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Authors:

Findling RL et al.

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Long-Term Effectiveness and Safety of Lisdexamfetamine Dimesylate in School-Aged Children with Attention-Deficit/ Hyperactivity Disorder

By Robert L. Findling, MD, Ann C. Childress, MD, Suma Krishnan, MS, MBA, and James J. McGough, MD

ABSTRACT

Introduction: Lisdexamfetamine dimesylate (LDX), a prodrug stimulant, is indicated for attention-deficit/hyperactivity disorder (ADHD) in children 6–12 years of age and in adults. In short-term studies, once-daily LDX provided efficacy throughout the day. This study presented here was conducted to assess the long-term safety, tolerability, and effectiveness of LDX in 6- to 12-year-olds with ADHD.

Methods: This open-label, multicenter, single-arm study enrolled children with *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision* criteria for ADHD. Following 1-week screening and washout periods, subjects were titrated to LDX 30, 50, or 70 mg/day over 4 weeks and placed on maintenance treatment for 11 months. The ADHD Rating Scale and Clinical Global Impression-Improvement scale measured effectiveness.

FOCUS POINTS

- Lisdexamfetamine dimesylate (LDX), a prodrug stimulant, is indicated for attention-deficit/hyperactivity disorder (ADHD) in children 6–12 years of age and in adults and, in short-term studies, once-daily LDX provided efficacy throughout the day.
- This open-label, multicenter, single-arm study was designed to assess the long-term safety, tolerability, and effectiveness of LDX 30, 50, and 70 mg/day in children 6–12 years of age with ADHD.
- The ADHD Rating Scale and Clinical Global Impression-Improvement scale were used as primary and secondary efficacy measures.
- The current results indicate that long-term LDX is generally well tolerated and effective in children with ADHD.

Results: Of 272 subjects receiving LDX, 147 completed the study. Most adverse events were mild to moderate and occurred during the first 4 weeks. There were no clinically meaningful changes in blood pressure or electrocardio-

Dr. Findling is director of Child and Adolescent Psychiatry at University Hospitals Case Medical Center in Cleveland, Ohio. Dr. Childress is affiliated with the Center for Psychiatry and Behavioral Medicine, Inc., in Las Vegas, Nevada. Ms. Krishnan is in Belvedere, California, and a former employee of New River Pharmaceuticals in Radford, Virginia. Dr. McGough is professor of clinical psychiatry at the Semel Institute for Neuroscience and Human Behavior and David Geffen School of Medicine at University of California—Los Angeles.

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Please direct all correspondence to: Robert L. Findling, MD, Director, Child and Adolescent Psychiatry, University Hospitals Case Medical Center, 11100 Euclid Ave., Cleveland, OH 44106; Tel: 216-844-1717, Fax: 216-844-5883; E-mail: robert.findling@uhhospitals.org.

graphic parameters. From baseline to endpoint, mean ADHD Rating Scale scores improved by 27.2 points ($P<.0001$). Improvements occurred during each of the first 4 weeks, and were maintained throughout. Based on Clinical Global Impression-Improvement scale scores, >80% of subjects at endpoint and >95% of completers at 12 months were rated "improved."

Conclusion: Long-term 30, 50, and 70 mg/day LDX was generally well tolerated and effective in children with ADHD.

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INTRODUCTION

The prevalence of attention-deficit/hyperactivity disorder (ADHD) is estimated at 8% to 10% in school-aged children.[1-3] Stimulants are most frequently used to treat ADHD and are regarded as first-line pharmacotherapy.[4] Their effectiveness and safety have been established in many clinical trials.[5] However, the lack of predictability and consistency associated with their bioavailability results in variable efficacy and duration of effect.[6-8] Further, abuse liability is a concern with the psychostimulants because these agents mediate reinforcing and euphoric effects if taken in high doses orally, or through nasal or parenteral routes.[9]

Lisdexamfetamine dimesylate (LDX [Vyvanse, Shire US Inc.]) is the first long-acting prodrug stimulant and is indicated for the treatment of ADHD.[10] LDX is a therapeutically inactive molecule. After oral ingestion, LDX is converted to l-lysine, a naturally occurring essential amino acid, and active d-amphetamine, which is responsible for the therapeutic activity. The conversion of LDX to d-amphetamine is not affected by gastrointestinal pH and is unlikely to be affected by alterations in normal gastrointestinal transit times.[10] LDX was developed with the goal of providing a duration of effect that is consistent throughout the day, with the potential for less abuse-related liking effects.

The short-term efficacy and safety of LDX in children 6–12 years of age have been established in clinical trials.[7,11] In short-term, placebo-controlled studies, LDX improved the symptoms of ADHD as early as the first week of treatment, and was well tolerated.[7,11] The fact that ADHD is a chronic condition pointed to the need for a study of LDX in long-term treatment. This study evaluates the long-term safety and effectiveness of LDX treatment in school-aged children up to 12 months.

METHODS

Participants

This long-term, open-label, multicenter, single-arm study enrolled children 6–12 years of age who met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision* criteria for a diagnosis of ADHD (combined or hyperactive subtypes) and who may or may not have received LDX treatment during a previous study.[7,11] Children were also required to be functioning at age-appropriate intellectual levels. Exclusion criteria included the presence of comorbid psychiatric illnesses, seizure disorder, or any general medical condition that might confound study results or contraindicate treatment. Also exclusionary were tic disorders, clinically significant electrocardiogram (ECG) or laboratory abnormalities, significant deviation from normal weight, hypertension, allergy to amphetamine, concomitant medications that could potentially interfere with the effectiveness and safety of amphetamines, or a concurrent illness that would preclude amphetamine use.

Parents or guardians of all prospective subjects signed an informed consent form, and all subjects gave assent after receiving written and oral information. This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice,[12] according to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines,[13] and the protocol was approved by the institutional review board of each institution.

Study Design

Following a 1-week screening and a 1-week washout period, subjects were titrated to LDX 30, 50, or 70 mg/day. Treatment was initiated at the minimum daily dose (30 mg), and subjects were seen weekly for the first 4 weeks, during which time doses could be increased or decreased in 20-mg/day increments to a maximum of 70 mg/day. The dose could be further adjusted at the monthly visits during the 11-month maintenance period. Subjects received one 30-, 50-, or 70-mg capsule orally per day in the morning.

The ADHD Rating Scale (ADHD-RS), consisting of 18 items, was completed by the investigator to assess ADHD symptomatology at each visit (visits 1–16). Each item was scored from 0–3, depending on the severity of symptoms.[14] Score on the Clinical Global Impression-Severity (CGI-S) scale established baseline global illness severity based on a 7-point scale ranging from 1 (no symptoms) to 7 (very severe symptoms). Score on the Clinical Global Impression-Improvement (CGI-I) scale, showing global improvement over time, was assessed at endpoint and at each postbaseline visit (2–16).[15] CGI-I score changes were rated on a 7-point scale, ranging from 1 (very much improved) to 7 (very much worse).[15]

Safety Assessments

Vital signs (blood pressure, heart rate, and body temperature), height, and weight were measured at all study visits. ECG parameters were assessed at the screening and baseline visits, and every 3 months thereafter. Clinical laboratory assessments of blood and urine were performed at screening, at 6 months, and at the final visit.

Statistical Analysis

The study planned to enroll at least 200 subjects in order to achieve at least 12 months of drug exposure for ~100 subjects. The intent-to-treat (ITT) population consisted of all subjects who received treatment and who had both a baseline score and at least one postbaseline primary efficacy assessment (ADHD-RS). Baseline measurements were collected at visit 1 except for subjects who completed a previous LDX study within 7 days of visit 1. The baseline measurements from that previous study were used for these subjects. The safety population was defined as all subjects who had enrolled in the washout phase or who entered from a previous study without a washout.

The primary outcome measure was the change in ADHD-RS from baseline to study endpoint for the ITT population using a paired *t*-test. For the paired *t*-test, the type I error rate for rejecting the null hypothesis (ie, that there were zero changes from baseline), was set at an alpha level of 0.05.

Descriptive statistics of the CGI (secondary efficacy measure) were summarized at baseline (CGI-S), and at each postbaseline visit and at study endpoint (CGI-I). The CGI-I was also analyzed for the proportion of subjects who were "improved" (CGI ≤2: "very much improved" or "much improved") and "not improved" (CGI ≥3).

The actual vital sign values obtained throughout the study were summarized using descriptive statistics. Vital sign outliers were defined as a change from baseline of systolic blood pressure (SBP) from <120 mmHg to ≥120 mmHg, diastolic blood pressure (DBP) from <80 mmHg to ≥80 mmHg, and pulse from <(mean + 2 SD) to ≥(mean + 2 SD) or from >(mean – 2 SD) to ≤(mean – 2 SD), where the mean and SD represented the baseline observations. Corrected QT (QTc) intervals for heart rate were calculated using Bazett's (QTc-B) and Fridericia's (QTc-F) formulae. ECG outliers were defined by cutoff values of ≥500 msec for QT, QTc-F, and QTc-B intervals. Increases in QT/QTc from baseline were categorized as ≥60 msec, 30–59 msec, and ≤29 msec for each postbaseline visit and endpoint.

Laboratory tests included hematology, biochemistry, and urinalysis. Descriptive statistics were presented for screening and endpoint values. The baseline for laboratory values was defined as the last valid assessment of the screening or baseline visits. For subjects who had enrolled in this study from a previous study, laboratory tests collected at the exit visit of the previous study were used as the screening values. Changes in laboratory tests from baseline were analyzed using a paired *t*-test. Findings of the physical examination were summarized for baseline and each visit.

Height and weight were measured at baseline and at each visit. Based on the 2000 Centers for Disease Control and Prevention Growth Chart of the United States, height and weight were normalized with respect to age and gender, and the normalized *z*-score and its change from baseline were calculated at each postbaseline visit and at endpoint.

RESULTS

Demographic and Baseline Characteristics

Of the 274 participants enrolled, 272 received LDX treatment. Of these, 271 had participated in previous double-blind trials of LDX (235 in an outpatient forced-dose titration trial[11]; and 36 in an analog classroom trial[7]), with approximately 95% participating in a previous study within 7 days of entering this study. Of the 272 treated subjects, 125 (46%) discontinued before completing this study; the primary reasons for discontinuation included withdrawal of consent (15.1%), loss to follow-up (13.6%), adverse events (AEs) (9.2%), lack of efficacy (4.0%), physician's decision (1.8%), protocol

violation (1.1%), sponsor's decision (0.4%), not eligible (0.4%), and other (0.4%).

Baseline and demographic characteristics are summarized in Table 1. Most subjects were male (69.5%) and white (52.6%). Mean age was 9.2 years. The majority (>90%) were diagnosed with combined subtype of ADHD; the average time since initial diagnosis was 2.3 years. Nine percent had prior therapy with amphetamines and 10% with methylphenidate; 73% had not received prior treatment for ADHD. During the study, the average rate of adherence, based on capsule count, was 91% for subjects who had previously received active study medication and 89% for those who had not. The most frequently prescribed dose of LDX was 50 mg/day (225 subjects), for a mean of 122.4 days. In addition, 133 subjects received LDX 70 mg/day for a mean of 175.7 days, and 272 subjects were prescribed LDX 30 mg/day for a mean of 71.8 days. Overall, the 272 subjects received LDX for a mean of 259 days.

TABLE 1.
Baseline and Demographic Characteristics of the Treated Population

Characteristics		LDX Treatment (n=272)
Sex, n (%)	Male	189 (69.5)
	Female	83 (30.5)
Race/Ethnicity, n (%)	White	143 (52.6)
	Black	70 (25.7)
	Hispanic	46 (16.9)
	Asian	3 (1.1)
	Native Hawaiian/Pacific Islander	2 (0.7)
	Native American	2 (0.7)
	Other	6 (2.2)
Age (years)	Mean±SD	9.2±1.8
Height (inches)	Mean±SD	54.2±4.2
Weight (pounds)	Mean±SD	78.2±23.1
Diagnosis, n (%)	Combined	262 (96.3)
	Hyperactive	10 (3.7)
Duration of disease (years)	Mean±SD	2.3±2.5
Duration of treatment in this study (days)	Mean±SD	259±133.6
Previous study treatment	LDX	197
	Placebo/None	75

LDX=lisdexamfetamine dimesylate; SD=standard deviation.

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Safety Analyses

Over the course of the study, 213 (78%) of 272 treated subjects experienced a total of 987 treatment-emergent AEs, 97.5% of which were mild or moderate in severity. The treatment-emergent AEs occurring in >5% of treated subjects are shown in Table 2; the majority occurred within the first 4 weeks. Of the AEs with a >5% incidence, insomnia and vomiting occurred more often in the patients receiving higher doses (for insomnia: 17% for 70 mg/day, 9% for 50 mg/day, and 4% for 30 mg/day; for vomiting: 6%, 4%, and 3%, respectively).

No deaths were reported in this study. Five serious AEs were reported in four subjects, one patient with mania and agitation (medical history included cerebral palsy and ongoing oppositional defiant disorder) and one each with lacerated spleen, acute dehydration, and gastroenteritis; all were deemed unrelated to study medication by the investigator. Twenty-five (9%) of the 272 subjects treated with LDX discontinued treatment due to AEs. The most common (>1%) reasons given for discontinuation were aggression, irritability, and decreased appetite (n=3 each; 1.1%).

For vital signs, mean (±SD) changes from baseline at endpoint were 1.4±13.7 beats per minute for pulse, 0.7 ±10.0 mmHg for SBP, and 0.6±8.3 mmHg for DBP. For ECG measures, mean changes from baseline at endpoint were 3.5±13.1 beats per min-

TABLE 2.
Treatment-Emergent Adverse Events Occurring in >5% of Subjects

Adverse Events	Subjects, n (%)
Any event	213 (78)
Decreased appetite	90 (33)
Headache	48 (18)
Weight decrease	48 (18)
Insomnia	47 (17)
Upper abdominal pain	29 (11)
Upper respiratory tract infection	29 (11)
Irritability	28 (10)
Nasopharyngitis	26 (10)
Vomiting	23 (9)
Cough	19 (7)
Influenza	16 (6)

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ute for heart rate, –0.2±10.2 msec for PR interval, –27.2±115.2 msec for RR interval, –1.0±5.8 msec for QRS interval, –3.4±23.0 msec for QT interval, 1.4±15.5 msec for QTc-F interval, and 4.2±19.3 msec for QTc-B interval; all of these changes were deemed clinically nonsignificant. At endpoint, 7.0%, 4.8%, and 6.6% of subjects had SBP, DBP, and pulse rate outliers, respectively. There were no apparent trends in vital sign outliers, and the medical monitor determined that they were not clinically meaningful.

Two subjects had a QT-interval change from baseline of ≥60 msec, one at month 3 and one at month 12, and two additional subjects had QTc-B interval changes from baseline of ≥60 msec at month 9; no subject had a QTc-F interval change of ≥60 msec. No patient showed a QT, QTc-F, or QTc-B interval ≥500 msec at any treatment visit. Abnormal ECGs, as described by the investigator, were observed in 33 subjects, but the medical monitor determined that none of the abnormal ECGs was clinically meaningful.

Similarly, no clinically significant changes were observed in laboratory values or findings from physical examinations. At endpoint, subject height had increased an average 1.5 inches (P<.05) and subject weight increased an average 0.6 pounds (P=NS vs baseline). When normalized using z-scores, which took expected growth into consideration, the average changes in z-score for height and weight at endpoint were –0.08 (P<.05 vs baseline) and –0.40 (P=NS vs baseline), respectively. The age- and sex-normalized mean change in weight from baseline in percentile was –13.4 over 1 year (average percentile at baseline and 12 months were 60.6 and 47.2, respectively).

Primary Efficacy Results

Compared with baseline, there was significant improvement in the ADHD-RS total score at endpoint. At endpoint, the mean ADHD-RS total score change from baseline was –27.2±13.0 points in the ITT population, a >60% change from baseline (P<.0001). Mean ADHD-RS inattentive subscale score at endpoint changed –13.4±7.0 points, a 60% change from baseline (P<.0001), while mean ADHD-RS hyperactivity score at endpoint changed –13.8±7.0 points, a 66% change from baseline (P<.0001).

Changes from baseline in ADHD-RS were observed at each postbaseline visit (P<.0001). After improvements during the first 4 weeks of study participation, the reductions in ADHD-RS scores were maintained throughout the subsequent 11 months of treatment (Figure 1).

Secondary Efficacy Results

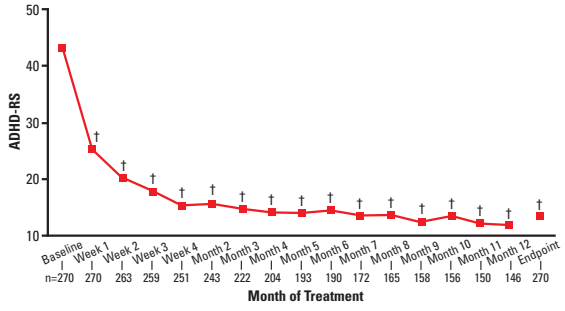
On the CGI-I scale, 81.1% of subjects in the ITT population were rated as improved at study endpoint (Figure 2). The percentage of subjects who improved increased weekly during the 4-week dose titration period (51.5% at week 1, 75.7% at week 2, 84.6% at week 3) to 90.0% by the time of dose stabilization at week 4. Thereafter, the percentage of subjects who improved remained at ~90% for each monthly assessment and was 95.9% for subjects completing 12 months of treatment.

DISCUSSION

This was the first long-term study to evaluate the effectiveness and safety of LDX in school-aged children. LDX treatment resulted in statistically and clinically significant improvements in the ADHD-RS total score. The improvements were seen during the titration period, and ADHD symptom reductions were observed over the remaining 11 months. For subjects who completed 12 months of treatment, mean ADHD-RS score was reduced >60% from baseline levels. In addition, >80% of the ITT population was rated as "improved" (CGI-I ≤2) at study endpoint on the CGI-I scale.

The safety findings of this long-term study are consistent with those observed in previous short-term studies of LDX.[11] LDX was found to be

FIGURE 1.
ADHD-RS average by each month of treatment*



* Results at each time point are reported for all subjects participating at that time point (n). Results at endpoint are last-observation-carried-forward results for the ITT population.

† P<.0001; paired t-test

ADHD-RS=Attention-Deficit/Hyperactivity Disorder Rating Scale; ITT=intent-to-treat.

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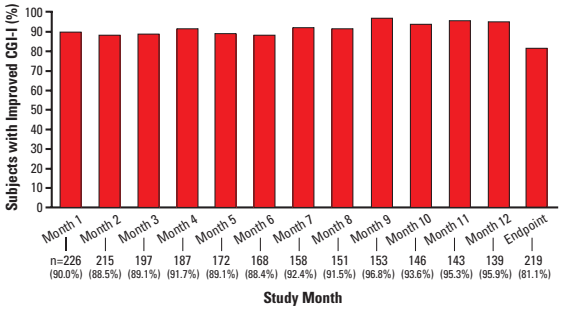
well tolerated for up to 12 months of treatment, with most reported AEs being mild to moderate in severity. The discontinuation rate due to AEs in this study was similar to other long-term follow-up studies with mixed amphetamine salts extended-release, osmotic-release methylphenidate, or atomoxetine.[16-18] Additionally, the current study found no clinically meaningful trends in pulse, blood pressure, or ECG measures after up to 1 year of LDX administration.

Although no significant long-term changes were evident in various cardiovascular parameters, clinicians should use good clinical judgment when prescribing stimulants to treat children with ADHD. The class labeling for these agents warns of serious cardiovascular AEs. Children and adolescents who are being considered for treatment with stimulants should have a careful medical history, including family history, and a physical examination to assess the presence of cardiovascular disease.

Height increased an average 1.5 inches ($P<.05$) and subject weight increased an average 0.6 pounds (P=NS vs baseline). However, consistent with other stimulants, there was a slowing in growth rate measured by body weight compared to age and sex controls. Therefore, growth should be monitored during treatment with stimulants.

This study had several limitations. First, subjects with many comorbid psychiatric diseases were excluded, as were those with abnormal blood pressure, or pulse values, subjects with cardiovascular disorders, and those with some other general medical conditions. Thus, the effects of long-term LDX use in patients with significant comorbid psychiatric or general medical conditions are not known. In addition, the study relied on collection of AE data through observation and open-ended inquiry and did not make use of a structured side-effects assessment. Failure to include the latter has been known to lead to underreporting of AEs. Also, since the majority of subjects had received LDX in a previous trial and chose to continue in a long-term, open-label study, it is likely that those who had acute AEs had already discontinued treatment. Thus, the low rates of AEs reported here might be biased toward use of LDX in individuals with acceptable levels of known tolerability.

FIGURE 2.
Percentage of subjects with improved CGI-I scale scores from baseline by treatment month*



* Results at each time point are reported for all subjects participating at that time point (n). Results at endpoint are last-observation-carried-forward results for the ITT population. CGI-I=all subjects rated "much improved" or "very much improved."

CGI-I=Clinical Global Impression-Improvement scale; ITT=intent-to-treat.

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CONCLUSION

The effective management of ADHD generally requires long-term treatment, and the findings presented here indicate that treatment with LDX was effective and generally well tolerated over 12 months. However, previous studies[10,19] have suggested that children who consistently receive medication have a temporary slowing in growth rate. Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining weight as expected may need to have their treatment interrupted.[10]

In conjunction with earlier findings,[7,11] the results of the present study add to, and support, the effectiveness and safety of LDX in the treatment of children with ADHD. ***CNS***

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