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KEY WORDS: Lisdexamfetamine dimesylate (LDX); attention-deficit/hyperactivity disorder (ADHD), adults; ADHD-RS-IV symptom subtype; amphetamine; stimulant; predominantly inattention; predominantly hyperactivity/ impulsivity; predominantly combined; clinical response

ORIGINAL RESEARCH

Attention Deficit Hyperactivity Disorder Subtypes and Symptom Response in Adults Treated With Lisdexamfetamine Dimesylate

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ABSTRACT

Objective: To evaluate the efficacy of lisdexamfetamine dimesylate in adults with attention deficit hyperactivity disorder symptom subtypes who exhibit predominantly inattention, hyperactivity/ impulsivity, or combined symptom clusters.

Design/Setting/Participants: This is a *post-hoc* analysis from a multicenter, one-year, open-label lisdexamfetamine dimesylate study in adults with attention deficit hyperactivity disorder previously completing two weeks or more in a four-week, randomized, placebo-controlled lisdexamfetamine dimesylate study, using Attention Deficit Hyperactivity Disorder Rating Scale IV symptom ratings as an attention deficit hyperactivity disorder subtype proxy (N=349).

Measurements: Attention Deficit Hyperactivity Disorder Rating Scale IV was measured at baseline of prior study and throughout the open-label study. Proxy subtypes were based on item scores of 2 (moderate) or 3 (severe), representing endorsement of at least six of nine symptoms on respective subscales; predominantly combined type endorsed at least six of nine symptoms on each subscale. Overall safety evaluations included treatment-emergent adverse events.

Results: At baseline, 93 of 345 participants exhibited predominantly inattention, 13 predominantly hyperactivity/ impulsivity, 236 combined symptom clusters, and three were unassigned. For the three subgroups, respectively, mean (standard deviation) Attention Deficit Hyperactivity Disorder Rating Scale IV total scores at baseline were 34.5 (4.02), 33.8 (3.27), and 43.6 (5.24); change from baseline to endpoint scores were -19.3 (9.48), -24.0 (7.22), and -27.3 (11.78). Mean (standard deviation) end-of-study lisdexamfetamine dimesylate dose was 57.7 (14.75), 53.1 (16.01), and 56.9 (14.94)mg/day, respectively.

Treatment-emergent adverse events (>5%) were upper respiratory tract infection (21.8%), insomnia (19.5%), headache (17.2%), dry mouth (16.6%), decreased appetite (14.3%), irritability (11.2%), anxiety (8.3%), nasopharyngitis (7.4%), sinusitis (6.6%), decreased weight (6.0%), back pain (5.4%), and muscle spasms (5.2%).

Conclusions: Lisdexamfetamine dimesylate was effective in participants with predominantly inattention, hyperactivity/ impulsivity, and combined attention deficit hyperactivity disorder symptom clusters. Groups exhibiting specific predominant subtype symptoms did not differ in clinical response to lisdexamfetamine dimesylate.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) has been characterized by the core symptoms of inattention, hyperactivity, and impulsivity.[1] As reviewed by Landgraf et al,[2] these ADHD core symptoms may lead to a variety of serious functional impairments across a person's life span, impacting education, work, family, and social interactions. ADHD presents in childhood but persists into adulthood in almost 60 percent of cases,[3] with an estimated prevalence of 4.4 percent in United States adults.[4] The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (*DSM-IV-TR*) defines three subtypes of ADHD: predominantly inattentive, predominantly hyperactive/ impulsive, and predominantly combined.[1]

In a study by Millstein et al,[5] a "proxy" diagnosis of the *DSM-IV-TR* ADHD subtypes based on structured diagnostic interviews of adult outpatients (N=149) with ADHD (using the *DSM-III-R* symptom criteria) provided insight into the clinical presentation of symptoms in the study population. The childhood ADHD diagnosis established approximately 23 percent of participants as of the predominantly inattentive subtype, two percent as of the predominantly hyperactive/ impulsive subtype, and 74 percent as of the predominantly combined subtype. ADHD symptoms exhibited in adulthood resulted in proxy symptom cluster assignments as predominantly inattention in 37 percent, predominantly hyperactivity/ impulsivity in two percent, predominantly combined symptom cluster in 56 percent, and not otherwise specified in five percent of the participants. These data suggested an increase of 14 percent in the predominantly inattention symptom cluster in adulthood over childhood ADHD, with 93 percent of the adults exhibiting symptoms of inattention.

Efficacy measures such as the Attention Deficit Hyperactivity Disorder Rating Scale (ADHD-RS) or the Swanson, Nolan, and Pelham rating scale (SNAP-IV) are often used to evaluate ADHD treatments in clinical trials to evaluate improvements from baseline of ADHD symptoms.[6–8] These aforementioned scales define efficacy as improvements in group averages over time; however, they do not give information on individuals, such as a percentage of individuals who achieve "excellent" clinical "response" due to treatment.[8,9] Clinical response may be defined by a prespecified level of percent improvements in symptoms or by a prespecified score on the efficacy measure, but because baseline severity levels may be unaccounted for, some individuals may continue to meet diagnostic criteria.[9,10]

To date, little is known about group-wide and individual clinical response to pharmacologic treatment of adults with ADHD by subtype or symptom clusters; yet studies[11,12] have compared treatment response by ADHD subtype in children with ADHD. These child ADHD studies[11,12] suggested that there was clinical improvement with psychostimulant treatment but there was no differential response as categorized by ADHD symptom subtypes. Overall, although these ADHD studies in children might provide some clinical perspective and suggest no differences in treatment response as related to psychostimulants, studies providing information on such comparisons in adults with ADHD are needed.

This *post-hoc* analysis was of data from a long-term (1 year) safety and effectiveness study and was undertaken to assess the long-term effects of the long-acting prodrug stimulant lisdexamfetamine dimesylate (LDX; Vyvanse®, Shire US Inc.), in adults with ADHD exhibiting symptom clusters of predominantly inattention, hyperactivity/ impulsivity, and combined subtypes. The effect of ADHD symptom clusters on achieving clinical response with LDX treatment was also assessed.

LDX is indicated for the treatment of ADHD in children (aged 6–12 years), in adolescents (aged 13–17 years), and in adults. Treatment with LDX has demonstrated efficacy in adults (aged 18–55 years) with ADHD in two randomized, placebo-controlled, short-term trials.[13,14] Also, LDX has been shown to be effective in the treatment of ADHD for up to 12 months in an open-label study in adults with ADHD.[15]

METHODS

Methodology of the study was previously reported in detail.1[5] This was an open-label, single-arm, multisite study[15] enrolling adults (aged 18–55 years) with ADHD who had completed at least two weeks of a previous four-week, randomized, double-blind, placebo-controlled, forced-dose titration study.[13,15] Clinical diagnosis of ADHD was based on a structured clinical interview using the Adult ADHD Clinical Diagnostic Scale (ACDS),[16] but assignment to an ADHD subtype was not recorded. Baseline ADHD-RS-IV and Clinical Global Impressions-Severity (CGI-S) Scale scores from the previous study were used as the baseline scores for this study. The baseline ADHD-RS-IV results were used to establish a proxy for ADHD subtype (see explanation of methodology in Statistical Analyses).

TABLE 1. Criteria for ADHD symptom clusters

SYMPTOM CLUSTER	INATTENTION SYMPTOMS	HYPERACTIVITY/ IMPULSIVITY SYMPTOMS
Predominantly inattention	≥6 of 9 items with severity rating of 2 or 3	<6 of 9 items with severity rating of 2 or 3
Predominantly hyperactivity/ impulsivity	<6 of 9 items with severity rating of 2 or 3	≥6 of 9 items with severity rating of 2 or 3
Predominantly combined	≥6 of 9 items with severity rating of 2 or 3	≥6 of 9 items with severity rating of 2 or 3

ADHD: attention deficit hyperactivity disorder

Safety data from the final visit of the previous four-week study were used as baseline for this study for participants enrolled within seven days of study completion and who were not taking any excluded medications. Otherwise, baseline safety data were recorded at the screening visit for this study. LDX was initiated at 30mg/day and titrated in 20-mg increments over four weeks to 30, 50, or 70mg/day based on investigator determination of adequate efficacy and tolerability. The dose-optimization period was followed by a long-term maintenance phase (11 months). Further dose adjustments (within the above parameters) were allowed at the discretion of the investigator.

Efficacy measures. The primary efficacy measure was the clinician-rated ADHD-RS-IV administered using adult prompts at each postbaseline visit. The ADHD-RS-IV contains 18 items designed to reflect ADHD symptoms based on *DSM-IV-TR* criteria and consists of two subscales, inattention (odd-numbered items) and hyperactivity/ impulsivity (even-numbered items). The ADHD-RS-IV total score can range from 0 to 54, with each item scored from 0 (no symptoms) to 3 (severe symptoms).

The secondary efficacy measure was the global severity of illness that was assessed using the CGI-S Scale, which consists of a 7-point scale ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill participants). Global improvement of illness was assessed using the CGI-Improvement (CGI-I) Scale, which also consists of a 7-point scale, ranging from 1 (very much improved) to 7 (very much worsened).

Safety analysis. Treatment-emergent adverse events (TEAEs) were assessed at all study weeks. TEAEs referred to events with onset after the first date of treatment and no later than three days following termination of treatment. Vitals signs analyses included systolic blood pressure (SBP), diastolic BP (DBP), and pulse, which were assessed at all study weeks. Electrocardiograms (ECGs) were performed at baseline visit and then at three-month intervals during the maintenance phase.

Statistical analyses. Efficacy analyses (n=345; intention-to-treat [ITT] population) were performed for all enrolled participants who were treated and had a baseline and at least 1 postbaseline primary efficacy measurement (ADHD-RS-IV total score). Safety analyses were performed for all enrolled participants who received at least one dose of study medication (n=349). At study entry, study participants were not classified by ADHD subtypes. Hence, *post-hoc* analysis categorized participants according to the presence of symptom clusters of inattention and/or hyperactivity/ impulsivity at baseline (Table 1). ADHD symptoms were classified as present if the ADHD-RS-IV items score indicated moderate (score of 2) or severe (score of 3) symptom presentation. Clinical response criteria, based on previously published parameters,[8,10] were stringently defined as a change in ADHD-RS-IV total scores of 30 percent or more from baseline and a CGI-I rating of 1 or 2, were assessed in the overall study population and by symptom cluster subgroup. Logistic regression modeling was performed with predominant symptom cluster, ADHD-RS-IV total score at endpoint, age, and gender as potential "predictors" of achieving response criteria.

RESULTS

Disposition and demographics. Detailed disposition, demographics, and primary efficacy and safety data were previously reported.[15] There were 349 participants who were enrolled and received at least one dose of LDX (i.e., safety population). Of the enrolled population, 345 participants (157 women and 188 men) were included in the efficacy analysis and 191 (54.7%) completed the study. There were 158 (45.3%) participants discontinued from the study in the safety population. The reasons for discontinuation were as follows: 28 (8.0%) due to TEAEs (at a rate of <1% a month); 11 (3.2%) due to lack of efficacy; 27 (7.7%) due to protocol violation; 41 (11.7%) lost to follow-up; 42 (12.0%) withdrew consent; 1 (0.3%) due to physician decision; 7 (2.0%) due to other reasons; and 1 (0.3%) participant died during the course of the study. According to the medical examiner's report, this death was due to acute cocaine and ethanol toxicity. Drug screen at autopsy indicated positive for cocaine and ethanol but negative for amphetamine.[15] Of the efficacy population (n=345) that was evaluated for predominant symptom clusters at baseline, three participants were diagnosed with ADHD by clinical diagnostic interview (per eligibility criteria), but did not meet *post-hoc* proxy diagnostic criteria (Table 2).

The final mean (SD) optimized dose of LDX was 57.7 (14.75), 53.1 (16.01), and 56.9 (14.94)mg/day for

predominantly inattention, hyperactivity/ impulsivity, and combined symptom cluster subgroups, respectively. The median final optimized LDX dose was 70, 50, and 70mg/day, for predominantly inattention, hyperactivity/ impulsivity, and combined symptom cluster subgroups, respectively. The proportion of female participants was higher in the predominantly hyperactivity/ impulsivity symptom cluster subgroup versus the predominantly inattention and combined subgroups (Table 2). Moreover, the proportion of younger adults (aged 18–29 years) was higher in the predominantly hyperactivity/ impulsivity symptom cluster subgroup and was lower in that group for older adult participants (aged ≥40 years) (Table 2). Due to the small number of participants in the predominantly hyperactivity/ impulsivity symptom cluster subgroup, however, these findings should be interpreted with caution.

The mean (SD) CGI-S scores, which were 4.5 (0.54) for the predominantly inattention subgroup, 4.5 (0.78) for the predominantly hyperactivity/ impulsivity subgroup, and 5.0 (0.63) for the predominantly combined subgroup, were comparable at baseline (Table 2). However, a higher proportion of participants had a CGI-S rating of 4 (moderately ill) at baseline in the predominantly inattention and hyperactivity/ impulsivity symptom cluster subgroups than in the predominantly combined subgroup and the overall study population (Figure 1). There was a higher proportion of participants who received a CGI-S rating of 5 (markedly ill) at baseline in the predominantly combined symptom cluster subgroup and overall study population in comparison with the predominantly inattention and hyperactivity/ impulsivity subgroups (Figure 1).

Efficacy. The baseline ADHD-RS-IV total scores were lower in the predominantly inattention and hyperactivity/ impulsivity symptom cluster subgroups (Figure 2). LDX treatment decreased ADHD-RS-IV total scores in all predominant symptom cluster subgroups (Figure 2). Mean percent reduction from baseline to endpoint was 55.9, 71.0, and 62.6 percent for the predominantly inattention, hyperactivity/ impulsivity, and combined symptom cluster subgroups, respectively, and was 61.1 percent for the overall study population. At endpoint, 285 of the 345 participants (82.6%) were classified as clinical responders (i.e., ADHD-RS-IV total score decrease of ≥30% from baseline and a CGI-I score of 1 or 2). Of the 93 participants who had predominantly inattention symptom cluster at baseline, 74 (79.6%) were classified as clinical responders at endpoint. All 13 (100%) participants who had predominantly hyperactivity/ impulsivity symptom cluster at baseline were classified as clinical responders at endpoint. At endpoint, of the 236 of participants who had combined type ADHD at baseline, 196 (83.1%) were classified as clinical responders. Also, 2 of the 3 participants who did not meet the proxy diagnostic criteria at baseline were classified as clinical responders at endpoint.

TABLE 2. Demographics and disposition by symptom cluster categories

PARAMETER	SYMPTOM CLUSTER		
	Predominantly Inattention	Predominantly Hyperactivity/ Impulsivity	Predominantly Combined
n (%)*	93 (27.0)	13 (3.8)	236 (68.4)
Sex, n (%)			
Male	56 (60.2)	5 (38.5)	126 (53.4)
Female	37 (39.8)	8 (61.5)	110 (46.6)
Age category (years), n (%)			
18–29	30 (32.3)	7 (53.8)	72 (30.5)
30–39	22 (23.7)	4 (30.8)	72 (30.5)
40–49	29 (31.2)	1 (7.7)	69 (29.2)
50+	12 (12.9)	1 (7.7)	23 (9.7)
Age (years), mean (SD)	36.7 (10.54)	31.3 (9.06)	35.7 (9.98)
Prior treatment,† n (%)			
LDX	70 (75.3)	12 (92.3)	211 (89.4)
Placebo	23 (24.7)	1 (7.7)	25 (10.6)
CGI-S, mean (SD)	4.5 (0.54)	4.5 (0.78)	5.0 (0.63)

LDX: lisdexamfetamine dimesylate; GCI-S: Clinical Global Impressions-Severity Scale.

*n=345; 3 participants (0.9%) from the study efficacy population were not evaluated for symptom clusters (unassigned).

†Prior treatment indicates treatment group in previous 4-week study.

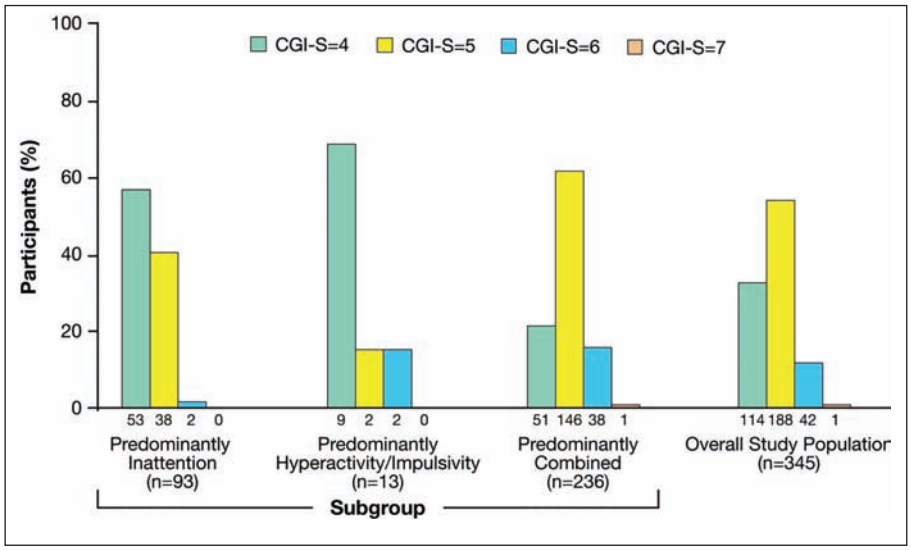

FIGURE 1. Distribution of CGI-S ratings at baseline by symptom cluster subgroup and overall study population. Numbers below bars indicate the number of participants in each CGI-S rating subgroup. CGI-S: Clinical Global Impressions-Severity Scale

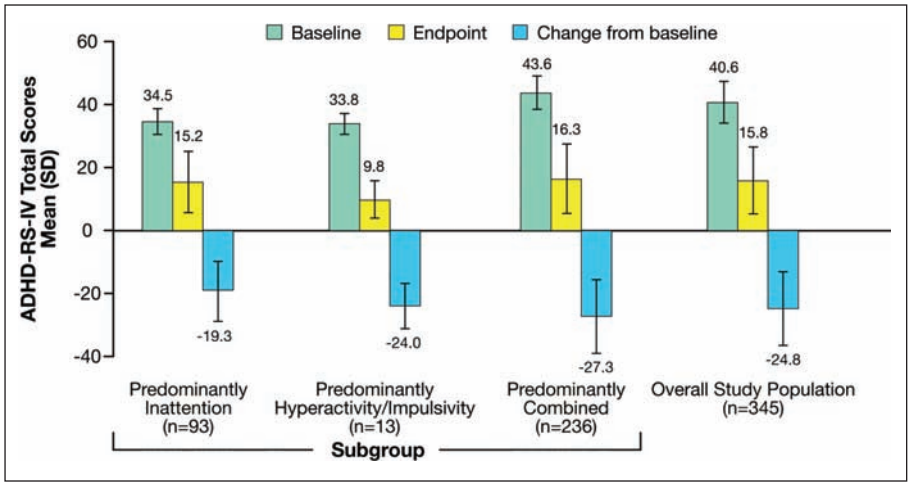

FIGURE 2. ADHD-RS-IV total scores by symptom cluster subgroup and overall study population; ADHD-RS-IV: ADHD Rating Scale IV

Logistic regression analysis showed that ADHD-RS-IV total score at endpoint, baseline predominant symptom cluster (combined greater than inattention), and gender (male greater than female) were statistically significant ($P \leq 0.05$) predictors of achieving responder status ($\geq$30% reduction in ADHD-RS-IV total score from baseline to endpoint and CGI-I rating at endpoint of 1 or 2). Because only three participants were unclassified at baseline, they were excluded from the analysis; because all participants with predominant hyperactivity/ impulsivity symptom cluster at baseline achieved responder status at endpoint, they were also excluded from the analysis.

Safety. *TEAEs.* Overall, 87.7 percent (306 of 349) participants experienced TEAEs in the safety population. TEAEs (incidence >5%) are reported in Table 3. Most TEAEs with LDX treatment were rated as mild to moderate in severity. Severe TEAEs occurred in 12.0% of the safety population. There were 12 severe TEAEs in 10 participants (2.9%) that were considered possibly or probably treatment related.

Vital signs and ECG parameters. At endpoint, small but statistically significant increases were noted in SBP and pulse (Table 4). At endpoint, mean (SD) change in heart rate from baseline was 3.4 (10.8)bpm. The mean (SD) change in QTcF interval from baseline at endpoint was 6.2 (18.1)msec ($P<0.0001$). At endpoint, 1 participant had a QTcF interval change 60msec or more from baseline. The QTcF interval reading at endpoint was 419msec for this study participant. There were no study participants who had a QTcF >480msec during the trial. The mean (SD) change in body weight at endpoint was -4.0 (10.5)Lb, with the greatest change at Month 10, which was -6.8 (11.4)Lb.

DISCUSSION

This *post-hoc* symptom clusters analysis resulted in assignment of predominant symptom clusters in all but three participants, allowing analysis of proxy ADHD subtype classification for the majority of participants. Overall distribution of participants with predominantly inattention symptom cluster, predominantly hyperactivity/ impulsivity symptom cluster, and predominantly combined symptom cluster was consistent with previous reports.[5] The study data suggested groups exhibiting specific predominant symptom clusters did not differ in clinical response to LDX treatment. However, these data suggested differences in selected subgroups for each symptom cluster. Data from the current adult LDX trial were consistent with previously reported studies[11,12] conducted in children with ADHD suggesting that there were no differential treatment responses by ADHD symptom subtype with psychostimulant treatment. In a double-blind, crossover, placebo-controlled study, children with combined type or predominantly inattention type ADHD improved versus placebo with psychostimulant treatment, regardless of ADHD subtype (predominantly inattention and combined).[11] Although both ADHD subtypes showed improvement, no differential symptom response between subtypes

were noted on a variety of behavioral questionnaires and clinical ratings.[11] A long-term, population-based ADHD study in children suggested that, regardless of *DSM-IV* ADHD subtype, there was no associated differential favorable treatment response to psychostimulant treatment.[12] However, another ADHD dose-response study[11] that categorized children with ADHD by subtype (inattention and combined) suggested that the relationship between subtypes and clinical response may be a dose-dependent effect. The study indicated that increased doses of a long-acting psychostimulant in participants with predominantly combined subtype improved inattention and hyperactivity symptoms, whereas in those with predominantly inattention subtype, improvement in symptoms occurred with lower doses and less benefit resulted from higher doses. Overall, these child study data suggest that there may not be differences in response with long-acting psychostimulant treatment; however, the effect may be dose-dependent. Further controlled, randomized psychostimulant studies in children and adults with ADHD as categorized by subtype need to be conducted to provide further insight.

The proportion of women with the predominantly hyperactivity/ impulsivity symptom cluster was higher than that of men. Previous data reported for children with ADHD suggested a lower proportion were of the predominantly hyperactivity/ impulsivity subtype in female subjects.[12,17,18] The difference observed between the current analysis and the childhood data may be related to a small subgroup sample size. It also may reflect a greater likelihood of female subjects with predominantly hyperactivity/ impulsivity symptom clusters to seek medical intervention or enroll in clinical trials. Additionally, ADHD that persists and does not attenuate with age may cause more severe impairment,[19] raising the possibility that adult women exhibiting the

TABLE 3. TEAEs with overall incidence >5%[15]

PREFERRED TERMINOLOGY (MEDDRA 9.1)	PARTICIPANTS REPORTING, N (%)			
	LDX 30 mg/day (n=349)	LDX 50 mg/day (n=323)	LDX 70 mg/day (n=238)	LDX Any Dose (N=349)
Any event	135 (38.7)	186 (57.6)	197 (82.8)	306 (87.7)
Anxiety	2 (0.6)	15 (4.6)	12 (5.0)	29 (8.3)
Back pain	7 (2.0)	3 (0.9)	10 (4.2)	19 (5.4)
Dry mouth	18 (5.2)	23 (7.1)	26 (10.9)	58 (16.6)
Decreased appetite	19 (5.4)	18 (5.6)	16 (6.7)	50 (14.3)
Headache	23 (6.6)	24 (7.4)	26 (10.9)	60 (17.2)
Insomnia	14 (4.0)	35 (10.8)	34 (14.3)	68 (19.5)
Irritability	9 (2.6)	20 (6.2)	17 (7.1)	39 (11.2)
Muscle spasms	5 (1.4)	7 (2.2)	9 (3.8)	18 (5.2)
Nasopharyngitis	6 (1.7)	11 (3.4)	13 (5.5)	26 (7.4)
Sinusitis	2 (0.6)	10 (3.1)	12 (5.0)	23 (6.6)
Upper respiratory tract infection	12 (3.4)	23 (7.1)	44 (18.5)	76 (21.8)
Weight decreased	4 (1.1)	8 (2.5)	9 (3.8)	21 (6.0)

TEAE: treatment-emergent adverse advent; MedDRA: Medical Dictionary for Drug Regulatory Affairs; LDX: lisdexamfetamine dimesylate, TEAE: treatment-emergent adverse event

Dose level indicates dosage of LDX being received by participants at the onset of TEAE.

TABLE 4. Vitals signs at baseline and endpoint[15]

TIME POINTS	SBP (mm Hg) Mean (SD)	DBP (mm Hg) Mean (SD)	Pulse (bpm) Mean (SD)
Baseline	117.3 (10.0)	75.4 (8.0)	74.1 (10.3)
Endpoint	120.5 (11.7)	76.8 (8.2)	77.1 (10.4)
Change from baseline	3.1 (10.7)*	1.3 (7.6)	3.2 (11.6)*

SBP: systolic blood pressure; DBP: diastolic blood pressure.

*Unadjusted P<0.0001 (paired t test).

predominantly hyperactivity/ impulsivity symptom cluster may have a more severely impairing form of ADHD. The proportion of adults with the predominantly hyperactivity/ impulsivity symptom cluster was higher in younger adults compared with older adults. This is consistent with previous findings that expression of hyperactivity may diminish with age.[20–22]

For the overall study population and those with combined-type symptom cluster, most participants were rated as markedly ill at baseline by the clinician global rating. For those with the predominantly inattention and the hyperactivity/ impulsivity symptom clusters, most participants were rated as moderately ill by the clinician global rating. The impact of more limited symptom cluster presentation (i.e., inattention only or hyperactivity/ impulsivity only) on global severity assessment by clinicians has not been evaluated. The lower perceived global symptom severity in an adult patient presenting with either predominantly inattention or predominantly hyperactivity/ impulsivity symptom clusters may impact recognition and diagnosis of ADHD and ultimate choice of treatment options. Thus, baseline severity in these analyses suggests that participants who exhibit either predominantly inattention or hyperactivity/ impulsivity symptom clusters may be perceived as less globally symptomatic in symptom severity than those with predominantly combined-type symptom cluster.

Similar to the findings on global illness severity, ADHD symptom scores suggested a similar trend. As expected, mean baseline ADHD-RS-IV total scores were somewhat lower for the predominantly inattention and hyperactivity/ impulsivity symptom cluster subgroups than for the predominantly combined subgroup and the overall study population. ADHD-RS-IV total scores with LDX treatment were similar regardless of symptom cluster subgroup, suggesting LDX was effective regardless of predominant symptom cluster observed at baseline. Most participants, regardless of predominant symptom cluster, achieved clinical response to LDX treatment. Interestingly, baseline symptom cluster and sex, as well as endpoint symptom severity by ADHD-RS-IV total score, were found to be predictors of response to LDX using logistic regression analysis. However, these findings should be interpreted with caution because our composite definition for responder status is based partially on a percentage decrease in ADHD-RS-IV score, so it may be more likely that those with higher baseline ADHD-RS scores (e.g., those with combined symptom cluster) would achieve such a responder criteria.

Clinical response, as defined by stringent criteria that incorporated global and symptom assessments to measure improvement over time in adults with specific symptom clusters, did not differ by subtype, regardless of baseline severity. ADHD subtype classifications may provide clinical value to the treatment of adults with ADHD, specifically to focus clinicians' awareness on the potential for underdiagnosis of patients with either predominantly inattention or predominantly hyperactivity/ impulsivity subtypes. A critical factor in the management of adult ADHD is the determination of symptom severity in balance with functional impairments. Global assessments may identify some aspects of ADHD symptoms or impairments that may not be classified by the symptom item assessments. Thus, using a percent reduction in ADHD-RS-IV total score from baseline as the only measure for defining clinical response may not be necessarily representative of response for participants who are severely ill at baseline. Although participants may have improved with treatment, they may still exhibit significant symptoms.[10] In this study, the stringent inclusion of a CGI-I criterion to define clinical response may help avoid classifying significantly symptomatic participants as clinical responders.

Rowland et al,[23] based on a community sample study of children with ADHD, suggested that a standardized criteria for defining ADHD subtypes (as well as the method ascertained to obtain that information) would improve comparisons of data across studies, and that an accurate distribution of subtypes would provide better understanding of study outcomes. However, this may not be the case in adults with ADHD, since subtypes are often clinician-determined (as in this study) compared with studies in children, in which subtype are determined by parent or teacher informants or a combination of both.

Clinical practice guidelines have established that although core symptoms are a reasonable method to diagnose ADHD in adults, the diagnostic criteria may not take into account other prominent and "impairing" symptom complaints.[24] ADHD management may benefit from focusing on a patient's "chief complaint," with particular focus on, for example, 2 to 3 symptoms or functional impairments that are the most bothersome to the patient. As reviewed by Gibbins et al,[24] children have been considered poor self-raters, and correlations between reports from secondary informants (i.e., parents and teachers) have not been decisive, whereas self-reports of most bothersome symptoms or functional impairments by adults with ADHD have been considered adequate, with information from secondary informants used to verify these symptoms and clinical response to treatment.

ADHD subtype studies may more accurately assess direct impact of one subtype on various functional outcomes versus another that was previously attributed to other causes or comorbid disorders. For example, a study using stringent smoking outcome criteria suggested that in adults with ADHD, symptoms of hyperactivity/ impulsivity were more likely than symptoms of inattention to

be associated with regular smoking.[25] However, other studies of adolescents with ADHD indicated the opposite—that, in general, inattention versus hyperactivity/ impulsivity was linked to smoking and substance abuse.[26–28] In one example, a study of adolescents with ADHD showed that the inattention subtype only was associated with a two-fold increase in risk for tobacco use.[26] This study determined that in early adolescence, inattention was significantly linked with tobacco use, even when other factors were controlled for, which included co-occurring conduct disorder, duration of tobacco use by age 12, poor parental communication in childhood, and African-American ethnicity (inversely predictive). It should be noted that in an analysis of data from the National Comorbidity Survey, a population-based prevalence study, current smoking rates and lifetime smoking prevalence were higher for those with lifetime mental illness or past-month mental illness than those with no mental illness.[29] These findings highlight the importance of considering the risks for comorbid substance use separately from the individual subtype of ADHD. Another study indicated that cocaine use in adult smokers with ADHD was associated with more severe symptomatology, specifically with increased hyperactivity/ impulsivity symptoms rather than symptoms of inattention.[30]

Limitations. A limitation of the current study is the open-label design, which may lack appropriate comparative reference arms and study controls. These *post-hoc* analyses were not statistically designed or powered to assess global severity, improvement measures, or clinical response with LDX treatment by ADHD symptom cluster subtypes. The small subgroup of participants in the predominantly hyperactivity/ impulsivity symptom cluster subgroup in comparison with those of the predominantly inattention and combined subgroups may have impacted the subsequent gender and age subgroup analyses.

Of importance, because the *DSM-IV-TR* diagnostic criteria were designed for diagnosing children with ADHD, they may not necessarily be representative of all adult symptoms or the severity level of particular items. In addition, the ADHD-RS-IV is designed to assess current ADHD symptoms, whereas the *DSM-IV-TR* classification of ADHD subtypes through the ACDS diagnostic interview requires respondents to have symptoms during childhood and during the six months preceding the interview.[16]

CONCLUSION

Long-term treatment with LDX was effective in improving ADHD symptoms in adult participants with predominantly inattention, hyperactivity/ impulsivity, and combined symptom clusters. Overall, percent reduction in ADHD-RS-IV scores from baseline at study endpoint between all study subgroups was comparable, regardless of ADHD subtype classification, as well as comparable with that in the overall study population. Groups exhibiting specific predominant subtype symptoms did not differ in clinical response to LDX treatment. The safety profile of LDX was consistent with that seen with other long-acting stimulants in the treatment of adults with ADHD.

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REFERENCES

1. American Psychiatric Association. Attention-deficit and disruptive behavior disorders. In: *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Text Revision.* Washington, DC: American Psychiatric Press Inc.; 2000:85–93.
2. Landgraf JM. Monitoring quality of life in adults with ADHD: reliability and validity of a new measure. *J Atten Disord.* 2007;11(3):351–362.
3. Barkley RA, Fischer M, Smallish L, Fletcher K. The persistence of attention-deficit/hyperactivity disorder into young adulthood as a function of reporting source and definition of disorder. J Abnorm Psychol. 2002;111(2):279–289.
4. Kessler RC, Adler L, Barkley R et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. *Am J Psychiatry.* 2006;163(4):716–723.
5. Millstein RB, Wilens TE, Biederman J, Spencer TJ. Presenting ADHD symptoms and subtypes in clinically referred adults with ADHD. *J Atten Disord.* 1997;2(3):159–166.
6. DuPaul GJ, Power TJ, Anastopoulos AD, Reid R. ADHD Rating Scale-IV: Checklists, Norms, and Clinical Interpretation. New York, NY: Guilford Press; 1998.
7. Swanson J, Lerner M, March J, Gresham FM. Assessment and intervention for attention-deficit/hyperactivity disorder in the schools. Lessons from the MTA study. *Pediatr Clin North Am.* 1999;46(5):993–1009.
8. Swanson JM, Kraemer HC, Hinshaw SP et al. Clinical relevance of the primary findings of the MTA: success rates based on severity of ADHD and ODD symptoms at the

end of treatment. *J Am Acad Child Adolesc Psychiatry.* 2001;40(2):168–179.
9. Frank E, Prien RF, Jarrett RB et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. *Arch Gen Psychiatry.* 1991;48(9):851–855.
10. Steele M, Jensen PS, Quinn DMP. Remission versus response as the goal of therapy in ADHD: a new standard for the field? *Clin Ther.* 2006;28(11):1892–1908.
11. Solanto M, Newcorn J, Vail L et al. Stimulant drug response in the predominantly inattentive and combined subtypes of attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol.* 2009;19(6):663–671.
12. Barbaresi WJ, Katusic SK, Colligan RC et al. Long-term stimulant medication treatment of attention-deficit/hyperactivity disorder: results from a population-based study. *J Dev Behav Pediatr.* 2006;27(1):1–10.
13. Adler LA, Goodman DW, Kollins SH et al, on behalf of the 303 Study Group. Double-blind, placebo-controlled study of the efficacy and safety of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder. *J Clin Psychiatry.* 2008;69(9):1364–1373.
14. Wigal T, Brams M, Gasior M et al, on behalf of the 316 Study Group. Randomized, double-blind, placebo-controlled, crossover study of the efficacy and safety of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder: novel findings using the adult workplace environment design. *Behav Brain Funct.* 2010;6:34.
15. Weisler R, Young J, Mattingly G et al, on behalf of the 304 Study Group. Long-term safety and effectiveness of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder. *CNS Spectr.* 2009;14(10):573–585.
16. Kessler RC, Green JG, Adler LA et al. Structure and diagnosis of adult attention-deficit/hyperactivity disorder: analysis of expanded symptom criteria from the Adult ADHD Clinical Diagnostic Scale. *Arch Gen Psychiatry.* 2010;67(11):1168–1178.
17. American Academy of Pediatrics Committee on Quality Improvement and Subcommittee on Attention-Deficit/Hyperactivity Disorder. Clinical practice guideline: diagnosis and evaluation of the child with attention-deficit/hyperactivity disorder. *Pediatrics.* 2000;105(5):1158–1170.
18. Wolraich ML, Hannah JN, Pinnock TY et al. Comparison of diagnostic criteria for attention-deficit hyperactivity disorder in a county-wide sample. *J Am Acad Child Adolesc Psychiatry.* 1996;35(3):319–324.
19. Lara C, Fayyad J, De GR et al. Childhood predictors of adult attention-deficit/hyperactivity disorder: results from the World Health Organization World Mental Health Survey Initiative. *Biol Psychiatry.* 2009;65(1):46–54.
20. Biederman J, Mick E, Faraone SV. Age-dependent decline of symptoms of attention deficit hyperactivity disorder: impact of remission definition and symptom type. *Am J Psychiatry.* 2000;157(5):816–818.
21. Hart EL, Lahey BB, Loeber R et al. Developmental change in attention-deficit hyperactivity disorder in boys: a four-year longitudinal study. *J Abnorm Child Psychol.* 1995;23(6):729–749.
22. Todd RD, Huang H, Todorov AA et al. Predictors of stability of attention-deficit/hyperactivity disorder subtypes from childhood to young adulthood. *J Am Acad Child Adolesc Psychiatry.* 2008;47(1):76–85.
23. Rowland AS, Skipper B, Rabiner DL et al. The shifting subtypes of ADHD: classification depends on how symptom reports are combined. *J Abnorm Child Psychol.* 2008;36(5):731–743.
24. Gibbins C, Weiss M. Clinical recommendations in current practice guidelines for diagnosis and treatment of ADHD in adults. *Curr Psychiatry Rep.* 2007;9(5):420–426.
25. Kollins SH, McClernon FJ, Fuemmeler BF. Association between smoking and attention-deficit/hyperactivity disorder symptoms in a population-based sample of young adults. *Arch Gen Psychiatry.* 2005;62(10):1142–1147.
26. Burke JD, Loeber R, Lahey BB. Which aspects of ADHD are associated with tobacco use in early adolescence? *J Child Psychol Psychiatry.* 2001;42(4):493–502.
27. Molina BS, Pelham WE, Jr. Childhood predictors of adolescent substance use in a longitudinal study of children with ADHD. *J Abnorm Psychol.* 2003;112(3):497–507.
28. Tercyak KP, Lerman C, Audrain J. Association of attention-deficit/hyperactivity disorder symptoms with levels of cigarette smoking in a community sample of adolescents. *J Am Acad Child Adolesc Psychiatry.* 2002;41(7):799–805.
29. Lasser K, Boyd JW, Woolhandler S et al. Smoking and mental illness: A population-based prevalence study. *JAMA.* 2000;284(20):2606–2610.
30. Saules KK, Pomerleau CS, Schubiner H. Patterns of inattentive and hyperactive symptomatology in cocaine-addicted and non-cocaine-addicted smokers diagnosed with adult attention deficit hyperactivity disorder. *J Addict Dis.* 2003;22(2):71–78. ■