatment with each medication: DS, six; pemoline, four; SR-20, four; 10 mg of methylphenidate b.i.d., one; no medication, seven. Of the boys for whom no medication was

TABLE 5. Percentages of Children Rated as Showing Side Effects by Medication Condition*

Side Effects Measured	Medication Condition				
	Placebo	10 mg Methylphenidate b.i.d.	SR-20 Ritalin q.a.m.	56.25 mg Pemoline q.a.m.	10 mg Dexedrine Spansule q.a.m.
Staff ratings					
Crabby, touchy	22.7	0	9.1	15	0
Whiny	22.7	4.8	9.1	10	18.2
Worried, anxious	4.5	0	0	0	0
Withdrawn	0	10.0	0	0	13.6
Dull, not alert	4.5	14.3	4.3	0	9.0
Drowsy, tired	4.5	9.5	4.5	0	13.6
Tearful, cries a lot	13.6	4.8	4.5	5.0	0
Jittery	0	0	0	0	4.5
Sad, depressed	4.5	0	0	0	4.5
Stomachaches, nausea	13.6	14.3	9.1	10.0	22.7
Headaches	9.1	0	0	0	22.7
Muscle aches	4.5	9.5	4.5	0	0
Rash	0	0	0	0	0
Weakness	4.5	0	4.5	0	0
Dry mouth	4.5	4.8	4.5	0	0
Loss of appetite	45.0	61.9	76.2	75.0	77.3
Vomiting	0	0	0	0	4.5
Fainting, dizziness	0	0	0	0	4.5
Eye/muscle twitches	4.5	4.8	9.1	4.8	4.5
Fingernail biting	9.1	4.8	4.5	0	4.5
Repetitive tongue movements	9.1	4.8	0	5.0	4.5
Picking	0	0	0	0	4.5
Distortion of vision	0	0	0	0	0
Parent ratings					
Difficulty falling asleep	5.3	5.9	18.8	42.1	20.0
Awake during the night	5.3	12.5	13.3	11.1	14.3
Nightmares	0	0	0	0	0
Bed wetting	0	5.6	0	0	6.3

* Abbreviations are expanded in the first footnote to Table 2.

recommended, all showed evidence of adverse response to medication.

DISCUSSION

The major findings of this pilot study can be briefly summarized. The three long-acting medications and standard methylphenidate were superior to placebo on most measures of social behavior from the medication assessment. There were relatively fewer effects on average measures from the classroom setting, but effects were relatively consistent across drugs. Overall, the drugs resulted in significant decreases in within-subject variability (that is, more consistent behavior) across days, with DS reducing variability on the most measures, while standard methylphenidate and SR-20 reduced within-subject variability the least. All four drug conditions had similar time courses, with effects from 1 to 9 hours after ingestion. Finally, there were individual differences in drug responsivity, with clinical medication recommendations spread across all drugs and no medication.

As Table 2 shows, all medications had similar effects on the daily frequency measures from the point system—increasing prosocial interactions and decreasing negative verbal and nonverbal behaviors. These results, then, replicate the findings we have reported in previous studies regarding the effects of stimulants on social behavior measures in the summer program.[28,30] Pemoline and DS had the most consistently beneficial effects, both increasing prosocial and decreasing antisocial behaviors, although the pemoline effect on positive peer interactions was accompanied by a large and significant increase in intrasubject variability across days. This increase warrants further exploration to determine whether it is reliably associated with pemoline or whether it is a function of inadequate randomization of drug order, side effect carryover (see below), or other factors. The finding that pemoline improves social interactions for at least some children with ADHD is consistent with our previous report about behavior on school playgrounds.[32]

The findings regarding aggressive behaviors are also consistent with what has been reported by

other groups of researchers in early studies with rating scale instruments[12] and with more recent investigations employing direct observations.[33–35] Stimulant drugs decrease aggression in children with ADHD, particularly in those who are highly aggressive. Given the concurrent and predictive importance of aggressive behavior,[36,37] stimulant-induced reductions in aggression are one of the most desirable of the drugs' effects on disruptive children with ADHD. It is, therefore, noteworthy that the three long-acting preparations were at least as efficacious as standard methylphenidate in reducing average frequencies as well as improving behavioral consistency across days on these dependent measures.

In contrast with our earlier findings, there were fewer drug effects on the classroom measures of functioning in this study, and the effects that were obtained were relatively smaller. Drug improved rule-following in the classroom, and all three long-acting medications were superior to placebo. Drug improved reading productivity (reading attempted), and 10 mg of methylphenidate and DS were significantly different from placebo by 26% and 22%, respectively. Reading accuracy improved slightly but nonsignificantly with all drugs. All medications improved seatwork percentage completion, but the effect for DS did not reach significance. Seatwork accuracy was improved only slightly with medication.

There are several possible reasons for the relatively smaller drug effects on class work than we have reported previously.[3,28,30] First, consider the possibility that the long-acting medications have less effect on academic performance measured over the course of a school day than standard methylphenidate. Given the prevailing belief that the major effect of methylphenidate is obtained during the drug's absorption phase,[19,25,38,39] this is a reasonable hypothesis. However, the CPT results reported herein—effects that were as large at 9 as at 2 hours postingestion—argue against this possibility. Alternatively, the mean milligram per kilogram equivalent of the medications in this study was 0.3 per morning dose. Many of the beneficial medication effects on classroom academic functioning that have been reported previously have been at 0.6 mg/kg doses,[3,40,41] meaning that higher doses might have yielded more benefit in the present study.

In contrast with these two possibilities, differences in subject characteristics between this study and our previous ones may account for the discrepant results. For example, the children in this study were older than those in our previous studies by 18 months to 2 years, and response to stimulant medication typically decreases with age.[42] Furthermore, there were fewer children in this sample with learning problems than in our previous studies, and there was, therefore, less room for improvement with medication in the current sample. Finally, there was a larger percentage of nonresponders to medication in the present sample than in our previous studies, and the presence of these nonresponders may have diluted drug effects on these classroom measures, which, as in the present study, typically yield smaller effects than measures of social behavior. In any case, the failure to find consistently beneficial effects on the classroom academic measures highlights the need for additional research on the long-acting stimulants.

Drug significantly improved both counselor and teacher ratings on the Abbreviated Conners Rating Scale. The follow-up contrasts showed that pemoline improved only the teacher ratings, DS improved both teacher ratings and counselor ratings, and the two forms of methylphenidate improved counselor ratings only. Drug also increased the percentage of days on which children received a positive daily report card, and all four medication conditions were superior to placebo. The changes in Conners ratings are smaller than those in many other medication studies because of the behavioral intervention in effect in the program, which results in relatively good behavior and, therefore, low ratings on placebo days. Drug effects were obtained nonetheless, and the long-acting medications, particularly pemoline and DS, had effects equivalent to or greater than those of standard methylphenidate.

These findings contradict common beliefs about at least one of the long-acting medications. By documenting that pemoline has effects on the second and third day of administration that are equivalent to those of the other medications, we have demonstrated that the conventional wisdom that pemoline requires 3 to 6 weeks to exert an effect is incorrect; our results support previous studies.[7,11,27] These results also demonstrate the feasibility of testing the long-acting medications by using the medication assessment protocol that we have used primarily with standard methylphenidate in the past.[30] All of the medications could be compared with placebo within the constraints of the 8-week summer treatment program, and significant drug effects and individual differences in response to medications could be detected.

However, several caveats of the results should be noted. Although it was feasible to manipulate the long-acting medications in the rapidly alternating fashion we used, the sleep problems noted for the long-acting medications (see Table 5) may limit the appropriateness of the procedure with these medications. Particularly with pemoline, some subjects had considerable difficulty falling asleep that did

not abate until the last night of a 3-day pemoline cycle. If the lack of sleep for those children influenced their behavior the following day, a likely possibility,[43] then the following day's medication condition may have been unduly influenced by the previous day's medication. In other words, even though there is no evidence for the beneficial behavioral or cognitive effects of stimulant medications carrying over until the following day, sleep difficulties, which were apparent in all of the long-acting medications, may have carryover effects that would contaminate subsequent medication conditions. Modifying the protocol in clinical settings to vary medications on a weekly basis should eliminate this problem.

The CPT results demonstrate that all medications had equivalently beneficial effects on a task that has become a standard in assessing stimulant effects in ADHD. However, these results also contradict somewhat the available information about some of the slow-acting medications. For example, SR-20 and DS both had significant effects on errors of omission at 1 hour and through 9 hours postingestion. This contrasts with both our previous study of SR-20,[28] which showed SR not having an effect on CPT until 3 hours postingestion, and Brown and colleagues'[25] study of DS, which showed effects only at 2 hours postingestion. Both previous studies had only 9 subjects, however, and the present results with an N of 22 may be a more veridical reflection of the medications' actual time courses. Furthermore, our data showed that all three long-acting medications had effects at 9 hours postingestion that were as great or nearly so as effects at 2 hours postingestion. Given the sleep problems noted for all three long-acting drugs, it would be useful to extend the times of the CPT time course testing to track evening medication effects.

As Table 3 reveals, 10 mg of methylphenidate reduced intraindividual variability on only two dependent variables, and SR-20 on five, compared with seven for pemoline and nine for DS. Both pemoline and SR-20 significantly increased within-subject variability on positive peer behaviors. Thus, all four drugs acted to reduce within-subject variability, thus increasing children's consistency in response over days, for at least some dependent measures. For the group as a whole, DS reliably resulted in the most consistent response to drug, with pemoline second, particularly compared with placebo and the standard methylphenidate. It was expected that the long-acting medications would produce less variable behavior within a day because they avoid the midday wearing off that is experienced with standard methylphenidate. However, the reduction in variability across days was unexpected. Others have argued that methylphenidate effects vary widely from day to day.[44] If the long-acting medications reduce this variability, they may have benefits that extend beyond their expected advantages.

This sample was relatively small and did not allow for meaningful analysis of individual differences in response as a function of diagnostic subgrouping, examination of which has become standard in the ADHD pharmacology area. Clearly, additional research with a larger sample is needed to determine, for example, whether these medications have differential effects on aggressive vs nonaggressive boys with ADHD.[33] However, it is noteworthy that there were clearly individual differences in responsiveness to the different stimulant preparations. When we considered the nature of each referred child's primary behavioral and cognitive difficulties, as well as the degree of improvement in these and other domains, we were able to discriminate among relatively more or less effective drugs for individuals, despite the relative similarity of the effects of the long-acting preparations when the group average medication effects were analyzed. As we have argued previously,[6,28,30] this finding that individual differences in response are often not reflected in averaged group data is becoming the rule rather than the exception in pediatric psychopharmacology, and it highlights the need for controlled, individualized assessments of stimulant effects in every medicated child.

It should be emphasized that our clinical recommendations for continued treatment resulted in recommmendation of one of the three long-acting medications for 14 of the 15 children for whom we recommended medication. If these results were to hold with a larger sample, the implication is that a very large number of children with ADHD should be receiving a long-acting form of stimulant. Given the small numbers of medicated children that actually receive them, as noted above, perhaps the majority of medicated children with ADHD are not receiving the most appropriate form of stimulant. This situation is especially salient for medicated children for whom there is difficulty—whether on the part of the school or the child—with midday dosing. Such problems could be avoided with the long-acting medications. Furthermore, if medication coverage is necessary for after-school hours, because of peer problems or participation in organized recreational activities, for example,[45] these results suggest that the three long-acting medications—all with effects lasting through 5:00 PM—might be the drugs of choice.

Finally, it should be noted that the results we have presented apply to the short-term effects of these medications. It is commonly assumed that the acute effects of standard methylphenidate are predictive of the effects of prolonged administration,

and at least one study has shown this to be true.[38] In contrast, one study has shown that the acute effects of SR-20 appear to dissipate after 6 months of continued administration.[46] Although pemoline, DS, and SR-20 have been studied in acute investigations, whether the acute effects maintain with continued administration is not clear. With DS and pemoline, which have long half-lives, it is possible that there is a build-up over time that means that continued administration of a dose that has a given acute effect may result in a larger effect over time. If this build-up is sufficiently large, then there might be a toxic or adverse effect of a dose that was initially therapeutic. Although such a situation could presumably be resolved by reducing the chronically administered dosage, the point is that the results of the initial assessment (such as the one we conducted) might not predict long-term response to the initial dose. Research directed at this possibility is clearly warranted before our results are accepted without qualification.

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ANTHONY TROLLOPE, THE ENGLISH NOVELIST, ON HOW HIS FATHER TRIED TO EDUCATE HIM DURING HIS CHILDHOOD

Anthony Trollope (1815–1882), in his autobiography, published posthumously in 1883, wrote as follows about his father's efforts to educate him from his babyhood until the age of seven years when he entered Harrow, one of England's great public schools.[1]

From my very babyhood, before those first days at Harrow, I had to take my place alongside of him as he shaved at six o'clock in the morning, and say my early rules from the Latin Grammar, or repeat the Greek alphabet; and was obliged at these early lessons to hold my head inclined towards him, so that in the event of guilty fault, he might be able to pull my hair without stopping his razor or dropping his shaving-brush. No father was ever more anxious for the education of his children, though I think none ever knew less how to go about the work. Of amusement, as far as I can remember, he never recognized the need. He allowed himself no distraction, and did not seem to think it was necessary to a child. I cannot bethink me of aught that he ever did for my gratification; but for my welfare,—for the welfare of us all,—he was willing to make any sacrifice. . . . As I look back on my resolute idleness and fixed determination to make no use whatever of the books thus thrust upon me, or of the hours, and as I bear in mind the consciousness of great energy in after-life, I am in doubt whether my nature is wholly altered, or whether his plan was wholly bad. In those days he never punished me, though I think I grieved him much by my idleness; but in passion he knew not what he did, and he has knocked me down with the great folio Bible which he always used.

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Noted by T.E.C., Jr, MD