Efficacy and Safety of Mixed Amphetamine Salts Extended Release (Adderall XR) in the Management of Attention-Deficit/Hyperactivity Disorder in Adolescent Patients: A 4-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study

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ABSTRACT

Background: The ability to recognize and diagnose attention-deficit/hyperactivity disorder (ADHD) has increased in recent years. The persistence of ADHD symptoms puts adolescents with ADHD at risk for long-term adverse psychosocial outcomes.

Objective: The primary goal of this study was to assess the efficacy and safety of mixed amphetamine salts extended release (MAS XR) in the management of adolescents with ADHD.

Methods: This was a Tweek, randomized, multicenter, double-blind, placebo-controlled, parallel-group, forced-dose-titration study. Adolescents aged 13 to 17 years with ADHD were randomized to 1 of 4 active treatments (MAS XR 10, 20, 30, or 40 mg/d) or to placebo. All doses were given in the morning. This study used a forced-dose-titration design in which patients randomized to the 10-mg/d group received 1 dose of 10 mg/d for 4 weeks. Patients randomized to the 20-mg/d group received 1 dose of 10 mg/d for the first week and 1 dose of 20 mg/d for the remaining weeks; patients randomized to the 30-mg/d group received 1 dose of 10 mg/d for the first week, 1 dose of 20 mg/d for the second week, and 1 dose of 30 mg/d for the remaining 2 weeks; and patients randomized to the 40-mg/d group received 1 dose of 10 mg/d for the first week, 1 dose of 20 mg/d for the second week, 1 dose of 30 mg/d for the third week, and 1 dose of 40 mg/d for the fourth week. The primary efficacy measure was change from baseline to end point in the ADHD Rating Scale-IV (ADHD-RS-IV) score. The secondary efficacy measure was the score on the Clinical Global Impressions-Improvement (CGI-I) scale for ADHD. ADHD-RS-IV total scores were analyzed post hoc in patients with low baseline ADHD-RS-IV severity (ie, patients with baseline ADHD-RS-IV total scores less than the median) and high baseline ADHD-RS-IV severity (ie, patients with baseline ADHD-RS-IV total scores greater than the median). Safety was assessed by recording adverse events, vital signs, and body weight at all study visits and 30 days after drug discontinuation.

Results: Of the 287 randomized adolescents, 258 completed the study. The intent-to-treat (ITT) population included 278 patients. The majority of patients were male (65.5%) and white (73.7%). The mean weight (57.8 kg [127.1 lb]) at baseline and the mean height (163.8 cm [64.5 in]) at screening were comparable across all MAS XR treatment groups. Patients in the placebo group had a mean weight of 59.8 kg (131.6 lb) and a mean height of 166.1 cm (65.4 in). Most (56.5%) of the patients had ADHD combined inattentive/hyperactive-impulsive subtype. Two hundred nineteen (78.8%) patients were treatment naive, and 59 (21.2%) had received treatment for ADHD within 30 days before screening. ITT analysis of the

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ADHD-RS-IV revealed statistically significant ($P < 0.001$) improvement in mean ADHD-RS-IV total scores in all 4 MAS XR treatment groups, compared with placebo, at all weeks throughout the 4-week study; the mean change from baseline to end point was -17.8 in the MAS XR 10- to 40-mg/d groups and -9.4 in the placebo group. Significant treatment effects were observed in both the ADHD-RS-IV inattentive ($P < 0.001$) and hyperactive-impulsive ($P < 0.001$) subscales from baseline. In patients with low baseline ADHD-RS-IV severity, statistically significantly ($P \leq 0.01$) greater improvements were observed in the MAS XR 20-, 30-, and 40-mg/d groups than in the placebo group; in patients with high baseline ADHD-RS-IV severity, statistically significantly ($P \leq 0.02$) greater improvements were observed in all active treatment groups compared with placebo. On the CGI-I scale at end point, a higher percentage of adolescents in all MAS XR treatment groups were considered improved (MAS XR 10 mg/d, 51.9% [$P < 0.01$]; 20 mg/d, 66.0% [$P < 0.001$]; 30 mg/d, 70.7% [$P < 0.001$]; 40 mg/d, 63.9% [$P < 0.001$]) compared with adolescents receiving placebo (26.9%). The most common adverse events in patients receiving MAS XR versus placebo were anorexia/decreased appetite (35.6% vs 1.9%), headache (16.3% vs 22.2%), insomnia (12.0% vs 3.7%), abdominal pain (10.7% vs 1.9%), and weightloss (9.4% vs 0%). Most adverse events were mild or moderate in intensity (97.5%); no serious adverse events were reported.

Conclusions: The adolescents with ADHD treated with 10- to 40-mg/d MAS XR up to 4 weeks had significant improvements in ADHD symptoms compared with those who received placebo. Results of this study suggest that once-daily dosing with MAS XR up to 40 mg was effective and well tolerated for the management of ADHD in these adolescents. (Clin Ther. 2006;28:266-279) Copyright © 2006 Excerpta Medica, Inc.

Key words: attention-deficit/hyperactivity disorder, ADHD, stimulant, amphetamine, mixed amphetamine salts extended release, Adderall XR, adolescents.

INTRODUCTION

The ability to recognize and diagnose attention-deficit/hyperactivity disorder (ADHD) has increased in recent years as a result of the application of diagnostic criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR),[1] the use of rating scales, an expansion of mental health services, and increased public awareness.[2] The estimated prevalence of ADHD is 2% to 18%,[3] and up to 65% of children with a diagnosis of ADHD continue to exhibit symptoms of the disorder into adolescence and adulthood.[4]

The persistence of ADHD symptoms puts adolescents with ADHD at risk for long-term adverse psychosocial outcomes. Adolescents with ADHD can experience substantial problems with academic, social, and behavioral functioning.[5] ADHD in adolescents has been associated with learning problems, academic failure, low self-esteem, impairments in relationships, deficits in social skills, nicotine use, alcohol and substance abuse, and an increased incidence of driving violations and motor vehicle accidents.[5-10] In addition, adolescents with ADHD are at risk for comorbid psychiatric conditions.[4,5,11-17]

ADHD treatment options include pharmacologic and psychosocial therapy, with stimulant therapy being the most widely prescribed and effective treatment for ADHD.[2,18-23] The results of multiple, randomized, controlled trials document the effectiveness of stimulant medications for the management of ADHD across age groups,[19,23-25] but most of the current ADHD research focuses on children 6 to 12 years of age.[26] Therefore, the scientific literature that specifically examines the efficacy and safety of stimulants in the treatment of adolescents with ADHD is very limited.[13,27]

Mixed amphetamine salts extended release (MAS XR)* is a once-daily, single-entity amphetamine approved by the US Food and Drug Administration for the management of ADHD in children aged 6 to 12 years and in adults. The primary objective of the current study was to assess the efficacy and safety of MAS XR in the management of adolescents with ADHD.

PATIENTS AND METHODS

The efficacy and safety of MAS XR in the management of adolescents with ADHD were examined in this 4-week, randomized, multicenter, double-blind, placebo-controlled, parallel-group, forced-dose-titration study.

Patients

Adolescents aged 13 to 17 years, weighing ≤75 kg (≤165 lb), who satisfied DSM-IV-TR[1] criteria for pri-

*Trademark: Adderall XR® (Shire Pharmaceuticals Inc., Wayne, Pennsylvania).

mary diagnosis of ADHD combined subtype (predominantly inattentive subtype or hyperactive-impulsive subtype), were eligible for the study. Key inclusion criteria were an intelligence quotient score ≥80, normal blood pressure (girls—systolic blood pressure, 128-132 mm Hg; diastolic blood pressure, 84-86 mm Hg; boys—systolic blood pressure, 130-140 mm Hg; diastolic blood pressure, 84-89 mm Hg),[28] electrocardiographic (ECG) findings within the normal range, and a willingness and ability to comply with protocol requirements in conjunction with a parent or caregiver. Adolescents who were known to be nonresponsive to stimulants (defined as no clinical improvement after trials of 2 stimulant medications, taken for at least 3 weeks each) or naive to stimulant treatment were eligible for enrollment.

Exclusion criteria included comorbid illness that could interfere with study participation or impact the efficacy and tolerability of MAS XR; a history of nonresponse to stimulant medication; a documented allergy or intolerance to MAS, MAS XR, or amphetamines; and medication use (not including ADHD medication) that could affect blood pressure or heart rate. Other exclusion criteria included a current comorbid psychiatric diagnosis except oppositional defiant disorder, hypertension, history of seizure disorder within the last 2 years, tic disorder, Tourette's syndrome, abnormal thyroid function, cardiac disorder, and significant laboratory abnormalities. In addition, patients with a history of drug abuse or who were current abusers of drugs or other substances or who had a parent or guardian who abused drugs were excluded.

All activities were conducted in accordance with the Declaration of Helsinki. The appropriate institutional review boards at each research site approved the study protocol, all amendments, and informed-consent forms. Before undergoing any activities pertaining to the study, written informed consent was obtained from each patient's parent/guardian, along with documentation of assent by the patient.

Study Design

The study consisted of a washout phase in which patients were required to discontinue all current ADHD medications for 1 week up to 4 weeks, depending on the medication the patient was taking. The washout period was followed by the double-blind treatment phase, during which patients were randomized in a 1:1:1:1:1 ratio to receive MAS XR 10, 20, 30, or 40 mg/d or placebo. All doses were given in the morning. This study used a forced-dose-titration design in which patients randomized to the 10-mg/d group received 1 dose of 10 mg/d for 4 weeks. Patients randomized to the 20-mg/d group received 1 dose of 10 mg/d for the first week and 1 dose of 20 mg/d for the remaining weeks; patients randomized to the 30-mg/d group received 1 dose of 10 mg/d for the first week, 1 dose of 20 mg/d for the second week, and 1 dose of 30 mg/d for the remaining 2 weeks; and patients randomized to the 40-mg/d group received 1 dose of 10 mg/d for the first week, 1 dose of 20 mg/d for the second week, 1 dose of 30 mg/d for the third week, and 1 dose of 40 mg/d for the fourth week. **Figure 1** illustrates the dosing schedule.

At screening and end point, patients underwent a physical examination, a brief neurologic examination, and a 12-lead ECG. Clinical laboratory tests, including hematology, blood chemistry, urinalysis, and thyroid function, were performed and height was recorded at screening and end point. A urine drug screen was performed at screening and baseline. Vital signs, including systolic and diastolic blood pressures, pulse, and sitting respiratory rate, were checked and body weight was measured at all study visits. Adverse events (AEs) were recorded at each visit.

Efficacy Measurements

The primary efficacy measure was the ADHD Rating Scale-IV (ADHD-RS-IV),[29] which consists of 18 items designed to reflect the presence of ADHD-related symptoms based on DSM-IV-TR criteria. ADHD-RS-IV total scores range from 0 to 54, with higher scores indicating more severe symptoms. The secondary efficacy measure was the Clinical Global Impressions (CGI) scale.[30] At screening and baseline, investigators administered a CGI-Severity (CGI-S) assessment to establish the severity of baseline ADHD symptoms. The CGI-S scale assesses the severity of the patient's condition on an 8-point rating scale ranging from 0 (not assessed) to 7 (among the most extremely ill). At each weekly study visit, improvement relative to baseline ADHD symptoms was assessed by the investigator using the CGI-Improvement (CGI-I) scale. The CGI-I scale is an 8-point scale ranging from 0 (not assessed) to 7 (very much worse), with 4 indicating no change.

ADHD-RS-IV total scores were analyzed post hoc according to intended dose separately for patients

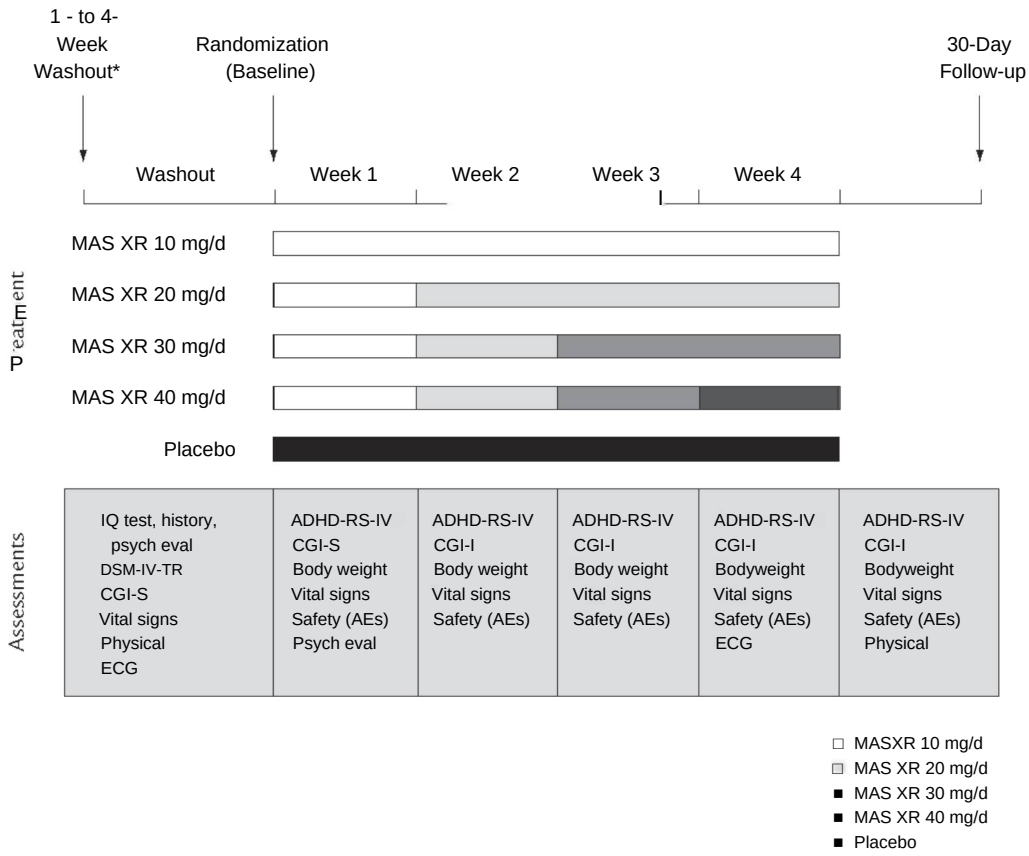

Figure 1. Dosing schedule. MAS XR = mixed amphetamine salts extended release; IQ = intelligence quotient; psych eval = psychiatric evaluation; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; CGI-S = Clinical Global Impressions-Severity; ECG = electrocardiogram; ADHD-RS-IV = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV; AEs = adverse events; CGI-I = Clinical Global Impressions-Improvement. *Length ofwashout period varied depending on previous treatment. Patients currently taking medication may have required a longer washout period (maximum, 4 weeks).

with low baseline severity (defined as patients with baseline ADHD-RS-IV total scores less than the median) and high baseline severity (defined as patients with baseline ADHD-RS-IV total scores greater than the median).

Safety Measurements

Safety was assessed by recording AEs, vital signs, and body weight at each study visit and 30 days after drug discontinuation. AEs were recorded using Coding Symbols for Thesaurus of Adverse Reaction Terms[31] terminology and were categorized as mild, moderate, or severe. ECGs were obtained at screening and end point.

Statistical Analyses

To detect an effect size of 0.78 on the ADHD-RS-IV scale between one MAS XR group and the placebo group at >95% power and an a level of 0.05 (2-tailed) using a 2-sample t test, it was necessary to randomize ~45 patients to each of the 5 treatment groups. The primary efficacy analysis was conducted on the change from baseline of the ADHD-RS-IV scores at the end point for the intent-to-treat (ITT) population using a 2-way analysis of covariance (ANCOVA) model. Each dose of study drug was compared with placebo using the ANCOVA model at the 0.05 level by including treatment (MAS XR 10, 20, 30, and 40 mg/d, and placebo), site, and the baseline score (covariate). The

least squares mean difference, the average of observations associated with MAS XR versus placebo, was calculated. To control the type I error rate at the 0.05 level and adjust for multiplicity, the significant treatment effect of each dose of MAS XR versus placebo was based on a closed testing procedure starting from the 40-mg/d dose. The analysis was conducted using SAS statistical software version 2.0 or higher (SAS Institute, Inc., Cary, North Carolina); type III estimation was reported. The ADHD-RS-IV total score from baseline through the final double-blind study visit was analyzed using the same model used for the primary efficacy analysis, allowing for an examination of the effects of dose titration for patients in the 10- and 40-mg/d treatment groups.

The secondary efficacy analyses were also conducted using the ITT population. The CGI-I scale was analyzed using a Cochran-Mantel-Haenszel test, adjusting for study site to examine the difference in the proportion of patients improved at treatment end point between MAS XR doses combined versus placebo. If the treatment effect was statistically significant ($P < 0.05$), each dose of MAS XR was compared with placebo at the 0.05 level using the same test. The significant treatment effect of each dose of MAS XR versus placebo was based on a closed testing procedure starting with the 40-mg/d dose. The patient's score on the CGI-I scale was analyzed as a dichotomous variable: improved (includes "very much improved" and "much improved") or not improved (includes all other assessments). Using the same analysis, the CGI-I score at end point was analyzed according to intended dose and final dose separately for the ITT patients with low and high ADHD-RS-IV scores at baseline.

The combined dosage groups were evaluated in the secondary analysis to first determine an overall effect on the CGI-I. If significance was determined in the overall analysis, then each dose group was analyzed for significance separately.

RESULTS

Study Population

The disposition of the 287 patients enrolled in the study is shown in **Figure 2;** 258 patients completed the study. Demographics and baseline characteristics for the patients in the ITT population are listed in **Table I.** The majority of patients were male (65.5%) and white (73.7%). The mean weight (57.8 kg [127.1 lb]) at baseline and the mean height (163.8 cm [64.5 in]) at screening were comparable across all MAS XR treatment groups. Patients in the placebo group were heavier, with a mean weight of 59.8 kg (131.6 lb), and taller, with a mean height of 166.1 cm (65.4 in).

Most (56.5%) of the patients were diagnosed with ADHD combined inattentive/hyperactive-impulsive subtype, and the disorder subtypes were distributed proportionally across all treatment groups. Of the 278 patients in the ITT population, 219 (78.8%) were treatment naive, and 59 (21.2%) had received treatment for ADHD within 30 days before screening. Approximately 30 patients weighing >75 kg (>165 lb) were randomized in a secondary cohort not evaluated here. The sample size in this cohort was not based on the power analysis; rather, it was based on an estimate of -10% to 15% of the adolescent study patients falling into this weight category and was intended to provide preliminary descriptive safety, efficacy, and dosing information for these patients.

Efficacy

ADHD Rating Scale

Patients in all groups had improvement in ADHD-RS-IV total scores from baseline to end point, but statistically significant ($P < 0.001$) improvements in the ADHD-RS-IV total score compared with the placebo group were found in all 4 MAS XR treatment groups (10, 20, 30, and 40 mg/d) beginning the first week of treatment. These statistically significant improvements in the MAS XR treatment groups were sustained throughout the 4-week treatment period. The mean ADHD-RS-IV total scores for the active treatment groups combined (MAS XR 10-40 mg/d) were significantly improved compared with placebo ($P < 0.001$). The mean change from baseline was -17.8 for all patients receiving MAS XR 10 to 40 mg/d and -9.4 for patients in the placebo group. The mean ADHD-RS-IV total scores were significantly ($P \leq 0.005$) improved for each active treatment group compared with placebo **(Figure 3).** The end point data for the subscales were also statistically significant (inattentive: MAS XR, -10.2; placebo, -6.1 [$P < 0.001$]; hyperactive-impulsive: MAS XR, -7.6; placebo, -3.2 [$P < 0.001$]).

When ADHD-RS-IV total scores were analyzed by intended dose separately for patients with low baseline severity and high baseline severity, the mean decrease was greater in patients with high baseline severity than in patients with low baseline severity for each MAS XR final dose **(Table II).** Pairwise compari-

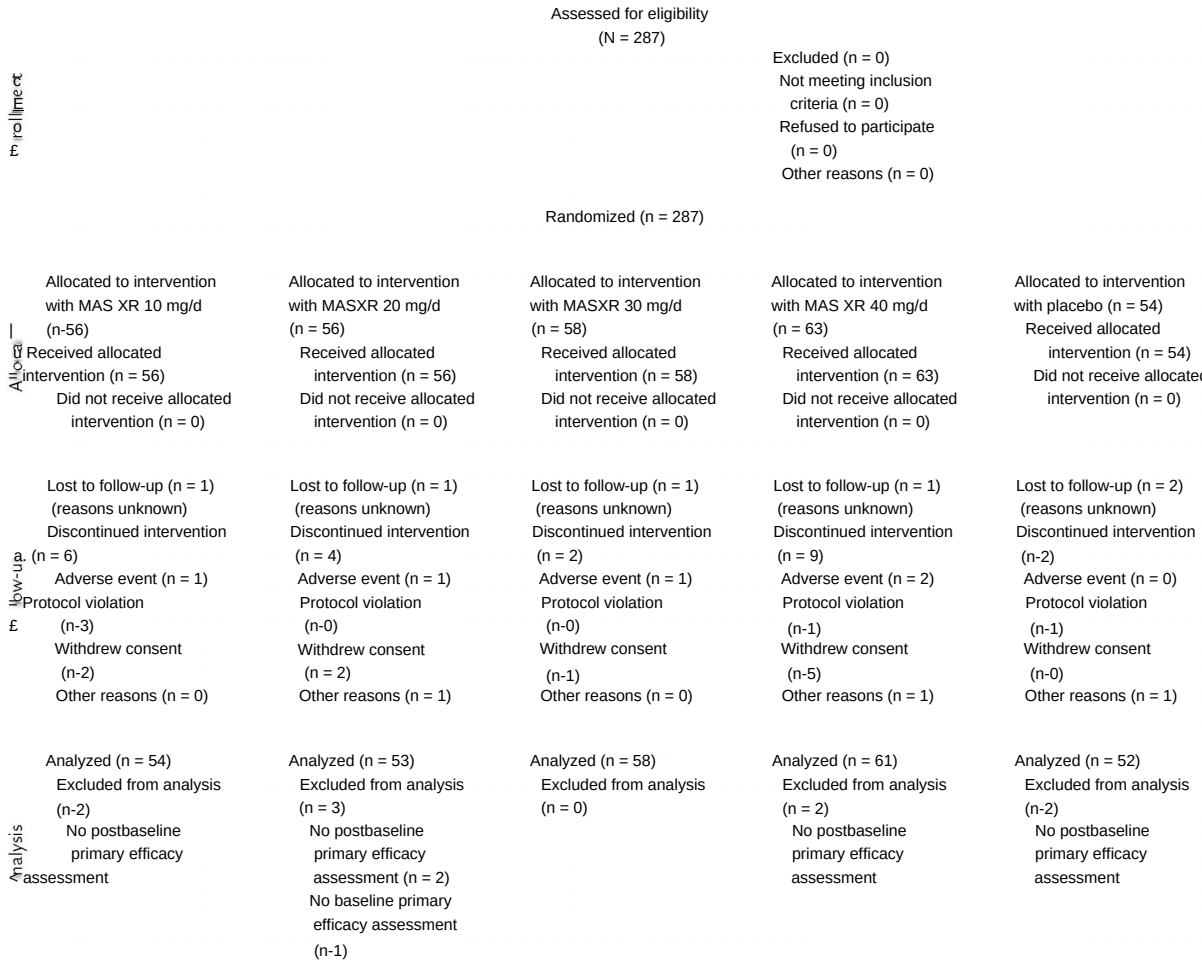

Figure 2. Patient disposition. MAS XR = mixed amphetamine salts extended release.

sons for the low baseline severity group revealed statistically significantly ($P \leq 0.01$) greater improvements in the MAS XR 20-, 30-, and 40-mg/d groups than in the placebo group, indicating that the 10-mg/d dose of MAS XR was the least effective treatment for patients with low baseline severity. Pairwise comparisons for the high baseline severity group revealed statistically significantly ($P \leq 0.02$) greater improvements in all active treatment groups compared with placebo.

Clinical Global Impressions Scale

At end point, more adolescents receiving MAS XR were considered improved than were adolescents receiving placebo **(Figure 4).** On the **CGI-I** scale at end point, a higher percentage of adolescents in all MAS XR treatment groups were considered improved (MAS XR 10 mg/d, 51.9% [$P < 0.01$]; 20 mg/d, 66.0% [$P < 0.001$]; 30 mg/d, 70.7% [$P < 0.001$]; 40 mg/d, 63.9% [$P < 0.001$]) compared with adolescents receiving placebo (26.9%).

Among patients with low baseline severity, 63.7% who were randomized to any dose of MAS XR were considered improved at end point compared with 29.2% of the patients receiving placebo. The treatment difference for patients with low baseline severity in the combined active treatment groups compared with the placebo group was statistically significant ($P < 0.005$); however, the proportion of patients considered improved at end point at only the 40-mg dose level was statistically significant compared with patients treated

Table I. Demographics and baseline characteristics of adolescent patients with attention-deficit/hyperactivity disorder (ADHD) (intent-to-treat population).

	MASXR 1 0 mg/d (n = 54)	MASXR 20 mg/d (n = 53)	MASXR 30 mg/d (n = 58)	MASXR 40 mg/d (n = 61)	Placebo (n = 52)	Total (N = 278)
Age, mean (SD), y	14.4 (1.2)	14.2 (1.2)	14.2 (1.2)	14.0 (1.2)	14.5 (1.3)	14.2 (1.2)
Age category, no. (%)						
13-14 y	30 (55.6)	37 (69.8)	37 (63.8)	44 (72.1)	31 (59.6)	179 (64.4)
15-17 y	24 (44.4)	16 (30.2)	21 (36.2)	17 (27.9)	21 (40.4)	99 (35.6)
Sex, no. (%)						
Male	33 (61.1)	37 (69.8)	38 (65.5)	39 (63.9)	35 (67.3)	182 (65.5)
Female	21 (38.9)	16 (30.2)	20 (34.5)	22 (36.1)	17 (32.7)	96 (34.5)
Race, no. (%)						
White	38 (70.4)	39 (73.6)	43 (74.1)	47 (77.0)	38 (73.1)	205 (73.7)
Black	10 (18.5)	9 (17.0)	8 (13.8)	6(9.8)	11 (21.2)	44 (15.8)
Hispanic	2(3-7)	3(5.7)	5 (8.6)	6(9.8)	3 (5.8)	19 (6.8)
Other	4 (7.4)	2 (3.8)	2 (3-4)	2 (3.3)	0(0)	10 (3.6)
Weight, mean (SD), lb	125.7 (22.5)	124.6 (20.4)	128.6 (18.8)	125.3 (22.5)	131.6 (18.2)	127.1 (20.6)
ADHD subtype, no. (%)						
Inattentive	20 (37.0)	25 (47.2)	20 (34.5)	26 (42.6)	23 (44.2)	114 (41.0)
Hyperactive-impulsive	3 (5.6)	1 (1.9)	1 (1.7)	2 (3.3)	0(0)	7(2.5)
Combined	31 (57.4)	27 (50.9)	37 (63.8)	33 (54.1)	29 (55.8)	157 (56.5)
Years since ADHD diagnosis, mean (SD)	5.3 (4.0)	5.1 (4.5)	4.9 (4.1)	5.7 (4.1)	4.4 (4.2)	5.1 (4.2)
Patients with recent prior ADHD treatment,* no. (%)	6 (11.1)	13 (24.5)	16 (27.6)	17 (27.9)	7 (13.5)	59 (21.2)

MASXR = mixed amphetamine salts extended release.
*Within 30 days before screening.

with placebo **(Table III).** Among patients with high baseline ADHD severity, 63.1% of those randomized to any dose of MAS XR were considered improved at end point compared with 25.0% of patients in the placebo group. The percentage of patients with high baseline severity who were considered improved at end point was statistically significantly greater for the patients in the MAS XR 20-mg/d (47.0%; P = 0.001), 30-mg/d (47.4%; P < 0.001), and 40-mg/d (36.5%; P = 0.02) groups than for those in the placebo group.

Safety Profile

Treatment-emergent AEs reported by >5% of randomized patients are shown in **Table IV.** AEs that occurred more frequently (>5% difference between combined MAS XR groups and placebo) in patients receiving MAS XR were anorexia/decreased appetite (35.6% vs 1.9% in the combined MAS XR treatment groups and placebo group, respectively), headache (16.3% vs 22.2%), insomnia (12.0% vs 3.7%), abdominal pain (10.7% vs 1.9%), and weight loss (9.4% vs 0%). No dose-response relationship was observed for abdominal pain or insomnia, although their incidence was highest in patients in the 40-mg/d treatment group. All cases of abdominal pain were mild or moderate in intensity and did not lead to discontinuation of the study drug. One patient reported severe insomnia, and 3 of 5 patients who discontinued the study due to AEs reported in-

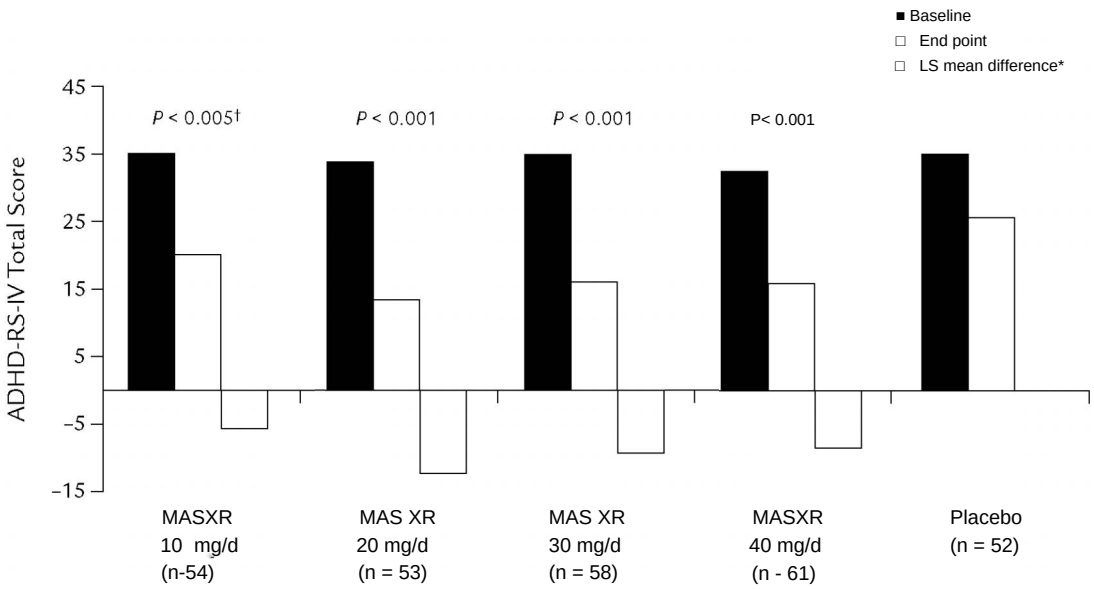

Figure 3. Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) total scores for mixed amphetamine salts extended release (MAS XR) treatment groups versus placebo. *A negative difference in least squares (LS) mean (active-placebo) indicates a positive effect of the active treatment versus placebo. tR value is based on type III sum of squares from an analysis of covariance model for the change from baseline in the ADHD-RS-IV score, including treatment and pooled center as fixed effects, and baseline value as a covariate. A closed testing procedure was used to test for a difference between each active treatment group and the placebo group, beginning with 40 mg versus placebo and stopping when significance (P < 0.05) was not reached.

somnia. The incidence of anorexia and weight loss increased with an escalation in dose up to 30 mg/d. All cases of anorexia were mild or moderate; 2 of the 5 patients who were discontinued from the study due to AEs had experienced anorexia.

AEs considered possibly or probably related to the study medication occurred in 33.3% of the patients receiving placebo and 56.2% of the patients treated with MAS XR. Most AEs were mild or moderate in intensity (n = 199 of 204 patients [97.5%]). The 5 AEs (1.7%) categorized by the investigator as severe were headache (n =1), diarrhea (n = 1), increased aspartate aminotransferase (AST) level (n =1), insomnia (n = 1), and twitching (n =1). With the exception of increased AST levels, all AEs were considered possibly or probably related to the study medication. There were no serious AEs reported.

Twenty-two patients (7.9%) reported weight loss as an AE, and 17 of these patients also reported anorexia as an AE. All cases of weight loss were mild or moderate, and no patient was discontinued from the study due to weight loss. Body weight decreased during the study in a dose-dependent manner in the MAS XR treatment groups, with the largest weight loss of 1.9 kg (4.1 lb) occurring in the 40-mg/d group. Weight was increased by 0.68 kg (1.5 lb; P = NS) in the placebo group during the study. There was no apparent correlation between weight at screening and the amount of weight lost during the study. Most reports of weight loss occurred during the first 2 weeks of treatment.

Overall changes in laboratory values, ECG findings, and physical and vital signs were not clinically significant. Neither sitting systolic nor diastolic blood pressure increased in any treatment group. Pulse rate was significantly increased from baseline relative to placebo among patients in the MAS XR 20-mg/d group after 4 weeks (4.9 beats/min; P = 0.023), but this change was not considered to be clinically significant. No dose-related trend in pulse rate was seen with MAS XR treatment. No statistically or clinically significant changes were observed in mean ECG parameters during the study.

Table II. Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) total score at end point according to final dose and baseline severity (intent-to-treat population).

	MASXR 10 mg/d (n=54)	MAS XR 20 mg/d (n = 53)	MAS XR 30 mg/d (n = 58)	MAS XR 40 mg/d (n = 61)	Placebo (n = 52)
Low severity					
No.	28	35	28	27	24
Mean change (SD)	-10.5 (7.9)	-15.7 (9.1)	-14.4 (8.2)	-12.9 (6.4)	-8.7 (8.3)
LS mean difference	-2.16	-7.83	-5.38	-6.62	
(95% CI)*	(-6.46 to 2.14)	(-11.90 to -3.75)	(-9.52 to -1.24)	(-10.93 to -2.32)	
Pt	0.323	<0.001	0.011	0.003	
High severity					
No.	28	25	29	26	28
Mean change (SD)	-18.9 (14.0)	-24.9 (13.1)	-24.0 (11.2)	-21.8 (13.6)	-10.0 (12.3)
LS mean difference	-8.18	-15.89	-13.66	-11.55	
(95% CI)*	(-14.88 to -1.47)	(-22.94 to -8.84)	(-20.50 to -6.82)	(-18.25 to -4.86)	
Pt	0.017	<0.001	<0.001	<0.001	

MASXR = mixed amphetamine salts extended release; LS = least squares.
*A negative difference in LS mean (active-placebo) indicates a positive effect of the active treatment over placebo,
tf value is based on type III sum of squares from an analysis of covariance model for the change from baseline in the ADHD-RS-IV score, including treatment and pooled center as fixed effects, and baseline value as a covariate. A closed testing procedure was used to test for a difference between each active treatment group and the placebo group, beginning with 40 mg versus placebo and stopping when significance ($P < 0.05$) was not reached.

DISCUSSION

The current study found that MAS XR has benefits in the management of adolescents with ADHD. Patients treated with MAS XR had significant improvements in ADHD symptoms compared with patients receiving placebo, as determined by the ADHD-RS-IV total scores and the CGI-I scale.

Significant statistical improvement was found in the total scores on the ADHD-RS-IV for adolescents in the MAS XR treatment groups beginning during the first treatment week and continuing throughout the 4-week study. The greatest improvement in symptoms was observed in the MAS XR 20-mg/d group, with ADHD-RS-IV total scores decreasing by >20 points from baseline to end point. Statistically significant treatment effects were detected in both the hyperactive-impulsive and inattentive subscales of the ADHD-RS-IV. Although patients with both high and low baseline severity scores had significant improvement in ADHD-RS-IV scores, patients with high baseline severity scores had a greater decrease in ADHD-RS-IV scores than did patients with low baseline severity scores. Furthermore, patients with ADHD inattentive subtype and patients with hyperactive-impulsive or combined ADHD had improvement in their symptoms, as reflected in the decrease in their ADHD-RS-IV total scores. These data suggest that treatment with MAS XR 10 to 40 mg/d benefits adolescents with both hyperactive-impulsive and inattentive symptoms of high and low severity.

Scores on the CGI-I scale further suggest the efficacy of MAS XR 10 to 40 mg/d in the treatment of adolescents with ADHD. There appeared to be a time-dependent treatment effect, with maximal improvement achieved by week 4. At that time, the percentage of patients considered statistically significantly improved ranged from 57.1% in the MAS XR 10-mg/d group to 70.0% in the MAS XR 20-mg/d group. Additional studies are needed to determine if adolescents treated with MAS XR demonstrate increased improvement in symptoms with longer courses of drug treatment and if the short-term effects of MAS XR are sustained over the long term in adolescents.

In the current study, adolescents treated with MAS XR 10 to 40 mg/d had a beneficial therapeutic response similar to that previously reported in children over the

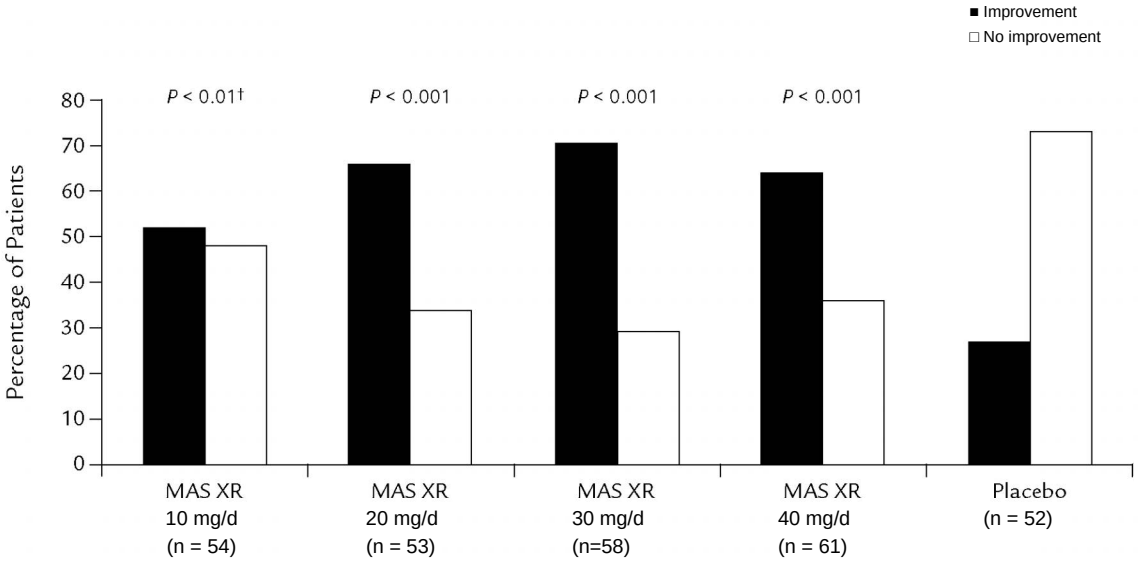

Figure 4. Dichotomized Clinical Global Impressions-Improvement (CGI-I) scores at end point in the intent-to-treat population: percentage of patients improved versus not improved.* MAS XR = mixed amphetamine salts extended release, improvement included CGI-I categories "very much improved" and "much improved"; no improvement included all other categories. 1P value was based on the general association Cochran-Mantel-Haenszel statistic with adjustment for pooled center comparing the treatment groups. A closed testing procedure was used to test for a difference between each active treatment group and the placebo group, beginning with 40 mg versus placebo and stopping when significance (P < 0.05) was not reached.

10- to 30-mg/d dose range.[32,33] However, the forced-dose-titration design of this study did not allow a determination of the maximum effective dose in adolescents. Adolescents in the 30- and 40-mg/d treatment groups did not receive their final assigned dose until the third and fourth week of the study, respectively; therefore, they may not have remained at the higher dose levels for an adequate length of time to realize increased efficacy and to achieve optimal dose levels. To better assess the efficacy of various doses of MAS XR in the treatment of adolescents with ADHD, additional studies should be conducted using an optimal-dose design in which study investigators can adjust the dosage of MAS XR individually in adolescents in 10-mg increments for the best possible efficacy and tolerability.

MAS XR was well tolerated at all doses studied, and the safety profile was similar to that observed in previous studies of younger patients with ADHD who were treated with MAS XR as well as in studies of other stimulants.[34-36] The most common AEs in this study were anorexia/decreased appetite, headache, insomnia, abdominal pain, and weight loss. These results are consistent with previous studies of MAS XR in children with ADHD.[32,33] In a study of 584 children aged 6 to 12 years who were diagnosed with ADHD, and which was designed to assess the safety and efficacy of MAS XR, the most common AEs were anorexia/decreased appetite (22%), headache (18%), insomnia (17%), abdominal pain (14%), and emotional lability (9%).[33] A similar pattern of common AEs emerged in a study of 51 school-aged children diagnosed with ADHD, conducted in an analog classroom environment, who were treated with MAS XR 10, 20, and 30 mg/d.[32] Common AEs included nervousness, anorexia/decreased appetite, insomnia, headache, and abdominal pain. In the current study, a dose-dependent increase in the incidence of anorexia was observed. Studies of other psychostimulants have reported a similar pattern of AEs.[19,34,35]

The beneficial results seen in this study are similar to those of other recent studies investigating the efficacy and safety of stimulant therapy in the treatment

Table III. Dichotomized Clinical Global Impressions-Improvement (CGI-I) at end point according to final dose and baseline Attention-Deficit/Hyperactivity Disorder Rating Scale-IV severity (intent-to-treat population).

	MAS XR 1 0 mg/d (n = 56)	MAS XR 20 mg/d (n = 60)	MAS XR 30 mg/d (n = 57)	MAS XR 40 mg/d (n = 53)	Placebo (n = 52)
Low severity					
No.	28	35	28	27	24
Improvement, no. (%)*	15 (53.6)	22 (62.9)	18 (64.3)	20 (74.1)	7 (29.2)
No improvement, no. (%)	13 (46.4)	13 (37.1)	10 (35.7)	7 (25.9)	17 (70.8)
% Difference with improvement versus placebo	24.4	33.7	35.1	44.9	
Pt	-	-	0.092	0.023	
High severity					
No.	28	25	29	26	28
Improvement, no. (%)*	13 (46.4)	18 (72.0)	21 (72.4)	16 (61.5)	7(25.0)
No improvement, no. (%)	15 (53.6)	7(28.0)	8 (27.6)	10 (38.5)	21 (75.0)
% Difference with improvement versus placebo	21.4	47.0	47.4	36.5	
Pt	0.129	0.001	<0.001	0.02	

MASXR = mixed amphetamine salts extended release.

■"■Improvement included CGI-I categories "very much improved" and "much improved." No improvement included all other categories.

tp value was based on the general association Cochran-Mantel-Haenszel statistic with adjustment for pooled center comparing the treatment groups. A closed testing procedure was used to test for a difference between each active treatment group and the placebo group, beginning with 40 mg versus placebo and stopping when significance (P < 0.05) was not reached.

of adolescents with ADHD. In an open-label study of adolescents and adults treated with 18 to 54 mg/d of OROS (ALZA Corporation, Mountain View, California) methylphenidate for up to 9 months, parents and investigators rated the treatment as good or excellent for >80% of patients on the Global Assessment of Effectiveness scale after 3 months of therapy.[35] In a multiphase study of adolescents with ADHD, patients who received OROS methylphenidate in doses up to 72 mg/d reported on the Conners-Wells Adolescent Self-report of Symptoms Scale that their symptoms were significantly improved (P = 0.001) after 6 weeks of therapy compared with patients receiving placebo.[36] Taken together, these studies suggest that stimulant therapy is a well-tolerated, effective treatment for reducing the symptoms associated with ADHD in adolescents.

Effective pharmacologic treatment options for adolescents with ADHD are critical, since ADHD can be considered a chronic condition, and health-related quality of life is significantly associated with ADHD-related symptoms.[37-39] Successful pharmacologic management of ADHD symptoms may prevent the manifestation of secondary problems that negatively impact an adolescent's quality of life.[13,40,41] For example, a recent meta-analysis of 6 studies of adolescents and young adults that examined the relationship between treatment with stimulants for ADHD and subsequent substance abuse concluded that children administered stimulant therapy for the management of

Table IV. All treatment-emergent adverse events reported by >5% of patients in any treatment group (all randomized patients). Values are given as number (%) of patients.

	MAS XR 10 mg/d (n = 56)	MASXR 20 mg/d (n = 56)	MAS XR 30 mg/d (n = 58)	MASXR 40 mg/d (n = 63)	Placebo (n = 54)
Anorexia/decreased appetite	13 (23.2)	19 (33.9)	26 (44.8)	25 (39.7)	1 (1.9)
Headache	8 (14.3)	7 (12.5)	14 (24.1)	9 (14.3)	12 (22.2)
1 nsomnia	5 (8.9)	8 (14.3)	4 (6.9)	11 (17.5)	2(3-7)
Abdominal pain	5 (8.9)	3 (5.4)	6 (10.3)	11 (17.5)	1 (1.9)
Dizziness	3 (5.4)	2(3.6)	4 (6.9)	4(6.3)	4 (7.4)
Nervousness	3 (5.4)	6 (10.7)	2 (3.4)	3 (4.8)	3 (5.6)
Emotional lability	2(3.6)	1 (1.8)	4 (6.9)	0(0)	0(0)
Somnolence	2(3.6)	1 (1.8)	2 (3.4)	6(9.5)	2(3-7)
Weight loss	1 (1.8)	5(8.9)	8 (13.8)	8 (12.7)	0(0)
Dry mouth	1 (1.8)	3 (5.4)	3(5.2)	3 (4.8)	0(0)

MAS XR = mixed amphetamine salts extended release.

ADHD have a reduced risk of future drug and alcohol abuse.[42]

Limitations

The primary end point for this study was the ADHD-RS-IV, and the main cohort of the study included patients weighing ≤75 kg. To detect an effect size of 0.78 on the ADHD-RS-IV scale between one active dose group and the placebo group at >95% power and an a level of 0.50 (2-tailed) using a 2-sample t test, it was necessary to randomize ~45 patients in each dose group. This yielded a total of -225 patients weighing ≤75 kg to be randomized for the main cohort in the double-blind portion of the study. Studies involving a sample size larger than 30 would be needed to evaluate the efficacy and safety of MAS XR in adolescents weighing >75 kg. In addition, studies of longer duration would confirm the findings observed in this 4-week study.

CONCLUSIONS

Overall, the results of this placebo-controlled, forced-dose-titration study indicated that statistically significant improvements in core ADHD symptoms occurred in these adolescents with ADHD who received MAS XR compared with placebo. Significant scores on the ADHD-RS-IV were reported in patients taking MAS XR 10, 20, 30, and 40 mg/d. Significantly more adolescents treated with MAS XR were considered improved at study end point compared with patients receiving placebo, as determined by the results on the CGI-I scale, and 63.3% of adolescents receiving active treatment with MAS XR were considered to be “much improved” or “very much improved.” The most frequently reported AEs were mild or moderate, and changes in vital signs were not clinically significant. Once-daily dosing with MAS XR up to 40 mg was effective and well tolerated for the management of ADHD in these adolescents.

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REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.
2. Olfson M, Gameroff MJ, Marcus SC, Jensen PS. National trends in the treatment of attention deficit hyperactivity disorder. Am J Psychiatry. 2003;160:1071-1077.
3. Rowland AS, Lesesne CA, Abramowitz AJ. The epidemiology of attention-deficit/hyperactivity disorder (ADHD): A public health view. Ment Retard Dev Disabil Res Rev. 2002;8:162-170.
4. Dulcan M. Practice parameters for the assessment and treatment of children, adolescents, and adults with attention-deficit/hyperactivity disorder. American Academy of Child and Adolescent Psychiatry. J Am Acad Child Adolesc Psychiatry. 1997;36(Suppl 10):85S-121S.
5. Rowland AS, Lesesne CA, Abramowitz AJ. The epidemiology of attention-deficit/hyperactivity disorder (ADHD): A public health view. Ment Retard Dev Disabil Res Rev. 2002; 8:162-170.
6. MannuzzaS, Klein RG. Diagnosis and longitudinal course of attention-deficit/hyperactivity disorder. Econ Neurosci. 2001;3:47-53.
7. Steinhausen HC, Drechsler R, Foldenyi M, et al. Clinical course of attention-deficit/hyperactivity disorder from childhood toward early adolescence. J Am Acad Child Adolesc Psychiatry. 2003;42:1085-1092.
8. Woodward LJ, Fergusson DM, Horwood LJ. Driving outcomes of young people with attentional difficulties in adolescence. J Am Acad Child Adolesc Psychiatry. 2000;39: 627-634.
9. Bagwell CL, Molina BS, Pelham WE Jr, Hoza B. Attention-deficit hyperactivity disorder and problems in peer relations: Predictions from childhood to adolescence. J Am Acad Child Adolesc Psychiatry. 2001 ;40:1285-1292.
10. Biederman J, Wilens T, Mick E, et al. Is ADHD a risk factor for psychoactive substance use disorders? Findings from a four-year prospective follow-up study. J Am Acad Child Adolesc Psychiatry. 1997;36:21 -29.
11. Biederman J, Faraone SV, Taylor A, et al. Diagnostic continuity between child and adolescent ADHD: Findings from a longitudinal clinical sample. J Am Acad Child Adolesc Psychiatry. 1998;37:305-313.
12. August GJ, Stewart MA, Holmes CS. A four-year follow-up of hyperactive boys with and without conduct disorder. Br J Psychiatry. 1983;143:192-198.
13. Barkley RA. Adolescents with attention-deficit/hyperactivity disorder: An overview of empirically based treatments. J Psychiatr Pract. 2004;10:39-56.
14. Mannuzza S, Klein RG, Bessler A, et al. Adult psychiatric status of hyperactive boys grown up. Am J Psychiatry. 1998; 155:493-498.
15. Biederman J, Faraone S, Milberger S, et al. A prospective 4-year follow-up study of attention-deficit hyperactivity and related disorders. Arch Cen Psychiatry. 1996;53:437-446.
16. Faraone S, Biederman J, Monuteaux MC. Further evidence for the diagnostic continuity between child and adoles-

cent ADHD. J Atten Disord. 2002;6: 5-13.
17. Molina BS, Pelham WEJr. Childhood predictors of adolescent substance use in a longitudinal study of children with ADHD. J Abnorm Psychol. 2003;112:497-507.
18. Findling RL, Dogin JW. Psychopharmacology of ADHD: Children and adolescents. J Clin Psychiatry. 1998; 59(Suppl 7):42-49.
19. Findling RL, Short EJ, Manos MJ. Developmental aspects of psychostimulant treatment in children and adolescents with attention-deficit/ hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2 001 ;40:1441 -1447.
20. Greydanus DE, Sloane MA, Rappley MD. Psychopharmacology of ADHD in adolescents. Adolesc Med. 2002; 13:599-624.
21. Swanson JM, Wigal S, Greenhill LL, et al. Analog classroom assessment ofAdderall in children with ADHD. J Am Acad Child Adolesc Psychiatry. 1998;37:519-526.
22. Wilens TE, Spencer TJ. The stimulants revisited. Child Adolesc Psychiatr Clin North Am. 2000;9:573-603.
23. SpencerT, Biederman J, Wilens T, et al. Pharmacotherapy of attention-deficit hyperactivity disorder across the life cycle. J Am Acad Child Adolesc Psychiatry. 1996;35:409-432.
24. Swanson JM, McBurnett K, Wigal T, et al. Effect of stimulant medication on children with attention deficit disorder: A "review of reviews." Exceptional Children. 1 993;60:154-1 61.
25. Greenhill LL, Halperin JM, Abikoff H. Stimulant medications. J Am Acad Child Adolesc Psychiatry. 1999;38:503-512.
26. SpencerTJ. ADHD treatment across the life cycle. J Clin Psychiatry. 2004; 65(Suppl 3):22—26.
27. Smith BH, Waschbusch DA, Willoughby MT, Evans S. The efficacy, safety, and practicality of treatments for adolescents with attention-deficit/hyperactivity disorder (ADHD). Clin Child Fam Psychol Rev. 2000 ;3:243-267.
28. Siberry GK, Iannone R, eds. The Harriet Lane Handbook: A Manual for Pediatric House Officers. 15th ed. St. Louis, Mo: Mosby; 2000.
29. DuPaulGJ, PowerT, Anastopoulos A, Reed R. The ADHD Rating Scale-IV Checklist, Norms and Clinical Interpretation. New York, NY: The Guilford Press; 1998.
30. Guy W, ed. Clinical Global Impressions (028-CGI). In: ECDEUAssessment Manual for Psychopharmacology. Revised, 1976. Rockville, Md: US Dept of Health, Education, and Welfare. Public Health Service, Alcohol, Drug Abuse and Mental Health Administration, National Institute of Mental Health Psychopharmacology Research Branch; 1976:217-222.
31. Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART). 5th ed. Rockville, Md: US Food and Drug Administration, Center for Drug Evaluation and Research; 1995.
32. McCracken JT, Biederman J, Greenhill LL, et al. Analog classroom assessment of a once-daily mixed amphetamine formulation, SLI381 (AdderallXR), in children with ADHD. J Am Acad Child Adolesc Psychiatry. 2003; 42:673-683.
33. Biederman J, Lopez FA, Boellner SW, Chandler MC. A randomized, double-blind, placebo-controlled, parallel-group study of SLI381 (Adderall XR) in children with attention-deficit/hyperactivity disorder. Pediatrics. 2002;110:258-266.
34. West SA, Muniz R, Quinn P, et al. The GRACE Study: An evaluation of girls, Ritalin, and ADHD. Poster presented at the Annual Meeting of the American Academy of Child and Adolescent Psychiatry; October 19-24, 2004; Washington, DC.
35. Stein MA, for the Concerta Community Use Study Group. OROS® methylphenidate for treatment of adolescents and adults with ADHD. Poster presented at the Annual Meeting of the American Academy of Child and Adolescent Psychiatry; October 1 6-19, 2003; Miami, Fla.
36. Wilens TE, McBurnett K, Bukstein O, et al. Multisite controlled study of OROS methylphenidate in the treatment of adolescents with attention-deficit/hyperactivity disorder. Arch Pediatr Adolesc Med. 2006;1 60:82-90.
37. Matza LS, Rentz AM, Secnik K, et al. The link between health-related quality of life and clinical symptoms among children with attention-deficit hyperactivity disorder. J Dev Behav Pediatr. 2004;25:166-174.
38. Sawyer MG, Whaites L, ReyJM, et al. Health-related quality of life of children and adolescents with mental disorders. J Am Acad Child Adolesc Psychiatry. 2002;41:530-537.
39. Weiss G, Hechtman L, Milroy T, Perlman T. Psychiatric status of hyperactives as adults: A controlled prospective 15-year follow-up of 63 hyperactive children. J Am Acad Child Psychiatry. 1985;24:211-220.
40. Lambert NM, Hartsough CS. Prospective study of tobacco smoking and substance dependencies among samples of ADHD and non-ADHD participants. J Learn Disabil. 1998;31: 533-544.
41. Barkley RA. Attention-Deficit Hyperactivity Disorder: A Handbook for Diagnosis and Treatment. 2nd ed. New York, NY: The Guilford Press; 1998.
42. WilensTE, FaraoneSV, BiedermanJ, Gunawardene S. Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. Pediatrics. 2003;111:1 79-185.

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