Lisdexamfetamine Dimesylate: The First Prodrug Stimulant

by DAVID W. GOODMAN, MD

AUTHOR AFFILIATIONS: Dr. Goodman is from the Adult Attention Deficit Disorder Center of Maryland, Johns Hopkins at Green Spring Station, Lutherville, Maryland; and Assistant Professor, Johns Hopkins University School of Medicine, Department of Psychiatry and Behavioral Sciences, Baltimore, Maryland.

ABSTRACT

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurobehavioral disorders affecting children. The symptoms often persist into adolescence and adulthood, causing significant impairments. ADHD often remains undiagnosed and untreated, and because of its potential long-term impact, recognition, diagnosis, and management in children have become increasingly important. Education about ADHD and the available therapy options is important for both the patient and the caregiver to achieve more effective treatment. Efficacy and safety data on stimulant medications have provided evidence for their effectiveness in treating ADHD. Although they remain the first-line treatment, the need for multiple daily dosing and concerns about the general risk profile of stimulants have led to the development of new agents, including once-daily formulations that provide prolonged duration of action. However, pharmacokinetic variability of these formulations can result in inconsistent effects in some patients. The use of prodrug technology and the development of the only prodrug stimulant, lisdexamfetamine dimesylate

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ADDRESS CORRESPONDENCE TO: David W. Goodman, MD, Johns Hopkins at Green Spring Station, 10751 Falls Road, Suite 306, Baltimore, MD 21093; E-mail: dgoodma4@jhmi.edu

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(LDX), provide a promising treatment option for ADHD with an improved overdose potential risk profile when compared to d-amphetamine. This review of LDX, which presents the efficacy, safety, and pharmacokinetic profile of this new class of stimulant, is designed to help the physician better understand the clinical use of this agent in treating ADHD.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is one of the most common behavioral disorders in childhood, estimated to occur worldwide in as many as eight percent to 12 percent of children.[1] Childhood ADHD persists into adolescence and adulthood in an estimated 10 percent to 70 percent of cases,[2–4] with impairing symptoms experienced by at least 50 percent of these patients.[1] A US epidemiologic adult ADHD study reported a prevalence of 4.4 percent, yet only a small fraction of adults with ADHD (10.9%) had received treatment prior to the survey.[5]

Stimulants have the most evidence for efficacy and safety for the treatment of ADHD and remain the first-line therapy for ADHD.[6] Concerns about the general risk profile of stimulant medications in clinical practice are common, including the association between ADHD and substance use disorder.[7] Tampering, including mechanical manipulation, of some formulations has allowed misuse through administration via intended or non-intended routes and has led to the need for the development of new agents,[8] including nonstimulants, developed as nonabusable alternatives for ADHD.

Since 2000, once-daily, modified-release stimulant formulations that provide prolonged delivery have been developed for the treatment of ADHD.[9] While it is not known if this pharmacokinetic variability contributes to therapeutic duration variability, formulations with less pharmacokinetic variability may provide more consistent clinical results.[10] More recently, development of long-acting formulations has included a prodrug stimulant representing a new class of agents for the treatment of ADHD that has less pharmacokinetic variability and the potential to produce more consistent clinical effects and less abuse potential.

PRODRUGS: A NEW CLASS OF STIMULANTS FOR THE TREATMENT OF ADHD

The concept of prodrugs as a useful formulation was proposed as early as 1958 by Adrien Albert, who described the alteration of the physiochemical properties of drugs to render them pharmacologically inactive until metabolized in the body to the active drug moiety.[11] By definition, a prodrug is a compound that undergoes biotransformation before exhibiting its therapeutic effect.[12,13] Some therapeutically effective prodrugs include the oral fluoropyrimidine chemotherapy agents, capecitabine and uracil, prodrugs of 5-fluorouracil, and the thienopyridine antiplatelet agents, ticlopidine and clopidogrel.

Lisdexamfetamine dimesylate (LDX, Vyvanse™; Shire US Inc.) is the only prodrug stimulant and is indicated for the treatment of ADHD in children aged 6 to 12 years. LDX is a therapeutically inactive molecule; after oral ingestion, it is converted to l-lysine, a naturally occurring essential amino acid, and active d-amphetamine, which is responsible for the drug's activity. LDX is unlike other long-acting stimulants in that it is not an encapsulated matrix or a bead formulation, but instead has extended-release characteristics because it is a prodrug.[9] LDX was developed with the goal of providing once-daily treatment with an extended duration of effect that is consistent throughout the day, with a reduced potential for abuse, overdose toxicity, and drug tampering.

SOLUBILITY AND PHARMACOKINETIC STUDIES OF LISDEXAMFETAMINE DIMESYLATE

***In-vitro* study.** The pH solubility profile of LDX in saturated buffered aqueous solutions (pH 1–13) was determined by a high-pressure liquid chromatography assay that was specific for LDX. Within a physiologically relevant pH range (pH 1–8), the solubility profile of LDX was not affected by the pH of the solution, and increasing the pH from 8 to 13 resulted only in modest reductions in LDX solubility.[14] The results suggest that the conversion of LDX to d-amphetamine should not be affected by gastrointestinal pH. Therefore, alkalinizing agents, such as sodium bicarbonate or other antacids, should not affect the absorption of LDX. Because LDX is a prodrug that is rapidly absorbed from the gastrointestinal tract and converted to d-amphetamine, it is not a controlled-release delivery vehicle and is unlikely to be affected by alterations in normal gastrointestinal transit times.

Phase I study. The pharmacokinetic profile of the LDX formulation was determined in a phase I, open-label, randomized, single-dose, three-treatment, three-period, crossover study.[14,15] This comprised three 1-week study periods with 7-day washout between doses. Eighteen healthy volunteers (9 males, 9 females) aged 18 to 55 years received a single LDX dose of 70mg under three dose conditions: (1) fasting and with capsule only; (2) solution containing capsule contents; and (3) intact capsule after a high-fat meal. The analysis showed that when LDX was administered in solution or as an intact capsule with or without food, d-amphetamine systemic exposure bioavailability was equivalent for all dosing conditions as evidenced by AUC and C_{max} values. However, significant differences in t_{max} values (mean hours±SD) were seen

TABLE 1. Pharmacokinetics of d-amphetamine after oral administration of 70mg/day of LDX or 30mg of MAS XR

	N	Mean±SD	Median	Range	%CV
C_{max} (ng/mL)					
LDX 70mg/day	8	155±31.4	164	99.9–187	20.3
MAS XR 30mg/day	9	119±52.5	96.9	49.8–218	44
T_{max} (hours)					
LDX 70mg/day	8	5.1±0.8	4.5	4.5–6.0	15.3
MAS XR 30mg/day	9	6.6±3.5	6	3.0–12.0	52.8
AUC (ng·h/mL)					
LDX 70mg/day	8	1326±285.8	1380	851.8–1618	21.6
MAS XR 30mg/day	9	1019±436.2	885	492.7–1899	42.8

%CV=coefficient of variance
Adapted with permission from Ermer, et al.[16]

between the fasted (3.8 ± 1.0) and fed (4.7 ± 1.1) conditions (p<0.001). Overall, these results demonstrated that LDX may be taken with or without food or dissolved in water and immediately consumed, without affecting the overall extent of absorption.

Phase II study. The inter-subject (patient to patient) pharmacokinetic variability of d-amphetamine after oral administration of LDX and mixed amphetamine salts (MAS XR; Adderall XR®) was determined in a phase II study.[16] Previous pharmacokinetic studies of MAS XR in healthy volunteers have shown considerable inter-subject variability in serum plasma d-amphetamine levels (C_{max}) over time.[10] This randomized, multicenter, double-blind, three-treatment, three-period, crossover study included children aged 6 to 12 years with a primary diagnosis of ADHD as defined by *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) criteria.[17] As a secondary trial objective, pharmacokinetic data were reported at the last visit for the largest patient cohort, eight patients who received 70mg/day of LDX and nine patients who received 30mg/day of MAS XR (equivalent d-amphetamine base doses) for one week. Levels of d-amphetamine reached median t_{max} in 4.5 hours (mean 5.1, range 4.5–6) for LDX and 6.0 hours (mean 6.6, range 3–12) for MAS XR (Table 1).[16] Corresponding percent coefficients of variation were 15.3 percent and 52.8 percent, respectively, meaning that the t_{max} is 3.5 times less variable with LDX than MAS XR. Mean (± SD) maximum plasma concentrations (C_{max}) were 155±31.4ng/mL for LDX and 119±52.5ng/mL for MAS XR. Corresponding coefficients of variation were 20.3 percent and 44.0 percent, respectively. Release of d-amphetamine was more predictable after oral administration of 70mg of LDX than 30mg of MAS XR as measured by t_{max} and C_{max}. Overall, LDX demonstrated low inter-subject variability of pharmacokinetic measures with consistent exposure to d-amphetamine.[16]

EFFICACY STUDIES WITH LISDEXAMFETAMINE DIMESYLATE

The efficacy and safety of LDX for the treatment of ADHD were established on the basis of results from two controlled clinical trials in children aged 6 to 12 years who met DSM-IV criteria for ADHD.[18–20]

Phase II study. Biederman and Boellner, et al., recently conducted a multicenter, double-blind, placebo-controlled, crossover-design, analog-classroom study in 52 children with ADHD aged 6 to 12 years (mean, 9.1±1.7 years).[18,20] After three weeks of open-label dose adjustment and optimization with 10, 20, or 30mg/day of MAS XR, subjects were randomly assigned in a crossover design to treatment with the same doses of MAS XR; equivalent LDX doses of 30, 50, and 70mg/day, respectively; or placebo once daily for one week. Efficacy was assessed by means of the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) Deportment Rating Scale, the Permanent Product Measure of Performance (PERMP) scale, and the Clinical Global Impressions-

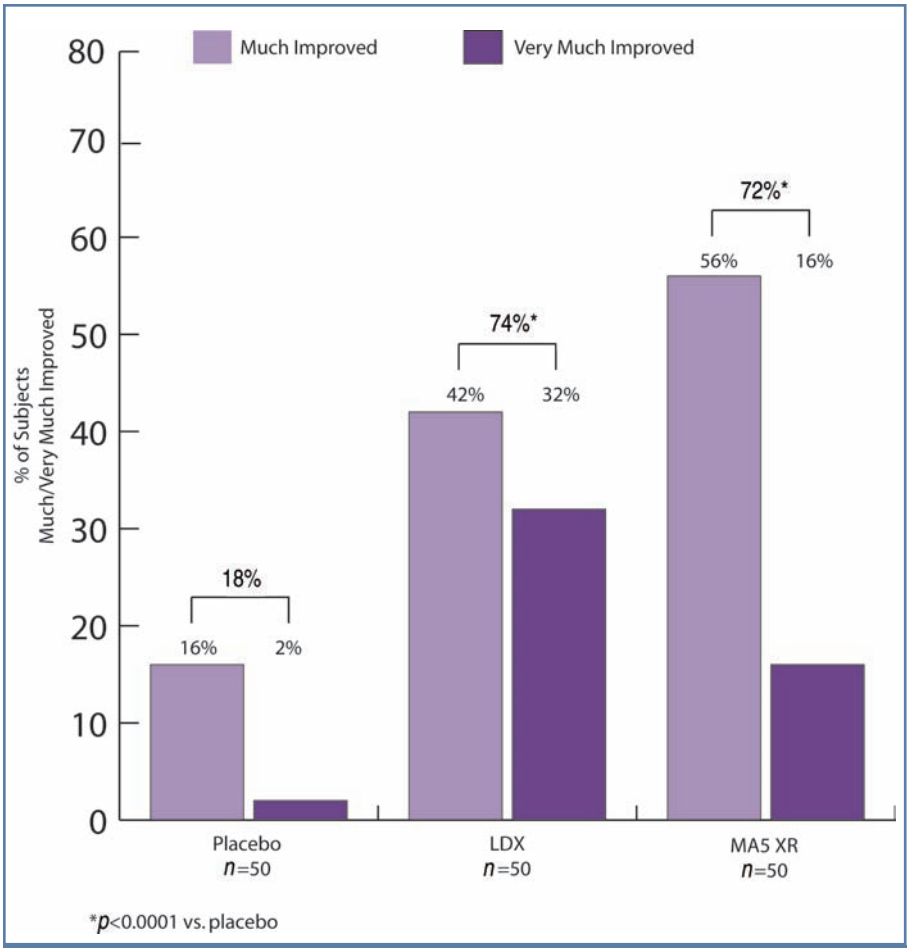

FIGURE 1. Clinical Global Impressions Scale - Mean improvement at assessment from baseline for intent-to-treat population who received placebo, LDX, or MAS XR.[18,20]

Adapted with permission from Boellner, et al.[20]

Improvement (CGI-I) scale. For each measure of efficacy (SKAMP, PERMP, and CGI-I scales), similar improvements were seen in children receiving LDX and MAS XR at each time point over 12 hours, and each treatment was significantly better at all doses than placebo ($p<0.0001$). On the CGI-I, ratings of very much improved or much improved were seen in 74 percent of subjects who received LDX and 72 percent of those who received MAS XR, compared with 18 percent of subjects receiving placebo (Figure 1). Thirty-two percent of subjects who received LDX were rated very much improved compared with 16 percent of subjects who received MAS XR and two percent of subjects who received placebo. Adverse events (AEs) were reported by 29 of the 52 subjects during the study. The most common AEs reported with MAS XR during the open-label, dose-titration phase were headache (15%), decreased appetite (14%), and insomnia (10%). During the double-blind phase, 16 percent of LDX-treated subjects, 18 percent of MAS XR-treated subjects, and 15 percent of placebo-treated subjects reported AEs. AEs that occurred during the double-blind phase with an incidence rate of ≥2 percent were insomnia (8%), decreased appetite (6%), and anorexia (4%) in LDX-treated subjects; decreased appetite (4%), upper abdominal pain (4%), vomiting (2%), and insomnia (2%) in MAS XR-treated subjects; and vomiting (4%), insomnia (2%), and upper abdominal pain (2%) in placebo-treated subjects. No serious AEs were reported.

Phase III study. Biederman, et al., also conducted a double-blind, multicenter, placebo-controlled, parallel-group study in 290 children (201 boys and 89 girls) aged 6 to 12 years (mean, 9±1.8 years) with a primary diagnosis of ADHD.[19] The children were randomly assigned to fixed-dose treatments consisting of oral doses of 30, 50, or 70mg/day of LDX or placebo once daily each morning for four weeks. A forced-dose design was employed for LDX treatments to assess the efficacy and tolerability of each individual dose as follows: 30mg for four weeks, 50mg (30mg/day for Week 1, with forced-dose escalation to 50mg/day for Weeks 2–4), or 70mg (30mg/day for Week 1, with forced-dose escalation to 50mg/day for Week 2 and 70mg/day for Weeks 3 and 4). Efficacy was assessed using the parent- and investigator-completed ADHD Rating Scale (ADHD-RS), the CGI-I, and the Conners Parent Rating Scale (CPRS). Of the 290 randomized patients, 230 completed the study (56 patients received LDX 30mg, 60 patients received LDX 50mg, 60 patients received LDX 70mg, and 54 patients received placebo). Significantly greater improvements in ADHD-RS total scores (mean change from baseline to endpoint) were seen with each of the three LDX doses compared with placebo ($p<0.001$ for all comparisons). Based on ADHD-RS scores at treatment endpoint, the effect sizes were 1.21, 1.34, and 1.60 in the 30-, 50-, and 70-mg groups, respectively, determined by the corresponding between-group differences. Throughout the study, assessment of symptomatic behaviors of ADHD using the CPRS in the morning (~10 AM), afternoon (~2 PM), and evening (~6 PM) showed significantly greater improvements ($p<0.01$) in symptom control throughout the day in each LDX dose group than in patients who received placebo. CGI-I scores were significantly

improved (p<0.0001) with all three doses of LDX compared with placebo; ratings of very much improved or much improved were seen in ≥70 percent of patients in the LDX treatment groups compared with 18 percent of patients who received placebo.

Overall, AEs in patients who received LDX were typical of amphetamine products.[19] The most frequently reported AEs among patients receiving LDX compared with placebo were decreased appetite (39% vs. 4%), insomnia (19% vs. 3%), upper abdominal pain (12% vs. 6%), headache (12% vs. 10%), irritability (10% vs. 0%), vomiting (9% vs. 4%), weight decrease (9% vs. 1%), and nausea (6% vs. 3%). Most AEs were mild to moderate and occurred in the first week of treatment. Treatment with LDX was not associated with statistically significant changes in laboratory values, mean electrocardiogram (ECG) values (including corrected QT intervals), and systolic or diastolic blood pressure measures.[21] There was a statistically significant change in pulse relative to placebo at endpoint, with each active treatment group showing an increase from baseline. The least-squares mean differences versus placebo in pulse rate from baseline to endpoint were 0.3±1.2 bpm for the LDX 30mg group (baseline pulse 82.2 bpm), 2.0±1.2 bpm for the 50mg group (baseline pulse 81.7 bpm), and 4.1±1.2 bpm for the 70mg group (baseline pulse 82.8 bpm) (p=0.0224, ANCOVA). No statistically significant changes from baseline were seen for any individual treatment week. Observed changes were not clinically meaningful and were consistent with results seen with other stimulant agents.

Long-term efficacy and safety of LDX-phase III study. A 12-month, open-label, single-arm study was conducted to determine the long-term efficacy and safety of LDX in children.[22] The intent-to-treat population consisted of 189 boys and 83 girls aged 6 to 12 years (mean, 9.2 years) with DSM-IV diagnosis for ADHD. Subjects were previously enrolled in a double-blind clinical study and may or may not have received prior treatment with LDX, except for one subject who was newly enrolled. After a one-week washout period, all subjects were started on 30mg/day of LDX and either maintained on this dose or titrated by the investigator to a dose of 50 or 70mg/day over a four-week period, based on effectiveness and tolerability. Treatment was maintained for up to 11 more months during which the doses could be changed for optimal effectiveness and tolerability; however, most of the dose changes occurred early in the study, suggesting that tolerance to medication did not occur.

Efficacy was assessed using the ADHD-RS scores at endpoint and from baseline over the course of treatment, and the CGI-I scale.[22] At endpoint (last observation), there was significant improvement (>60%, p<0.0001) in ADHD-RS total scores compared with baseline. Beginning at week 4, reductions in ADHD-RS total scores occurred and were seen throughout the 12-month treatment period. Using a clinician-completed rating scale (CGI), more than 80 percent of the patients were rated as much improved or very much improved by study endpoint. Additionally, more than 95 percent of those who completed 12 months of treatment were improved.

LDX was generally well tolerated, with most of the treatment-related AEs occurring during the first eight weeks of treatment. AEs reported in 10 percent or more of the patients included decreased appetite, weight decrease, headache, insomnia, upper abdominal pain, upper respiratory infection, nasopharyngitis, and irritability. During the second eight weeks of treatment, only decreased appetite and weight decrease occurred in more than five percent of subjects. No statistically or clinically significant changes in ECG values or blood pressure were seen over the study period.[23] The mean changes from baseline were 0.3 to 3.5 bpm for pulse; -1.8 to 1.0mmHg for systolic blood pressure; and -1.0 to 0.7mmHg for diastolic blood pressure. The mean increases from baseline in heart rate ranged from 1.8 to 5.2 bpm. Mean changes in QT/QTc intervals ranged from -4.7 to -1.8msec for QT, -0.4 to 2.2msec for QTc-F, and 1.1 to 6.4 msec for QTc-B. Twenty five (9%) of the 272 LDX-treated subjects discontinued treatment because of AEs, including three for decreased appetite, three for irritability, three for aggression, two for anxiety, and two for decreased weight. There were no discontinuations related to ECG findings.

LDX is the only product for the treatment of ADHD that includes abuse liability data in the product label. Support for the reduced abuse potential of LDX relative to immediate-release d-amphetamine has been shown in two abuse liability studies in human subjects.

ABUSE LIABILITY DATA

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abuse potential of LDX relative to immediate-release d-amphetamine has been shown in two abuse liability studies in human subjects.[24,25]

The abuse potential of oral LDX and d-amphetamine was compared in 38 adult non-ADHD subjects who had a history of stimulant abuse.[24] In the double-blind, placebo-controlled, crossover study, oral doses of 50mg, 100mg (equivalent to 40mg of d-amphetamine), and 150mg of LDX and 40mg of d-amphetamine sulfate were administered. For the primary measure of subjective responses on a scale of the drug-liking effects, the Drug Rating Questionnaire-Subject (DRQS) Liking Scale, the maximum post-dose change in score from baseline was significantly greater in the subjects who received d-amphetamine 40mg than the equivalent 100-mg dose of LDX ($p<0.05$) when compared to placebo. Mean drug-liking scores peaked between 1.5 and 2 hours post-dose in subjects who received d-amphetamine and between 3 and 4 hours post-dose in subjects who received LDX, in keeping with the slower rise in LDX blood level. At a higher dose of LDX (150mg; equivalent to 1.5 times the dose of d-amphetamine used in this study), the maximum drug-liking score was similar to that after 40mg of d-amphetamine; however, the peak effect of LDX was two hours later than that of d-amphetamine, reflecting a slow ascent in serum level.

In the second double-blind crossover study, equivalent intravenous doses of 50mg of LDX and 20mg of d-amphetamine were administered over a two-minute period at 48-hour intervals to nine adult non-ADHD subjects who had a history of drug abuse.[25] Intravenous LDX at doses of 50mg did not produce significantly different liking scores as measured by the DRQS Liking Scale compared with placebo ($p=0.29$). In contrast, equivalent doses of 20mg of intravenous d-amphetamine did have significantly more liking effects than placebo ($p=0.01$). Mean peak behavioral and subjective effects were observed at 15 minutes post-dosing for d-amphetamine and between 1 and 3 hours for LDX.

CONCLUSION

Recognition, diagnosis, and management of ADHD in children have become increasingly important in the primary care setting. Stimulants remain the first-line treatment for ADHD, but the need for multiple daily dosing can be problematic for some patients when using short-acting stimulants. Concerns about the general risk profile of stimulant medications have led to the need for the development of new agents, including once-daily stimulant formulations that provide a prolonged duration of action and may have a reduced potential for risk of abuse. Although long-acting formulations have been shown to be effective in treating ADHD, pharmacokinetic variability can theoretically result in inconsistent duration of action across patients. The recent development and approval of LDX, the only prodrug stimulant, represents a new class of agents for the treatment of ADHD. Clinical evidence supports the effectiveness of LDX in the treatment of children with ADHD, while exhibiting reduced pharmacokinetic variability in maximum concentration and time to maximum concentration, and a tolerability profile similar to that of other long-acting stimulants. LDX has been shown to provide significant symptom control throughout the day for children with ADHD. In human abuse liability studies, LDX produced lower subjective responses on a test of drug-liking effects than dose-equivalent immediate-release d-amphetamine. In human abuse liability studies with oral and intravenous administration, LDX produced lower subjective responses on a test of drug-liking effects in adult substance abusers compared to dose-equivalent immediate-release d-amphetamine.[24,25] The reduced drug-likability is a unique attribute of LDX relative to other stimulant preparations and is cited in the prescribing information.[26]

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