ORIGINAL ARTICLE

Efficacy of a Mixed Amphetamine Salts Compound in Adults With Attention-Deficit/ Hyperactivity Disorder

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Background: We report on a controlled trial of a mixed amphetamine salts compound (Adderall, dextroamphetamine sulfate, dextro-, levoamphetamine sulfate, dextroamphetamine aspartate, levoamphetamine aspartate, and dextroamphetamine saccharate) in the treatment of adult attention-deficit/hyperactivity disorder (ADHD).

Methods: This was a 7-week, randomized, double-blind, placebo-controlled, crossover study of Adderall in 27 well-characterized adults satisfying full *DSM-IV* criteria for ADHD of childhood onset and persistent symptoms into adulthood. Medication was titrated up to 30 mg twice a day. Outcome measures included the ADHD Rating Scale and the Clinical Global Impression Score. Comorbid psychiatric disorders were assessed to test for potential effects on treatment outcome.

Results: Treatment with Adderall at an average oral dose of 54 mg (administered in 2 daily doses) was effective and well tolerated. Drug-specific improvement in ADHD symptoms was highly significant overall (42% decrease on the ADHD Rating Scale, $P<.001$), and sufficiently robust to be detectable in a parallel groups comparison restricted to the first 3 weeks of the protocol ($P<.001$). The percentage of subjects who improved (reduction in the ADHD rating scale of ≥30%) was significantly higher with Adderall treatment than with a placebo (70% vs 7%; $P=.001$).

Conclusions: Adderall was effective and well tolerated in the short-term treatment of adults with ADHD. More work is needed to evaluate the long-term effects of Adderall, or other amphetamine compounds, in the treatment of adults with ADHD.

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In children with attention-deficit/hyperactivity disorder (ADHD), the literature suggests that the percentage of responders is comparable between the stimulants.[1] However, crossover studies of dextroamphetamine and methylphenidate (6 studies, 274 subjects) reveal differences in response on the individual level. Of responders, 52% responded equally well to both, 25% preferentially to amphetamine, and 23% to methylphenidate.[2-7] However, these differences in response may be because of either efficacy or adverse effects.

In adults with ADHD, controlled studies have reported an average response of 54% of subjects both to methylphenidate (6 studies, 139 subjects) and pemoline (2 studies, 93 subjects).[8] To our knowledge, the only previous controlled trial of amphetamines in adults with ADHD was a recent short-term study of dextroamphetamine in adults with broadly defined ADHD indicating efficacy.[9] In addition, there is a controlled study in normal men[10] as well as several case studies[11,12] and open series[13,14] in adults with ADHD. For example, in a placebo-controlled, single-dose crossover study of dextroamphetamine in normal men (N=31), Rapoport et al[10] reported improved cognitive performance. In an open, 6-week trial of dextroamphetamine in 18 adults with ADHD, dramatic changes were reported in behavior, but not on cognitive measures.[13]

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Despite the well-documented efficacy of stimulant drugs in the treatment of ADHD, their short duration of action commonly requires a 3-times-daily dosing schedule to obtain a daylong clinical effect. In children with ADHD the prevalence of after-school stimulant use has increased.[15] Such after-school dosing has been recommended for ADHD-associated nonacademic adaptive dysfunctions in daily living, communication, and socialization skills.[16] Similar adaptive dysfunctions are salient in adults with ADHD. Thus, a simplified dosing regimen with a longer-acting compound could be particularly important for adults with ADHD.

SUBJECTS AND METHODS

SUBJECTS

Subjects were 30 outpatient adults with ADHD between 19 and 60 years of age ascertained from clinical referrals. To be included, subjects had to satisfy full diagnostic criteria for *DSM-IV* ADHD based on clinical assessment confirmed by structured diagnostic interview. Attention-deficit/hyperactivity disorder diagnoses, including age of onset by 7 years, were determined by self-report as well as school records and report by others as available. We excluded potential subjects if they had any clinically significant chronic medical conditions, abnormal baseline laboratory values, IQ less than 80, delirium, dementia, or amnestic disorders, any other clinically unstable psychiatric conditions (ie, bipolar disorder, psychosis), drug or alcohol abuse or dependence within the 6 months preceding the study, previous adequate trial of Adderall, or current use of psychotropics. We also excluded pregnant or nursing females. This study was approved by the institutional review board and all subjects completed a written informed consent before inclusion in the study.

PROCEDURE

This was a double-blind, placebo-controlled, randomized, crossover trial, comparing Adderall with placebo. There were two 3-week treatment periods separated by 1 week of washout to minimize carryover effects of medication. During washout, subjects received placebo pills to maintain the blind. The order of treatment (Adderall, placebo, or placebo, Adderall) was randomized by the research pharmacy. Weekly supplies of Adderall or placebo were dispensed by the pharmacy in identical-appearing 10-mg capsules. Study physicians prescribed medication under double-blind conditions in twice-a-day dosing (7:30 AM, 2:30 PM). Compliance was monitored by pill counts at each physician visit. Study medication was titrated up to 20 mg/d (10 mg twice daily) by week 1, 40 mg/d (20 mg twice daily) by week 2, and 60 mg/d (30 mg twice daily) by week 3, unless adverse effects emerged. Although drug or placebo status was randomized, dose within each phase was not. Study treatment was always titrated from low to high dose to avoid exposure to high initial doses of active medication and to minimize adverse effects. Other psychoactive medications were not permitted during the protocol.

ASSESSMENT

Before inclusion in the study, patients underwent a comprehensive clinical assessment that included a psychiatric evaluation by a board-certified adult and child psychiatrist (T.S., T.W., J.P., K.G., R.D., and A.P.), a structured diagnostic interview, a medical history, and laboratory assessments (liver function tests, complete blood counts, and electrocardiograms). The structured diagnostic interview used was the Structured Clinical Interview for *DSM-IV*,[28] supplemented for childhood disorders by modules (*DSM-IV* ADHD and conduct disorder) from the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children (Epidemiologic Version).[29] Diagnostic raters estimated a level of ADHD impairment (mild, moderate, or severe) by assessing the degree of dysfunction (social, familial, academic, and occupational) specifically attributable to the ADHD symptoms.

To have been given a full diagnosis of adult ADHD, the subject must have (1) met full *DSM-IV* criteria (at least 6 of 9 symptoms) for inattentive or hyperactive/impulsive subtypes[30] by the age of 7 years as well as currently (within the past month); (2) described a chronic course of ADHD symptoms from childhood to adulthood; and (3) endorsed a moderate or severe level of impairment attributed to the ADHD symptoms. Diagnostic reliability of the structured interviews was established by having 3 experienced, board-certified child and adult psychiatrists diagnose the conditions of 35 subjects from audiotaped interviews made by the assessment staff. The mean κ was 0.91. A κ of 1.0 was obtained for ADHD with a 95% confidence interval of 0.8 to 1.0.

To assess intellectual functioning, we administered subtests of the Wechsler Adult Intelligence Scale, Revised[31] and the Wide Range Achievement Test, Revised.[32] Learning disabilities[33] were defined by the procedure recommended by Reynolds[34] that provides a statistical method for operationalizing the difference between achievement and intelligence scores. Family history was determined by questioning the subject about the presence of psychiatric disorders in first- or second-degree relatives. Socioeconomic status was measured by the Hollingshead Four-Factor Index of

There are sustained-release preparations available for both methylphenidate and dextroamphetamine (spansules). While some reports have indicated an equal response to methylphenidate immediate-release and sustained-release,[4,17,18] others have not.[19-22] Dextroamphetamine spansules may be more consistently effective[4]; however, few studies have examined effectiveness beyond 4 hours.[4,23] While relatively long-acting, pemoline has been relegated to second-line status because of concerns about hepatotoxicity.[24]

An additional longer-acting amphetamine product is the mixed amphetamine salts compound, Adderall. Adderall consists of 25% levoamphetamine and 75% dextroamphetamine in 4 salts. Recent controlled studies in children have reported that Adderall is as effective as methylphenidate immediate-release in the improvement of behavior in classroom and recreational settings and in increased academic performance, and that the time course of the response is longer, as shown in detailed pharmacodynamic studies.[25,26] While there has been no direct comparison between Adderall and dextroamphetamine, there are theoretic reasons for potential differences. Previous reports comparing levoamphetamine with dextroamphetamine have suggested that some children respond preferentially to each isomer.[27]

We now report results of a randomized, placebo-controlled clinical trial of an amphetamine (Adderall) in the treatment of adults with ADHD. We hypothesized that a twice-daily dosing regimen of Adderall at clinically relevant doses will be effective in the treatment of adults with ADHD and provide adequate daylong coverage of their symptoms.

Social Status,[35] with low values indicating high socioeconomic status.

To assess change during treatment, board-eligible or board-certified psychiatrists used the following scales. Overall severity and change in severity of ADHD was assessed with the Clinical Global Impression Scale.[36] The Clinical Global Impression Scale includes global severity (1, not ill, to 7, extremely ill) and global improvement (1, very much improved, to 7, very much worse) scales. The ADHD Rating Scale,[37] shown to be sensitive to drug effects in pediatric[38] and adult[39-42] populations, assesses each of the 18 individual criteria symptoms of ADHD in *DSM-IV* on a severity grid (0, not present; 3, severe; overall minimum score, 0; maximum score, 54). Five raters independently reviewed audiotaped interviews of 5 subjects. An intraclass correlation of 0.99 was obtained for interrater reliability of the ADHD symptom checklist. For depression, we used the 17-item Hamilton Depression Scale (HAM-D) (minimum, 0; maximum, 52)[43] and the Beck Depression Inventory (minimum, 0; maximum, 63).[44] For anxiety, we used the Hamilton Anxiety Scale (HAM-A) (minimum, 0; maximum, 56).[45] The presence of adverse experiences was elicited by open-ended questions at each visit. We administered the HAM-D, HAM-A, and Beck Depression Inventory before and after each arm of the study. All other symptom rating scales were administered weekly. Raters were blind to treatment assignment.

Since ADHD has been associated with cognitive impairments,[46] we included neuropsychological measures to test for potential drug effects on cognition. Based on our review of the literature and our previous neuropsychologic studies with ADHD children and adults,[46] we selected neuropsychological tests that measure sustained attention, response inhibition, set shifting and categorization, selective attention and visual scanning, and organization and recall of visual constructions. The test battery included an auditory version of the Continuous Performance Test,[47,48] the Stroop test,[49] and the Rey-Osterrieth Complex Figure.[50] This neuropsychological battery was administered 3 times, at baseline and after each arm of the study.

SUBJECT CHARACTERISTICS

One hundred three prospective participants applied for entry into the study. Of these, 30 were enrolled. Of the 73 who were not enrolled, 17 did not complete the initial evaluation; 14 were excluded because of current substance or alcohol abuse; 12 did not meet full *DSM-IV* criteria for ADHD; 11 met entry criteria but were unable to commit to the demands of a controlled study; 12 were excluded for medical conditions and/or current use of concomitant medications (4 seizures, 3 sensory motor impairment, 2 hypertension, and 3 other); and 7 were excluded for unstable psychiatric conditions or current use of psychotropics (3 psychosis, 1 bipolar, and 3 depression).

Of the 30 subjects enrolled in the study, 27 (90%) completed it. Three subjects did not complete the first treatment arm: 1 after the first week and 2 after the second week, and were not included in the final analyses. These 3 patients were receiving placebo and never received Adderall. Thus, the final sample consisted of 15 men and 12 women (age: mean±SD, 38±9.3 years). Seventy-eight percent (21/27) met criteria for ADHD combined type in childhood (44% [12/27] currently) and 22% (6/27) met criteria for ADHD predominantly inattentive type in childhood (56% [15/27] currently). No one met criteria for ADHD predominantly hyperactive-impulsive type. Ten (37%) of the 27 subjects had been diagnosed as having ADHD previously and had received other medications (8 other stimulants; 2 desipramine).

STATISTICAL ANALYSIS

The primary outcome measures were the ADHD Rating Scale and the Clinical Global Impression Scale. Improvement was defined either as a 30% reduction in the ADHD Rating Scale or "much" or "very much improved" on the Clinical Global Impression Scale. For statistical tests of change between 2 points in time, we used the McNemar test (for binary data), the paired *t* test (for continuous data), or the Wilcoxon signed rank test (for ordinal data). For analyses that used all of the time points in our data set, we used random effects, cross-sectional time-series models using the method of generalized estimating equations (GEE) as described by Liang and Zeger[51] and Zeger et al[52] These models estimated main effects of drug (Adderall vs placebo), time (week in study), and order (Adderall first vs placebo first), as well as interactions among these effects. Significance was set at the .05 level and all tests were 2-tailed.

RESULTS

As depicted in **Table 1**, 93% (N=25) of ADHD subjects had at least 1 lifetime comorbid psychiatric disorder. The mean±SD number of comorbid diagnoses was 2.9±2.5 per subject. Baseline ratings of depression (HAM-D, 4.3, and Beck Depression Inventory, 6.2) and anxiety (HAM-A, 6.0) were low. Using standard cutoff points for moderate severity on ratings of depression (HAM-D, >16; Beck Depression Inventory, >19) and anxiety (HAM-A, >21), only 11% (N=3) of subjects had baseline scores of depression or anxiety that were moderately severe or worse. Sixty-seven percent of ADHD adults had 1 or more first- or second-degree relatives with ADHD. Despite average to above-average intelligence (mean±SD, 108±11), 37% of the subjects required tutoring in school and 19% had repeated at least 1 grade.

EFFICACY

Averaged across both periods, at week 1 the average daily doses of Adderall and placebo were both 20 mg; by week 2, 38.5 mg and 40 mg; by week 3, 53.7 mg and 59.3 mg, respectively. Examining the first and second periods separately, inspection of the **Figure** shows some evidence of a carryover effect in that the mean value of the ADHD Rating Scale of the medication-first group at week 4 (placebo-washout) did not fully return to the baseline (Figure, B). However, the order effect (medication first vs medication second) was not significant (random effects: $z=0.99$, $P=.32$). Despite the weak order effect, we found a

Table 1. Clinical and Demographic Characteristics of Sample (N = 27)*

Demographics		
Male, No. (%)	15 (56)	
White, No. (%)	26 (96)	
Age, mean (SD), y	38.8 (9.27)	
Socioeconomic status, mean (SD)†	2.0 (0.73)	
	Past	**Current**
Psychiatric disorders, No. (%)		
Major depression with severe impairment	2 (7)	1 (4)
Major depression with at least moderate impairment	12 (44)	3 (11)
Multiple anxiety disorders (≥2)	5 (19)	1 (4)
At least 1 anxiety disorder	14 (52)	7 (26)
Substance dependence	4 (15)	. . .
Alcohol dependence	7 (26)	. . .
Antisocial personality disorder	6 (22)	0 (0)
Conduct disorder	6 (22)	0 (0)
Any comorbid disorder	25 (93)	6 (22)
Past GAF, mean (SD)	53 (5.05)	
Current GAF, mean (SD)	61 (4.58)	
Family history of disorders, No. (%)		
ADHD	18 (67)	
Depression	15 (56)	
Anxiety	10 (37)	
Antisocial personality	3 (11)	
Substance abuse dependence	11 (41)	
Cognitive testing, mean (SD)		
Wechsler Adult Intelligence Scales		
Freedom from distractibility IQ	102 (12.05)	
Full-scale IQ	108 (11.32)	
Achievement scores, mean (SD)		
WRAT subscale percentiles		
Arithmetic	47 (23.85)	
Reading	60 (22.64)	
Academic underachievement, No. (%)‡		
Arithmetic	7 (26)	
Reading	0 (0)	
School failure, No. (%)		
Repeated grade	5 (19)	
Placement in special class	2 (7)	
Tutoring	10 (37)	

*GAF indicates Global Assessment of Functioning; ADHD, attention-deficit/hyperactivity disorder; WRAT, Wide Range Achievement Test; and ellipses, not applicable.

†Socioeconomic status was measured by the Hollingshead Four-Factor Index of Social Status,[35] with low values indicating high socioeconomic status.

‡Learning disabilities[33] were defined by the procedure recommended by Reynolds,[34] which provides a statistical method for operationalizing the difference between achievement and intelligence scores.

significant effect of drug for both the first period (week 0-3: Adderall, 15; placebo, 12; $z=5.5$, $P<.001$) and the second period (week 4-7: Adderall, 12; placebo, 15; $z=5.7$, $P<.001$). In addition the average change scores (ADHD Rating Scale) were similar in each period of the study (35% vs 51% decrease while receiving Adderall and 5% vs 7% increase while receiving placebo; first vs second period, respectively). While none of the subjects worsened while receiving Adderall, 55% (15/27) worsened while receiving placebo.

In addition, we analyzed the results after combining the first and second period. Response to Adderall attained significance by the first week of treatment ($z=3.1$, $P=.002$), with further improvement by week 2 ($z=5.6$, $P<.001$) and week 3 ($z=6.3$, $P<.001$). Overall, there was a very significant drug by time interaction for ADHD symptoms ($z=6.4$, $P<.001$) without significant main effects of drug (Adderall or placebo) or time (baseline and weeks 1, 2, and 3).

To further evaluate the absolute rate of improvement, we analyzed end-of-treatment results (averaged across both periods) using a preestablished definition of improvement of more than a 30% reduction on the ADHD Rating Scale (see the "Subjects and Methods" section). Using this definition, 70.4% (19/27) of patients showed improvement of ADHD symptoms while receiving Adderall compared with only 7.4% (2/27) who were receiving placebo ($\chi^2_1=13.8$, $P<.001$). Similarly, when improvement was defined as much or very much improved on the Clinical Global Improvement Scale, 66.7% (18/27) of patients receiving Adderall were rated as improved compared with only 3.7% (1/27) receiving placebo ($\chi^2_1=14.2$, $P<.001$). In addition, Adderall treatment significantly reduced the Global Severity Scale ratings of ADHD (4.7±0.7 to 3.4±1.0; $z=4.3$, $P<.001$). In contrast, placebo did not (4.6±0.7 to 4.4±0.9; $z=0.8$, $P=.45$).

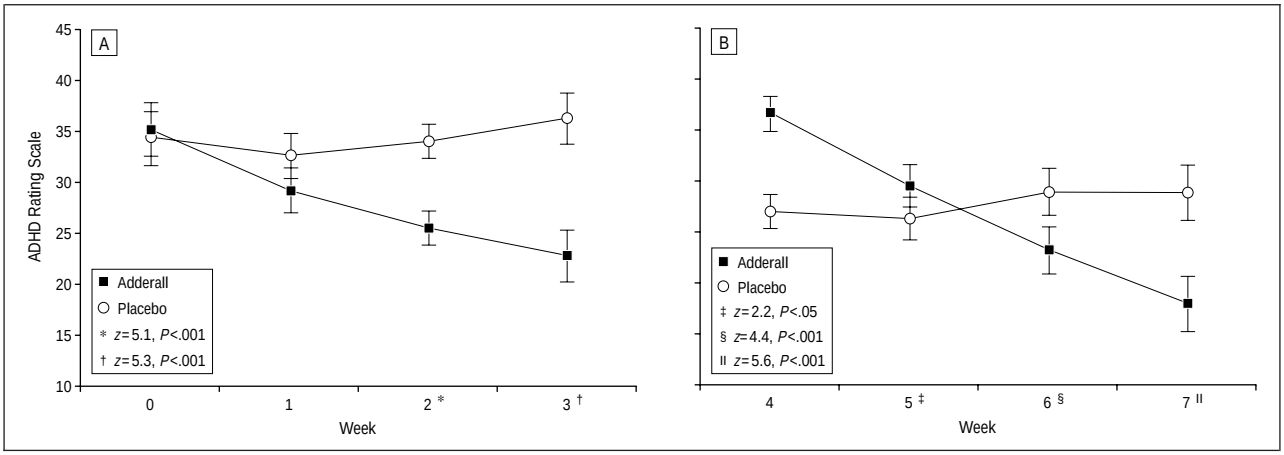
Adderall treatment (averaged across both periods) was associated with clinically and statistically significant improvement of all but 2 of the 18 individual ADHD symptoms, with the notable effects observed for symptoms in both subclusters of hyperactivity/impulsivity and inattention (**Table 2**). However, fewer of the individual hyperactive/impulsivity items would achieve significance when corrected for multiple comparisons. In contrast, the effect of placebo on individual ADHD symptoms was negligible.

Other than race and socioeconomic status, our sample represented a group of adults with diverse clinical characteristics (Table 1). Therefore, we examined each of these characteristics as potential confounders. While we did not have sufficient power to fully examine this issue, a detailed analysis revealed no effects of ADHD subtype (combined vs predominately inattentive), sex, age, history of comorbid disorders, lifetime history of treatment, current comorbid disorders, or positive family history of psychiatric disorder on rates of improvement while receiving Adderall or placebo. As mentioned earlier, baseline ratings of depression (HAM-D, BDI) and anxiety (HAM-A) were very low and were not affected by treatment with Adderall.

At baseline, adults with ADHD in this study performed comparably with non-ADHD adults on some cognitive tests (Rey-Osterrieth Complex Figure, Stroop [Interference condition]). On other tests (Stroop [Word and Color], and Continuous Performance Test) adults with ADHD were found to have mild difficulty at baseline with equal improvement while receiving medication and placebo (**Table 3**).

ADVERSE EFFECTS

Adverse effects were reported on the entire sample, at any time during treatment and tabulated in **Table 4**. Adderall was well tolerated and no serious adverse effects were observed. Of individual adverse effects reported, only Adderall-associated appetite suppression and agitation reached



The controlled study of Adderall in adult attention-deficit/hyperactivity disorder (ADHD). Fifteen participants were randomized to Adderall and 12 to placebo during the first period (A). During the second period (B), the 15 participants who were given Adderall were crossed over to placebo, and the 12 participants who were given placebo were crossed over to Adderall.

Table 2. Individual Symptom Scores on the Attention-Deficit/Hyperactivity Disorder Scale at Baseline and at the End of Treatment of the Placebo and Adderall Conditions

	Baseline, Mean (SD)		End of Treatment, Mean (SD)	
Symptom Cluster*	Placebo	Adderall	Placebo	Adderall
Hyperactivity/Impulsivity				
Has difficulty remaining seated	1.22 (0.8)	1.78 (0.9)	1.56 (0.9)	0.96†‡§ (0.6)
Is fidgety	1.44 (0.8)	1.89 (0.8)	1.63 (0.8)	1.15‡§ (0.8)
Has difficulty playing quietly	1.11 (0.9)	1.48 (0.9)	1.19 (0.8)	0.93‡§ (0.8)
Talks excessively	1.33 (1.0)	1.63 (1.0)	1.41 (1.1)	1.00†‡§‖ (0.8)
Interrupts or intrudes	1.52 (0.8)	1.67 (0.8)	1.41 (0.9)	0.93†‡§‖ (0.9)
Blurts out answers	1.19 (0.9)	1.67 (0.7)	1.56‖¶ (1.0)	0.78†‡§ (0.7)
Has difficulty waiting turn	1.48 (1.0)	2.00 (0.9)	1.70 (1.0)	1.04†‡§ (0.9)
Often "on the go"/acts like driven by a motor	1.48 (1.0)	1.78 (1.0)	1.52 (1.0)	0.96†‡§‖ (0.9)
Hyperactivity/restlessness	1.41 (0.9)	1.63 (1.0)	1.63 (1.0)	0.96†‡§‖ (0.7)
Hyperactivity/impulsivity (overall)	1.35 (0.6)	1.72 (0.5)	1.51 (0.7)	0.97†‡§‖ (0.6)
Inattentiveness				
Has difficulty sustaining attention	2.41 (0.6)	2.37 (0.6)	2.30 (0.6)	1.37†‡§ (0.8)
Has difficulty following instructions	2.00 (0.8)	2.15 (0.7)	1.97 (0.8)	1.45†‡§‖ (0.9)
Is easily distracted	2.33 (0.6)	2.44 (0.6)	2.37 (0.7)	1.52†‡§ (0.8)
Loses things	1.78 (0.8)	2.11 (0.8)	2.00 (0.9)	1.04†‡§ (0.8)
Does not listen	1.93 (0.7)	2.15 (0.7)	1.89 (0.8)	1.04†‡§ (0.8)
Fails to pay close attention to details	1.96 (0.7)	2.26 (0.7)	1.93 (1.0)	1.34†‡§ (0.9)
Has difficulties organizing	2.07 (0.9)	2.30 (0.9)	2.04 (0.08)	1.45†‡§ (0.8)
Avoids or strongly dislikes mental tasks	1.81 (0.7)	2.37 (0.8)	2.15 (0.8)	1.45†‡§ (0.9)
Is often forgetful	1.78 (0.8)	2.15 (0.7)	1.85 (0.7)	1.30†‡§ (0.8)
Inattentiveness (overall)	2.01 (0.5)	2.26 (0.5)	2.05 (0.6)	1.33†‡§ (0.7)

*Rating scale symptom scores range from 0 to 3 (0, "not a problem"; 1, "mild problem"; 2, "moderate problem"; 3, "severe problem").
†Adderall vs placebo treatment by Wilcoxon signed rank test.
‡$P = .04$.
§End of treatment vs baseline by Wilcoxon signed rank test.
‖$P = .05$.
¶For this comparison, the value at end point while receiving placebo was significantly worse than baseline.

our threshold for significance (Table 4). All patients who received active medication completed the study. Six patients receiving Adderall did not reach or were not able to remain on the final target dose of 60 mg because of subjective adverse effects that included anxiety (n=3), fatigue (n=1), increased obsessive symptoms (n=1), and confusion (n=1). However, these patients were able to tolerate a lower dose. One patient did not tolerate 60 mg of placebo because of insomnia. In addition, significant but a clinically small difference was observed with Adderall treatment in diastolic blood pressure (76 vs 71 mm Hg) ($t_{25}=2.6$, $P=.02$). While weight decreased an average of 1.8 kg (4 lb) (167 vs 163 lb [75 vs 73 kg]) ($t_{25}=5.8$, $P<.001$), weight loss was not of clinical significance in any individual patient.

COMMENT

In a double-blind study of amphetamines in adults with ADHD, we found that treatment with the mixed amphetamine salts product Adderall, administered twice daily

Table 3. Neuropsychological Functioning at Baseline and at the End of Treatment of the Placebo and Adderall Conditions*

	Baseline	Placebo	Adderall
Stroop Test			
Word T-Score	44.3 (9.7)	48.3†‡ (9.6)	49.9†§ (8.7)
Color T-Score	41.0 (8.7)	43.6†‖ (9.4)	46.0†§ (8.2)
Color Word T-Score	43.4 (10.4)	49.5†¶ (11.1)	48.6†‖ (11.8)
Interference T-Score	49.7 (6.6)	53.1†‖ (7.6)	50.1 (7.8)
Rey-Osterrieth Complex Figure			
Copy Organization	10.4 (3.4)	10.5 (3.3)	9.6 (3.4)
Copy Accuracy	63.6 (4.3)	63.5 (3.5)	64.0 (2.1)
Delay Organization	7.1 (3.9)	8.6 (3.7)	8.2 (4.1)
Delay Accuracy	41.5 (10.0)	51 (10.4)	50.3 (7.8)
Continuous Performance Test, No.			
Hits	76.7	84.5	85.7†‖
Omissions	20.6	14.4	12.7†‖
Late	2.78	1.04	1.39

*Values are mean (SD) unless otherwise indicated.
†Vs baseline by Wilcoxon signed rank test.
‡$P<.05$.
§$P<.0001$.
‖$P<.01$.
¶$P<.001$.

Table 4. Adverse Events While Receiving Adderall and Placebo

Adverse Event	Drug, No. (%)	Placebo, No. (%)	χ^2*	*P*
Insomnia	10 (37)	4 (14.8)	3.6	.06
Loss of appetite	8 (29.6)	3 (11.1)	5.0	.03
Depression	1 (3.7)	2 (7.4)	1.0	.32
Anxiety	7 (25.9)	4 (14.8)	1.8	.18
Headache	3 (11.1)	2 (7.41)	0.33	.56
Dry mouth	4 (14.8)	3 (11.1)	1.0	.32
Agitation	6 (22.2)	2 (7.4)	4.0	.05
Fatigue	1 (3.7)	1 (3.7)	0.0	>.99
Indigestion	1 (3.7)	2 (7.4)	1.0	.32
Urinary tract infection	1 (3.7)	0 (0.0)	1.0	.32
Gastrointestinal pain	1 (3.7)	0 (0.0)	1.0	.32
Panic attack	1 (3.7)	0 (0.0)	1.0	.32
Nausea	1 (3.7)	0 (0.0)	1.0	.32
Sinus problems	0 (0.0)	1 (3.7)	1.0	.32
Bronchitis	0 (0.0)	1 (3.7)	1.0	.32
Cough	0 (0.0)	1 (3.7)	1.0	.32
Confusion	1 (3.7)	0 (0.0)	1.0	.32
Light-headed	1 (3.7)	0 (0.0)	1.0	.32

*Using McNemar exact test.

at an average oral daily dose of 54 mg, was well tolerated and effective. Although this was a crossover design, reduction in ADHD symptoms was sufficiently robust to be detectable in a parallel group comparison during the first 3 weeks of the protocol ($P<.001$). These results confirm the study hypothesis and suggest that Adderall is a well-tolerated and effective treatment for adults with ADHD.

Although the duration of drug action was not measured directly, our results suggest that twice-daily dosing of Adderall may be comparable with methylphenidate using a thrice-daily dosing.[39] Subjects in our study indicated that twice-daily dosing was sufficient to cover the entire day and there was no subjective sense of medication "wear-off" in between doses.

These results extend to amphetamines other findings documenting a highly similar pattern of drug responsivity between children and adults with ADHD to anti-ADHD medications including methylphenidate,[39] pemoline,[42] desipramine,[40] tomoxetine,[41] and bupropion.[53] The similarities in drug response across the life span provide further support for the informativeness of trials of adults with ADHD in drug development programs for ADHD.

Traditional analyses in clinical trials examine outcome using a cutoff score. We used a 30% cutoff of ADHD symptoms (ADHD Rating Scale) to define improvement. In another report, we have addressed the issue of cutoffs by use of a novel analytic technique, the drug-placebo response curve, that examines the entire range of symptom change scores.[54] In addition, in this study the negligible overall response to placebo was composed of individuals who improved and individuals who worsened. Another pharmacotherapy study of adults with ADHD also revealed worsening while receiving placebo.[54]

Although we evaluated a range of neuropsychological outcomes using a battery of tests that measures executive functions, most subjects performed well on this battery. The relative good function at baseline is consistent with other studies showing adult ADHD to be associated with mild neuropsychological deficits.[46] This created a "ceiling" effect that did not allow the detection of medication-associated cognitive improvements. The development of tests that are more sensitive to neuropsychological dysfunction in ADHD adults may be required to assess fully the effect of pharmacological treatments.

The absence of meaningful associations between Adderall treatment and ratings of anxiety and depression indicate that Adderall-associated ADHD improvement was unlikely to be secondary to improvement in comorbid depression or anxiety in our sample. They also indicate that Adderall treatment was not associated with worsening of anxiety or depression in this sample that had a frequent history of comorbidity with these disorders. While we did not have sufficient statistical power to fully examine the effects of potential confounding factors, the absence of sex and comorbidity effects in the treatment response of adults with ADHD is consistent with prior studies with other medications, and does not support the practice of excluding comorbid cases in clinical trials of adults with ADHD.

Although none of our subjects suffered from preexisting hypertension, patients with poorly controlled hypertension may not be eligible for stimulant treatment until their blood pressure is well controlled. Special monitoring may be required in patients with borderline hypertension receiving Adderall or other stimulant drugs. Until more is known about long-term treatment in adults, periodic assessment of blood pressure may be warranted in patients exposed to stimulants.

The results of this study should be viewed in light of methodological limitations. These include the rela-

tively small subject size, use of a crossover design, and a relatively short exposure to medication. While studies in children suggest a rapid response to stimulants, in clinical practice a more gradual dose escalation is the rule. In our study, the dose was increased weekly; thus we cannot disentangle dose and time effects. It is possible that continued exposure would lead to increased effectiveness of long-term Adderall treatment. While the use of a crossover design provides increased statistical power, the evidence of a minor carryover effect would suggest that in future studies, a longer washout period or a parallel design may be more optimal. Nevertheless, reduction in ADHD symptoms was robust enough to be detectable in a parallel group comparison. Despite their robustness, our results could not address the impact of Adderall on functioning and quality of life. Such information is critical to further inform the risk vs benefit analysis of treatment with Adderall. Longer studies with appropriate instrumentation assessing these domains will be needed to address these important issues.

Despite these limitations, this study has shown that Adderall significantly improved ADHD symptoms and was well tolerated. These promising initial results provide support for further studies of Adderall or other amphetamine compounds in the treatment of adult ADHD using a wide range of doses over an extended period of treatment and with more detailed assessment of functioning and quality of life.

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