Double-Blind, Placebo-Controlled Study of Single-Dose Amphetamine Formulations in ADHD

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ABSTRACT

Objective: To compare the efficacy and time course of single morning doses of Adderall®, extended-release, and immediate-release dextroamphetamine sulfate. **Method:** Thirty-five children with attention-deficit/hyperactivity disorder, combined type, were given Adderall, immediate-release dextroamphetamine, dextroamphetamine Spansules®, and placebo in a randomized, double-blind, crossover study. Behavior ratings, locomotor activity measurements, and academic measures were obtained over a period of 8 weeks. **Results:** All three drugs exhibited robust efficacy versus placebo on nearly all measures. The effects of dextroamphetamine Spansules were less robust in the morning, particularly compared with Adderall, but they lasted 3 to 6 hours longer, depending on the measure. Although parent behavior ratings and locomotor activity showed improvements up to 12 hours after single doses of all three drugs, the number of math problems attempted and completed correctly 4 hours after dosing were only robustly increased by Spansules. **Conclusions:** Both immediate-release amphetamines demonstrated earlier onset of effects, but dextroamphetamine Spansules showed more sustained effects that were present on a wider range of measures. *J. Am. Acad. Child Adolesc. Psychiatry*, 2001, 40(11):1268–1276. **Key Words:** attention-deficit/hyperactivity disorder, dextroamphetamine, Adderall®, psychostimulants.

Stimulants are the drugs of choice for the pharmacological treatment of attention-deficit/hyperactivity disorder (ADHD), and the most frequently prescribed agent remains methylphenidate (MPH), with a positive response rate exceeding 70% (Spencer et al., 1996). Several controlled crossover studies suggest that nearly all children with combined-type ADHD who are nonresponders to MPH respond favorably to dextroamphetamine sulfate and vice versa (Arnold, 1996; Arnold et al., 1978; Elia et al., 1991; Sharp et al., 1999). In the past few years, a mixture of 75% dextroamphetamine and 25% levoamphetamine (Popper, 1994) has been aggressively marketed under the trade name Adderall®, attaining an estimated 29% of market share in 2000 (Goodman and Nachman, 2000). Initial marketing efforts emphasized the existence of four distinct salts and suggested that they provided differential rates of absorption and thus longer efficacy (Richwood Pharmaceutical Company, unpublished prescribing information on Adderall tablets, 1997). Recent manufacturer-sponsored trials have compared Adderall and immediate-release MPH (Pelham et al., 1999; Pliszka et al., 2000; Swanson et al., 1998), but there have been no comparisons between Adderall and either immediate-release or extended-release formulations of dextroamphetamine sulfate. On the basis of similar terminal half-lives for dextro- and levoamphetamine (Hutchaleelaha et al., 1994), we hypothesized that Adderall would be comparable in efficacy and time course with immediate-release dextroamphetamine, that Adderall and immediate-release dextroamphetamine would be more effective than the same dose of extended-release dextroamphetamine in the morning, but that the effects of extended-release dextroamphetamine would last longer than those of Adderall and immediate-release dextroamphetamine.

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METHOD

Subjects

We examined 21 boys and 14 girls (mean age 9.1 ± 1.5, range 6.9–12.2 years) with a history of severe hyperactivity, impulsivity, and

inattention who met *DSM-IV* criteria for combined-type ADHD. In addition to the diagnosis of ADHD, 10 children also met criteria for oppositional defiant disorder, 12 for an anxiety disorder, 3 for enuresis, 2 for dysthymic disorder, and 6 for a learning disorder. Children were recruited from local schools. Exclusion criteria included Full Scale IQ less than 80 on the WISC-III (Wechsler, 1991) or the presence of a chronic medical or neurological disease including Tourette's disorder, chronic tic disorder, pervasive developmental disorders, and mood or anxiety disorders requiring current treatment. The sample consisted of 18 whites, 9 African Americans, 7 Latinos, and 1 Asian American. Fifteen subjects were naive to stimulant treatment prior to participation in the study (Table 1).

Assessment

Systematic telephone screenings were conducted by a research social worker to determine that ADHD symptoms were present in at least two settings. Conners Parent and Teacher Rating Scales were then obtained (Conners, 1997). Additional tools used in the screening process included the Child Behavior Checklist and Teacher's Report Form (Achenbach and Ruffle, 2000). Subjects who met study diagnostic criteria and who had a Conners Teacher Rating Scale Hyperactivity factor score of 70 or greater were sent copies of consent and assent by mail and invited to visit the program. Written informed consent and assent were obtained during this initial face-to-face interview. All psychotropic medications were discontinued prior to beginning the study, which was approved by our institutional review board.

TABLE 1
Demographic Characteristics

	Mean	SD
Age (years)	9.1	1.5
WISC-III		
Verbal standard score	102.5	13.6
Performance standard score	96.6	14.5
Full Scale standard score	99.8	13.0
CBCL Attention Problems *T* score	72.5	10.2
TRF Attention Problems *T* score	72.3	10.8
	n	**%**
Sex		
Male	21	60
Female	14	40
DSM-IV diagnoses		
ADHD, combined type	35	100
ODD	10	29
Anxiety disorder	12	34
Enuresis	3	9
Dysthymia	2	6
Learning disorder	6	17
Prior stimulant treatment	20	57
Methylphenidate	11	31
Methylphenidate SR	3[a]	9
Adderall	3	9
Immediate-release dextroamphetamine	2	6
Dextroamphetamine Spansules	2	6

Note: CBCL = Child Behavior Checklist; TRF = Teacher's Report Form; ADHD = attention-deficit/hyperactivity disorder; ODD = oppositional defiant disorder; SR = sustained release.

[a] Includes one subject taking both methylphenidate and methylphenidate SR.

Procedure

Children participated in a research school 5 days per week consisting of formal academic instruction from 9 A.M. to 12:30 P.M. and therapeutic recreation (sports, art therapy, structured social skills sessions) from 1 P.M. to 3 P.M. Behavior management techniques were used extensively within the program, although parent training was not provided.

During a 3-week medication-free observation period, a physical and neurological examination was performed and routine laboratory studies were obtained (complete blood cell count, electrolytes, urinalysis, liver function test, thyroid studies). A psychoeducational evaluation, consisting of the WISC-III and the Woodcock-Johnson Achievement Battery-Revised (Woodcock and Johnson, 1989), was performed by a clinical psychologist. A child and adolescent psychiatrist confirmed the final *DSM-IV* diagnoses by combining information from the structured psychiatric interview (Diagnostic Interview for Children and Adolescents-Child and Parent versions, revised) (Reich, 2000), teacher and recreation therapist ratings of hyperactive behavior, parent ratings, and staff observations.

Double-blind medications were administered for 8 weeks, followed by 2 weeks of open treatment optimization. Each child received 2 weeks each of Adderall, immediate-release dextroamphetamine, dextroamphetamine Spansules, and placebo in random order. Active drugs were given in two doses, one per week. Doses, selected before randomization, were based on age, weight, prior medication experience, and symptom severity. The overall mean low dose was 7.8 mg (range 5–25 mg, 0.24 mg/kg) and the mean high dose was 12.8 mg (range 10–30 mg, 0.39 mg/kg). The dose order was randomized across subjects, but the same order, either increasing (n = 18) or decreasing (n = 17), was used for a given subject. Given the absence of comparative data, we administered equal doses of all three drugs to the first 24 subjects. The last 11 subjects received equal doses of both immediate-release formulations, but we increased the dextroamphetamine Spansules doses by 5 mg to more closely approximate clinical use patterns (Table 2).

Medications and placebo were contained in identical capsules packaged in dated, coded blister packs by a research pharmacy service and were administered by parents at home at a mean time of 7:16 A.M. (SD = 21 minutes), on weekdays and at breakfast on weekends. Subjects who had not previously received stimulants were first treated with immediate-release dextroamphetamine (2.5–5 mg daily for 3 days)

TABLE 2
Dose Schedule

	Dosage Level (mg)					
First 24 subjects						
Adderall	5	10	15	20	25	30
Dextroamphetamine	5	10	15	20	25	30
Dextroamphetamine Spansules	5	10	15	20	25	30
Last 11 subjects						
Adderall	5	10	15	20	25	
Dextroamphetamine	5	10	15	20	25	
Dextroamphetamine Spansules	10	15	20	25		

Note: Two doses were selected for each patient from the listed options. The order of the doses (increasing or decreasing) was randomly selected and applied to all active drugs for each subject. Drug sequence, including placebo, was assigned randomly.

prior to beginning double-blind trials to rule out idiosyncratic responses and minimize adverse effects from starting on a relatively high dose.

Dependent Measures

Teachers provided weekly ratings of classroom behavior (between 9 A.M. and noon) using the Hyperactive/Impulsive factor of the Conners Teacher Rating Scale (Conners, 1997). The recreation therapist provided weekly scores on the Hyperactivity factor of the Children's Psychiatric Rating Scale (Fish, 1985). Academic measures were also obtained each day at 11 A.M., about 4 hours after medication administration. Students performed a 5-minute timed math task, consisting of arithmetic problems with difficulty levels selected individually for each child. The number of correct and total responses was recorded daily and summed weekly. The nurse coordinator recorded weekly weights and vital signs and assessed medication side effects using the Stimulant Side Effect Rating Scale (Barkley et al., 1990). Parents recorded time of administration of coded medication and provided a weekly rating of adverse effects (Barkley Side Effect Rating Scale). Parents of the 28 most recently enrolled subjects were asked to provide ratings of hyperactive/impulsive behavior (Conners Parent Behavior Rating Scale) for the hours 4 P.M. to 7 P.M. Weekly telephone contact and medication slips signed daily by parents confirmed compliance. Motor activity was assessed with an Actometer worn on the nondominant wrist (Actiwatch, Sun River, OR).

Adderall and immediate-release dextroamphetamine were obtained commercially. When the study began, Smith-Kline Beecham was in the process of modifying the manufacturing process for extended-release dextroamphetamine capsules. Pending Food and Drug Administration approval (obtained in February 1999) for the new aqueous process, Smith-Kline Beecham provided dextroamphetamine Spansules at no cost and without restrictions. No funding was sought or received from any commercial entity.

Statistical Analysis

Parametric analyses used SPSS 10.0 for Windows (SPSS, 1999). A mixed repeated-measures analysis of variance (ANOVA) was used to initially examine the two between factors (dose order [increasing versus decreasing], dosage equivalence [same dosage versus 5 mg higher dose for Spansules]), and the within factors of drug (4 levels) and dose (2 levels), and interactions. Nonsignificant between-subject factors were removed from subsequent analyses. Significant ANOVA results were explored with a priori defined pairwise contrast analyses, corrected for multiple comparisons. All tests were two-tailed, with nominal overall significance set at $p < .05$ for each measure.

Daytime Actometer data were divided into 12 hourly periods from 9 A.M. (beginning of school) to 9 P.M. (earliest bedtime), averaged over weekdays (Monday–Friday) and log-transformed (ln [x + 1]). Because of substantial missing data with this measure, primarily from Actometer breakage, complete data are available for only 22 subjects. The 22 subjects with complete data did not differ from the remaining subjects on age or any severity measures ($p > .40$). Post hoc drug-drug and drug-placebo hourly contrasts were corrected for 72 multiple comparisons with significance set at $p < .0007$.

The Actiwatch Sleepwatch software (Mini Mitter Company, 1999) calculates total presumed sleep duration (Sadeh et al., 1994, 1995), which was averaged for the week nights of each study week.

Missing weekly weights (6%) were calculated by interpolation. Children with other missing data for a measure were excluded from analyses for that measure. Complete parent data were available for 20 or fewer subjects, depending on the measure. There were no demographic or severity differences between the subjects with and without completed parent reports.

RESULTS

We enrolled 38 children, 3 of whom were excluded prior to randomization because of a history of chronic motor and vocal tics, IQ < 80, and abnormal EEG findings, respectively. The remaining 35 subjects completed the double-blind trial. All subjects met *DSM-IV* criteria for ADHD, combined type. See Table 1 for additional subject characteristics. Medication compliance, as documented by parent records noting date and time of medication administration, exceeded 93% (SD = 11.8%). Documented compliance was low for two subjects (46% and 57%). Although their data are included in all analyses, we verified that they did not represent statistical outliers (Table 3).

Between-Group Factors

Dose order (increasing versus decreasing) was randomly determined for each subject, and the same sequence was used for all three active medications. Significant three-way interactions (dose order by drug by dose) were found for weight and recreation therapist ratings of hyperactivity/impulsivity, as noted below. Dose order was not a significant factor with any other main effects or interactions for any other measure.

Similarly, we compared the first 24 subjects, all of whom received the same dosages for all three drugs, with the last 11 subjects, who received Spansule doses that were 5 mg higher than the immediate-release formulations. Only parent-reported adverse effects showed a significant difference between groups ($F_{1,17} = 9.15$, $p = .008$), with a greater number of adverse effects reported in the subgroup with complete data that received a higher Spansule dose ($n = 4$). No other significant main effects or interactions were observed for any measures. Accordingly, analyses for all other measures were collapsed across the two groups (maximum $n = 35$).

Hyperactivity Ratings

There was a significant effect of medication on the Conners Teacher Hyperactivity factor score ($F_{3,32} = 15.70$, $p < .001$), obtained in the classroom between 9 A.M. and 12:30 P.M. Contrast analysis revealed that immediate-release dextroamphetamine, which did not differ significantly from Adderall, decreased teacher-rated hyperactivity significantly more than dextroamphetamine Spansules ($p = .025$). Higher doses were significantly more effective than lower doses for all three medications ($F_{1,34} = 5.38$, $p = .03$).

In afternoon recreation therapy (1 P.M. to 3 P.M.), ANOVA revealed a significant main effect of drug on

TABLE 3
Means, Standard Deviations, and Analyses of Variance

Measure	Mean (SD)								ANOVA		
	Adderall		Dex-Span		I-R Dex		Placebo		*F*	*df*	*p*
CTS	50.6	(5.6)	53.7	(9.1)	50.5	(5.4)	63.1	(12.6)	15.7	3,32	.000
CPRS	2.8	(1.0)	2.3	(1.0)	2.5	(1.1)	3.8	(1.1)	35.0	3,29	.000
CPS	58.3	(13.1)	60.0	(15.6)	60.5	(14.7)	68.0	(14.5)	5.8	3,12	.01
Weight (kg)	32.6	(8.0)	32.5	(7.9)	32.7	(8.0)	33.3	(8.3)	13.4	3,32	.000
Sleep (hr)	7.6	(0.7)	7.2	(0.5)	7.4	(0.7)	7.8	(0.6)	9.9	3,19	.000
TAP	171.6	(56.4)	187.0	(60.9)	177.4	(42.9)	147.7	(50.7)	6.3	3,32	.002
TCP	164.6	(55.9)	177.6	(61.1)	167.6	(41.2)	140.2	(51.3)	5.6	3,32	.003
SERS-N#	3.3	(2.0)	2.9	(1.8)	2.6	(1.8)	2.0	(1.9)	3.9	3,23	.02
SERS-N sev	2.7	(1.5)	3.1	(2.0)	2.7	(1.7)	1.8	(1.2)	3.6	3,23	.03
SERS-P#	6.3	(2.7)	6.7	(2.9)	6.4	(3.5)	5.9	(3.2)	0.3	3,15	.82
SERS-P sev	3.2	(1.2)	3.7	(1.5)	3.2	(1.6)	2.8	(1.5)	2.2	3,15	.13

Note: ANOVA = analysis of variance; Dex-Span = dextroamphetamine Spansules; I-R Dex = immediate-release dextroamphetamine; CTS = Conners Teacher Rating Scale Hyperactivity *T* score obtained from 9 A.M. to 12:30 P.M.; CPRS = Children's Psychiatric Rating Scale Hyperactivity factor score obtained between 1 P.M. and 3 P.M.; CPS = Conners Parent Rating Scale Hyperactivity *T* score obtained between 4 P.M. and 7 P.M.; TAP = total attempted math problems; TCP = total correct math problems, obtained at 11 A.M.; SERS-N and SERS-P, Barkley's Side Effect Rating Scale, nurse and parent forms, respectively. For SERS-N and SERS-P, # indicates number of adverse effects reported, and "sev" indicates mean severity of reported adverse effects.

the Hyperactivity factor of the Children's Psychiatric Rating Scale ($F_{3,29} = 34.96$, $p < .001$). A higher dose was significantly more effective than a lower dose ($F_{1,31} = 8.65$, $p = .006$). Across doses, all three active drugs were significantly more effective than placebo (Bonferroni corrected pairwise comparisons, $p < .001$). In addition, dextroamphetamine Spansules decreased hyperactive behavior significantly more than Adderall ($p = .04$). Spansules and immediate-release dextroamphetamine did not differ significantly. The significant interaction between drug, dose, and order was due mainly to weaker effects of high-dose Adderall when it was given before low-dose Adderall and a lack of dose-related improvement for Adderall in the increasing-dose group ($F_{3,26} = 4.81$, $p = .009$). By contrast, both dextroamphetamine formulations produced dose-related improvements, regardless of the dosing schedule.

Because of parent work schedules and variable after-school child-care arrangements, complete late afternoon (4 P.M. to 7 P.M.) parent ratings of hyperactive behavior were available for only 15 subjects. Analyses revealed a significant drug effect ($F_{3,12} = 5.84$, $p = .01$); Bonferroni adjusted pairwise comparisons revealed significant improvements versus placebo for dextroamphetamine Spansules ($p = .007$), and Adderall ($p = .03$), with a trend for immediate-release dextroamphetamine ($p = .053$). A higher dose was significantly more effective than a lower dose ($F_{1,14} = 8.04$, $p = .01$).

Academic Measures

Timed academic tasks were performed each weekday at 11 A.M. Stimulants significantly increased the number of math problems attempted and number of problems done correctly ($F_{3,32} = 6.25$, $p = .002$ and $F_{3,32} = 5.58$, $p = .003$, respectively). Immediate-release dextroamphetamine and dextroamphetamine Spansules both significantly increased the number of problems attempted relative to placebo ($p = .01$ and $p = .003$, respectively). Improvements on Adderall did not reach significance; drug-drug differences were not statistically significant.

Accuracy also improved; the number of problems done correctly significantly increased over placebo with immediate-release dextroamphetamine ($p = .02$) and dextroamphetamine Spansules ($p = .003$). Adderall did not differ significantly from placebo, and no significant between-drug differences were found. A higher dose did not significantly improve the number of problems attempted or problems done correctly.

Locomotor Activity

As shown in Figure 1, stimulants significantly decreased locomotor activity ($F_{3,54} = 5.50$, $p = .002$). Besides the highly significant although trivial effect of time of day, the interaction of time and drug was also significant ($F_{33,594} = 2.15$, $p = .004$). Pairwise contrasts revealed significant decreases in activity for all three drugs relative to placebo from 9 A.M. to 7 P.M. Dextroamphetamine Spansules and

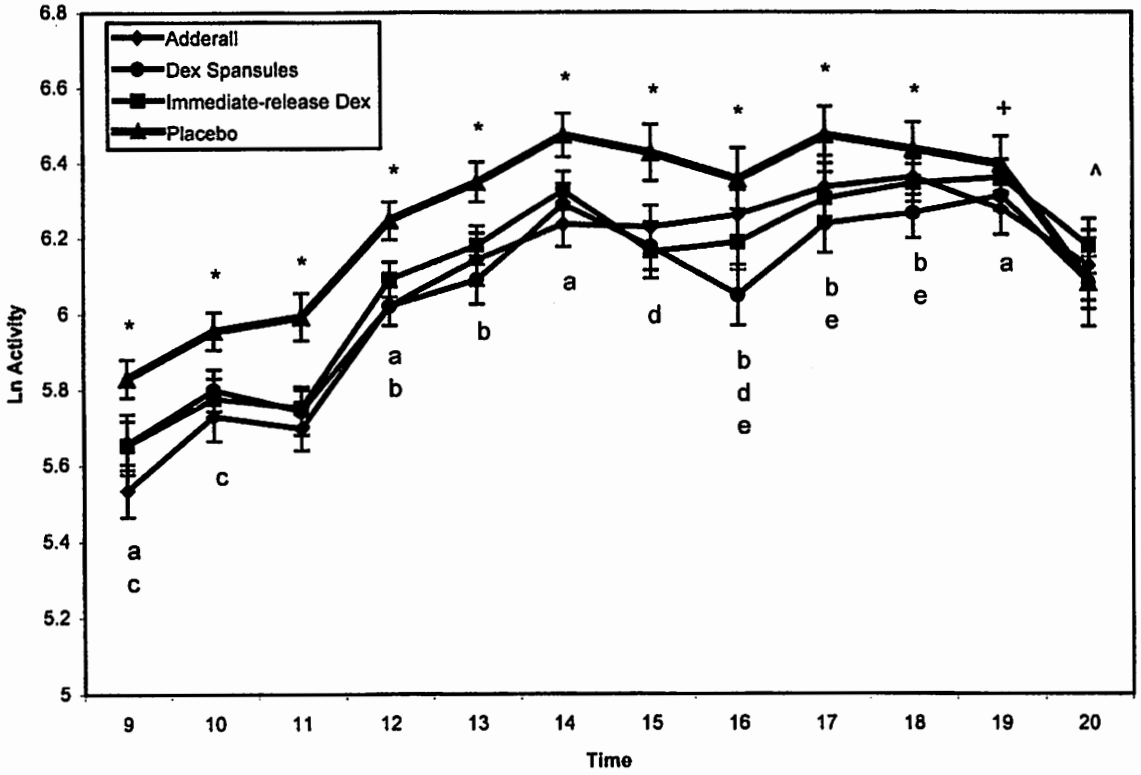

Fig. 1 Hourly log-transformed Actometer means and standard errors for 22 children with complete data; values averaged across weekdays and doses. Hourly intervals begin at indicated times. Bonferroni corrected significant pairwise comparisons ($p < .0007$) are indicated as follows: *all stimulants better than placebo; +dextroamphetamine Spansules and Adderall better than placebo; ^immediate-release dextroamphetamine worse than placebo; [a]Adderall better than immediate-release dextroamphetamine; [b]dextroamphetamine Spansules better than immediate-release dextroamphetamine; [c]Adderall better than dextroamphetamine Spansules; [d]immediate-release dextroamphetamine better than Adderall; [e]dextroamphetamine Spansules better than Adderall.

Adderall significantly reduced activity below placebo levels until 8 P.M. ($p < .0007$). Immediate-release dextroamphetamine significantly *increased* activity relative to placebo from 8 P.M. to 9 P.M. ($F_{10,208} = 4.85$, $p < .0001$).

Adderall significantly reduced activity relative to immediate-release dextroamphetamine from 9 A.M. to 10 A.M., and relative to dextroamphetamine Spansules from 9 A.M. to 11 A.M. ($p < .0001$). Adderall was comparable with both dextroamphetamine preparations between 11 A.M. and 2 P.M. but was significantly more effective than immediate-release dextroamphetamine between 2 P.M. and 3 P.M. ($p < .0001$). Immediate-release dextroamphetamine was significantly more effective than Adderall between 3 P.M. and 5 P.M. ($p < .0006$). However, the reverse was true from 7 P.M. to 8 P.M. ($p < .0001$).

Dextroamphetamine Spansules were significantly more effective than both immediate-release formulations between 4 P.M. and 7 P.M. ($p < .0001$). Spansules were also more effective than immediate-release dextroamphetamine between noon and 2 P.M. ($p < .0001$).

Sleep Measures

Overall, stimulants significantly decreased presumed sleep duration ($F_{3,19} = 9.92$, $p < .001$). While both dextroamphetamine Spansules and immediate-release dextroamphetamine significantly decreased sleep duration compared with placebo ($p < .001$, and $p = .02$, respectively), sleep duration on Adderall did not differ significantly from placebo ($p = .47$).

Adverse Effects

Parents and nursing staff recorded the magnitude of adverse effects on the 17-item Barkley Side Effect Rating Scale (0 = absent; 9 = serious), although nurses did not rate sleep and nightmares. Nurse ratings ($n = 29$) revealed a significantly increased number of adverse effects ($F_{3,23} =$

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