

Placebo-Controlled Evaluation of Amphetamine Mixture—Dextroamphetamine Salts and Amphetamine Salts (Adderall): Efficacy Rate and Side Effects

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ABSTRACT. *Objective.* The primary objective of this study was to determine the efficacy rate of Adderall in children newly diagnosed with attention-deficit/hyperactivity disorder (ADHD). A secondary objective was to address the severity of side effects associated with Adderall treatment in children with ADHD using the Barkley Side Effects Questionnaire (BSEQ).

Design. Randomized, double-blind, placebo-controlled crossover trial.

Setting. A large rural tertiary care clinic.

Patients. Participants were prospectively recruited from children 5 to 18 years of age referred for academic and/or attention problems; 154 children who met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for ADHD were enrolled.

Interventions. Two doses of Adderall (0.15 mg/kg/dose and 0.3 mg/kg/dose) were compared with placebo in separate 2-week trials. Participants received each dosage regimen twice daily for 7 consecutive days.

Measurements and Main Results. Efficacy rates were determined by comparing Adderall with placebo during the low-dose crossover sequence and also during the high-dose crossover sequence. The criteria that defined a positive response to Adderall relative to placebo (with each patient serving as their own control) included an indication of response by at least 1 of 2 parent measures of children's behavior or at least 2 of 5 teacher measures of children's behavior. The Adderall efficacy rate was determined based on parent criteria alone, teacher criteria alone, and by a more stringent definition of response that required concurrence between parent and teacher criteria. The Adderall response rate in this study ranged from 59% when requiring concurrence between parent and teacher observers, to 82% when based on parent criteria alone. Overall, 137 of 154 participants (89%) showed a positive response by either the parent or teacher response criteria.

Parents completed a modified version of the BSEQ during each week of the trial. Appetite, stomachaches,

and insomnia were rated as worse by parents while children were receiving either dose of Adderall; headaches were rated as worse when children were receiving the higher dose of Adderall. Parents rated certain side effects, including staring/daydreaming, sadness, euphoria, and anxious/irritable, as worse during placebo regimens.

Conclusions. We found that Adderall is highly efficacious in our population of youth diagnosed with ADHD. In addition, Adderall is well-tolerated with a side effect profile similar to that reported for other psychostimulants. *Pediatrics* 2001;107(1). URL: <http://www.pediatrics.org/cgi/content/full/107/1/e10>; *attention-deficit/hyperactivity disorder, side effects, efficacy rate, Adderall.*

ABBREVIATIONS. ADHD, attention-deficit/hyperactivity disorder; ACTeRS, ADD-H Comprehensive Teachers' Rating Scale; CTRS-28, Conners' Teachers' Rating Scale (28 items); CPRS-48, Conners' Parent Rating Scale (48 items); BSEQ, Barkley Side Effects Questionnaire; CBCL, Child Behavior Checklist; SD, standard deviation.

Attention-deficit/hyperactivity disorder (ADHD) is the most commonly diagnosed neurobehavioral disorder of childhood and is estimated to affect 5% to 11% of school-aged children.¹ Although various specialists may be involved in the care of children with ADHD during the continuum of diagnosis and management, the primary care physician frequently performs the initial evaluation of a child with the disorder. Therefore, pediatricians should be cognizant of the efficacy rates and side effect profiles of all currently available psychostimulant medications.

Psychostimulants have served as the primary mode of treatment of ADHD with reported efficacy rates of ~70%.² For the past 2 decades, methylphenidate (Ritalin, Novartis, East Hanover, NJ) and dextroamphetamine (Dexedrine, SmithKline Beecham, Philadelphia, PA; DextroStat, Shire Richwood Inc, Florence, KY) have been used for the management of ADHD. A product comprised of mixed amphetamine salts (Adderall, Shire Richwood Inc) has been marketed for the treatment of ADHD since 1994. Each Adderall tablet contains equal milligram portions of *d*-amphetamine saccharate, *d,l*-amphetamine aspartate, *d*-amphetamine sulfate, and *d,l*-amphetamine sulfate.³ This combination of salts and isomers results in a 3:1 ratio of dextro to levoamphetamine.⁴ In >4000 patients with ADHD enrolled in an open-

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Preliminary results of this study were presented at the following meetings: American Academy of Neurology; April 6, 1999; Toronto, Canada; Child Neurology Society; October 22–24, 1998; Montreal, Canada; CHADD's Annual International Conference on ADHD; October 15–17, 1999; Washington, DC; and the American Academy of Child and Adolescent Psychiatry; October 21, 1999; Chicago, IL. Abstract of preliminary results was published in *Neurology*. 1999;52(suppl 2):A154

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label trial of Adderall, reported side effects were typical of other psychostimulant medications and included decreased appetite, insomnia, and headaches.⁴ No research has been conducted to address the differences between mixed salts of amphetamine and dextroamphetamine spansules.

The prevalence of ADHD among school-aged children as well as the recently recognized persistence of the disorder into adolescence and adulthood requiring long-term treatment with psychostimulant medications have contributed to the inclusion of Adderall in the "Top 200" list of most frequently prescribed medications in the United States.⁵ Recent comparative trials indicate that Adderall is at least as efficacious as Ritalin.⁶⁻¹⁰ Potential advantages to the use of Adderall in the treatment of ADHD include the following: a longer duration of action than Ritalin⁶; a dose-dependent duration of action⁸; a reduction in the need for in-school dosing of a psychostimulant⁹⁻¹¹; and a smoother course of clinical action.¹² At the conclusion of a comparison trial of Adderall and Ritalin, Pelham and colleagues⁶ recommended Adderall by a ratio of 3:1 for continued medication treatment in children with ADHD. However, review of the literature reveals that no study involving large numbers of children in a naturalistic setting has systematically and prospectively addressed efficacy rates and side effects associated with this mixture of amphetamine salts, compared with placebo in a randomized, double-blind manner.

This prospective study was initiated in 1997 to determine the efficacy rate and side effect profile of Adderall in the treatment of children newly diagnosed with ADHD from a private, rural, outpatient clinic. The double-blind, placebo-controlled, within-subject crossover methodology applied in this trial has proven effective in research settings as well as general clinical practice applications.¹³ In a previous placebo-controlled trial of Ritalin conducted at our institution, we found this study design to be an effective clinical method to identify medication responders and to evaluate stimulant side effects.¹⁴

METHODS

Participants

Participants were recruited prospectively from children 5 to 18 years of age referred to the Marshfield Clinic (Marshfield, WI) for assessment of academic and/or attention problems. All participants were newly diagnosed and stimulant-naive.

Instruments

The following instruments were completed at the end of each week to assess the patients' response to medication. The first 3 instruments were also used to assess patient behaviors at baseline.

- ADD-H Comprehensive Teachers' Rating Scale¹⁵ (ACTeRS)
- Conners' Teachers' Ratings Scale¹⁶ (CTRS-28; 28 items)
- Conners' Parent Rating Scale¹⁶ (CPRS-48; 48 items)
- Narratives—structured comments provided by parents and teachers. (See "Response Evaluation" section.)
- Barkley Side Effects Questionnaire¹⁷ (BSEQ)

Eligibility Criteria

The protocol was approved by the institutional review board of the Marshfield Medical Center. Written informed consent was obtained from parents before enrolling a child in the study. Par-

ticipants 7 years of age and younger were given a modified "Assent Form" to sign, written in age-appropriate language.

At the time of initial appointment, an extensive medical history form was completed by the family. The Child Behavior Checklist (CBCL)¹⁸ served as an initial screening measure for comorbid conditions during this portion of the examination. The results of the CBCL are given in Table 1. The physician and the neuropsychologist each interviewed the family independently, framing their interview questions around the 18 behavioral items from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for ADHD. The physician also completed a physical and neurological examination. The neuropsychologist evaluated the patient for comorbid disorders of mood, anxiety, and conduct. Consultation then occurred between the physician and neuropsychologist regarding their findings. Both physician and neuropsychologist reviewed the results from previsit questionnaires sent to the family (CTRS, CPRS, and ACTeRS) to ensure that the results were consistent with eligibility criteria. (See Table 2 for these baseline test data.)

To be categorized as either ADHD subtype impulsive or combined (impulsive and inattentive), at least 3 of the following 5 criteria had to be met:

1. ACTeRS Attention Score at or below the 25th percentile;
2. ACTeRS Hyperactivity Score at or below the 25th percentile;
3. CTRS-28 Inattention/Passivity Scale 2 or more standard deviations (SDs) above the mean;
4. CTRS-28 Hyperactivity Index 2 or more SDs above the mean;
5. CPRS-48 Hyperactivity Index 2 or more SDs above the mean.

To be categorized as ADHD subtype inattentive, the child had to also meet at least 2 of the following 3 criteria:

1. ACTeRS Attention Score at or below the 25th percentile;
2. CTRS-28 Inattention/Passivity scale >1.5 SDs above the mean;
3. Teacher narrative that suggests problems with careless mistakes, organization skills, maintenance of routines, loss of materials, and failure to finish work.

Children with a history of seizures, mental retardation, or other significant neurologic history were not eligible for the study.

Response Evaluation

At the end of each week of the double-blind, crossover trial, parents were asked to complete the CPRS, the BSEQ, and a structured behavioral narrative. The classroom teacher completed the CTRS, the ACTeRS, and a structured behavioral narrative.

The narratives were structured to elicit behavioral observations in areas thought to be sensitive to medication effects (eg, time on task, following directions, etc). (See Fig 1 for a sample narrative.) Narratives were judged independently by 2 of the clinical investigators who were blinded to the treatment condition. The narratives were scored as positive if the narrative suggested improvement and negative if the narrative did not suggest improvement from prestudy conditions. If the clinical investigators disagreed on the scoring of the narrative, they would confer to reach agreement. A positive narrative response was one criterion for the identification of Adderall responders.

Although not commonly used in research of this type, the narrative forms have not only become a standard part of the

TABLE 1. Child Behavior Checklist

| | <i>n</i> | Mean | SD | Minimum | Median | Maximum |
|-------------------|----------|------|------|---------|--------|---------|
| Withdrawn | 140 | 58.2 | 8.2 | 50.0 | 57.5 | 81.0 |
| Somatic | 140 | 57.2 | 7.8 | 41.0 | 56.0 | .0 |
| Anxious/depressed | 140 | 60.6 | 9.2 | 50.0 | 60.0 | 7.0 |
| Social problem | 140 | 61.4 | 9.9 | 50.0 | 60.0 | 4.0 |
| Thought problem | 140 | 61.4 | 7.4 | 50.0 | 64.0 | 9.0 |
| Attention problem | 140 | 70.5 | 8.1 | 50.0 | 70.0 | 1.2 |
| Delinquent | 140 | 60.5 | 9.2 | 50.0 | 61.0 | 5.0 |
| Aggressive | 140 | 63.4 | 11.1 | 50.0 | 62.0 | 5.0 |
| Total | 132 | 63.8 | 9.5 | 26.0 | 65.0 | 83.0 |
| External | 132 | 60.4 | 11.6 | 32.0 | 62.0 | 88.0 |
| Internal | 132 | 59.8 | 10.5 | 32.0 | 60.0 | 81.0 |
| Total competency | 93 | 37.5 | 6.4 | 17.0 | 37.0 | 56.0 |

TABLE 2. Baseline Test Data

| | <i>n</i> | Mean | SD | Minimum | Median | Maximum |
|--------------------------------------|----------|------|------|---------|--------|---------|
| Parent Conners' Hyperactivity Index | 146 | 75.6 | 12.8 | 42.0 | 76.0 | 100.0 |
| Teacher Conners' Inattention | 151 | 66.4 | 9.7 | 45.0 | 66.0 | 99.0 |
| Teacher Conners' Hyperactivity Index | 151 | 70.5 | 12.0 | 44.0 | 70.0 | 100.0 |
| Teacher ACTeR's Attention | 150 | 10.2 | 10.8 | 1.0 | 7.0 | 65.0 |
| Teacher ACTeR's Hyperactivity | 150 | 19.4 | 20.2 | 1.0 | 13.0 | 73.0 |

clinical evaluation process, but also are included as a descriptor of response for the following reasons:

1. The narratives capture a description of the child's core behaviors and overall functioning both on and off medication in real world terms, providing highly compelling documentation of drug efficacy.
2. Teachers and parents have reported that they "like being able to write something" in addition to responding to questionnaires.
3. Many general practitioners use this type of informal methodology in their practice.

The following criteria were used to classify a child as an Adderall responder:

1. The parent reported a 1 SD improvement in the CPRS-48 Hyperactivity Index or gave a positive narrative comment, and
2. The teacher reported at least 2 of the following 5:
 - 10% improvement in ACTeRS Attention Score,
 - 10% improvement in ACTeRS Hyperactivity Score,
 - 1 SD improvement on the CTRS-28 Inattention/Passivity Scale,
 - 1 SD improvement on the CTRS-28 Hyperactivity Index,
 - a positive narrative comment.

A child was considered an Adderall responder by the strict response criteria if criteria 1 and 2 were met while receiving either a low dose (0.15 mg/kg) or a high dose (0.3 mg/kg) of Adderall twice daily, compared with response during the corresponding placebo regimen. Children meeting criteria 1 were considered responders by parent response criteria, while those meeting criteria 2 were considered responders by teacher response criteria.

Dosing and Preparation of Study Medications

Identically appearing Adderall and placebo capsules were prepared by the research pharmacy at the Marshfield Medical Research Foundation. Each patient dose was calculated on a mg/kg basis rounded up to the nearest 2.5-mg dose. Active dosage forms were compounded by placing a 10-mg Adderall tablet, one half of a tablet (5 mg), or one quarter of a tablet (2.5 mg) in an opaque capsule and packing the capsule with lactose powder. Matching placebos were prepared by filling a capsule corresponding in size to the active dosage form with an appropriate weight of lactose powder to prevent differentiation between drug and placebo regimens. A sufficient quantity of Adderall and placebo capsules were dispensed in containers distinguishable only by the label corresponding to the appropriate week of the study. Patients were instructed to take 1 capsule twice daily (7 AM and 1 PM) from the appropriate container for each 7-day week of the study. Patients were also instructed to swallow the capsules whole and not crush or break the capsule.

Randomization

A computer program written by our biostatistics staff used a random number generator to create the randomization list, blocked by treatment sequence, which was maintained by the

investigational pharmacy. On determining eligibility and obtaining informed consent, participants were randomized to receive a sequence of Adderall/placebo or placebo/Adderall. In each sequence, the participant received the low dose (0.15 mg/kg/dose) of Adderall before receiving the high dose (0.3 mg/kg/dose). The study design is illustrated in Fig 2. Participants received capsules in 4 bottles labeled only by week, with each bottle containing Adderall (or the corresponding placebo dose) in 2 daily doses (maximum dose 40 mg/day) for 7 consecutive days beginning on a Saturday. Because Adderall has a relatively short half-life of 4 to 8 hours,¹² dosing regimens were alternated over 4 successive weeks without a washout period. Through these procedures, both clinical staff and participants were blinded to the treatment sequence and only knew that each participant's trial would include both drug and placebo weeks. Only at the end of the 4-week trial was the blind broken.

Statistical Analyses

Simple estimates of efficacy were calculated based on the available data (number of responders/number of patients with response data available). However, because some parent or teacher ratings were missing for either dosage regimen, not all participants could be evaluated on both low and high Adderall doses. Including all valid data and not excluding participants with missing results is in keeping with standard practice for the analysis of randomized clinical trials and helps to avoid possible biases that might otherwise be introduced if, for example, the participants most likely to complete the trial¹⁹ were those with the best response. To determine an estimated efficacy rate using incomplete data, an Estimation Manifestation algorithm was used to compute maximum likelihood estimates.²⁰ Confidence limits on the maximum likelihood estimates were determined using the bootstrap method.²¹

Efficacy rates by gender and age group were compared using χ^2 tests. The differences in individual side effect rates were evaluated using the Wilcoxon signed-rank tests, without adjustment for multiple comparisons. The Wilcoxon rank-sum test was used to perform crossover analyses²² of differences in the continuous rating scales for Adderall versus placebo, and Hodges-Lehmann²³ estimates of the treatment effect were computed with approximate 95% confidence limits. κ statistics were used as a means of validating the narratives by determining their association with the better established rating scales. Analyses were deemed statistically significant at the 5% level of significance ($P < .05$). Data management and analyses were performed using SAS software (SAS, Cary, NC).²⁴

RESULTS

Demographics

A total of 154 children met diagnostic criteria for entrance into the study. Participants ranged in age between 5 and 16 years; 113 of the participants (73%) were boys and 41 (27%) were girls. Given the clinic's location in a rural, agricultural setting, nearly all of the patients enrolled in the study were white. The majority of the participants were in a regular classroom; 18 (12%) were enrolled in exceptional educational needs programs such as a learning disabled or an emotionally disabled program. Nuclear family history of ADHD, learning disabilities, or depression was reported in 41 participants (27%). The demographic data are presented in Table 3.

The majority of children ($n = 76$; 49%) were diagnosed with the combined type of ADHD; 56 (36%) with the inattentive type; and 22 (14%) with the hyperactive/impulsive type of ADHD. Diagnostic and comorbidity data are presented in Table 4.

Efficacy

Of the 154 children enrolled in this study, 115 had complete data for all dosing regimens throughout

Double Blind Placebo Crossover Study

Child's Name

Date

Week 1

Week 2

Name of person completing this form

Week 3

Week 4

In addition to the questionnaires that were completed regarding this child's behavior we are giving you additional room to make any other observations that you may have during each of the weeks the child is participating in the study.

Play with other children

Patience with games/school work

Following directions

General appearance

Other

Fig 1. Structured narrative questions.

the 4-week duration of the trial. Both parent and teacher response data were available for another 28 patients for at least 1 of the 2-week comparison periods (low or high dose). Therefore, the total number of children with response data available for both observers on at least 1 dose was 143 of the 154 children enrolled.

The simple estimates of Adderall efficacy rates for all participants evaluated during at least 1 (high or low) dosing regimen were as follows: 54% (78/143) based on the response by the strict criteria (parent and teacher concur); 81% (121/149) based on parent response criteria; and 73% (106/146) based on teacher response criteria. A detailed breakdown of patient response is illustrated in Fig 3. Overall, 137 of 154 participants (89%) displayed a positive response to Adderall by either parent or teacher criteria.

The maximum likelihood estimates of efficacy were similar to simple estimates of efficacy based on participants for whom complete data were available. The maximum likelihood estimates (efficacy rates

adjusted for missing data) were 59% based on the strict response criteria; 82% based on parent response criteria; and 77% based on teacher response criteria.

No significant difference in Adderall efficacy rates was found among genders or ADHD diagnostic subtypes. A statistically significant difference in the efficacy rate of Adderall was found among the 3 age groups ($P = .036$). Children 5 to 7 years of age had an efficacy rate based on the strict criteria of 60% versus 71% for children 8 to 9 years of age and 48% for children 10 years of age and older. These results are presented in Table 5.

Utility of the Narratives

Of collateral interest was the utility of the structured narrative in measuring response. κ statistics were used to measure the agreement with respect to response of the parent and teacher narratives with the corresponding continuous rating scales. In all cases, the narratives were significantly associated

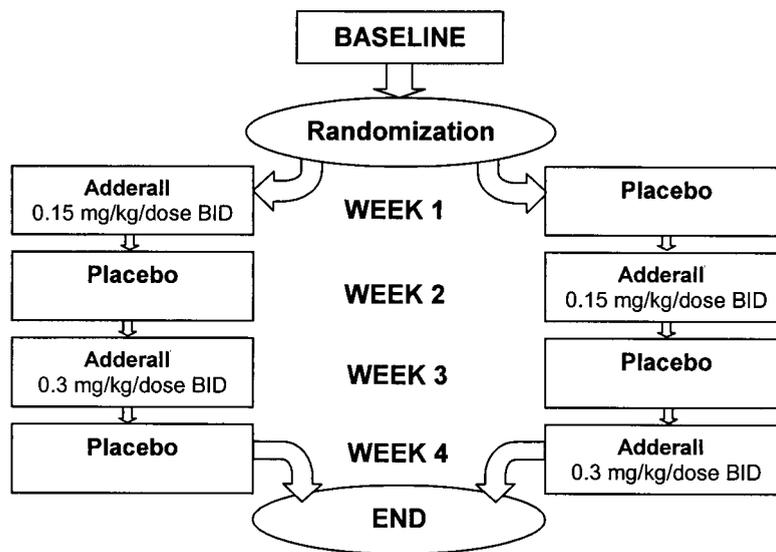


Fig 2. Study design.

TABLE 3. Demographics

| | Number of Patients <i>n</i> (%) |
|--------------------------|------------------------------------|
| Gender | |
| Male | 113 (73) |
| Female | 41 (27) |
| Age range (y) | |
| 5–7 | 58 (38) |
| 8–9 | 45 (29) |
| ≥10 | 51 (33) |
| Grade in school | |
| Kindergarten–3 | 90 (58) |
| 4–8 | 55 (35) |
| 9–12 | 9 (6) |
| Grade placement | |
| Regular | 136 (88) |
| Learning disabled | 11 (7) |
| Special education | 2 (1) |
| Emotional disabled | 4 (3) |
| Learning and emotional | 1 (1) |
| Family history (nuclear) | |
| ADHD | 41 (27) |
| Learning disabilities | 29 (19) |
| Depression | 35 (23) |

TABLE 4. Diagnoses and Comorbidity

| | Number of Patients <i>n</i> (%) |
|--------------------|------------------------------------|
| ADHD subtype | |
| Hyper/impulsive | 22 (14) |
| Inattentive | 56 (36) |
| Combined | 76 (49) |
| Comorbidity | |
| Reading disability | 26 (17) |
| Mood disorder | 7 (5) |
| Anxiety, general | 2 (1) |
| Anxiety, other | 1 (1) |
| Conduct | 2 (1) |
| Oppositional | 37 (24) |
| Chronic tic | 2 (1) |
| Tourette | 3 (2) |
| Other | 18 (12) |

with the continuous measures, with κ ranging from .48 to .66.

The effect of the narratives on the observed response rates was determined by recalculating response without the narratives. This left only a single measure of response for the parent observer (the CPRS Hyperactivity Index), which reduced the parent response such that 54 rather than 78 participants were responders by the strict response criteria. Elimination of the narrative had less impact on the teacher response, however, which involved 4 other measures; the overall response by either parent or teacher would have declined by only 5 responders, reducing the overall response from 137/154 (89%) to 132/154 (86%).

Adderall Effects on Rating Scales

The general effects of Adderall on the continuous rating scales used to measure response were evalu-

ated in both the low- and high-dose periods. All 5 scales showed highly significant ($P < .001$) improvement on both low- and high-dose Adderall. Table 6 presents estimates of the overall treatment effect with 95% confidence limits. The estimates all show improvement on Adderall (median decreases in the Conners' scales and median increases in the ACTeRS scales). The estimated treatment effects on high dose were larger for all scales and were significantly larger for all but the CPRS Hyperactivity Index.

Side Effect Profile

Appetite, stomachaches, and insomnia were rated as worse by parents while children were receiving either the high or low dose of Adderall, compared with placebo. Decreased appetite and insomnia were much more of a problem on the high dose than on the low dose. When children were receiving either dose of Adderall, staring/daydreaming was rated as improved by parents. Sadness/unhappiness as well as euphoria were rated as improved while children were receiving the low dose of Adderall, and while children were receiving the high dose of Adderall, anxiety and irritability were rated as improved. These results are illustrated in Figs 4 and 5.

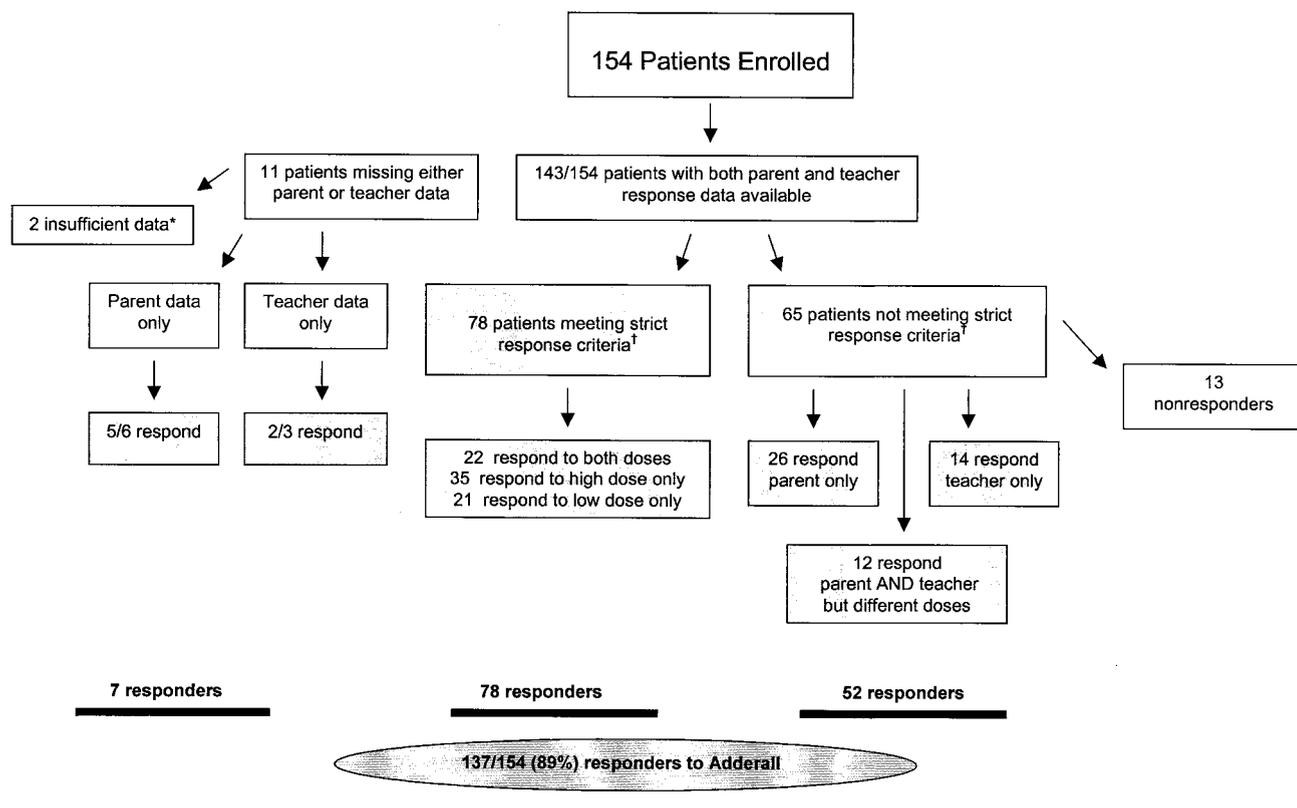


Fig 3. Response to Adderall. *Two participants had insufficient data to evaluate efficacy of dose by parent or teacher. †Strict criteria require that response criteria by both parent and teacher must be met at the same dose.

TABLE 5. Adderall Efficacy by Age Group* According to Strict Response Criteria

| Age (Years) | n | Efficacy Rate (95% Confidence Interval)† | Total |
|-------------|-----|--|-------|
| 5-7 | 55 | 60% (46-74) | 33.00 |
| 8-9 | 43 | 71% (55-86) | 30.53 |
| ≥10 | 45 | 48% (30-65) | 21.60 |
| All | 143 | 59% (50-69) | 84.37 |

* Response rates are significantly different by age group at $P = .036$.

† Maximum likelihood estimates for Adderall efficacy rate with 95% confidence interval.

Occurrence of these side effects was found to be similar by gender and diagnostic group. When side effects were evaluated by age group, insomnia was reported significantly more often in the 10 years of age and older group than in the younger age groups while on the high dose of Adderall ($P = .011$). One participant dropped out of the study because of changes in the preexisting tic disorder.

DISCUSSION

The Adderall response rate in this study ranged from 59% when requiring concurrence between parent and teacher observers, to 82% when based on parent criteria alone. This is consistent with the commonly reported response rate of approximately 70% for any one stimulant medication used in the treatment of ADHD.^{2,25} This efficacy rate is also consistent with the rate observed in our investigation of Ritalin¹⁴ that used the same response criteria and

TABLE 6. Continuous Response Measures in the Adderall Trial Estimates* of Effect Size: Adderall Minus Placebo

| | Median | (95% Confidence Interval) |
|--------------------------------------|--------|---------------------------|
| Low dose | | |
| Parent Conners' Hyperactivity Index | -8.5 | (-11.5, -6.0) |
| Teacher Conners' Inattention Index | -4.0 | (-5.5, -2.0) |
| Teacher Conners' Hyperactivity Index | -5.0 | (-7.5, -2.5) |
| Teacher ACTeR's Attention | 8.0 | (4.5, 12.0) |
| Teacher ACTeR's Hyperactivity | 7.5 | (4.5, 11.0) |
| High dose | | |
| Parent Conners' Hyperactivity Index | -10.0 | (-12.5, -7.0) |
| Teacher Conners' Inattention Index | -8.0 | (-10.0, -6.0) |
| Teacher Conners' Hyperactivity Index | -11.0 | (-13.0, -8.5) |
| Teacher ACTeR's Attention | 20.0 | (15.0, 25.0) |
| Teacher ACTeR's Hyperactivity | 18.5 | (14.0, 22.5) |

* Hodges-Lehmann estimates of the treatment effect with approximate 95% confidence intervals.

study design. The placebo-controlled, within-subject, crossover methodology used in this trial accounts for any placebo response by defining a positive response to Adderall as improvement greater than that observed during the corresponding placebo regimen. The estimates of stimulant efficacy commonly reported in the literature apply to group effects, whereas the placebo-controlled, crossover design used herein informs the clinician about response in the individual patient.

The strict response criteria used in this investiga-

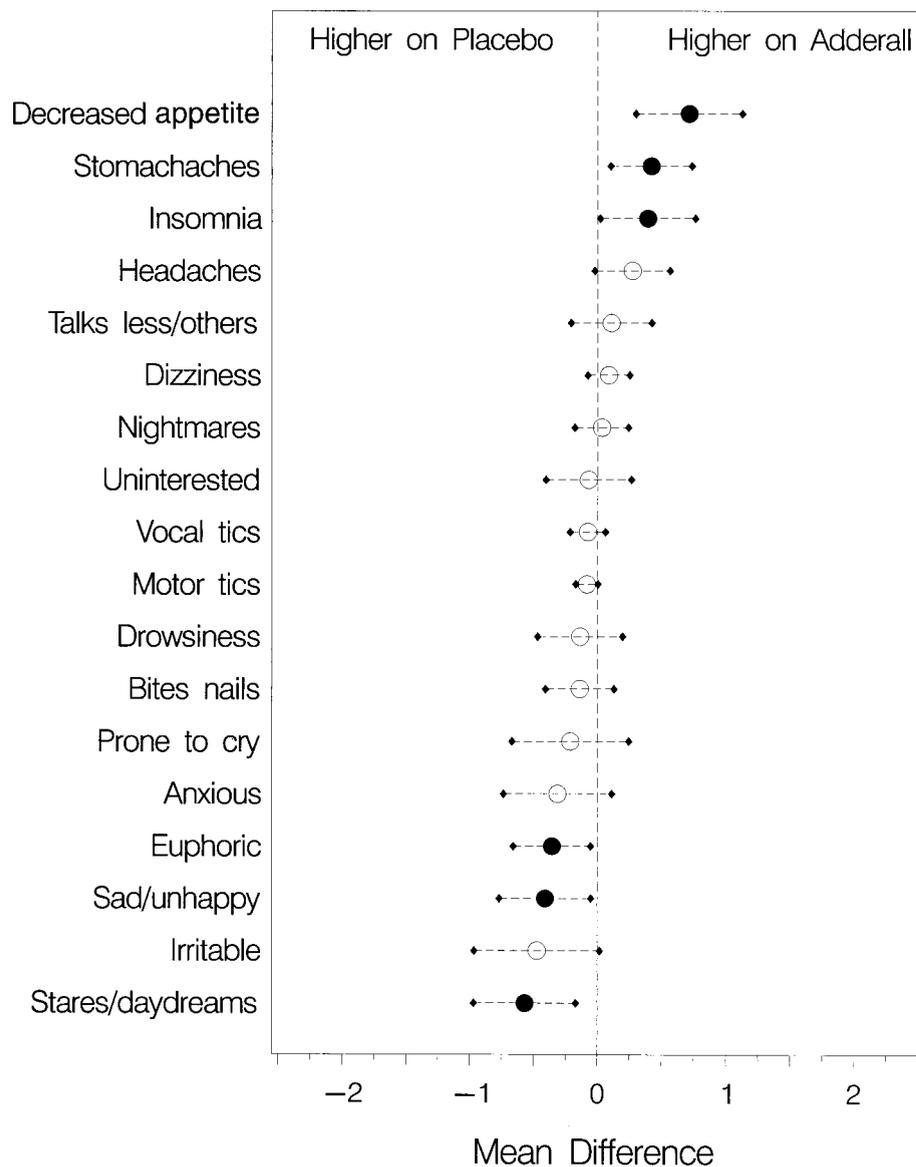


Fig 4. Mean difference in symptoms (Adderall minus placebo) on low dose, with 95% confidence limits. Filled circles (●) show means that are significantly different from zero ($P < .05$).

tion to define response to Adderall required that a child's behavioral improvement be documented in 2 environments—the classroom setting as well as the home. Studies in which higher efficacy rates were reported typically documented behavioral improvement in only one of these settings. In our study, the estimated efficacy rate for Adderall was 82% based on parent criteria alone and 77% based on teacher criteria alone. These higher efficacy rates based on behavioral improvement in only one domain are consistent with other literature reports. Our use of the stringent criteria requiring behavior improvements in both school and home environments was based on the fact that ADHD is a pervasive disorder affecting multiple domains of functioning, and *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria require that symptoms be present in at least 2 of 3 contexts. The recent practice guidelines of the American Academy of Pediatrics strongly suggest that data from 2 environments be included in

making treatment decisions.²⁷ Ideally, efficacy of a stimulant or any other medication or intervention for the treatment of ADHD should be based on response in more than one domain. However, literature reports reveal that depending on the behavioral dimension being rated, the degree of concurrence between parents and teacher may be modest, ranging between .30 and .50.²⁶ Therefore, the efficacy of any stimulant medication based on concurrence of parent and teacher response data is likely to be lower than the commonly reported response rate of 65% to 75% that is based on parent, teacher, and/or research raters.²⁶ In the current trial, Adderall efficacy rates based on parent or teacher response criteria were similar to the commonly reported response rates for other stimulant medications.

No significant differences in Adderall efficacy rates were found among genders or ADHD diagnostic subtypes. However, analysis was limited by the small sample size in each category. Future investiga-

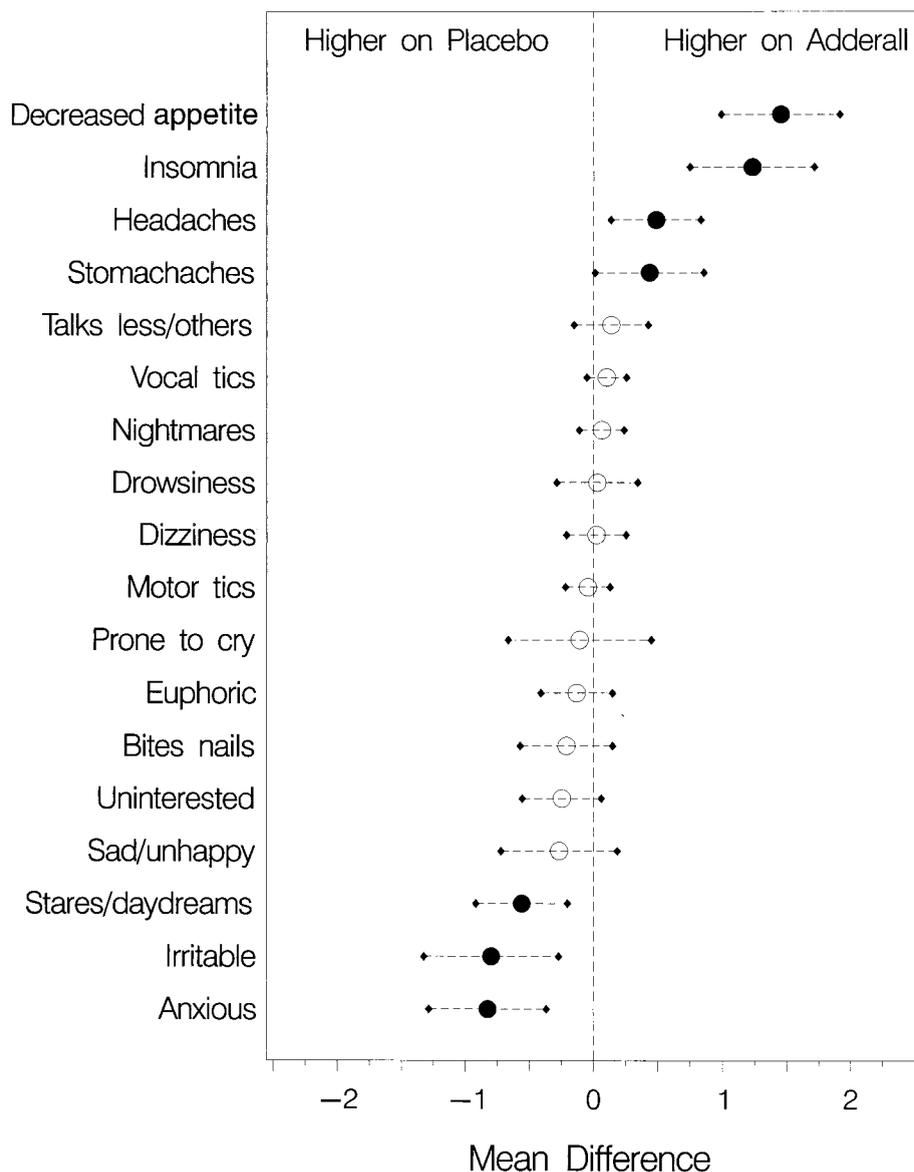


Fig 5. Mean difference in symptoms (Adderall minus placebo) on high dose, with 95% confidence limits. Filled circles (●) show means that are significantly different from zero ($P < .05$).

tions may clarify the existence of any differences in efficacy rates of stimulants by gender or diagnosis. In addition, the limited variation in ethnicity (nearly all participants were white, with a small number of American Indian participants), may limit generalizability of the findings.

Statistically significant differences in Adderall efficacy were found among age groups. In the group of children 8 to 9 years of age, 71% responded to Adderall, whereas children 5 to 7 years of age had an efficacy rate of 60%, and 48% of children 10 of age and older responded. Although these findings are statistically significant, the clinical significance of this differential efficacy rate by age is difficult to interpret without replication of these findings.

A possible limitation of the crossover design used in this study was the potential for carryover or halo effects to attenuate the observed treatment response. Given the short half-life of Adderall, such carryover would not be expected to result from the drug itself

but might result from observer bias. For example, if a child took Adderall in week 1 and responded well, an observer might react so positively that favorable ratings would persist into week 2, reducing the observed response to Adderall. It is considered that these effects would be minimized, however, by the fact that evaluations were obtained at the end of the week. Statistical tests of the rating scales showed no evidence of carryover, although such tests have limited statistical power.²⁸

The side effect profile of Adderall seems to be similar to that of other psychostimulants.^{14,17,29} Appetite suppression, stomachache, and sleep disturbances occurred during both Adderall dosage regimens. Headaches were reported more frequently when children were receiving the higher dose of Adderall, indicating that this side effect may be dose-dependent.

Three of the behaviors considered to be side effects according to the modified BSEQ actually improved

patient population on Adderall and follow-up experience increase.

The adverse effects of stimulant medications tend to be relatively mild and Adderall does not differ in this respect. The adverse effects associated with Adderall in this study were similar to those reported for other stimulant medications.^{14,17,29} The transition from medication to placebo week was not associated with any negative side effects. The adverse effects of stimulant medications are well known to physicians and management of these side effects is not complicated—a dose reduction, dose division, or a change in the time of dosage administration is often sufficient to alleviate any problems. In some cases, a switch to a different stimulant medication may be required because of the intraindividual and interindividual variation in terms of the frequency and severity of stimulant side effects. During comparison trials of Adderall and methylphenidate, Pelham and colleagues^{6,7} noted that side effects of both stimulants dissipated with continued treatment. Use of a stimulant side effect rating scale such as the BSEQ (Fig 6) before initiation of stimulant therapy can provide the physician with a baseline against which parental reports of stimulant side effects can be measured.

In addition to efficacy and potential side effects, 2 other factors should be considered when prescribing a stimulant medication: compliance and security. First, patients struggle with compliance to the 2 times or 3 times daily dosing schedules typically associated with methylphenidate. Compliance is especially difficult for many adolescent patients. Second, schools typically cannot provide a secure environment for storage of a schedule II medication. This factor is of great concern to parents and school officials given the potential for abuse of stimulant medications by youth not diagnosed with ADHD.³⁰ The longer duration of Adderall may make it the preferred stimulant for many youth diagnosed with ADHD.

Further investigations are necessary to address optimal dosing regimens, compliance, and long-term efficacy of Adderall. The recently released National Institutes of Health Consensus Development Conference Statement on ADHD³¹ emphasized the paucity of long-term prospective controlled studies that address the safety and efficacy of stimulant medications in children and adolescents. We believe that the methodology described herein can be adapted to determine long-term maintenance of response to psychostimulants for the treatment of ADHD. We have initiated an extensive, longitudinal follow-up investigation designed to determine the maintenance of behavioral response to Adderall among our patients. A new or rechallenge double-blind, placebo-controlled, crossover trial (after a week of washout), will be initiated with participants 18 to 24 months after the initial efficacy trial for this purpose.

Effective treatment of ADHD requires compliance as well as response to the medication. We believe that adaptation of our methodology to include measures of medication compliance will demonstrate

that improved long-term outcomes are caused by the stimulant medication itself.

CONCLUSION

This study demonstrates that Adderall is highly efficacious in youth newly diagnosed with ADHD. In this trial, >80% of our patients exhibited a positive response to Adderall. The number of side effects that increased while participants were receiving Adderall was small and was limited to stomachache, appetite suppression, sleep disturbances, and headaches. Behaviors including anxiety, irritability, and daydreaming improved while patients were receiving Adderall. For all of these reasons, Adderall is a good option for primary care physicians when considering medical management alternatives for the treatment of youth with ADHD.

Additionally, this study replicated our previous finding that a randomized, placebo-controlled, double-blind trial is a viable methodology for the study of treatment options in children with ADHD in a naturalistic setting. Future research is necessary to better delineate long-term efficacy rates of Adderall and optimal dosing regimens.

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Placebo-Controlled Evaluation of Amphetamine Mixture—Dextroamphetamine Salts and Amphetamine Salts (Adderall): Efficacy Rate and Side Effects

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