

Once-a-Day Concerta Methylphenidate Versus Three-Times-Daily Methylphenidate in Laboratory and Natural Settings

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ABSTRACT. *Objective.* Methylphenidate (MPH), the most commonly prescribed drug for attention-deficit/hyperactivity disorder (ADHD), has a short half-life, which necessitates multiple daily doses. The need for multiple doses produces problems with medication administration during school and after-school hours, and therefore with compliance. Previous long-acting stimulants and preparations have shown effects equivalent to twice-daily dosing of MPH. This study tests the efficacy and duration of action, in natural and laboratory settings, of an extended-release MPH preparation designed to last 12 hours and therefore be equivalent to 3-times-daily dosing.

Methods. Sixty-eight children with ADHD, 6 to 12 years old, participated in a within-subject, double-blind comparison of placebo, immediate-release (IR) MPH 3 times a day (tid), and Concerta, a once-daily MPH formulation. Three dosing levels of medication were used: 5 mg IR MPH tid/18 mg Concerta once a day (qd); 10 mg IR MPH tid/36 mg Concerta qd; and 15 mg IR MPH tid/54 mg Concerta qd. All children were currently medicated with MPH at enrollment, and each child's dose level was based on that child's MPH dosing before the study. The doses of Concerta were selected to be comparable to the daily doses of MPH that each child received. To achieve the ascending rate of MPH delivery determined by initial investigations to provide the necessary continuous coverage, Concerta doses were 20% higher on a daily basis than a comparable tid regimen of IR MPH. Children received each medication condition for 7 days. The investigation was conducted in the context of a background clinical behavioral intervention in both the natural environment and the laboratory setting. Parents received behavioral parent training and teachers were taught to establish a school-home daily report card (DRC). A DRC is a list of individual target behaviors that represent a child's most salient areas of impairment. Teachers set daily goals for each child's impairment targets, and parents provided rewards at home for goal attainment. Each weekday, teachers completed the DRC, and it was used

as a dependent measure of individualized medication response. Teachers and parents also completed weekly standardized ratings of behavior and treatment effectiveness. To evaluate the time course of medication effects, children spent 12 hours in a laboratory setting on Saturdays and medication effects were measured using procedures and methods adapted from our summer treatment program. Measures of classroom behavior and academic productivity/accuracy were taken in a laboratory classroom setting during which children completed independent math and reading worksheets. Measures of social behavior were taken in structured, small-group board game settings and unstructured recess settings. Measures included behavior frequency counts, academic problems completed and accuracy, independent observations, teacher and counselor ratings, and individualized behavioral target goals. Reports of adverse events, sleep quality, and appetite were collected.

Results. On virtually all measures in all settings, both drug conditions were significantly different from placebo, and the 2 drugs were not different from each other. In children's regular school settings, both medications improved behavior as measured by teacher ratings and individualized target behaviors (the DRC); these effects were seen into the evening as measured by parent ratings. In the laboratory setting, effects of Concerta were equivalent to tid MPH and lasted at least through 12 hours after dosing. Concerta was significantly superior to tid MPH on 2 parent rating scores, and when asked, more parents preferred Concerta than preferred tid IR MPH or placebo. Side effects on children's sleep and appetite were similar for the 2 preparations. In the lab setting, both medications improved productivity and accuracy on arithmetic seatwork assignments, disruptive and on-task behavior, and classroom rule following. Both medications improved children's rule following and negative behavior in small group board games, as well as in unstructured recess settings. Individual target behaviors also showed significant improvement with medication across domains in the laboratory setting. Children's behavior across settings deteriorated across the laboratory day, and the primary effect of medication was to prevent this deterioration as the day wore on. Results support the use of background behavioral treatment in clinical trials of stimulant medication, and illustrate the utility of a measure of individualized daily target goals (ie, the DRC) as an objective measure of medication response in both the laboratory and natural school settings.

Conclusion. This investigation clearly supports the efficacy of the Concerta long-acting formulation of MPH for parents who desire to have medication benefits for their child throughout the day and early evening. Effects

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of a single morning dose lasted throughout the school day and into the evening hours, and were present for both social behavior with peers and academic performance in the classroom. Effects on multiple measures, by multiple informants, and in multiple settings, were similar to those of a standard preparation of MPH given 3 times a day. These effects lasted throughout a 12-hour period, providing coverage of school, afternoon, and evening behavior with a single morning dose. Measures of evening behavior in the laboratory setting included arithmetic productivity (analogous to homework), and recess settings (analogous to home and neighborhood recreational activities). Some parents prefer behavioral interventions to medication for use at home, and some children with ADHD neither need nor tolerate medication in the evening. For those who do need a full 12 hours of medication coverage, based on the results of this study, Concerta would seem to be the choice. This study provides a model for clinical trials of new psychoactive drugs for children: assessments by multiple raters, in both natural and ecologically valid laboratory settings, across a range of domains of impairment and settings, examining a large number of objective, reliable measures of behavior, and in a context of ongoing behavioral treatment. *Pediatrics* 2001;107(6). URL: <http://www.pediatrics.org/cgi/content/full/107/6/e105>; *attention-deficit/hyperactivity disorder, pharmacological treatment, methylphenidate, long-acting preparations*.

ABBREVIATIONS. ADHD, attention-deficit/hyperactivity disorder; CNS, central nervous system; IR, immediate release; MPH, methylphenidate; bid, twice a day; tid, 3 times a day; DSM IV, Diagnostic and Statistical Manual-Fourth Edition; ODD, oppositional defiant disorder; CD, conduct disorder; DRC, daily report card; qd, every day; SD, standard deviation; STP, summer treatment program; SKAMP, Swanson, Kotkin, Agler, M-Flynn, and Pelham; AE, adverse events; ES, difference between the least square means of treatment 1 and treatment 2 divided by the estimate of inpatient variation; bpm, beats per minute.

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. Children with ADHD experience severe and chronic impairment in daily life functioning, including academic problems, disruptive behavior, and problematic relationships with parents, teachers, and peers. Its high prevalence and potential for a poor long-term course make ADHD a major public health problem for which effective treatment is necessary.¹ Only 2 interventions for ADHD are evidence-based: medication with a central nervous system (CNS) stimulant^{2,3} and behavior modification.⁴ CNS stimulants are the most widely used pharmacological treatments for ADHD, and the only pharmacologic agents with Federal Drug Administration approval for the disorder.

Immediate-release (IR) methylphenidate (MPH) has been the primary stimulant used in the treatment of children with ADHD for the past 30 years and is well documented in the literature as demonstrating efficacy. However, IR MPH has several limitations related to its time course of action. For example, it is rapidly absorbed, yielding effects within 30 minutes, peaking after 2 hours, and typically only lasting ~4

hours.⁵⁻⁹ Thus, children usually take morning and midday doses, with many children receiving an after-school dose to cover evening hours. The implications of such a dosing schedule are twofold. First, a standard regimen of breakfast and lunchtime dosing of IR MPH may leave a child experiencing a trough in medication level during some times of the day. As the morning dose wears off, inattention may increase during late-morning classes. Similarly, when the midday dose is wearing off, the child may experience difficulty concentrating on after-school homework.

A second problem related to the short duration of effect of IR MPH relates to compliance with midday and late afternoon dosing. Taking medication during school hours is an event that many children with ADHD would like to avoid. With the absence of nurses in many schools, other school staff must administer medication, and that is often done unreliably.¹⁰ In other schools, administrative policies prohibit school personnel from administering psychoactive medication or controlled substances,¹¹ thus requiring children with ADHD—who tend to be disorganized and fail to remember things—to remember to go to a designated place in school at the appropriate time to take their midday pills, or even to go to their lockers and take their pills themselves. Administration of a third daily dose of IR MPH—typically given after school—is made difficult by the fact that children may be on a school bus, in after-school child care, or in sports or other leisure extracurricular activities (eg, Scouts) when the dose should be administered. Coupled with the data showing that stimulant medications have beneficial acute effects on peer interactions in recreational settings,^{12,13} the consensus that problematic peer interactions is one of the major difficulties faced by children with ADHD^{14,15} has highlighted the potential importance of a later afternoon dose of medication to treat impairment in peer settings. Difficulties in administration are one of the likely factors that contribute to the fact that the vast majority of treated children with ADHD take medication for only 1 or 2 months.¹⁶

Given the dosing limitations of IR MPH, preparations with a longer effective duration of action have been developed and used for at least 20 years. Ritalin-SR, which has been evaluated in only a handful of studies, was designed to exert an effect equivalent to two 10-mg tablets of IR MPH given 4 hours apart. However, the time course of Ritalin-SR appears to be variable, and individual responsiveness to the preparation may be highly variable.^{6,17,18} Other preparations and medications (eg, Dexedrine Spansule, d-amphetamine, Adderall, pemoline) have shown longer durations of action than IR MPH—up to 9 hours^{6,8,19-21}—but have also been infrequently studied and have not been as frequently prescribed, compared with IR MPH.

All previous work with extended-release or long-acting stimulants has focused on formulations (such as those noted above) designed to last from breakfast throughout a school day (7-9 hours)—that is, the equivalent of a twice-a-day (bid) regimen of IR MPH. Twice-daily IR MPH and equivalent preparations do

not exert a major effect on functioning at home in the evening hours.^{7,8,22} There is a growing awareness that children with ADHD are impaired in the home domain, in the peer contacts that occur after school and in the evenings, and in their ability to perform homework tasks. As a consequence, a growing trend has been to prescribe a third daily dose of IR MPH in the late afternoon. Estimates based on surveys of prescription practices are that 38% of medicated children with ADHD are receiving a 3 times a day (tid) dosing regimen or equivalent (Physician Drug and Diagnosis Audit, November 1999). However, the increasing trend toward tid dosing has outpaced the research documenting the efficacy of such a dosing regimen on home behavior in the evening. To our knowledge, only 3 studies of stimulant effects on evening behavior have been conducted.^{8,23,24} These studies—1 conducted in an inpatient unit, 1 in an outpatient clinic, and 1 in a summer treatment program—had relatively small samples and varied methodologies, but all tended to show that a late-afternoon stimulant dose had beneficial effects on evening behavior without substantive side effects. Pelham and colleagues⁸ showed that the dose of IR MPH that was necessary to produce beneficial effects on parent ratings of evening behavior was the same as the morning and midday doses, as opposed to the half-sized late afternoon IR MPH dose that is often prescribed.²⁵

Given the limitations of IR MPH and of the existing extended-release products, and the trend toward tid dosing, ALZA Corporation and Crescendo Pharmaceuticals Corporation recently developed a long-acting delivery form of MPH (Concerta) that is designed to provide efficacy for approximately 12 hours after dose administration, a time period equivalent to a tid dosing schedule of IR MPH. The current study is part of a research program describing the development, efficacy, effectiveness, and safety of Concerta compared with standard IR MPH given tid and with placebo. First, a series of studies were conducted to determine what drug delivery pattern throughout a 12-hour period would produce an overall effect analogous to IR MPH and would be maintained for 12 hours.^{26,27}

Next, this study was undertaken to evaluate the time course, efficacy, effectiveness, and safety of the new formulation. Time course and efficacy were assessed in laboratory classroom and play settings in which multiple objective measures of drug response could be gathered at fixed times throughout a 12-hour period on Saturdays. Effectiveness was documented by parents in the children's home setting and by children's community school teachers at school on weekdays. Short-term measures of safety (side effects) were assessed by parents, teachers, and physician in all settings. Because children's response to stimulant medication varies across measures, settings, and domains,^{28,29} it was important to include a wide variety of settings and levels of those variables in this first study of the novel form of MPH.

An important methodologic consideration in trials of stimulant medication on ADHD has been whether to include a concurrent, evidence-based behavioral

intervention. It has been clearly established that behavioral and psychostimulant interventions often have beneficial combined effects.^{30,31} Leading researchers and professional organizations generally agree that 1) stimulants should be used with children with ADHD after appropriate psychosocial and psychoeducational interventions have been conducted and are insufficient, and 2) stimulants should be used in conjunction with these other interventions.^{1,32} Indeed, classroom behavioral interventions are typically required components of the federally mandated 504 plans and individual education plans for children with ADHD in many school districts throughout the country. Similarly, many parents use behavioral procedures such as "time-out" with their children with ADHD, having acquired such skills from the many available materials for these parents.³³ However, there is considerable variability in the implementation of behavioral treatments in natural settings, with many children living in families and attending schools in which no behavioral interventions are being done and medication is prescribed without systematic behavioral treatments. Thus, to address questions about the efficacy of Concerta in settings in which behavioral treatments are likely to be used, a background regimen of behavioral treatment was implemented in the current study so that variability in behavioral treatment across families and schools would be controlled. Thus, this study is analogous to the many studies of long-acting stimulants that the current authors have conducted in summer treatment program settings.^{6,7,8,18}

METHODS

Participants

Participants included 70 children between the ages of 6 and 12 (mean: 9.1) with a *Diagnostic and Statistical Manual-Fourth Edition (DSM-IV)* diagnosis of ADHD (any subtype). Children were recruited via a number of sources, including advertisement; physician, agency, and school referral; and parent referral. Parents of the participants gave informed consent for their children to participate, and children assented to the procedures. Families and schools received monetary compensation for their cooperation with study procedures. Two children were discontinued from the study because parents administered nonstudy IR MPH during the first week of the study; they thus did not have complete data for inclusion in the efficacy analyses. The sample was 89% male and 94% white.

Diagnostic information was obtained using the National Institute of Mental Health Diagnostic Interview Schedule for Children Version IV³⁴ completed with parents, and the Swanson, Nolan, and Pelham³⁵ and Disruptive Behavior Disorders³⁶ parent and teacher rating scales. In addition to meeting *DSM* diagnostic criteria for ADHD, 43% of the sample met criteria for oppositional defiant disorder (ODD), and an additional 37% of the sample met *DSM-IV* criteria for conduct disorder (CD). Children had to meet *DSM* diagnostic criteria using a rule in which a symptom was defined as present if either parents or teachers endorsed it, with overlap between raters on at least 1 symptom.

All participants were required to be medicated with MPH on entry to the study and must have been receiving a stable dose for at least 4 weeks before the beginning of the study. Total daily doses ranged from 10 to 60 mg (mean: 25; daily mg/kg dose mean: 0.75, standard deviation [SD]: 0.34) with 81% of the sample receiving <30 mg per day; 57% of the sample was receiving bid dosing or equivalent Ritalin-SR at enrollment, and 43% were on a tid dosing schedule.

Exclusionary criteria included the following: presence of any medical condition that would contraindicate the use of stimulant medication; presence of any physical condition or severe learning difficulty that would interfere with participation in the laboratory classroom assessment (eg, IQ below 80 as determined by the Wechsler Intelligence Scale for Children at screening); receiving additional medication (beyond MPH) for ADHD; receiving any medication having CNS effects, anticonvulsants, or investigational medications; having reached menarche; and having blood pressure at or above the 95th percentile for age and height. Table 1 lists diagnostic and descriptive information.

Procedures

This study consisted of a within-subject, double-blind, cross-over comparison of three drug conditions: placebo, IR MPH given 3 times daily, and Concerta given once in the morning. Each child received each medication condition for a 7-day period (Sunday–Saturday), with order of conditions randomized across participants. Three separate cohorts of ~24 children each completed the study between January and May 1998. The cohorts did not differ from each other on diagnostic or demographic characteristics. During Monday through Friday of each week, the children remained in their regular home and school settings. All the participants came to the study site for a practice Saturday laboratory session day in which they completed the activities described below, with the goal of minimizing any learning effects and to make certain that all academic work was assigned at appropriate ability levels. Two weeks later, the children returned for the study itself, which took place over 3 successive Saturdays. Five of the participants missed 1 of the laboratory session days because of illness or

inclement weather. All available data were included in the analyses.

Baseline Behavioral Treatment

To provide a standard background of behavioral treatment against which medication effects could be evaluated, the medication manipulation in the present investigation was conducted after a program of clinical behavioral treatment had been conducted with parents and teachers and with a concurrent behavioral intervention in the laboratory setting. A brief course (4–6 sessions) of behavioral parent training³⁷ was provided, in which parents were taught how to use behavioral techniques in the home setting. Parents were required to attend at least 4 sessions to participate in the study. Similarly, each child's teacher received 1 to 4 clinical contacts (average number of visits = 2) during which a consulting teacher worked with each child's teacher to establish a daily report card (DRC) and to consult on other classroom management strategies.³⁸

The DRC listed precisely defined individual target behaviors for which the child could earn positive or negative marks throughout his or her school day.³⁹ Establishing the DRC involved having the teacher select target problem behaviors that were unique to each child (eg, following classroom rules), establishing criteria for goal attainment (eg, no more than 3 rule violations per period), having the child take his or her report daily to parents, and having parents provide a positive consequence at home when the DRC was positive (see *Comprehensive Textbook of Psychiatry/VII*⁴⁰ for a description of how to establish a DRC). Use of a DRC as a dependent measure of drug response provides objective data regarding children's individualized presenting problems.⁴¹

Medication Procedures

Three dosing levels of medication were used: 5 mg of IR MPH tid/18 mg of Concerta once a day (qd); 10 mg of IR MPH tid/36 mg of Concerta qd, and 15 mg of IR MPH tid/54 mg of Concerta qd. The dose level used for each child was based on that child's MPH dosing before the study, and the doses of Concerta were selected to be comparable to the daily doses of MPH that each child received. Children who were receiving a bid regimen of MPH before the study had a third daily dose added in the immediate-release MPH week of the study. To achieve the ascending rate of MPH delivery determined by initial investigations to provide the necessary continuous coverage,^{26,27} Concerta doses are 20% higher on a daily basis than a comparable tid regimen of IR MPH; for example, the 18-mg Concerta tablet is equivalent to a 5-mg tid IR MPH regimen. Seventeen participants received the 5-mg IR/18-mg Concerta doses, 39 received the 10-mg IR/36-mg Concerta doses, and 14 received the 15-mg IR/54-mg Concerta doses. Thus, the average child in the study received 35 mg of Concerta or 29 mg of MPH/d. Average mg/kg/d doses were 0.88 (standard deviation [SD]: 0.32) in the IR MPH condition and 1.05 (SD: 0.38) in the Concerta condition.

Using a double-dummy placebo procedure, study capsules were administered to each child 3 times a day (4 capsules at 7:30 AM, 1 capsule at 11:30 AM, and 1 capsule at 3:30 PM). During the Concerta condition, 1 to 3 of the 7:30 AM capsules contained Concerta (depending on the child's dose level—only 18-mg capsules were available) and the remaining capsules were inactive. During the IR MPH condition, 1 each of the 7:30 AM, 11:30 AM, and 3:30 PM capsules contained IR MPH (5, 10, or 15 mg per capsule) and the remainder were inactive. In the placebo condition, all capsules were inactive. Medication was dispensed to parents each Saturday. Parents administered Sunday doses and the weekday 7:30 AM doses, school personnel administered the 11:30 AM doses, and parents or other caregivers administered the 3:30 PM doses. Parents and school personnel kept records of the times each dose was given. On Saturdays, study staff members administered all medication and kept dosing records. Compliance with medication administration was virtually 100% across all conditions.

Weekly Dependent Measures and Data Collection

The dependent measures used in the natural setting included weekly teacher and parent ratings, and the daily, individualized reports of each child's performance on a list of targeted behavior goals (the DRC described above). Each day, the child's teacher completed the DRC and sent a copy home with the child. The

TABLE 1. Participant Characteristics

Measure	Mean	SD
Age (y)	9.1	1.6
Full-scale IQ (WISC-III)	104.8	11.7
Reading achievement (WIAT)	104.1	13.2
Math achievement (WIAT)	98.8	12.9
Spelling achievement (WIAT)	96.3	12.9
DISC hyperactive/impulsive symptoms endorsed	8.3	1.1
DISC inattention symptoms endorsed	7.1	2.0
Parent SNAP ratings ³⁵		
Inattention	2.26	0.40
Hyperactivity/impulsivity	1.96	0.70
Oppositional/defiant	1.56	0.68
Parent DBD Ratings ³⁶		
Inattention	2.15	0.46
Hyperactivity/impulsivity	1.83	0.67
Oppositional/defiant	1.28	0.65
Conduct disorder	0.26	0.26
Parent IOWA Conners ratings ^{42,43}		
Inattention/overactivity	10.42	3.02
Oppositional/defiant	7.28	4.00
Parent abbreviated Conners rating ⁴⁴	18.06	5.56
Teacher SNAP ratings ³⁵		
Inattention	2.04	0.63
Hyperactivity/impulsivity	1.62	0.89
Oppositional/defiant	1.56	0.68
Teacher DBD ratings ³⁶		
Inattention	1.82	0.79
Hyperactivity/impulsivity	1.47	0.86
Oppositional/defiant	0.75	0.73
Teacher IOWA Conners ratings ^{42,43}		
Inattention/overactivity	9.65	3.81
Oppositional/defiant	4.07	4.28
Teacher abbreviated Conners rating ⁴⁴	14.96	7.54
Teacher peer relations rating	5.33	5.07

WISC-III indicates Wechsler Intelligence Scale for Children—Third Edition; WIAT, Wechsler Individual Achievement Test; DISC, Diagnostic Interview Schedule for Children; SNAP, Swanson, Nolan and Perham; DBD, disruptive behavior disorders. Children received WISC-III and WIAT testing at screening unless they had recent testing scores. Values are based on original 70 participants.

percentage of positive marks (that is, the percentage of individualized goals attained daily) on a child's DRC was used as an individualized behavioral measure of medication response. On Fridays, teachers completed an Inattention/Overactivity With Aggression (IOWA) Conners Rating Scale,^{42,43} which yields information in 10 items about 2 distinct behavioral dimensions: 1) inattention, impulsivity, and overactivity; and 2) oppositional-defiant behavior. The rating scale also included items used to compute the Abbreviated Conners Rating Scale score,⁴⁴ and items assessing peer relations from the SNAP Rating Scale.⁴⁵ Teachers also completed a global assessment of how well they thought the treatment given that week worked for the child.

Study staff members collected the rating scale, weekly DRCs, and medication records from schools each Friday via fax, phone, or personal visit. Staff members collected 100% of the possible data from community school teachers using these methods. One participant missed 2 days of school because of suspension, and another missed 1 full week of school and laboratory session (ie, 1 medication condition) because of illness.

Parents also completed IOWA and Abbreviated Conners Rating Scales. They brought these ratings and their dose logs to the study site each Saturday morning, where they also completed a series of global questions regarding possible side effects, sleep quality, and appetite.

Laboratory Sessions

Overview

To evaluate onset and duration of action in the current study, we used or adapted procedures that we have used in many previous studies in the classroom and recreational settings used in our Summer Treatment Program (STP)^{46–48} These procedures have been used in numerous trials of stimulant efficacy in ADHD and have demonstrated reliability.^{6,7,13,18,28,41,47} Children were grouped by age into 2 groups of approximately 12, each supervised by 4 trained counselors during the day. Parents dropped off their children at approximately 6:45 AM, and children received breakfast, lunch, and dinner at the site. Children participated in classroom activities, structured recreational activities, meals, and recess periods throughout the day (Table 2). Parents returned to the site to pick up their children at 8:15 PM.

Classroom Periods

At 9 times throughout the day (see Table 2), the children participated in a 30-minute classroom period, staffed by a special

education teacher and 2 teacher aides. During each classroom period, the children completed a 10-minute timed math task and a 10-minute timed reading task that were selected to be appropriate for each child's instructional level. The first and last 5 minutes of each class period were spent in reviewing classroom rules and structure and in providing behavioral feedback.

A behavioral management system was in place during the classroom periods, consisting of response-cost and reward components.^{46,49} Children lost points on any violation of the posted classroom rules (eg, remain in assigned seat, obey adults), and earned points for working hard and for accuracy. Teachers recorded frequencies of rule violations, numbers of math problems attempted, and numbers of math problems completed correctly for each classroom period, and these served as dependent measures for the study. Children had individualized behavior goals related to rule-following and academic productivity, and staff members gave feedback to the children's parents at the end of the day in the form of a DRC. Independent observers watched the children from behind a 1-way mirror using an observation code⁴⁹ adapted from the Classroom Observation Code for Attention Deficit Disorders observation system⁵⁰ and recorded disruptive and on-task behavior.

After each classroom period, the teacher completed a Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale⁵¹ that assessed various aspects of attention and behavior in the classroom. At the end of the day, the teacher completed an IOWA Conners rating scale that summarized each child's behavior over all 9 classroom periods.

Structured Recreation Periods

Four times during the day (Table 2), children participated in 25- to 30-minute recreation periods during which they played board games in groups of 4, each supervised by 1 counselor. All board games were familiar, age-appropriate, turn-taking games (eg, "Sorry," "Chutes and Ladders") in which the children were attempting to be the first to reach the goal. Games were randomized so that each child played a different game with different peers each period. Supervising counselors were assigned to specific games. The supervising counselor quickly explained the rules and gave a rules sheet to the children. During the game, the counselor answered questions, interacted minimally with the children, encouraged the children to work out disputes among themselves, and did not play the game. To encourage competition during the games, staff members awarded prizes (small toys) to the child who won each game or were farthest ahead at the end of the period.

The counselors implemented a modification of the STP point system,⁴⁶ awarding points for appropriate behavior (eg, good sportsmanship) and removing points for inappropriate behaviors (eg, teasing or breaking rules). Children also received time outs for specified behaviors. Children who met behavioral criteria (followed rules 80% of the time) earned extra free-play time at the end of the day. Individualized behavior goals (set during the initial practice laboratory session) were summarized on a DRC that was given to parents at the end of the day. At the end of the day, counselors completed IOWA Conners rating scales. Observers used the same code as was used in the classroom setting.

Recess Periods

For 3 periods during the day (Table 2), children engaged in 20- to 30-minute free-play periods structured as school-like recess⁴⁶ during which they played indoor games (eg, ball-darts, dodgeball) in a large room. Children were supervised by the classroom aides, who recorded rule violations and assigned 1-minute "benchings" for every violation. The independent observers used the identical observation code with the omission of on-task behavior.

Integrity and Reliability

Procedures were standardized and a senior staff member completed fidelity checklists in classroom and recreational settings, sampled across time periods, each Saturday. Reliability was computed by correlating frequency counts from the counselors and the reliability observer. Correlations ranged from 0.43 to 1.00 ($M = 0.72$); mean differences ranged from 0 to 1.72 (mean: 0.31). Independent observers collected reliability data for ~20% of the observation intervals in the classroom and recreational settings. Phi coefficients were computed (mean: 0.60 for on-task in the classroom; mean: 0.74, 0.70, and 0.83 for observed negative behavior in the classroom, board game, and recess settings, respectively). In

TABLE 2. Daily Laboratory School Schedule

Time	Activity
7:30–7:45	HR and BP check/administer medication
7:45–8:10	Recreation
8:15–8:45	Class
8:50–9:05	HR and BP check
9:05–9:20	Snack/free time
9:20–9:50	Class
9:55–10:25	Recreation
10:30–11:00	Class
11:05–11:25	Recess
11:30–11:55	HR and BP check/administer medication
12:00–12:20	Lunch
12:30–1:00	Class
1:05–1:20	HR and BP check
1:25–1:55	Recreation
2:05–2:35	Class
2:35–2:50	Free time
2:50–3:10	Recess
3:20–3:55	HR and BP check/medication/snack
4:00–4:30	Class
4:35–5:00	Recreation
5:00–5:15	HR and BP check
5:15–5:45	Class
5:55–6:15	Dinner
6:20–6:50	Class
6:55–7:05	HR and BP check
7:10–7:40	Class
7:45–8:15	Recess

HR indicates heart rate.

addition, counselors, teachers, and observers completed weekly reliability quizzes as a means of ongoing calibration to the behavioral codes, and weekly staff meetings were held.

Dependent Measures

For the purposes of Federal Drug Administration approval, teacher rating scales in the natural setting (IOWA inattention/overactivity [I/O]) and the laboratory classroom (SKAMP attention) were defined as primary outcome measures. To provide a comprehensive illustration of medication effects across classroom and social settings, a number of other dependent measures were gathered.

Natural Setting

Dependent measures from the natural setting included: 1) teacher and parent IOWA Conners ratings, 2) teacher and parent abbreviated Conners ratings, 3) teacher peer relations ratings, 4) teacher and parent global effectiveness ratings, and 5) individualized DRC percentages. Measures 1 through 4 were collected once at the end of each week. Measure 5 was collected daily and averaged across the week.

Laboratory Classroom

Measures included 1) frequencies of rule violations, 2) math problems completed, 3) math problems percentage correct, 4) teacher SKAMP ratings, 5) observed on-task behavior, 6) observed disruptive behavior, 7) records of individualized target behaviors (DRC goals), and 8) teacher end-of-day IOWA Conners ratings. Measures 1 through 7 were completed for each of the 9 classes and were used to assess the time course of each drug condition. Measure 9 was used to assess the overall effectiveness of that day's condition.

Structured Recreation

Measures included 1) frequencies of rule violations, 2) frequencies of negative behaviors (eg, teasing peers, interrupting, complaining), 3) observed disruptive behavior, 4) observed on-task behavior, 5) records of individualized target behaviors (DRC), and 6) counselor end-of-day IOWA-Conners ratings. Measures 1 through 5 were completed for each of the 4 game periods and were used to assess the time course of each drug condition. Measure 6 was used to assess the overall effectiveness of the condition received that day.

Recess

Measures included 1) frequencies of rule violations, and 2) observed disruptive behavior. Recess periods were scheduled during parts of the day when the tid doses of IR MPH were likely to be decreasing in strength and at the last period of the day, to assess whether there were any differences between the drug conditions at those times of day.

Daily Behavior

Data from the point system were aggregated across the day, including board game periods, mealtimes, and unstructured transition times. These frequencies were used to assess the overall efficacy of each medication condition, and included 1) percentage following activity rules; 2) noncompliance; 3) interrupting; 4) complaining; 5) positive peer behaviors (helping, sharing, and ignoring provocation); 6) conduct problems (lying, stealing, destruction of property, and aggression); and 7) negative verbalizations (verbal abuse to staff, teasing peers, and swearing). These measures were identical to those employed in numerous stimulant drug studies conducted in our summer treatment programs.^{6-8,49}

Safety

Reports of adverse events (AE) were collected via spontaneous reports. Additionally, each Saturday parents completed questions regarding AEs, sleep quality, appetite, and tics. Sleep quality for the week was rated as poor, fair, good, or excellent. Food intake for the week relative to usual food intake (ie, the week immediately preceding the study) was rated as less, usual amount, or more. AE data were analyzed across settings. Additionally, vital signs (blood pressure and pulse rate) were measured predose and at 1 hour after each medication dosing period throughout the day.

RESULTS

Mixed-effects analyses of variance (analysis of variance) models were used for the analysis of each efficacy measurement. This analysis of variance

model included the fixed-effect factors of treatment, sequence, and period, and the random-effect inter- and inpatient factors. Pairwise comparisons were also performed between placebo and each of the active drug conditions, and between the 2 active drug conditions. All statistical tests for the efficacy variables were performed at the $P = .05$ significance level. Because the time course of the study included different levels of drug concentration in blood, a treatment \times time interaction was expected to be significant; therefore, planned comparisons were conducted separately at each time point. The issue of performing statistical tests on multiple efficacy endpoints was not formally addressed by an adjustment of critical significance level. Multiplicity did not appear to be a concern because significant treatment differences versus placebo were consistently observed for all efficacy measures with high significance ($P < .001$), as described below.

Natural Setting

There was an overall effect of drug ($P < .001$) for all the dependent measures taken in the natural setting (see Fig 1 and Table 3). Pairwise comparisons of each drug with placebo showed that both tid IR MPH and Concerta were significantly improved relative to placebo ($P < .001$ for all measures) on all measures. There were only differences between Concerta and tid IR MPH for 2 of the parent ratings (I/O and Abbreviated Conners), with ratings in the Concerta condition superior to those in the tid IR MPH condition ($P < .05$). The magnitude of the drug effects (ES: difference between the least square means of treatment 1 and treatment 2 divided by the estimate of inpatient variation)^{52,53} was quite large across measures. Effect sizes on the ADHD symptoms (IOWA I/O), which are indicative of the symptoms for which all participants were selected, and on the individualized target behaviors of the DRC, were quite large (2.0). Effect sizes on ODD symptoms and peer relations problems, which were present in only a subset of participants, were lower; 1.3 for ODD symptoms and 1.4 for peer relations. The size of the Concerta/IR differences on the parent ratings was much smaller, with an ES of 0.4 on the I/O factor. At the end of the study (before removing the treatment blind), parents were asked to choose which of the treatment weeks they preferred. Forty-seven percent of the sample chose the Concerta week; 31% chose the tid IR MPH week, 15% chose their previous MPH treatment, and the remainder chose placebo or had no preference.

Laboratory Sessions

Classroom Setting

Time course effects are depicted in Fig 2. Significant results of pairwise comparisons are noted with subscripted letters. Significant differences between drug and placebo were generally found for both IR MPH and Concerta across dependent measures beginning at 9:20 AM (the earliest they could have been detected given the time of drug administration), and then throughout the remainder of the day through

Fig 1. Means (+ standard error) for parent and community teacher measures as a function of medication condition.

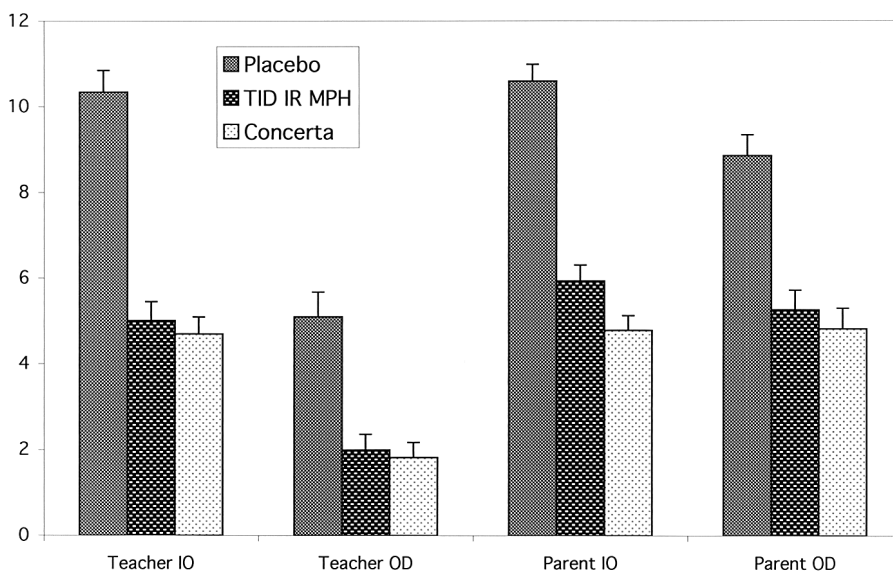


TABLE 3. Means and SDs for Dependent Measures From the Natural Setting

Measure	Placebo Mean (SD)	tid IR MPH Mean (SD)	Concerta Mean (SD)
Teacher Ratings			
Inattention/overactivity	10.34 (4.21)	5.00 (3.69)*	4.69 (3.31)*
Oppositional/defiant	5.09 (4.85)	1.99 (3.03)*	1.81 (2.98)*
Abbreviated Conners	16.40 (7.74)	7.94 (5.83)*	7.82 (5.92)*
Peer interactions	4.29 (4.63)	4.03 (4.74)*	3.41 (4.67)*
Global effectiveness:			
Poor	69.1%	10.3%	10.4%
Fair	14.7%	32.4%	22.4%
Good	14.7%	36.8%	44.8%
Excellent	1.5%	20.6%	22.4%
Daily report card % positive	61.17 (24.22)	84.36 (15.76)*	86.06 (13.52)*
Parent ratings			
Inattention/overactivity	10.59 (3.28)	5.93 (3.09)*	4.78 (2.86)*‡
Oppositional/defiant	8.85 (4.04)	5.26 (3.85)*	4.82 (4.00)*
Abbreviated Conners	19.91 (6.02)	11.41 (6.23)*	9.49 (6.50)*‡
Global effectiveness			
Poor	73.5%	8.8%*	5.9%*
Fair	22.1%	26.5%*	27.9%*
Good	2.9%	50.0%*	39.7%*
Excellent	1.5	14.7%*	26.5%*

Inattention/overactivity and oppositional/defiant subscales of the IOWA Conners Rating Scale (42, 43) scores range from 0–15 (most deviant). Abbreviated Conners Rating Scale (44) scores range from 0–30 (most deviant). Peer relations scores range from 0–21 (most deviant). Global efficacy ratings presented as percentages of respondents.

* Significantly different from placebo.
‡ Significantly different from tid MPH.

7:00 PM. Individual measures showed some variations throughout the day. Only 2 significant differences between the 2 active drug conditions were seen, and both were during the first classroom period.

Structured Recreation Setting

There were significant drug effects on measures of rule violation frequency, negative behavior frequency, observed disruptive behaviors, and individualized target behaviors (DRC) for the latter 3 of the 4 periods (Table 4). Both active drug conditions were significantly different from placebo in these periods, with effect sizes ranging from 0.4 to 0.8 (mean: 0.5), and were not significantly different from each other. No drug effects were expected in the 7:45 AM period,

because the children had just received medication. After the first period, rates of observed on-task behavior were uniformly very high; although there were significant differences between placebo and drug for 2 of the periods, the differences were not clinically important (ie, changes from 94% or 96% to 98%).

Recess Setting

For rule violations, there were significant overall effects of drug for the first 2 periods. For these periods, both medication conditions were significantly different from placebo (ES: 0.45 and 0.6). There was no significant effect during the 7:45 PM period (12 hours, 15 minutes after the first drug administration), perhaps attributable to a dramatic increase in

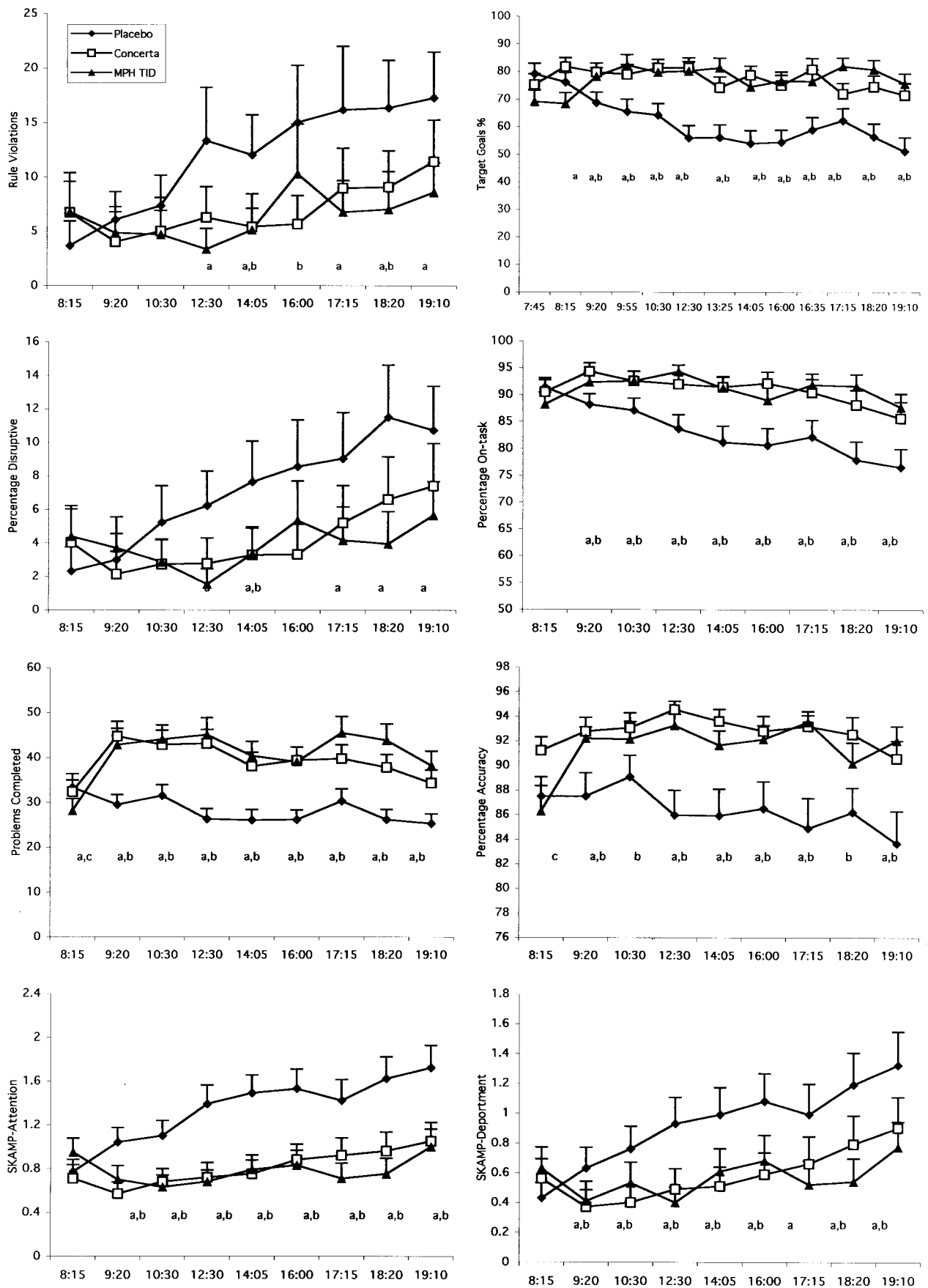


Fig 2. Means (+ standard error) for major dependent measures from the laboratory sessions. a) tid IR MPH significantly different from placebo. b) Concerta significantly different from placebo. c) Concerta significantly different from tid IR MPH. For Rule Violations, Percentage Disruptive, and SKAMP ratings, lower scores indicate improved behavior. For Problems Completed, Target Goals %, Percentage On-Task, and Percentage Accuracy, higher scores indicate improved behavior. Target Goals % incorporates both classroom and structured recreational periods.

TABLE 4. Means and SDs for Behavioral Measures from Recreational Activities

Measure	Period	Placebo	tid IR MPH	Concerta
Counselor measures				
Rule violations	7:45–8:10	2.53 (2.63)	2.83 (3.10)	2.21 (2.38)
	9:55–10:25	4.00 (4.45)	2.58 (3.08)*	2.70 (2.78)*
	1:25–1:55	5.87 (8.72)	2.17 (2.44)*	2.39 (2.65)*
	4:35–5:00	4.21 (4.51)	2.84 (3.57)*	2.53 (2.79)*
Negative behavior	7:45–8:10	1.53 (2.61)	4.86 (20.87)	1.73 (2.07)
	9:55–10:25	3.62 (7.70)	1.14 (2.17)*	1.14 (2.46)*
	1:25–1:55	6.25 (15.47)	0.98 (1.79)*	2.45 (6.07)*
	4:35–5:00	4.76 (7.83)	2.83 (7.88)*	1.58 (2.86)*
Individual target goals	7:45–8:10	79.05 (32.5)	69.01 (34.97)	75.13 (33.18)
	9:55–10:25	65.44 (37.14)	82.30 (29.8)*	78.91 (31.2)*
	1:25–1:55	56.13 (38.52)	81.25 (30.2)*	74.22 (32.4)*
	4:35–5:00	58.82 (38.23)	76.43 (35.3)*	80.73 (33.8)*
Observer measure				
negative behavior	7:45–8:10	3.24 (4.41)	4.00 (4.58)	4.21 (6.09)
	9:55–10:25	6.99 (11.17)	2.13 (3.79)*	2.97 (4.62)*
	1:25–1:55	8.96 (17.05)	2.17 (3.53)*	3.47 (5.62)*
	4:35–5:00	8.91 (14.22)	4.61 (7.19)*	2.86 (5.84)*

Observer negative behavior = percentage of intervals coded by independent observer. Rule violations and negative behavior = counselor-recorded frequency.

* Significantly different from placebo.

TABLE 5. Means and SDs for Recess Measures

Measure	Period	Placebo	tid IR MPH	Concerta
Rule violations	11:05	0.81 (1.35)	0.44 (0.79)*	0.36 (0.72)*
	2:50	1.10 (1.43)	0.66 (1.06)*	0.52 (0.85)*
Negative behavior	7:45	2.07 (3.01)	1.42 (1.58)	1.53 (2.21)
	11:05	10.37 (13.21)	7.48 (12.04)	8.56 (13.26)
	2:50	14.03 (17.70)	10.13 (14.74)*	7.65 (11.19)*
	7:45	13.76 (17.65)	8.88 (12.60)*	7.73 (10.55)*

Negative behavior = percentage of intervals observed by independent observer. Rule violations = frequency count by recess aides.

* Significantly different from placebo.

variability at that time period (Table 5). In contrast, observers' records of disruptive behaviors showed significant effects of drug for the 2:50 PM and 7:45 PM periods (ES: 0.3–0.54; mean: 0.43) only. Comparisons between placebo and Concerta were significant for both of these periods; tid MPH was significantly different from placebo only during the last period. The 2 drugs did not differ significantly from each

other on either measure across periods (mean ES: 0.11).

Overall Daily Behavior

The results of this analysis closely parallel the findings for the individual activities (Table 6). There were significant effects of drug on all behavior fre-

TABLE 6. Means and SDs for Overall Daily Measures (Laboratory Sessions)

Measure	Placebo	tid IR MPH	Concerta
Behavior frequencies			
Following rules	47.5% (25.8)	60.2% (22.3)*	61.3% (23.2)*
Noncompliance	5.76 (16.53)	2.73 (9.16)*	2.14 (5.45)*
Interruption	21.60 (39.07)	10.5 (17.04)*	10.58 (17.71)*
Complaining/whining	15.45 (28.29)	6.95 (13.37)*	6.67 (17.04)*
Positive peer behaviors	10.52 (7.99)	9.86 (5.43)	9.20 (6.24)
Conduct problems	3.81 (13.52)	1.53 (6.53)*	0.60 (2.02)*
Negative verbalizations	18.27 (37.26)	9.29 (31.68)*	7.14 (26.03)*
Teacher rating			
Inattention/overactivity	5.01 (4.48)	2.75 (3.73)*	2.59 (3.91)*
Oppositional/defiant	2.18 (4.39)	1.19 (3.72)*	1.30 (3.79)
Abbreviated Conners	7.03 (7.07)	4.03 (6.31)*	3.75 (6.66)*
Peer interactions	0.24 (0.62)	0.15 (0.49)	0.15 (0.44)
Counselor rating			
Inattention/overactivity	7.95 (3.85)	6.31 (3.24)*	6.10 (3.10)*
Oppositional/defiant	3.63 (4.57)	2.58 (3.70)*	2.36 (3.29)*
Abbreviated Conners	12.70 (7.15)	9.91 (6.15)*	9.26 (5.73)*
Peer interactions	0.77 (0.74)	0.56 (0.56)*	0.49 (0.48)*

Inattention/overactivity and oppositional/defiant subscales of the IOWA Conners Rating Scale (42, 43). Abbreviated Conners Rating Scale (44).

* Significantly different from placebo.

quency counts except positive peer interactions, with ES ranging from 0.3 to 1.5, and nearly all ratings (ES ranging from 0.3–1.1). Teacher ratings of peer interactions were not significantly different between any of the drug conditions (likely attributable to the limited amount of peer interaction possible in the classroom setting). The 2 drugs did not differ on any measure.

Safety Measures

No serious adverse events were reported, and no participants were discontinued from the study for reasons related to AEs. Few AEs were reported (none were severe), and numbers of occurrences were similar across medication conditions (Table 7). With the exception of accidental injury and respiratory symptoms, all events were judged possibly or probably related to study treatment. The most common AEs experienced by children on both Concerta and tid IR MPH were headache and abdominal pain. Four participants had reports of motor tics during the study, all during the tid IR MPH treatment: 3 had motor tics of moderate severity and 1 had a vocal tic (humming) of mild severity. Two of these reports were of new or worsened tics, which were not judged to be serious by the study physician.

With regard to sleep, no significant differences were seen between placebo and either drug, or between the 2 active drugs. Excellent sleep was reported for 12%, 13%, and 7% of children on the placebo, Concerta, and tid IR MPH conditions, respectively; good sleep was reported for 57%, 47%, and 65% of the children in these conditions. Fair sleep was reported for 21%, 24%, and 21% of children, and poor sleep for 10%, 16%, and 7% of children.

Usual appetite was reported for 59%, 77%, and 66% of the children in the placebo, Concerta, and IR MPH conditions, respectively; an additional 37%, 6%, and 10% of the sample in each condition reported eating more than usual. Thus, appetite loss (relative to prestudy medicated state) occurred in 4% of the sample in the placebo condition, compared with 18% in the Concerta condition and 24% in the IR MPH condition. Pairwise analyses using a dichotomy of less than usual versus same/more than usual (McNemar's test) showed significant differences between both active drug conditions and placebo ($P =$

.013 for Concerta/placebo; $P = .001$ for IR MPH/placebo); the 2 active drug conditions did not differ significantly from each other.

Maximal and minimal diastolic blood pressure means were both significantly higher for the Concerta (62.6 mm Hg, 52.1 mm Hg) and IR MPH tid (63.0 mm Hg, 51.8 mm Hg) treatments than for placebo (60.7 mm Hg, 50.1 mm Hg; $P < .05$). The mean maximal pulse rate was significantly ($P < .001$) faster for both the Concerta (106.1 beats per minute [bpm]) and the IR MPH tid (106.8 bpm) treatments than for placebo (102.1 bpm) as well. There were no significant differences between Concerta and IR MPH tid on blood pressure or pulse.

DISCUSSION

This study was undertaken to examine the effects of a novel extended-release formulation of MPH, Concerta, with comparisons to placebo and a standard tid dosing regimen of MPH. On all the measures collected, across a variety of domains, settings, and sources, both tid IR MPH and Concerta produced improvement relative to placebo, which was significant in most cases. In the natural setting, the 2 drug conditions did not differ significantly from each other with the exception of 2 of the 3 parent ratings of ADHD behaviors (on which Concerta was preferred). Results of the laboratory study indicated that Concerta was superior to placebo and not significantly different from tid IR MPH, even at 12 hours after dosing.

The fact that Concerta had significant effects through 12 hours after administration in the laboratory setting and on measures of evening behavior in the natural setting indicates that the span of action of Concerta is sufficiently long and comparable to tid IR MPH. The only measure on which there was a significant difference between the 2 active drug conditions was on parent ratings, on which Concerta was preferred to the tid condition. However, the effect size of this difference was much smaller (0.4) than the ES of either tid IR or Concerta to placebo (1.2–2.0). These results thus add to the small literature documenting that active medication in the late afternoon and evening would be helpful for problems in the evening. Children with ADHD are significant stressors to their parents,^{55–57} and behavior improved in the evening may be important not only for

TABLE 7. AEs Seen in at Least Two Percent of Children in Any Treatment Group*

AE	Placebo	tid IR MPH	Concerta	Total
Headache	16 (23.2%)	11 (15.9%)	8 (11.8%)	22 (31.4%)
Abdominal pain	8 (11.6%)	12 (17.4%)	9 (13.2%)	20 (28.6%)
Upper respiratory tract infection	3 (4.3%)	3 (4.3%)	2 (2.9%)	8 (11.4%)
Accidental injury	2 (2.9%)	3 (4.3%)	1 (1.5%)	6 (8.6%)
Vomiting	2 (2.9%)	2 (2.9%)	2 (2.9%)	5 (7.1%)
Twitching	0 (0.0%)	4 (5.8%)	0 (0.0%)	4 (5.7%)
Diarrhea	1 (1.4%)	2 (2.9%)	0 (0.0%)	3 (4.3%)
Pharyngitis	0 (0.0%)	2 (2.9%)	1 (1.5%)	3 (4.3%)
Rhinitis	0 (0.0%)	2 (2.9%)	1 (1.5%)	3 (4.3%)
Dizziness	0 (0.0%)	1 (1.4%)	2 (2.9%)	2 (2.9%)
Urinary incontinence	2 (2.9%)	1 (1.4%)	0 (0.0%)	2 (2.9%)

* AE mapping was based on the COSTART IV thesaurus. AE reports were tabulated under the treatment the child was receiving at AE onset.

the ADHD child, but also for his or her parents. Parent-child interactions, compliance with commands, and parental stress are affected positively by stimulants,^{58–60} and difficulties with completing homework, chore completion, and sibling interactions may be improved by stimulants. Some parents choose behavioral approaches (eg, time out, reward systems), which are effective alternatives to help in these problem areas with their children in the evening.^{61–62} In addition, some children with ADHD neither need nor tolerate medication in the evening. However, the present data show that if nonpharmacologic approaches are unsuccessful, stimulant medication is an important adjunctive treatment for the home setting, and the once-daily dosing of Concerta may be preferable to tid IR MPH. Similarly, children will benefit from a long-acting preparation when they participate in after-school sports activities or neighborhood peer interactions.

Other stimulant preparations require administering medication in the late afternoon or early evening, both times that may be difficult for many children and families. Indeed, compliance with treatment is a pervasive problem that would seem to be minimized with an effective, once-daily, preparation.^{63,64} For example, compliance with medications has been shown to improve from 59% on a tid regimen to 83.6% on a once-daily regimen.⁶⁵ With once-a-day administration in the morning, neither the child, school staff, nor after-school care providers need to remember to administer additional doses during the day. Clinical lore suggests that children may be embarrassed by trips to the nurse's office for medication and may skip doses as a result. Because many of these difficulties worsen in middle and junior high schools, once-a-day dosing would seem to have particular usefulness in this population. IR MPH tid has a clearly beneficial effect on young adolescents on measures analogous to those we used in this study,^{66,67} although such studies have not yet been performed with Concerta. In this study, children took (placebo) pills 3 times a day, including lunchtime and after-school doses. Therefore, preference ratings were made without taking into account the fact that a once-a-day preparation would eliminate the need for dosing at school and after school.

An area worthy of discussion is how the present results relate to existing literature on MPH effects on children with ADHD. First, it is noteworthy that medication had significant effects on parent- and teacher-rated IOWA oppositional/defiant behavior in addition to effects on ADHD symptoms. This finding is consistent with literature documenting that stimulant effects extend to at least 1 very important domain of concurrent impairment in children with ADHD—oppositional and defiant behavior as rated by parents and teachers.^{12,49} The results also highlight the fact that stimulant effects are salient in children with ADHD comorbid with either ODD or CD (80% of the children in the current study had ADHD comorbid with ODD and CD), as only these children had baseline/placebo ratings on the IOWA Conners O/D subscale that were sufficiently high to be lowered with medication.

Second, our comprehensive laboratory school methodology for assessing efficacy and time course effects of stimulant medication replicates earlier studies documenting that stimulants have beneficial acute effects on daily classroom activities, including arithmetic tasks⁶⁸ and individualized classroom goals.⁴¹ Such effects have been documented in summer treatment program classrooms,^{6,7,41,49,69} in regular community school settings,²⁹ and in laboratory classrooms.^{20,70} Such findings on objective indices of work performance no doubt give rise to teacher ratings of improved task completion. Unfortunately, these acute effects, despite the fact that they continue in adolescence,⁶⁶ have not yet been shown to translate into long-term gains in academic achievement, even with long-term stimulant use.²⁵

A third point relevant to the extant literature concerns our measures of peer interactions in recreational settings. Previous studies have involved examinations of dyadic interactions⁷¹ and structured large-group interactions.^{8,13,72} These studies have generally shown that stimulants decrease rule violations, aggression, interruption, and other behaviors bothersome to peers. In contrast, only a single study has examined a small group setting⁷³ and only one a large-group unstructured setting.¹² Because small groups make up the majority of the settings in which children with ADHD interact with peers, and because interaction with peers in small groups (eg, board games) and in unstructured peer settings is clearly problematic for children with ADHD,⁷⁴ the absence of information on stimulant effects in both small-group and recess activities has been a major deficit in the literature. The data from this study demonstrate that stimulant medication (both IR MPH and Concerta) had beneficial effects on negative peer interactions during board game periods, as well as during unstructured group recess periods. Furthermore, as Table 4 and Fig 2 show, both medication conditions caused substantial increases in the percentage of individualized target behavior goals that children reached in the board game setting (individualized goals were not established for recess periods). These beneficial medication effects occurred throughout the day into the evening, times when children with ADHD are likely to engage in board games and free play with neighbors and siblings. Although behavioral interventions, such as summer treatment programs, are arguably the treatment of choice for dysfunctional peer relationships in children with ADHD,^{48,75} the present results suggest that stimulant medication has an important adjunctive role for this domain of impairment. Both tid IR MPH and Concerta seem to offer substantial benefit to children with ADHD in these peer contexts. As in the case of academic productivity, whether these acute changes in peer interactions will translate into long-term changes in peer relationships remains a question that merits investigation.

As Table 6 illustrates, medication effects during the classroom and peer settings extended to the entire laboratory assessment day. These daily totals summarize peer settings, meals and snacks, vital sign assessment periods, and transitions. They are thus

analogous to the daily frequency counts that we have reported in numerous studies of medication effects in our summer treatment program setting,^{6–8} and reveal the same results we have reported in that context—improvements in rule-following and in a variety of behavioral interactions with adults and peers, as well as in counselor and teacher ratings.

Parents reported appetite loss relative to placebo for both drug conditions, and the 2 drug conditions were similar. For children for whom evening medication is needed, strategies such as high calorie snacks can be used to minimize weight reduction or lack of weight gain associated with appetite loss. Although earlier studies have suggested that the reductions in weight and height gain associated with stimulant use are not problematic in the long-term, those studies were typically conducted with bid dosing schedules. Whether long-term tid medication or Concerta will result in a reduction in growth velocity awaits assessment.

Notably, parents did not report differential sleep or appetite problems for the 2 active drug conditions. Although assessments of sleep difficulty were admittedly crude, the fact that sleep difficulty was reported in only a minority of children (and not differentially) means that late-afternoon doses of stimulants roughly equivalent to 5 to 15 mg of IR MPH apparently did not disrupt sleep in the majority of children in this study. This finding is consistent with the small number of studies that have evaluated tid IR dosing of MPH.^{8,23,24} However, all children in this study were taking MPH before entry. Presumably, children whose sensitivities to MPH included problematic sleeping would not have been taking MPH and thus would not have been enrolled in this trial. Therefore, sleep problems associated with late-afternoon or evening stimulant medication may be underestimated and call for additional investigation.

Several points about the methodology that we used in this study merit comment, as we believe they offer information for future clinical trials of psychoactive medication for children. First, the time course measures reveal that there are substantial changes in children's behavior over time in the laboratory settings—both in the classroom and in the 2 recreational settings. Children were on-task less, more disruptive, violated more rules, and were less likely to achieve target goals as the day wore on. As the tables and graphs illustrate, a primary effect of medication was to prevent this deterioration in behavior. Our companion study evaluating normal children's behavior in this setting shows that non-ADHD children do not deteriorate over the course of the day.⁷⁴ The implication of these patterns is that brief, 1-time assessments are likely to underestimate both differences from controls and medication effects. We have previously argued that this is a benefit of our use of a 9-hour STP day to assess medication effects and a liability of brief pediatric/psychiatric office visits.²⁸

The time course data also provide new insight into the nature of ADHD. As discussed previously, unmedicated children in this study showed deterioration across an entire day of naturalistic activities. Such deterioration is similar to the typical ADHD

performance decrement over the course of a 20-minute vigilance task. This finding argues that an explanation for ADHD is not likely to be a simple deficit in 1 or more of the core symptoms of inattention, impulsivity, or activity level. Instead, these deficits must interact with factors associated with maintaining appropriate behavior and attention across settings and long periods of time. For example, children with ADHD may pay attention and inhibit impulses when their interest level or novelty is high or when they are motivated to exert substantive effort because of external incentives.⁷⁶ However, if novelty wears off and interest wanes over lengthy exposure, or if the cost of exerting effort exceeds the value of external incentives, then the children's behavior may deteriorate as our figures demonstrate. Parents often report that an antecedent to their children's behavior problems is fatigue, which certainly increased over the lengthy laboratory study days. Perhaps the ability of the children to switch gears (eg, from games to classroom) decreased with successive introductions of the activities. Alternatively, perhaps staff members' ability to recognize antecedents to inappropriate behavior and provide consequences consistently deteriorated as the day progressed. Such notions warrant investigation, and our data suggest that settings including multiple, ecologically valid activities over entire days may be more valuable than restricted laboratory tasks in studies designed to evaluate these hypotheses.

Second, it is important to note that the present results were obtained with a clinically implemented regimen of behavior therapy as a background intervention at home (parent training), in school (teacher consultation, DRC), and in the laboratory setting (point system, DRC, time out). Despite this concurrent intervention, the magnitude of the medication effects in our study are comparable to those reported by Swanson and colleagues,⁷⁷ who conducted the same study in a different laboratory and community setting but without the protocol-defined behavioral interventions. However, the behavioral measurements that were obtained in this study were lower (less severe) than those obtained in the Swanson study, perhaps attributable to the additive effect of the behavioral treatment. For example, the final community teacher IOWA I/O score obtained for Concerta in this study (4.7) was substantially lower than that obtained in the Swanson study (6.7), with the difference representing an effect size of >0.5 (Swanson mean–Pelham mean/Swanson SD). These results are consistent with many others showing that combined behavioral and pharmacologic treatments are generally superior to unimodal treatments when low to moderate dosages of stimulants and behavior therapy are combined.^{4,31}

The present results thus illustrate that investigations of stimulant effects in children can routinely be done by examining the incremental value of medication beyond a baseline behavioral intervention without compromising the evaluation of the drug's efficacy. Because behavioral interventions, the only evidence-based treatment for ADHD other than CNS stimulants, are commonly used in the community by

parents and teachers, they constitute the background against which medication effects are measured in clinical practice. To best mirror clinical practice, therefore, clinical trials of stimulants should include some form of behavioral intervention as a background. By using a standardized dose of a clinical behavioral intervention, we have removed some of the variance attributable to differences in background behavioral treatments and yielded clear incremental effects of medication. Because a behavioral condition is more beneficial than placebo alone, and because a combined approach to treatment is substantially more beneficial and acceptable to parents than medication alone,^{25,78} clinical trials of new psychoactive medications that use behavioral treatments as the background interventions would seem to have advantages both in terms of participant retention and from an ethical perspective.

A third methodologic note concerns our use of individualized target behavior goals (DRCs) as dependent measures. Although teacher rating scales are ubiquitously used in drug studies with children as well as in clinical applications, DRCs represent a feasible alternative that yield more interpretable and stable data than ratings alone, without the need to use extensive and labor-intensive structured observations made by ancillary staff. ADHD children are 4 to 5 times more likely to reach their daily targets when they are medicated,⁴¹ and such changes can be clearly depicted graphically, demystifying drug responsiveness for teachers, parents, and physicians. For example, knowing that a child's DRC goal attainment increases from 50% to 80% is more understandable than is a reduction of 3 points on a rating scale. In the present study, the effect size yielded on the DRC measure of target behaviors was only slightly less than that yielded on teacher ratings of ADHD symptoms, and larger than that shown on teacher ratings of oppositional behavior and peer relations. Target behaviors typically included measures of work completion, rule-following, noncompliance, oppositional behaviors, and peer interactions—all measures of the impairment associated with ADHD rather than ADHD symptoms. Because reduced impairment, not reduced symptoms, is the goal of treatment for ADHD, individual target behaviors are better measures of treatment effects than are standard teacher rating scales—particularly for symptoms or areas of impairment that are not well represented on rating scales and/or are unique to the child. This may be especially important in evaluating the utility of medication in a predominantly inattentive ADHD child, a subtype in which medication effects have been less studied but DRC targets can easily be established.

Most of our ADHD medication studies have been conducted in the context of an 8-week summer treatment program. The current study demonstrates the exportability of settings and measures used in that program to a laboratory setting. The measures of peer interactions, typically applied to outdoor sports activities, are sensitive to medication effects in the context of indoor, small-group, board games. Given the importance of peer difficulties in the current

presentation and long-term outcome of children with ADHD, assessment of treatment effects on such measures of acute functioning is of paramount importance.

Finally, the total daily dosage of Concerta was 20% greater than that for the tid IR MPH condition. As our data and those from the parallel study show,⁷⁷ such a total daily dose of Concerta produces the same behavioral effects as the amount of tid IR MPH that we used. However, the bioavailability of Concerta does not necessarily yield 20% higher blood levels of MPH. It may be that lower absorption in the intestine necessitates higher doses to yield the same blood levels as well as the same behavioral effect, meaning that no more medication is active in the Concerta formulation than in IR MPH.

CONCLUSION

This investigation clearly supports the efficacy of the Concerta long-acting formulation of MPH for parents who desire to have medication benefits for their child throughout the day and early evening. Effects of a single morning dose lasted throughout the school day and into the evening hours, and the effects on multiple measures, by multiple informants, and in multiple settings, were similar to those of a standard preparation of MPH given 3 times a day. This study provides a model for clinical trials of new psychoactive drugs for children: assessments by multiple raters, in both natural and ecologically-valid laboratory settings, across a range of domains of impairment and settings, examining a large number of objective, reliable measures of behavior, and in a context of ongoing behavioral treatment.

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