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Lisdexamfetamine dimesylate: A prodrug stimulant for the treatment of ADHD in children and adults

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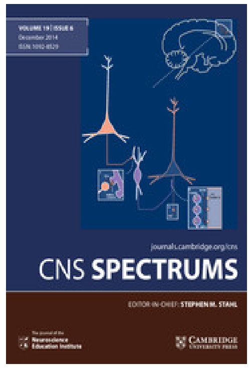

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is a highly genetic neuropsychiatric disorder that can cause impairment at school, work, home, and in social relationships. Once considered a childhood disorder, as many as 65% of children with ADHD continue to exhibit symptoms into adulthood. While a mainstay of ADHD patient care, immediate-release stimulant use has been constrained by concerns about safety, tolerability, and issues related to nonmedical use and abuse. These concerns have prompted interest in developing modified versions or new delivery systems for stimulants. Prodrugs have been used in pharmaceutical development to optimize delivery of an active drug or to minimize toxicity. Prodrugs are pharmacologically inactive compounds that require in vivo conversion to release therapeutically active medications. Lisdexamfetamine dimesylate (LDX) is an inactive, water-soluble prodrug in which d-amphetamine is bonded to l-lysine, a naturally occurring amino acid. After oral ingestion, LDX is metabolized into l-lysine and active d-amphetamine. This review of LDX presents the efficacy, safety, and pharmacokinetic profile of this novel stimulant medication,

FOCUS POINTS

- Once-daily stimulant medications continue to be the first-line treatment for attention-deficit/hyperactivity disorder (ADHD).
- Lisdexamfetamine dimesylate (LDX) is the first long-acting prodrug stimulant indicated for the treatment of ADHD. Clinical evidence supports the safety and efficacy of LDX for the treatment of ADHD in children 6–12 years of age and adults.
- No significant cardiovascular effects or effects on sleep quality have been observed in studies of adults taking LDX. Clinical data suggest that LDX is generally well tolerated in children and adults, with a safety profile consistent with long-acting stimulant use.

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and is intended to help clinicians understand its role in treating children and adults with ADHD.

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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a highly heritable neuropsychiatric disorder associated with significant impairments in occupational, academic, neuropsychological, and social functioning.[1] ADHD is commonly diagnosed in children and adolescents, and affects 3% to 7% of children in the United States.[2,3] Children with ADHD may experience significant social, emotional, and academic problems, including low self-esteem, poor peer relationships, delinquency, and substance abuse. Evidence shows that ADHD often runs in families, with a heritability of 76%.[2,4] Children and adolescents with ADHD often present with comorbid psychiatric disorders, including major depression, anxiety disorders, conduct disorder, and oppositional defiant disorder.[5] ADHD in adolescents is also associated with suboptimal academic achievement and a greater use of illicit drugs.[5]

While once thought of as a childhood disorder, ADHD symptoms persist into adulthood in up to 65% of children with ADHD.[6] Diagnostic criteria for ADHD in adults are still based on the 18 symptoms that were originally identified in children with ADHD. These diagnostic symptoms are centered around disruptions in attention and/or hyperactivity-impulsivity that are prevalent in children with ADHD.[3] Inattention is a key component of the behaviors associated with ADHD in both children and adults. Adults with ADHD may present with poor time management or a lack of attention to detail. Patients are easily distracted, find it difficult to concentrate, and are forgetful when faced with tasks that they find monotonous or boring.[7,8] Hyperactivity, while a common feature among children with ADHD, is likely to be less overt in adults. Rather than the constant activity seen in children, adults are more likely to report restlessness, difficulty sitting through meetings, and a feeling of being chronically "on the go."[3,8] They may have a sloppy workspace and may avoid work that is challenging or requires a maintained focus. Patients with impulsive tendencies have great difficulty waiting in line, will interrupt conversations, may act without thinking, or experience emotional volatility.[3,7,8]

The estimated prevalence of ADHD in adults throughout the US is ~4.4%, or 9 million adults.[9] ADHD in adults is highly comorbid with mood disorders, anxiety disorders, and substance-use disorders (SUDs). In the National Comorbidity Survey Replication,[9] only 10.9% of adults with ADHD were currently receiving treatment for ADHD, although as many as 53.1% of women and 36.5% of men were being treated for other comorbid mental health or substance-related disorders. Adults with ADHD frequently present in crisis and are often initially diagnosed with mood and anxiety disorders, temper problems, or substance abuse. Clinicians frequently treat the presenting crisis and miss the underlying problems from ADHD. Untreated ADHD then creates a pervasive pattern of repeated difficulties or impairment. Continuing impairment from ADHD may cause individuals to struggle with academic, career, and personal goals, or may cause significant difficulty within interpersonal relationships.

Functional imaging studies and cognitive neuroscience have focused on disruptions in brain regions normally involved in attention/cognition, executive function, working memory, response inhibition, and/or reward/motivation. Structural imaging studies have identified smaller volumes in the frontal cortex, cerebellum, and subcortical structures in adults and children with ADHD compared with those without ADHD.[1] Additionally, neuroanatomic studies in children with ADHD have shown delayed maturation in the prefrontal cortex, an area known to be involved with executive function and working memory.[10]

UNMET NEEDS IN THE TREATMENT OF ADHD

Pharmacotherapy continues to be the mainstay of treatment for ADHD.[2] All US Food and Drug Administration-approved medications for the treatment of ADHD enhance the physiological effects of either norepinephrine, dopamine, or both. ADHD stimulants are all derived from various preparations of either methylphenidate (MPH) or amphetamines. MPH is felt to exert its clinical effect by blocking the reuptake of dopamine and norepinephrine, while amphetamines are felt to work by both blocking reuptake and enhancing release of dopamine and norepinephrine. Immediate-release (IR) and extended-release (ER) formulations of MPH, mixed amphetamine salts (MAS-XR), and dex-

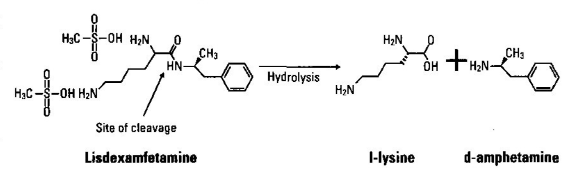
troamphetamine are available as pharmacologic treatment options.

Despite the efficacy of short-acting stimulants, they can "wear off" during the day, which may increase symptoms of inattention during late morning or afternoon activities.[11] Therefore, multiple doses during the day may be required to achieve continuous symptom management. Generally, longer-acting ER formulations may eliminate the need for in-school medication administration and provide ongoing clinical effect during the school day.[12] Long-acting stimulants have traditionally been created utilizing mechanical delivery systems or beaded preparations. Although these improved treatment options exist, unmet therapeutic needs remain, including consistent delivery of medication, adequate duration of action, and reduced potential for abuse.

PRODRUG STIMULANT LISDEXAMFETAMINE DIMESYLATE

Lisdexamfetamine dimesylate (LDX), the first long-acting prodrug stimulant, is indicated for the treatment of ADHD in children (approved in 2007) and adults (approved in 2008).[13] LDX is a therapeutically inactive, water-soluble molecule. After oral ingestion, LDX is converted to l-lysine and active d-amphetamine (Figure 1),[14] which is responsible for the therapeutic effect. LDX is thought to be primarily absorbed intact in the small intestines and into the portal circulation, where hydrolysis is thought to occur by enzymatic cleavage mediated by enzymes primarily found on the red blood cells.[15,16] Hydrophilic drugs, such as the prodrug LDX, are thought to be unable to permeate the blood-brain barrier. While this specific hypothesis has not been tested with LDX, the requirement for enzymatic cleavage to free the d-amphetamine

FIGURE 1.
Chemical structure of lisdexamfetamine dimesylate[14]



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may help explain the consistent pharmacokinetic parameters, the sustained duration of action, and the decreased abuse likeability scores, which will be detailed in the remainder of this review.

Pharmacokinetic and Formulation Studies

Nonclinical in vivo and in vitro studies have been conducted to investigate the absorption[16] and hydrolysis[15,16] of LDX using rodent and human tissues. Results of these studies suggest that absorption of LDX occurs primarily in the small intestine and that conversion of LDX into active d-amphetamine occurs primarily in the blood. Intact LDX was readily absorbed through duodenal, jejunal, and ileal intestinal segments, and underwent presystemic enzymatic conversion to active d-amphetamine in rodents.[16] LDX was converted to amphetamine in the presence of rat and human whole blood, but conversion did not occur in plasma or human white blood cells or platelets.[15,16] In vitro studies of enzymatic conversion by human blood cell fractions demonstrated that LDX was converted into active d-amphetamine by red blood cells.[15,16]

In an open-label study,[17] six healthy adult volunteers 22–52 years of age were administered a single oral 70 mg dose of 14C-radiolabelled LDX in solution following a fast of at least 10 hours. Blood samples were drawn predose and at time points up to 120 hours postdose. Plasma pharmacokinetic analysis was conducted for active d-amphetamine and the intact parent compound, LDX. Analysis showed LDX to be quickly absorbed and extensively converted to d-amphetamine. Systemic exposure to d-amphetamine was ~20-fold higher than systemic exposure to intact LDX, which exhibited rapid elimination with a mean apparent terminal elimination half-life of 0.47 hours.[17] Urinary excretion was the predominant route of elimination of radioactivity, with ~96% of the oral dose radioactivity recovered in the urine over a period of 120 hours. Of the radioactivity recovered in the urine, 41.5% of the dose was related to amphetamine, 24.8% to hippuric acid, and 2.2% to intact LDX. Plasma concentrations of unconverted LDX were low and transient, generally becoming nonquantifiable by 8 hours after administration.[17]

Shojaei and colleagues[18] reported that the absorption of LDX to d-amphetamine was not affected by pH in an in vitro study. Krishnan and Zhang[14] reported the results of a randomized, open-label, three-period crossover study of 18

healthy adult volunteers. A single LDX dose of 70 mg was administered to each subject under three conditions: fasting, a solution containing the capsule contents, and an intact capsule after a high-fat meal. The results demonstrated that systemic exposure to d-amphetamine was bioequivalent when administered with or without food or in solution. This finding suggests that LDX is not likely to be affected by changes in gastrointestinal transit times.[14]

LDX, unlike other currently approved long-acting stimulant formulations, does not rely on encapsulated matrix or beaded formulations to prolong the absorption period of the active drug.[19] MAS-XR is an example of a mechanically formulated capsule that contains two types of drug-containing beads; one bead designed to be released immediately and the other to be released in the lower intestine, where pH levels are higher.[20] This formulation creates a pH-dependent delivery system designed to give a double-pulsed delivery of amphetamine, which prolongs the release of the medication.[20] Using this technology, consistent drug delivery may be compromised by alterations in gastric pH due to coadministration with proton pump inhibitors.[21]

When compared with MAS-XR, LDX pharmacokinetics were significantly more consistent when coadministered with the proton pump inhibitor omeprazole.[21] Regarding other drug-drug interactions, d-amphetamine, the active ingredient in LDX, is known to inhibit monoamine oxidase.[13] The ability of d-amphetamine and its metabolites to inhibit various cytochrome P450 (CYP) isozymes and other enzymes has not been adequately elucidated. In vitro experiments with human microsomes indicate minor inhibition of CYP2D6 by amphetamine and minor inhibition of CYP1A2, 2D6, and 3A4 by one or more metabolites, but there are no in vivo studies of CYP enzyme inhibition.[13] In a study[22] conducted to analyze potential inhibitory drug-drug interactions with the seven major CYP isoforms using pooled human liver microsomes, neither concentration-dependent nor mechanism-based inhibition of human CYP isoforms was demonstrated for LDX during in vitro testing.

LDX has predictable pharmacokinetic characteristics. Three published studies[23-25] have examined the pharmacokinetic variability and dose proportionality of LDX. Biederman and colleagues[23] compared the interpatient pharmacokinetic variability of d-amphetamine after administration of LDX (30, 50, or 70 mg/day) and MAS-XR (10, 20, or 30 mg/day) in children with a primary diagnosis of ADHD. LDX demonstrated considerably lower interpatient variability of pharmacokinetic measures compared with MAS-XR, indicating consistent d-amphetamine pharmacokinetics between patients. For example, the mean maximum observed drug concentration (Cmax) values for d-amphetamine following MAS-XR (30 mg) or LDX (70 mg) administration were 119±52.5 ng/mL and 155±31.4 ng/mL, respectively (Figure 2).[23,24] As measured by coefficient of variance, the interpatient variability of C_{max} following LDX administration was lower than that observed following MAS-XR administration (20.34 ng/mL and 43.96 ng/mL, respectively), indicating that LDX may provide more consistent drug delivery.[23] A further pharmacokinetic study of healthy adults confirmed low interpatient variability in pharmacokinetic values and also demonstrated low intrapatient variability in values when measured over all doses within individual subjects.[25]

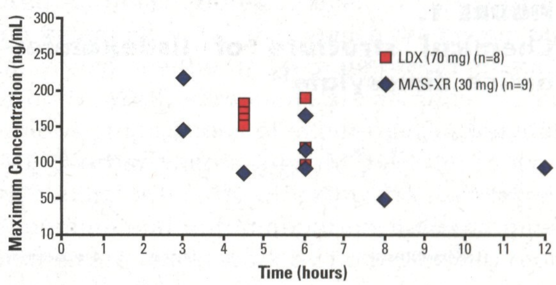
Efficacy Studies

The efficacy of LDX for the treatment of ADHD has been demonstrated in three controlled clinical trials[23,26,27] and two open-label trials[28,29] in children, as well as two randomized, controlled trials[30,31] and one open-label trial[32] in adults (Table).

Studies in Children

Biederman and colleagues[23] conducted a multicenter, randomized, double-blind, placebo-controlled, analog classroom crossover study of 52 children 6–12 years of age with ADHD. After 3

FIGURE 2.
Time to peak plasma d-amphetamine concentration in individual patients following LDX (70 mg) and MAS-XR (30 mg)[24]



LDX=lisdexamfetamine dimesylate; MAS-XR=mixed amphetamine salts extended-release.

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weeks of open-label dose adjustment and optimization with 10, 20, or 30 mg/day of MAS-XR, the children received, in randomized order, 1 week each of their optimized dose of MAS-XR, an approximately equivalent dose of 30, 50, or 70 mg of LDX, and placebo.[23] The primary efficacy measure was the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP)-Deportment[33] rating scale. Secondary efficacy measures included the Permanent Product Measure of Performance (PERMP)[34] derived measures and the Clinical Global Impressions (CGI) scale.[35] Treatment with LDX and MAS-XR significantly improved measures of efficacy on the SKAMP-Deportment and PERMP-Attempted (both *P*<.0001) scales. A post-hoc analysis[36] showed that at 12 hours postdose, LDX produced significantly greater improvement compared with MAS-XR on both PERMP-Attempted and PERMP-Correct measures (*P*<.05; Figure 3).[23,36] On the CGI scale, ratings of very much improved or improved were noted in 74% of children who received LDX and 72% of children who received MAS-XR versus 18% of those who received placebo.[23] Additionally, CGI ratings of very much improved were noted in 32% of children who received LDX and 16% of children who received MAS-XR versus 2% of those who received placebo.[37]

Biederman and colleagues[26] also conducted a double-blind, multicenter, placebo-controlled, parallel-group study in 290 children (6–12 years of age) with a primary diagnosis of ADHD.

TABLE.
Trials of LDX Efficacy

Study	Trial Type	Duration	Interventions	Primary Outcome Measure	Efficacy Outcome
Children					
Biederman et al, 2007[23]	RCT n=52	4 weeks	Open-label MAS-XR 10/20/30 mg LDX 30/50/70 mg Placebo	SKAMP-Deportment[33]	*P*<.0001 vs placebo *P*<.0001 vs placebo
Biederman et al, 2007[26]	RCT n=290	4 weeks	LDX 30/50/70 mg, forced titration Placebo	ADHD-RS-IV[38]	*P*<.001 vs placebo
Wigal et al, 2008[27]	RCT n=129	6 weeks	LDX 30/50/70 mg Placebo (4 week, open-label, dose-optimization phase followed by 2 week crossover phase)	SKAMP[33]	*P*<.005 vs placebo
Findling et al, 2008[28]	Open-label n=272	1 year	LDX 30/50/70 mg	ADHD-RS-IV[38]	Overall: >60% reduction from baseline *P*<.0001
Findling et al, 2008[29]	Open-label, dose-optimization n=318	7 weeks	Open-label LDX 20/30/40/50/60/70 mg	ADHD-RS-IV[38]	Mean change in ADHD-RS-IV total scores[38] from baseline was significant (*P*<.0001)
Adults					
Adler et al, 2008[30]	RCT n=420	4 weeks	LDX 30/50/70 mg Placebo	ADHD-RS-IV[38]	Overall: 40%–45% reduction from baseline *P*<.0001 vs placebo
Brams, 2009[31]	RCT n=142	13 weeks	LDX 30/50/70 mg Placebo	PERMP[34]	*P*<.0001 vs placebo
Weisler et al, 2009[32]	Open-label, single-arm extension n=345	1 year	LDX 30/50/70 mg	ADHD-RS-IV[38]	Mean change in ADHD-RS-IV total scores[38] from baseline was significant (*P*<.0001)

LDX=lisdexamfetamine dimesylate; RCT=randomized clinical trial; MAS-XR=extended-release mixed amphetamine salts; SKAMP=Swanson, Kotkin, Agler, M-Flynn, and Pelham rating scale; ADHD-RS-IV=Attention-Deficit/Hyperactivity Disorder Rating Scale Version IV; PERMP=Permanent Product Measure of Performance.

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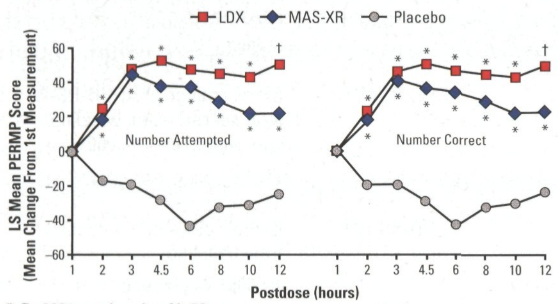
Children were randomly assigned to receive LDX (30, 50, or 70 mg/day) with forced dose titration or placebo for 4 weeks. Efficacy was assessed using the ADHD Rating Scale Version IV (ADHD-RS-IV),[38] the Conners' Parent Rating Scale (CPRS),[39] and the CGI; tolerability was also assessed throughout the study. Significantly greater improvements in ADHD-RS-IV scores were seen with each of the three LDX doses throughout the day compared with placebo (P<.001 for all comparisons).[26] The effect sizes of treatment with LDX were 1.39, 1.42, and 1.73 for 30, 50, and 70 mg/day of LDX, respectively.[40] LDX showed similar significant improvements in both the inattention and hyperactivity subscales of the ADHD-RS-IV. Using the CPRS at home, parents of patients in each LDX dose group reported significantly greater improvements in symptom control throughout the day (morning, ~10 AM; afternoon, ~2 PM; evening, ~6 PM). Compared with placebo (18%), CGI-Improvement (CGI-I) ratings of very much improved or much improved were seen in ≥70% of children receiving LDX.[26]

Wigal and colleagues[27] evaluated the efficacy of LDX in 129 school-aged children with ADHD in a 6 week, randomized, double-blind, placebo-controlled, analog classroom crossover study. Significant improvements on SKAMP-Deportment scores, the primary efficacy measure, were noted in the active treatment group compared with placebo (P<.005) beginning at 1.5 hours postdose and persisting up to and including 13 hours.[27]

Findling and colleagues[28] conducted a 12 month, open-label study to determine the long-term efficacy of LDX in children. The intent-to-treat (ITT) population included 272 children 6–12 years of age with previously diagnosed ADHD, some of whom may have received LDX during a prior study.[23,26,28] After a 1 week screening period and a 1 week washout period, subjects were titrated to 30, 50, or 70 mg/day of LDX over 4 weeks and then placed on a maintenance dose for 11 months. Week 4 reductions in the ADHD-RS-IV total score were maintained throughout the 12 month treatment period (Figure 4).[28] At endpoint, the ADHD-RS-IV total score change from baseline was -27.2 points (>60% reduction; P<.0001).[28]

Findling and colleagues[29] also conducted an open-label, 7 week, dose-optimization study of daily LDX doses up to 70 mg in 318 children 6–12 years of age with ADHD. Subjects were dosed to optimal symptom response and tolerability. The primary efficacy assessment was the ADHD-RS-IV, and secondary assessments included the CGI-I and the Parent Global Assessment (PGA). Because symptoms of ADHD in children are often accompanied by deficits in executive functioning and abnormalities in emotional expression,[41,42] additional secondary measures included the Expression and Emotion Scale for Children (EESC)[43] and the Behavior Rating Inventory of Executive Function (BRIEF)–Parent Form.[44] At

FIGURE 3.
Change in children's PERMP scores over 12 hours[23,36]



* P<.0001 vs placebo; N=50.

† P<.0001 vs placebo and P<.05 LDX vs MAS-XR.

Study was not designed to compare LDX and MAS-XR groups.

Adapted from Biederman et al, 2007,[23] with permission from Elsevier, and Lopez et al, 2008.[36]

PERMP=Permanent Product Measure of Performance; LS=least squares; LDX=lisdexamfetamine dimesylate; MAS-XR=mixed amphetamine salts extended-release.

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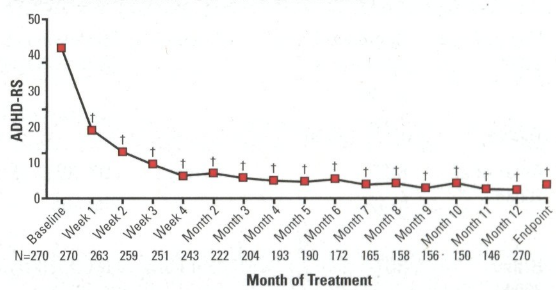
FIGURE 4.
Children's ADHD-RS-IV average by each month of treatment[28]*



* 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 intent-to-treat population.

† P<.0001; paired t-test.

Used with permission from Findling et al, 2008.[28]

ADHD-RS-IV=Attention-Deficit/Hyperactivity Disorder Rating Scale Version IV.

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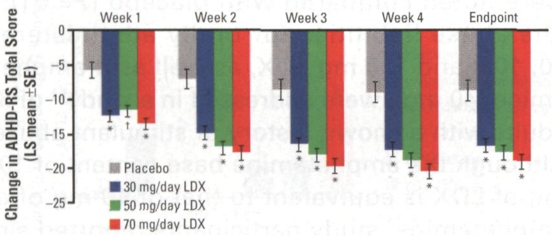
endpoint, the mean change in ADHD-RS-IV total scores from baseline was significant ($P<.0001$).[29] By weeks 2–3 of the study, most subjects showed improvement by clinician-rated CGI-I and parent-rated PGA. Also at endpoint, the mean EESC total and subscale scores and the BRIEF Global Executive Composite scores were significantly improved. Overall, LDX was effective as rated by both investigator and parental assessment.[29]

Studies in Adults

Adler and colleagues[30] evaluated the efficacy of LDX in 420 adults with moderate-to-severe ADHD. The study was a randomized, double-blind, placebo-controlled, parallel-group, 4 week study with forced dose escalations. After a 7–28 day washout period, patients received 30, 50, or 70 mg/day of LDX or placebo for 4 weeks. Baseline symptom severity as measured by ADHD-RS-IV with adult prompts ranged from 39.4 (placebo) to 41.1 (LDX groups).[30] Treatment with LDX at all three doses was significantly more effective than placebo, with a mean reduction in ADHD-RS-IV scores of 16.2–18.6 points in the active treatment groups compared with 8.2 after placebo ($P<.0001$ versus placebo).

Significant changes in ADHD-RS-IV scores ($P<.001$) were observed after the first week of LDX treatment and continued at each postbaseline visit (Figure 5).[30] Each week during the dose titration period, a significantly greater proportion of subjects in each active treatment group had a reduction in ADHD-RS-IV total score of ≥30% ($P<.01$). Treatment effect sizes at endpoint versus placebo, calculated using mean changes in ADHD-RS-IV scores, were 0.73, 0.89, and 0.99 for the 30, 50, and 70 mg groups, respectively.[30] The investigators also measured the efficacy of LDX using the CGI-I scale. On this scale, the percentages of adults taking LDX rated by investigators as improved or very much improved at endpoint were 57% (30 mg), 62% (50 mg), and 61% (70 mg), significantly more ($P<.01$) than with placebo.[30]

FIGURE 5.
Change from baseline in adult ADHD-RS-IV scores in the intent-to-treat population[30]



* $P<.0001$ vs placebo; † $P<.001$ vs placebo.

Reprinted by permission from Adler et al, 2008.[30] Copyright 2008, Physicians Postgraduate Press.

ADHD-RS-IV=Attention-Deficit/Hyperactivity Disorder Rating Scale Version IV; LS=least squares; LDX=lisdexamfetamine dimesylate.

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In a separate presentation of the short-term adult data,[30] Adler and colleagues[45] analyzed the effect of LDX on sleep quality using the Pittsburgh Sleep Quality Index (PSQI). At baseline, patients with ADHD generally had global PSQI scores >5, suggesting that they were poor sleepers. LDX was not associated with statistically significant changes in overall sleep quality.[45]

Additional post hoc subpopulation analyses[46] of these adult data[30] revealed that LDX treatment was effective and generally well tolerated in 36 patients with a history of depression or mood disorders not currently requiring treatment with antidepressants. LDX produced similar improvements in ADHD-RS-IV and CGI-I scores in those with and without a history of depressive disorders.[46] In another exploratory post hoc analysis,[47] LDX produced similar improvements in ADHD-RS-IV and CGI-I scores in subjects with and without a history of SUD. Lastly, when the data were assessed as a function of gender,[48] LDX treatment produced significant improvements in ADHD-RS-IV scores for both male and female subjects when compared with same-sex subjects treated with placebo.

The efficacy and duration of effect of LDX in adults with ADHD have also been assessed in a randomized, double-blind, placebo-controlled crossover study[31] in a simulated workplace environment. Three doses of LDX (30, 50, and 70 mg) were compared with placebo in 142 adults with ADHD. When compared with those given placebo, patients treated with LDX demonstrated significant improvement in average total PERMP scores (289.5 and 312.9, respectively; $P<.0001$) and significantly better mean PERMP total scores at each postdose assessment from 2–14 hours ($P<.01$ for all).[31]

Long-term LDX treatment efficacy in adults was evaluated in a 12 month, open-label, single-arm, long-term extension study[32] of LDX 30, 50, or 70 mg/day for 4 weeks, and then continued for 11 months with dose adjustments made as necessary. Patients treated with LDX showed significant improvements in ADHD-RS-IV total scores relative to baseline at all vis-

its, beginning as early as week 1.[32] At endpoint, 84% of patients had CGI-I scores showing improvement relative to baseline, indicating that LDX efficacy was sustained throughout the year. LDX treatment was also associated with statistically significant improvements in global PSQI scores.[32]

Safety and Tolerability Studies

In the multicenter, randomized, double-blind, placebo-controlled, analog classroom crossover study[23] of 52 children 6–12 years of age with ADHD, the most common adverse events (incidence >2%) in children who took LDX included insomnia, decreased appetite, and anorexia. In the double-blind, multicenter, placebo-controlled, parallel-group study[26] of 290 children 6–12 years of age with a primary diagnosis of ADHD, most adverse events were mild to moderate and occurred during the first week; these included decreased appetite, insomnia, upper abdominal pain, headache, irritability, vomiting, weight loss, and nausea. In the 6 week, randomized, double-blind, placebo-controlled, analog classroom crossover study[27] of LDX in 129 school-aged children with ADHD, small mean increases in blood pressure and small weight reductions consistent with the known effects of stimulant use were observed.

LDX was well tolerated during the 12 month duration of the open-label study[28] of 272 children 6–12 years of age with previously diagnosed ADHD. Most reported adverse events (97.5%) were mild or moderate in severity. Of the adverse events with a >5% incidence, most occurred within the first 4 weeks of treatment. Insomnia and vomiting were seen at a higher incidence in patients who received higher doses of LDX (17% for 70 mg/day, 9% for 50 mg/day, and 4% for 30 mg/day for insomnia; and 6%, 4%, and 3% for vomiting, respectively). No patient showed a QTc interval ≥500 msec at any treatment visit and no observed abnormal electrocardiographic measurements were considered clinically meaningful by the investigators.[28] Lastly, in an open-label, 7 week, dose-optimization study[29] of daily LDX doses up to 70 mg in 318 children 6–12 years of age with ADHD, LDX was generally well tolerated, with a safety profile consistent with long-acting stimulant use.

The most common adverse events in the randomized, double-blind, placebo-controlled, parallel-group, 4 week study[30] of adults with forced dose escalations were decreased appetite, anorexia, insomnia, nausea, diarrhea, anxiety, feeling jittery, and dry mouth. Analysis of the cardiovascular effects of LDX showed no effects on QTcF measurements or clinically meaningful trends for systolic or diastolic blood pressure.[49] During the dose-optimization phase of the double-blind, placebo-controlled crossover study[31] in a simulated workplace environment, the most frequently reported adverse events (≥5%) for adult patients were decreased appetite, dry mouth, headache, insomnia, upper respiratory tract infection, irritability, nausea, anxiety, and feeling jittery. In the 12 month, open-label, single-arm, long-term extension study[32] of LDX 30, 50, or 70 mg/day for 4 weeks, and then continued for 11 months with dose adjustments made as necessary in adults, LDX was well tolerated; most adverse events occurred early in treatment and were of mild or moderate severity. Subjects showed a mean increase of ~3.2 beats/minute from baseline to endpoint. The mean changes in systolic and diastolic blood pressure from baseline to endpoint were 3.1 and 1.3 mmHg, respectively.[32]

Abuse-Liability Studies

LDX is currently the only FDA-approved product for the treatment of ADHD that includes abuse-liability data in the product label.[13] In a double-blind, placebo-controlled, abuse-liability study,[50] equivalent intravenous doses of 50 mg of LDX and 20 mg of d-amphetamine were administered to adults without ADHD and with a history of drug abuse. A 50 mg dose of LDX administered intravenously did not produce abuse-liking effects significantly different than placebo; however, after intravenous administration of 20 mg of IR d-amphetamine, significantly greater increases in abuse-related liking scores were noted compared with placebo (P=.01).[50] The abuse liabilities for orally administered 50, 100, and 150 mg LDX, as well as d-amphetamine (40 mg), were addressed in a study[51] of 36 adults with a known history of stimulant abuse. Although the amphetamine base content of 100 mg of LDX is equivalent to that of 40 mg of d-amphetamine, study participants reported significantly lower mean abuse-related liking scores with LDX 100 mg than with d-amphetamine 40 mg (Figure 6; P<.05).[51] Abuse-related liking scores of LDX at a dose corresponding to a 50% higher amphetamine base (LDX 150 mg) were similar to d-amphetamine 40 mg.[51]

CLINICAL PLACEMENT

LDX is a long-acting prodrug, amphetamine-based stimulant which can be used once daily for children or adults with ADHD.[13] Particular areas where LDX is unique and may therefore be the preferred agent include:

Coverage across the lifespan. LDX is FDA approved and has significant efficacy at the same dosages in both children and adults with ADHD.[23,26-32]

Water solubility. LDX is FDA approved to be dissolved in water.[13] When dissolved in water, LDX maintains its sustained duration of action and has a slightly sweet taste.

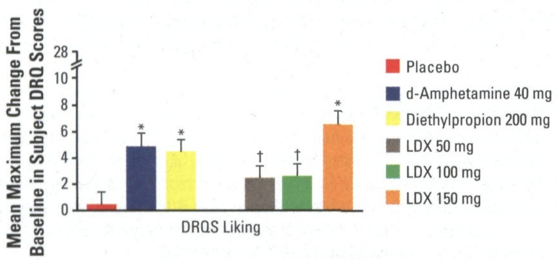
Consistent pharmacokinetics. The enzymatic conversion of LDX into d-amphetamine is primarily due to enzymes on the red blood cells[15,16] and is not affected by changes in gastric pH or transit time.[14,18,21]

Sustained duration of action. LDX has demonstrated efficacy at 12 and 13 hours postdose in pediatric clinical trails[23,27] and up to 14 hours in an adult clinical trial.[31] These results suggests that LDX has the longest proven efficacy of any stimulant indicated for use in the treatment of ADHD in children or adults.

Lack of worsening of sleep quality. Sleep quality was prospectively measured in an adult LDX clinical trial.[30,45] After 4 weeks of treatment, self-reported daytime functioning had significantly improved for patients treated with LDX, no worsening of sleep parameters was observed, and transient insomnia, which was a common side effect, gradually resolved in most patients.[30,45]

Reduced potential for substance abuse. LDX is a preferred agent for patients or families with a history of substance abuse. Oral or intravenous administration of LDX has been associated with less likeability than similar doses of d-amphetamine.[50,51] LDX cannot be ground or dissolved into a short-acting stimulant.[51]

FIGURE 6.
Maximum mean change in DRQS liking score from baseline[51]



* *P*<.01 vs placebo; † *P*<.05 vs d-amphetamine.

Reprinted from Jasinski and Krishnan, 2009,[51] with permission from SAGE Publications.

DRQS=Drug Rating Questionnaire–Subject; LDX=lisdexamfetamine dimesylate.

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CONCLUSION

ADHD is a common neurobehavioral disorder that typically presents first in childhood and often persists into adulthood, causing significant impairments in multiple domains of function. Treatment strategies include the use of stimulant and nonstimulant medications, as well as adjunctive cognitive-behavioral skills training and psychotherapy. Despite a long history of proven efficacy, the need for multiple daily doses can be problematic for patients when using short-acting stimulants. Additionally, concerns about the general risk profile of stimulants have led to the need for new, once-daily formulations that provide a prolonged duration of action.

While long-acting stimulants are effective in treating ADHD, increased pharmacokinetic variability may result in inconsistent efficacy both within individual patients from day to day and between patients. This enzymatic process by which LDX is converted into d-amphetamine in the blood results in very consistent pharmacokinetics that are less effected by gastric contents, gastric pH, or gastrointestinal transit time than are other long-acting stimulants. LDX requires a physiologic enzymatic conversion and represents the first of a novel class of agents for treating ADHD in children and adults. Clinical evidence supports the effectiveness and tolerability of LDX in adults and children. Additionally, LDX offers the benefits of less pharmacokinetic variability and a tolerability profile consistent with long-acting stimulant use.

The measures used in clinical trials of LDX reflect the *DSM-IV* symptom cluster for ADHD and demonstrate significant improvements over placebo throughout the day. LDX was effective in pediatric studies, with significant improvements in behavior, attention, quality of work, and number of attempted and correct math problems up to 13 hours postdose. At home, parent-rated improvements in symptom control were reported throughout the day up to 6 PM. In addition, robust effect sizes have been shown in both pediatric and adult studies with LDX 30, 50, and 70 mg. Among children, there was no worsening of mean emotional expression scores. Children

also showed improvement in parent ratings of executive function. Analyses of adult subjects over 4 weeks showed no significant cardiovascular effects or effects on sleep quality. In patients with a history of depression or SUD, LDX produced similar improvements in ADHD-RS-IV and CGI-I scores compared with subjects who were not depressed or substance abusers. In human abuse-liability studies, LDX produced lower subjective drug-liking responses than dose-equivalent IR d-amphetamine. Results of long-term, open-label studies in children and adults have shown LDX to be effective in improving symptoms of ADHD over a range of doses while being generally well tolerated, with a safety profile consistent with long-acting stimulant use. *CNS*

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