Review of Lisdexamfetamine Dimesylate in Adults With Attention-Deficit/Hyperactivity Disorder

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ABSTRACT: Lisdexamfetamine dimesylate (LDX) is the first prodrug stimulant used for the treatment of attention-deficit/hyperactivity disorder (ADHD) dosed once daily. Due to its long-acting properties, LDX remains pharmacologically inactive until an enzymatic process predominantly associated with red blood cells converts it to the active ingredient, D-amphetamine and the amino acid lysine. The efficacy of LDX over placebo has been demonstrated in several studies in adults with moderate to severe ADHD with significant improvements noted in ADHD rating scales, Clinical Global Improvement scores, and assessments of executive function, for all doses of LDX (30-70 mg daily). Lisdexamfetamine dimesylate has demonstrated efficacy at 14 hours post dose in adults and may be used as a long-acting stimulant for managing ADHD symptoms, which may extend late into the day. Lisdexamfetamine dimesylate has demonstrated a safety profile consistent with long-acting stimulants use. Relevant English language articles were identified through computerized searches of MEDLINE (PubMed and EMBASE) from 1995 to 2016 using the following search terms: lisdexamfetamine dimesylate, attention-deficit hyperactivity disorder, NRP104, and Vyvanse.

KEYWORDS: Lisdexamfetamine, dimesylate, attention-deficit hyperactivity disorder, ADHD, NRP 104, vyvanse

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by inappropriate levels of inattention, hyperactivity, and/or impulsiveness at higher levels than typically observed in individuals at comparable age and development.[1] Attention-deficit/hyperactivity disorder generally presents in children and adolescents with 99% of the patients being diagnosed before age 16,[2] and up to 60% of individuals may have symptoms that persist to adulthood, necessitating long-term treatment.[3] Globally, the number of children affected with ADHD ranges from 3% to 11%,[1,4] whereas adults are affected at a rate of 2.5% to 5.2%.[5]

The disorder may negatively affect the individual's life, leading to significant impairments in educational, vocational, interpersonal and social functioning, as well as conflicts with family, friends, teachers, and co-workers.[6] Deficits in executive function (EF) and how patients manage their goal-oriented and purposeful tasks in daily life may be affected, leading to disorganization, impaired workflow prioritization, decrease in work efficiency, as well as a decreased ability to focus on tasks and control emotional responses.[6,7]

Treatment guidelines of ADHD include multimodal treatment, using both pharmacologic and psychoeducational/behavioral interventions. Amphetamine and non-amphetamine stimulants (eg, methylphenidate) have proven to be effective in reducing ADHD core symptoms and improving functionality in children and adults and are most often prescribed for this disorder. Stimulants are class II–controlled substances and have a potential for abuse, making them less desirable choices for some patients and prescribers. Although all stimulants are associated with a high abuse potential, the long-acting formulations are associated with a lower abuse potential compared with the shorter acting formulations. Long-acting preparations improve compliance and may decrease the potential for abuse, misuse, or recreational use.[8] In addition, long-acting preparations may minimize the daily peaks and troughs of therapeutic effects associated with the shorter acting agents and also minimize the potential for rebound symptoms later in the day.[9,10]

Lisdexamfetamine dimesylate (LDX) is an amphetamine prodrug that undergoes a biochemical conversion following administration to its active form, D-amphetamine. Lisdexamfetamine dimesylate is approved for ADHD use in children, adolescents, and adults in the United States (Vyvanse), Canada (Vyvanse), Denmark (Elvanse), Finland (Elvanse) Germany (Elvanse), Ireland (Tyvense), Norway (Elvanse), Spain (Elvanse), Sweden (Elvanse), and United Kingdom (Elvanse) and in children in Brazil (Venvanse).[11–13] In addition, it is approved for binge eating disorder in adults in the United States.[14]

Pharmacologic and Pharmacokinetic Aspects

Lisdexamfetamine dimesylate is a water-soluble prodrug of the single isomer—D-amphetamine and L-lysine—that remains

pharmacologically inactive until it undergoes enzymatic hydrolysis predominantly by red blood cells converting the pharmacologically inactive molecule to the active drug moiety, D-amphetamine.[15] Substantial hydrolysis occurs even at low hematocrit levels,[16] and one in vitro study noted that the biotransformation is unaffected in sickle cell pathology.[15] Following administration, conversion of LDX to D-amphetamine occurs in approximately 1.5 hours, with duration from 1.5 to 13 hours in children and 2 to 14 hours in adults.[9,17] The active moiety crosses the blood-brain barrier and increases noradrenergic and dopaminergic neurotransmission thereby exerting its therapeutic effects.[17] The long-term release of the drug results in a homogeneous action, allowing for a similar effect noted 90 minutes to 14 hours after administration.[18] Food does not affect the observed area under the curve or peak plasma concentration but does prolong time to peak plasma concentration by approximately 1 hour. Levels of D-amphetamine are proportional to the LDX dose, exhibiting low intraindividual and interindividual variability.[19] Saturation is unlikely to occur at therapeutic doses due to its high-capacity enzymatic process; however, at doses greater than 130 to 150 mg, saturation of enzymatic hydrolysis can be seen resulting in decreased levels and suggesting reduced potential for toxicity in an overdose.[9]

Lisdexamfetamine dimesylate is not affected by variations in absorption related to changes in normal gastrointestinal transit times or variations in gastric pH.[20] However, acidic drugs (eg, ascorbic acid) may decrease levels of D-amphetamine; likewise, basic drugs (eg, sodium bicarbonate) may increase levels of D-amphetamine. Lisdexamfetamine dimesylate is not metabolized by cytochrome P450 enzymes and unlikely to be involved in drug interactions involving CYP enzymes or P-glycoprotein; however, it is contraindicated during or within 2 weeks following the administration of monoamine oxidase inhibitors.[16,21] Both LDX and D-amphetamine are renally eliminated and are not dialyzable, and dose reductions are recommended in patients with severe renal impairment or end-stage renal disease.[19]

Efficacy

Short-term trials

The efficacy and safety of once-daily LDX in adults (aged 18-55 years) diagnosed with ADHD according to *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision) criteria was demonstrated in short-term, randomized, double-blind, placebo-controlled multicenter studies incorporating a parallel-group[22,23] or crossover design.[24] Additional crossover, open-label trial,[25] as well as placebo-controlled studies comparing LDX with mixed amphetamine salts immediate-release (MAS-IR) tablets have also demonstrated the benefits of the stimulant compared with placebo (Table 1 summarizes the efficacy and safety studies of lisdexamfetamine dimesylate in adults with ADHD).[26,27]

The first trial by Adler et al[22] established the efficacy of LDX in adults and resulted in LDX being the first ADHD medication approved by the Food and Drug Administration (FDA) for adults in the United States. In this 4-week trial, patients were randomized to receive once-daily LDX 30, 50, or 70 mg, or placebo for a forced-dose titration of 3 weeks, followed by a 1-week maintenance phase. At study end point, compared with baseline, all doses of LDX demonstrated significant improvements in ADHD Rating Scale Version-IV (ADHD-RS-IV) scores and in Clinical Global Impressions Improvement (CGI-I) scores, compared with placebo ($P < .0001$; $P < .01$, respectively).

A post hoc analysis of the above study noted that of the 414 participants in the overall study population, 41 had previously been treated with amphetamines; of which 36 remained symptomatic with ADHD-RS-IV >18 scores at screening.[36] Mean changes at end point from screening ADHD-RS-IV total scores were −5.5 and −14.8 for those 36 participants receiving placebo and LDX, and in the overall study population, the mean change from baseline to end point in ADHD-RS-IV total score was reported at −7.8 for patients who received placebo and −17.5 for patients treated with LDX. Thus, patients in whom ADHD symptoms may not be optimally managed with amphetamines, LDX may be a potential alternative as efficacy outcomes in prior amphetamine-treated patients were consistent with those of the overall study population.

The second pivotal trial was a 10-week study by Adler et al[23] which used a 4-week dose-optimization period where patients were randomized to receive LDX 30, 50, or 70 mg/d based on efficacy and tolerability. All patients had EF deficits as assessed by baseline Behavior Rating Inventory of Executive Function-Adult version (BRIEF-A) Global Executive Composite (GEC) *T* scores of ≥65. In context of acceptable tolerability, optimal dose was achieved if patients demonstrated ≥30% reduction from baseline in total score on the ADHD-RS-IV with adult prompts and reported CGI-I ratings of 1 or 2, corresponding to very much improved or much improved, respectively. At week 10, LDX compared with placebo was associated with significantly greater improvements in ADHD-RS-IV total scores ($P < .0001$), with greater reductions from baseline in mean BRIEF-A GEC *T* scores ($P < .0001$), and with significantly greater improvements in all the measure's 9 clinical subscales from baseline ($P \leq .0056$). Significantly, more patients treated with LDX rated as improved on the CGI-I ($P \leq .0125$) beginning at week 1 through week 9, and at week 10, 79% of LDX-treated participants were rated as improved, compared with 34.7% of patients receiving placebo ($P < .0001$).

A post hoc analysis of the above study[33] examined the effects of LDX on quality of life (QOL) using the Adult ADHD Impact Module (AIM-A) and the Adult ADHD QOL (AAQoL), both participant-perceived QOL measures. Relative to the reductions in primary outcomes of BRIEF-A GEC and ADHD-RS-IV, there were significant improvements in AIM-A scores with treatment of LDX compared with placebo

Table 1. Summary of efficacy and safety studies of lisdexamfetamine dimesylate in adults with ADHD.

REFERENCE	STUDY DESIGN, DURATION	STUDY POPULATION: NO. OF PATIENTS (N), REGIMENS	PRIMARY EFFICACY END POINTS/ASSESSMENTS AND SELECTED SECONDARY RESULTS	ADVERSE EVENTS
Adler et al[22]	R, DB, PC, PG; 4-wk study: forced dose titration × 3 wk, followed by 1-wk maintenance	N = 420 (18-55 y) LDX: 30 mg/d (119) LDX: 50 mg/d (117) LDX: 70 mg/d (122) placebo (62) for 4 wk	ADHD-RS-IV total score improvement from baseline, LDX vs placebo: LDX: 30 mg/d: –16.2 vs –8.2 LDX: 50 mg/d: –17.4 vs –8.2 LDX: 70 mg/d: –18.6 vs –8.2 (all, *P*'s < .0001) CGI-I score: significantly improved from baseline for all three LDX doses (57%, 62%, and 61%) vs placebo (29%) (all, *P*'s < .01)	For all doses of LDX most common vs placebo: decreased appetite (27% vs 2%), dry mouth (26% vs 3%) insomnia (19% vs 5%. Others: diarrhea (7% vs 0%), nausea (7% vs 0%), anorexia (5% vs 0%), anxiety (5% vs 0%)
Weisler et al[28]	OL, single-arm, MC (extension of Adler et al[22])	N = 349 (18-55 y) LDX: 30 mg/d (61) LDX: 50 mg/d (113) LDX: 70 mg/d (175)	Mean change in ADHD-RS-IV total score from baseline to end of study period: –24.8 (*P* < .0001) CGI-I: 84% improvement PSQI: overall mean change from baseline to end point: –1.3 (*P* < .0001)	LDX at 30, 50, and 70 mg doses: upper respiratory tract infection (3%, 7%, 19%), insomnia (4%, 11%, 14%), headache (7%, 7%, 11%), dry mouth (5%, 7%, 11%), decreased appetite (5%, 6%, 7%), decreased weight (1%, 3%, 4%)
Wigal et al[24]	4-wk OL dose optimization followed by R, DB, MC, PC: 2-wk crossover	N = 142 (18-55 y) Dose optimization phase: LDX: 30 mg/d (28) LDX: 50 mg/d (70) LDX: 70 mg/d (44) Later: N = 127 LDX/placebo (63) Placebo/LDX (64)	PERMP total (post-dose average): difference from LDX and placebo: 23.4 (*P* < .0001). PERMP total score significantly greater for LDX from 2 to 14 h vs placebo (*P* < .001) ADHD-RS-IV total scores mean change at dose-optimization end point was –11.5 (*P* < .0001) CGI-I score improved with LDX (76.5%) vs placebo (23.1%) (*P* < .0001)	LDX vs placebo: fatigue (1% vs 12%), upper respiratory tract infection (2% vs 8%), decreased appetite (4% vs 2%), dry mouth (4% vs 1%), headache (2% vs 3%)
Brams et al[29]	Patients maintained on LDX for >6 mo: 3-wk OL phase, followed by a 6-wk R, DB, withdrawal phase	N = 116 (18-55 y) LDX: 30, 50, 70 mg/d (56) Placebo (60)	Symptom relapse: LDX (8.9%) vs placebo (75%) (*P* < .0001) ADHD-RS-IV scores: LS mean change from baseline of withdrawal phase to end point: LDX (1.6 [1.39]) vs placebo (16.8 [1.35]) (*P* < .0001) LDX vs placebo: LS mean difference in adjusted change from baseline of withdrawal phase: –15.2 (–19.1 to –11.4)	LDX during OL phase, LDX during withdrawal phase vs placebo: headache (3%, 14% vs 5%), increased appetite (0%, 2% vs 3%), insomnia (2%, 5% vs 5%), upper respiratory tract infection (3%, 9% vs 0%)
Mattingly et al[30]	Post hoc analysis of Weisler et al[28]	N = 342 (18-55 y) Predominant ADHD subtypes: Inattention (n = 93) Hyperactivity/impulsivity (n = 13) Combined (n = 236)	ADHD-RS-IV mean (SD) change from baseline to end point for predominantly inattention –19.3 (9.48), hyperactivity/impulsivity –24.0 (7.22), and combined symptom clusters –27.3 (11.78) subgroups, respectively	As reported previously

(Continued)

Table 1. (Continued)

REFERENCE	STUDY DESIGN, DURATION	STUDY POPULATION: NO. OF PATIENTS (N), REGIMENS	PRIMARY EFFICACY END POINTS/ASSESSMENTS AND SELECTED SECONDARY RESULTS	ADVERSE EVENTS
Biederman et al[31]	R, DB, PC, PG: 6 wk	N = 61 (18-26 y) LDX: 30-70 mg/d (31) Placebo (30)	LDX vs placebo: ADHD-RS-IV total score improvement from baseline: –18.4 vs –5.4, CGI-I: 68% vs 27%, and GAF: 7.5 vs 2.9 (all, *P*'s < .001) LDX vs placebo: faster reaction times (*P* = .026), reduced likelihood of having collision in driving simulator (23% vs 47%) (*P* = .048)	LDX vs placebo: decreased appetite (61% vs 7%), mucosal dryness (29% vs 3%), tension/jitteriness (26% vs 7%), insomnia (23% vs 3%), headache (16% vs 3%) LDX vs placebo from baseline to end point: change in pulse (15.8 vs –0.6, *P* < .0001)and QTc interval (9.7 vs 0.6, *P* = .01)
DuPaul et al[32]	DB, PC, CO: 5 wk: 5 phases, each 1 wk: no-drug baseline, placebo, LDX at doses: 30, 50, 70 mg	N = 40 (18-23 y) LDX: 30-70 mg/d (24) Controls (without ADHD) (26)	CAARS: for all LDX doses, ratings significantly lower than baseline for inattention/memory problems, hyperactivity/restlessness, and ADHD index (*P* < .01) CTP-II: significant main effects for dosage for commission errors, hit reaction time-standard error (*P* = .02) BRIEF-A: for all LDX doses, significant improvement (*P* < .01) CVLT-II: significant linear trends for 4 scores (*P* ≤ .02) SCL-90-R: significant linear and cubic trends in decrease scores with increasing dosage for most scores (*P* ≤ .02) SAS-SR: no significant effects noted on social functioning EESC-C: no significant main effects (no dosage impact on affect or emotional expression)	Most commonly reported adverse side effects include decreased appetite and trouble sleeping (percentages not available) No significant changes in SBP or pulse; mild increase in SBP (not clinically significant)
Adler et al[23]	R, DB, MC, PC,PG: 10 wk	N = 159 (18-55 y) LDX: 30-70 mg/d (79) Placebo (80)	ADHD-RS-IV total score improvement from baseline: LDX vs placebo (–21.4 vs –10.3, *P* < .0001) Reductions from baseline in mean BRIEF-A GEC T-scores: LDX vs placebo (–22.3 vs –11.2, *P* < .0001 CGI-I score: improved vs placebo (*P* < .0125)	Most common LDX vs placebo: decreased appetite (33% vs 6%), dry mouth (32% vs 8%), headache (25% vs 3%), insomnia (13% vs 4%). Other: diarrhea (8% vs 3%), anorexia (5% vs 0%), nausea (3% vs 6%)
Adler et al[33]	Post hoc analysis of Adler et al. (2013)	As above	From baseline to week 10, LDX vs placebo: greater improvement on all AIM-A global multi-item domain scales (all, *P*'s < .0302) Improvements for total AAQoL score (LS mean difference: 21.0)	As reported above
Adler et al[25]	R, OL,12 wk: 4-wk optimization period, followed by 8-wk maintenance phase	N = 40 (18-55 y) LDX: 30-70 mg/d	ADHD-RS: significant decrease in total scores from baseline (47%, *P* < .001) ASRS: decrease in total scores (42%, *P* < .001) TASS: decrease in total scores in-clinic and in evening (47% and 53%, respectively, *P* < .001) AMRS: reductions of 53% in-clinic assessment and 61% in evening, *P* < .001 IA and HI subscale scores: significant improvement (*P* < .005) WRAADDS: improvement with 39% in-clinic and 79% evening reductions (*P* < .001) AMSES: smooth effect throughout day with no differences in doses noted	For all doses of LDX most common adverse events: insomnia (80%), headache (53%), loss of appetite (53%), and dry mouth (43%)

Table 1. (Continued)

REFERENCE	STUDY DESIGN, DURATION	STUDY POPULATION: NO. OF PATIENTS (N), REGIMENS	PRIMARY EFFICACY END POINTS/ASSESSMENTS AND SELECTED SECONDARY RESULTS	ADVERSE EVENTS
Adler et al[27]	SB (patient-blind), PC, crossover, 14 wk: 1-wk washout, LDX × 5 wk followed by placebo × 3 wk, then OL with MAS-IR × 5 wk	N = 21 (19-55 y) LDX: 30-70 mg/d MAS-IR (10-15 mg 3 times daily)	ADHD-RS total score: decrease from baseline (LDX: 49%, MAS-IR 45%) NS ADHD-RS IA and HI scores: decreased for LDX (50%, 47%) and for MAS IR (47%, 43%) NS CGI-S score: LDX (32%) vs MAS-IR (24%) ($P < .02$) Improvements noted with both LDX and MAS-IR but NS differences between the two agents: BRIEF, PSQI	Both LDX and MAS-IR well tolerated: dry mouth, anxiety, jitteriness, fatigue, and insomnia. No clinically significant changes in weight, blood pressure, pulse
Ginsberg et al[34]	Post hoc analysis of Adler et al[22] and Weisler et al[28]	As previously reported	From baseline to endpoint 82%, 85%, and 88% very much/much improved (CGI-I of 1 or 2) in CGI-S categories of 4, 5, and ≥6 Greater baseline symptom severity having increased mean change in ADHD symptoms ($P < .0001$) CGI-S score 4, 5, ≥6 scores: clinical response in 79%, 84%, and 88%, respectively, and symptomatic remission criteria in 64%, 65%, and 72%, respectively	Upper respiratory tract infection (22%), insomnia (20%), headache (17%), dry mouth (17%), decreased appetite (14%), irritability (11%)
Martin et al[26]	R, DB, PC, 3-period crossover (7 d each)	N = 18 (18-55 y) LDX: 50 mg/d, MAS-IR 20 mg/d, and placebo × 7 d each in randomized order	Improvement in PoA scores for LDX and MAS-IR vs placebo (3 to 16 h post dose on day 7, with maximum improvement 5 h post dose) CAARS scores unchanged with LDX and MAS-IR (vs placebo) at all postdose time points CDR-CBT: little change following LDX or MAS-IR (vs placebo)	LDX, MAS-IR, placebo: dry mouth (33%, 24%, 18%), decreased appetite (16.7%, 24%, 6%), increased heart rate (11%, 0%, 0%), dyspnea (6%, 12%, 0%), headache (5.6%, 5.9%, 17.6%)
Waxmonsky et al[35]	3-wk OL, LDX titration trial, followed by phase 1 DB, PC (within-subjects evaluation), then phase 2 parent-blinded treatment of LDX or placebo × 4 wk	N = 30 parent (mean age: 40.7 y)-child/adolescent (5-12 y) dyads LDX: 30, 50, or 70 mg/d	Change in rate of parenting behaviors coded during the parent-child interaction tasks Phase 1—reduction in negative talk by parents ($P = .0066$), reduction in children's negative behaviors in homework phase ($P = .0154$) Phase 2—increases in praise by parents, reductions in parental commands, reduction in children's inappropriate behaviors (all, P's < .05) ADHD-RS total score: decrease from baseline in parental ADHD symptoms vs placebo ($P < .005$)	LDX 30, 50, 70 mg: loss of appetite (56%, 61%, 69%), headaches (36%, 28%, 31%), dry mouth (30%, 33%, 56%), trouble sleeping (20%, 22%, 31%), irritability (16%, 17%, 25%), buccal-lingual movement (16%, 28%, 25%) Decreased weight over time ($P < .05$), no significant group differences in cardiovascular parameters

Abbreviations: AAQoL, Adult ADHD Quality of Life Scale; ADHD-RS-IV, ADHD Rating Scale Version IV; AIM-A, Adult ADHD Impact Module; AMRS, Adult ADHD Medication Rebound Scale; ASRS, ADHD Self-Report Scale; BADDS, Brown Attention-Deficit Disorder Scale; BRIEF-A, Behavior Rating Inventory of Executive Functioning-Adult Version; CAARS, Connors' Adult ADHD Rating Scales-Short form; CDR-CBT, Cognitive Drug Research Computerized Battery of Tests; CGI, Clinical Global Impression scores; CGI-I, Clinical Global Impression Improvement scores; CGI-S, Clinical Global Impression Severity of Illness Scale; CTP-II, Connors' Continuous Performance Test; CVLT-II, California Verbal Learning Test-second edition; DB, double blind; DBP, diastolic blood pressure EESC-C: Expression and Emotion Scale-College Student Version; GAF, Global assessment of functioning scale; GEC, Global Executive Composite; HI, hyperactivity/impulsivity symptoms; IA, inattentive symptoms; LDX, lisdexamfetamine dimesylate; LS, least squares; MAS-IR, mixed amphetamine salts immediate release; MC, multicenter; NS, non significant; OL, open label; PC, placebo-controlled; PERMP, Permanent Product Measure of Performance; PG, parallel group; PoA, power of attention; PSQI, Pittsburgh Sleep Quality Index; R, randomized; SAS-SR, Social Adjustment Scale-Self Report; SB, single-blind; SBP, systolic blood pressure; SCL-90-R, Symptom Checklist 90-Revised; SKAMP, Swanson, Kotkin, Agler, M-Flynn, and Pelham; TASS, Time-Sensitive ADHD Symptom Scale; WRAADDS: Wender-Reimherr Adult Attention Deficit Disorder Scale.

in subscales of Performance and Daily Functioning, Impact of Symptoms: Daily Interference, Impact of Symptoms: Bother/Concern, and Relationships/Communications, Living with ADHD, and General Well-Being ($P \leq .0302$). In addition, for AAQoL, the least squares (LS) mean difference for total score was 21, and improvement was observed from baseline with LDX compared with placebo for all AAQoL subscales: Life Productivity, Psychological Health, Life Outlook, and Relationships.

A 2-week placebo-controlled crossover trial by Wigal et al[24] used a simulated Adult Workplace Environment (AWE) design and demonstrated the maintenance of therapeutic effects of LDX from 2 to 14 hours post dose in adults with ADHD, as noted by improvements in the Permanent Product Measure of Performance (PERMP) scores, a 10-minute skill adjusted math test, compared with placebo. Participants entered a 2-week randomized, double-blind, placebo-controlled crossover phase after completing a 4-week open-label dose optimization with LDX at doses from 30 to 70 mg/d. Executive functioning was assessed with PERMP total score at baseline and 2 to 14 hours post dose. Patients treated with LDX had greater improvement in average PERMP total scores, as measured by difference in LS mean at 23.4 ($P < .0001$). The PERMP total scores were greater at all post dose time points from 2 to 14 hours for adults on LDX compared with placebo ($P < .001$). In addition, the PERMP-Attempted (PERMP-A) and PERMP-Correct (PERMP-C) scores at post dose time points were significantly improved for adults who received LDX compared with placebo at each time point ($P \leq .0031$). The ADHD-RS-IV total scores improved from baseline ($P < .0001$) and the CGI-I scores suggested that 76.5% of participants improved while taking LDX and 23.1% of participants improved on placebo ($P < .0001$). A post hoc analysis of this study noted LS mean effect sizes of 0.9 for PERMP-A and 0.8 for PERMP-C for all post dose sessions, and medium to large effect sizes with LDX were maintained from 2 to 14 hours for all PERMP assessments.[37] The sustained efficacy of LDX throughout the day and into the evening hours demonstrated its benefit as one of the longest acting stimulant preparations, making it a viable treatment option in managing ADHD symptoms throughout the day. Another post hoc analysis of the AWE study assessed improvements in QOL using patient-reported AIM-A, a QOL assessment consisting of 4 global items, 5 multi-item subscales compromising 6 domains and 5 economic impact items, and noted that LDX significantly improved overall QOL at study end point compared with baseline, and no significant differences were observed in either age or sex.[38]

A 14-week trial comparing the efficacy of LDX, at doses up to 70 mg/d with MAS-IR, at doses up to 45 mg/d was undertaken by Adler et al[27] in a crossover design. Following 1 week of single-blind placebo, patients received either LDX or MAS-IR for 5 weeks and then were switched over to the other stimulant after a 3-week washout period. Both treatments resulted in significant improvements in the primary outcome measure of ADHD-RS scores and did not differ significantly from each other: LDX at 48.7% and MAS-IR at 45.1%. The CGI-Severity of Illness (CGI-S) scores were significantly reduced for the LDX group compared with the MAS-IR group ($P < .02$). In addition, LDX compared with MAS-IR demonstrated a trend in superiority in all the BRIEF major components: the overall measure of EF (GEC), behavior regulation (Behavioral Regulation Index [BRI]), and meta-cognition (Metacognition Index [MCI]) (trend at $P < .06$).

In a 12-week, randomized, open-labeled trial by Adler et al,[25] 40 patients underwent a 4-week optimization period with LDX 30, 50, or 70 mg/d for efficacy and tolerability, followed by an 8-week maintenance phase. From baseline to end of study period, there was a 47% reduction in the mean total ADHD-RS score ($P < .001$), with significant improvement in inattentive and hyperactive/impulsive subscale scores ($P < .005$). Secondary outcome measures of ADHD Self-Report Scale (ASRS) v1.1 Symptom Checklist significantly improved from baseline to study end point (42% reduction), as well as total scores of Time-Sensitive ADHD Symptom Scales (TASS), with reductions in 47% (in-clinic) and 53% (evening) (all P's $< .001$). This study also evaluated the Adult ADHD Medication Smoothness of Effect Scale (AMSES), a self-reported scale used to assess the consistency and duration effect of ADHD medications throughout the day, and the Adult Medication Rebounds Scale (AMRS), another self-reported scale used to assess the return of symptoms, emotional over reactivity, irritability, and medication "wear-off" throughout the day. Both the AMSES and AMRS had high internal consistency and demonstrated that LDX had a smooth and consistent effect throughout the day at lower and higher doses, with no reported worsening of symptoms in the evening, suggesting no symptom rebound with LDX.

Martin et al[26] in a pilot study (18 participants, mean age: 31 years) examined the sensitivity and responsiveness of the Cognitive Drug Research-Computerized Battery of Tests (CDR-CBT), a set of standardized, validated neruopsychometric tasks, for assessing cognitive function in adults with ADHD prior to and up to 16 hours post dose following either LDX 50 mg/d or MAS-IR 20 mg/d for 7 days. The primary outcome, the composite power of attention score improved with both stimulants compared with placebo, and improvements were first noted 2 and 3 hours post dose with MAS-IR and LDX, respectively, and persisted for up to 16 hours post dose, with maximum reductions with both stimulants occurring 5 hours post dose at day 7. The delayed 1-hour difference in efficacy onset noted between MAS-IR and LDX may necessitate an earlier administration of LDX in some patients.

Long-term trials

Brams et al[29] conducted a 6-week placebo-controlled, randomized, withdrawal study and provided evidence of long-term efficacy of LDX in adults. Patients stable on LDX at 30, 50, or

70 mg daily for ≥6 months who had Adult ADHD-RS-IV with prompts total score <22 and CGI-S ratings ≤3 at screening entered into a 3-week, open-label treatment phase, followed by a 6-week double-blind randomized withdrawal phase, where they received the same dose of LDX or were switched to placebo. Primary end points included ≥50% increase in ADHD-RS-IV and a ≥2-point increase in CGI-S score. At baseline, ADHD-RS-IV scores were similar in patients randomized to LDX or placebo and significantly improved in patients treated with LDX vs placebo ($P < .0001$). Patients who were stable previously on LDX and were randomized to placebo (LDX withdrawal) had a 75% relapse rate in symptoms, compared with 8.9% of participants continuing on LDX treatment ($P < .0001$). In addition, most of the relapses occurred within the first 2 weeks of the study period. The higher relapse rates for those who had treatment withdrawn, compared with those who continued on the stimulant noted the benefit of continuing long-term treatment in those who responded to short-term treatment.

Weisler et al[39] in a post hoc analysis of the above study explored the relationship between ADHD symptoms and global clinical assessment of functionality and the implications for patient assessment in clinical practice. Compared with those participants who were maintained on their stable LDX dose during the withdrawal phase, higher ADHD-RS-IV and higher CGI-S ratings were observed in the participants switched to the placebo. As the CGI-S scores increased (ie, worsened), so did the ADHD symptoms, with a positive linear relationship among ADHD symptoms and global illness ratings, correlating a dependence factor between the two.

Weisler et al[28] conducted an open-label, single-arm extension study originally undertaken by Adler et al[22] where all patients, irrespective of prior exposure of LDX began a 4-week dose-titration period with LDX dosed from 30 to 70 mg daily, followed by a maintenance phase for 11 months where the dose could be increased or decreased as deemed by the investigator. The mean change in ADHD-RS-IV total score from baseline to end of study period was −24.8 ($P < .0001$), which corresponded to a 60.7% mean relative improvement from baseline ($P < .0001$). Participants, who received LDX previously compared with those who were LDX naïve, had mean improvements in ADHD-RS-IV total scores of 61.6% and 55.1%, respectively. Likewise, at end point, 84.1% of patients noted an improvement in overall functioning as measured by the CGI-I, with similar responses noted in both the prior LDX-treated patients and LDX-naïve patients (84.8% and 79.6%, respectively). A post hoc analysis of this trial noted that LDX was effective in improving symptoms of ADHD in patients who exhibited predominantly inattention, hyperactivity/impulsivity, or combined symptom clusters, and clinical response did not differ among these different groups exhibiting specific predominant subtype symptoms.[30]

A 12-month open-label extension study[34] examined the impact of baseline severity on efficacy of LDX in patients from the trials undertaken by Weisler et al[28] and Alder et al.[22] Clinical response was defined as a decrease ≥30% in ADHD-RS-IV from baseline and a CGI-I score of 1 or 2, whereas symptomatic remission was noted as ADHD-RS-IV ≤18. Patients from the short-term trial[22] and the long-term trial[28] at study end point demonstrated increased symptom improvement as noted by clinical response criteria achieved by 78.9% to 88.4% and symptomatic remission achieved by 64.0% to 72.1% of participants. This long-term extension study demonstrated LDX's increased degree of clinical response and symptom improvement in patients with greater baseline symptom severity.

Executive Function

Analysis by Weisler et al[40] of the previous study by Adler et al[23] reported on the level of agreement between self-rated and informant-rated executive functioning deficits and clinician-rated and informant-rated ADHD symptoms over the 10-week study period with LDX compared with placebo. The primary efficacy measure was the BRIEF-A self-reported measure of EF ratings, a measure of EF behaviors with 75 items, which is also used to calculate GEC scores, and 2 indices: the BRI and the MCI. Participant ratings of improvement in executive functioning deficits were 2-fold greater than those of informant ratings at study week 10/early termination. Informant-rated EF deficits, using BRIEF-A GEC and Index *T* scores, improved significantly more with LDX compared with placebo treatment and in a similar manner to self-reported EF deficits. The LS mean treatment difference for GEC, BRI, and MCI noted significant improvement with LDX over placebo at −11.2, −8.4, and −11.6, respectively, all P's ≤ .0002).

In a post hoc analysis of the AWE study, the effects of LDX on EF impairment in adults with ADHD were evaluated by assessing changes from baseline using the Brown Attention-Deficit Disorder Scale (BADDS) total scores.[41] At study end point, BADDS total and cluster scores were significantly reduced compared with baseline ($P < .0001$), and 62.7% of participants had a BADDS total score <50 with 78.9% reliably improved compared with 1.4% reliably worsened. Likewise, another post hoc analysis of the AWE study noted the mean BADDS total score from baseline to dose-optimization week 4 decreased from 74.3 to 40.9 for all LDX doses ($P < .0001$), and the optimal response was observed in 67% of the patients based on BADDS scores at week 4.[42]

In a double-blind, placebo-controlled crossover study, DuPaul et al[32] evaluated LDX in college students with ADHD over 5 weekly phases: baseline with no drug, placebo, and LDX at 30, 50, and 70 mg/d. Matched controls without any ADHD psychopathology were included to compare LDX effects for students with ADHD with students without medication. Self-reported rating scales of functioning and direct assessment of ADHD symptoms and verbal learning/memory were analyzed, and LDX relative to no medication baseline and placebo was associated with significant reductions in ADHD symptoms as

assessed via Conners' Adult ADHD Rating Scales (CAARS) and improvement in executive functioning for nearly all BRIEF-A subscales (both, $P < .001$), with similar effects for psychosocial functioning, using the Symptom Checklist 90-Revised (SCL-90-R) ($P < .02$). Specific aspects of executive functioning, which improved with LDX, were noted for BRI, MCI, GEC, including inhibition, initiation, working memory, planning and organizing, task management, and organization of materials.

Parental treatment with LDX on parent-child interactions

Waxmonsky et al[35] examined the effects of parental treatment with LDX on parent-child interactions in 20 participants and their children (aged 5-12 years), both diagnosed with DSM-IV ADHD. Medication titration consisted of a 3-week open-label dose-optimization phase of LDX with 30 mg/d titrated to 70 mg/d. Phase 1 was a 2-week placebo-controlled lab-based interaction trial (first lab session—parent on LDX, second lab session—parent on placebo), which assessed within-subject evaluations of immediate effects of LDX (2-10 hours post dose) and phase 2 was a 1-month parent-blinded placebo or LDX trial followed by a third interaction task, which assessed between-subjects evaluations. The primary end point measured was a change in rate of parenting behaviors coded during the parent-child interaction tasks. In phase 1, there were significant reductions in negative talk by parents ($P = .0066$) and in children's negative behaviors in the homework phase only ($P = .0154$). In phase 2, there was a statically significant increase in praise by parents, and reductions in parental commands, and in children's inappropriate behaviors ($P < .05$, for all). Although not significant, there were also reductions in parental verbalizations, moderate increases in parental responsiveness, and reductions in the ratio of commands to verbalizations during the non-homework task. In addition to use of LDX being associated with significant reductions in children's negative behaviors and improvements in multiple parenting behaviors adversely affected by ADHD, significant reductions in parental ADHD symptoms compared with placebo were also observed ($P < .005$).

Using parent-adolescent dyads from the above-mentioned study, Babinski et al[43] recruited 5 subjects with ADHD who also were parents of adolescents with ADHD. In this 3-week open-label, dose-optimization trial, LDX was noted to improve some aspects of parenting behaviors during 3 parent-child interaction tasks. Task 1 was neutral discussion between parent and child, and parents on LDX displayed a lower command to verbalization ratio, which was statistically significant ($P = .04$), and associated with a large decrease in the number of commands, and moderate increases in verbalizations and responsiveness, although the latter were not significant. Statically significant effects were noted during tasks 2 and 3, associated with problem discussion and homework assignment, respectively. Lisdexamfetamine dimesylate was associated with a large increase in verbalizations and moderate decrease in ratio of commands to verbalizations as well as an increase in total commands with little change in verbalizations, resulting in an increase in the ratio of commands to total verbalizations.

Driving Performance

Biederman et al[31] in a double-blind, placebo-controlled trial assessed the impact of LDX on driving performance in young adults with ADHD using a validated driving simulation paradigm. Participants were randomized to LDX or placebo for 6 weeks following a baseline driving simulation and completed another driving simulation at study end point. Compared with placebo, posttreatment with LDX revealed positive effect on reaction time across 5 surprise events and significantly fewer accidents. In addition, compared with placebo, LDX was associated with significantly faster reaction times (91% faster) and lower rate of simulated driving collisions. In a post hoc analysis of the above study, Biederman et al[44] assessed the impact of LDX on driving behaviors in the participants using a US version of the Manchester Driving Behavior Questionnaire (DBQ). At week 6, compared with placebo, LDX was associated with significantly lower DBQ errors ($P < .02$) and lapses ($P < .02$). A decrease in DBQ violations was also noted, although not significant ($P = .16$).

Effect of Age and Sex on Results

Age-related differences in symptom presentations have been documented, with older patients demonstrating more pronounced inattentive symptoms relative to symptoms of hyperactivity/impulsivity. Symptoms of hyperactivity/impulsivity tend to decrease with increasing age, whereas symptoms of inattention tend to persist and are more constant with increasing age. Weisler et al[45] in their analysis of similarly designed 4-week trials in children (aged 6-12 years) and adults (aged 18-55 years) noted that the inattention items on the ADHD-RS-IV rating scales were numerically higher than hyperactivity/impulsivity items among older children and adults, especially those aged 40 to 55 years. The end point ADHD-RS-IV scores decreased in both children and adults, and the age-by-sex subgroup analysis noted both symptoms of inattention and hyperactivity/impulsivity decreased with active treatment in all subgroups. In adult men and women, aged 18 to 39 years, all 18 mean item scores on the ADHD-RS-IV decreased numerically in patients treated with LDX compared with placebo, and in the subgroup of men and women aged 40 to 55 years, the end point mean item scores also decreased, although with more variability, as decreases were also noted in the placebo groups.

Safety

The most commonly reported adverse event in patients who received LDX during the short-term trials was a decrease in appetite, reported at 26.5%[22] and 32.9%,[23] although weight loss was not consistently reported in these trials. Other commonly reported adverse events were insomnia (11%-19%), and nausea

(2.5%-12.5%). Although headache and nasopharyngitis were reported in trials, their frequency was similar to that observed in the placebo-treated groups. The overall rates of treatment emergent adverse events (TEAEs) for patients treated with LDX were also similar across the different age groups from previous trials reported.[46] However, dry mouth was commonly reported by adults (up to 32%),[23] whereas less than 6% of children and adolescents reported this adverse event.[46]

Long-term trials noted that the most common TEAEs were similar to those reported in the short-term trails: insomnia (20%), decreased appetite (14%), headache (17%), dry mouth (17%), irritability (11%), and muscle spasms (5%). During the open-label extension study,[28] 87.7% of patients experienced adverse events, and similar percentages were noted between LDX-naïve patients and those who had received LDX previously. Upper respiratory tract infection, insomnia, headache, dry mouth, decreased appetite, and irritability were the most commonly reported adverse events reported. Postmarketing safety data are consistent with the earlier reported adverse events, and poison centers have reported patients presenting with insomnia, dystonia, hallucinations, jitters, tachycardia, and chest pain.[47] It should be noted that patients with underlying psychosis and/or preexisting cardiac complications were excluded from the earlier phase 1 and 3 trials, and as use of LDX increases in the real-world setting, adverse events such as hallucinations and cardiac events may occur and patients at risk need to be monitored.

During the 6-week placebo-controlled, randomized withdrawal trial, TEAEs were reported in 48% of the patients receiving LDX compared with 30% of the patients on placebo. Treatment emergent adverse events with incidence ≥5% in the stimulant-treated group compared with placebo were headache (14.3% vs 5%), insomnia (5.4% vs 5%), and upper respiratory tract infection (8.9% vs 0%).[29] No histopathologic changes have been noted in any studies with LDX, and findings regarding toxicology are unremarkable and consistent with changes in behavioral activity associated with stimulant exposure, as is loss of appetite and reductions in weight gain and growth measurements.[16]

A 6-month study where LDX was titrated to 70 mg/d in 15 patients (aged 18-60 years) used comprehensive, provocative physiological testing including resting transthoracic echocardiogram and noninvasive cardiopulmonary exercise testing and did not find clinically meaningful changes in cardiac structure or function at rest or during peak exertion. Likewise, no significant mean changes in metabolic and ventricular variables were noted.[48] A decrease in left ventricular (LV) dimensions was observed; however, a more sensitive measure of LV size, a change in LV volume, was not noted. No changes were observed in oxygen uptake (gold standard measure of cardiorespiratory fitness) and oxygen pulse (noninvasive estimate of stroke volume). At maximum exertion, diastolic blood pressure was significantly increased in hypertensive patients ($P < .003$), but not in healthy subjects, which may require further studies to elucidate the cause.

Safety data from the study by Adler et al[49] of LDX on cardiovascular parameters in 420 medically healthy adults with ADHD were analyzed, and no significant differences for mean systolic or diastolic blood pressure in any LDX dose group vs placebo were noted. Although LDX was associated with predictable but modest increases in pulse and heart rate (both, $P < .05$), beginning at week 2 and persisting through week 4, no meaningful effects on electrocardiogram (ECG) parameters such as PR, PP, and QT intervals were noted. Likewise, LDX compared with placebo from baseline to study end point was associated with small but significant increases in pulse (mean change: 15.8, $P < .001$) and QTc interval (corrected QT interval) (mean change: 9.7, $P = .01$), although no serious adverse events were reported during the study period.[31]

Ermer et al[20] evaluated the safety of LDX in healthy older adults and noted that the drug's safety profile was consistent with prior data in healthy younger adults aged 18 to 55 years. No vital sign differences were noted between men and women, and no trends in pulse or blood pressure changes were observed according to age. Maximal mean increases in pulse in patients aged 55 to 64 years and 65 to 74 years occurred 12 hours post dose and 5.5 hours post dose in patients aged ≥75 years. The mean change from baseline pulse ranged from −5.0 to 14.7, −4.3 to 9.5, and −3.0 to 14.7 beats per minute in participants aged 55 to 64, 65 to 74, and ≥75 years, respectively. Likewise, 12 hours post dose, the following mean changes from time-matched baseline systolic and diastolic blood pressure, respectively, were noted in participants aged 55 to 64 years (−3.9 to 18.5 mm Hg; −2.5 to 8.3 mm Hg), 65 to 74 years (−2.1 to 14.5 mm Hg; −0.8 to 9.4 mm Hg), and ≥75 years (−5.9 to 16.0 mm Hg; −0.6 to 9.5 mm Hg).

In a postmarketing surveillance from a total of 9525 adverse events associated with LDX reported to the FDA between January 2004 and March 2017, 11 cases (0.12%) of cardiomyopathy were reported; most were men, aged 10 to 19 years of age, taking the drug for 6 to 12 months.[50] Because adults have a greater likelihood of structural cardiac abnormalities compared with children, use of stimulants should be used with caution in adults with serious cardiac problems. As with other stimulants, a black box warning addressing the potential for abuse and dependence exists with LDX, a class II–controlled substance, and patients should be assessed for risk of abuse prior to prescribing the stimulant and monitored for signs of abuse and dependence while on therapy. In addition, misuse of amphetamine stimulants may cause sudden death and serious cardiovascular adverse events. Likewise, stimulants are associated with peripheral vasculopathy and patients with Raynaud's phenomenon may be at increased risk for complications.

Misuse/Abuse

Lisdexamfetamine dimesylate is chemically stable in water and at room temperature and resistant to buffering even under extreme hydrolytic conditions, making alteration of

the LDX molecule difficult, costly, and laborious.[13] Previously reported abuse liability studies support the reduced abuse potential of LDX administered orally at doses ≤150 mg or intravenously at doses ≤50 mg, compared with D-amphetamine immediate-release 40 mg oral or 20 mg intravenous doses, respectively.[21] Pharmacokinetic profiles following oral and intranasal administration of LDX in healthy adults demonstrated similar systemic exposures of D-amphetamine concentrations.[51] As D-amphetamine is released slowly from the prodrug LDX, it does not produce the subjective "rush" experienced by drug abusers and may offer reduced abuse potential relative to immediate-release D-amphetamine.[16] Compared with other stimulants, LDX demonstrates a more moderate reinforcing effect in drug self-administration and a more time-dependent effect in drug discrimination studies. Surveys using the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) system in the United States noted the abuse potential of LDX to be very low, with no increases demonstrated between 2007 and 2011.[52]

Place in Therapy

Lisdexamfetamine dimesylate is the first prodrug approved for managing ADHD across the life span of children, adolescents, and adults. Its long duration of effect allows for once-daily dosing encouraging medication compliance while also providing sufficient efficacy for the average work or school day. Lisdexamfetamine dimesylate has demonstrated low intrapatient and interpatient variability in the systemic exposure of D-amphetamine, with changes in gastric acidity and gastrointestinal transit times having minimal if any impact on the absorption of LDX. Unlike MAS-XR, which requires an acidic environment to dissolve the enteric-coated beads, LDX may be dissolved in water for patients who may have difficulty swallowing the capsule. In addition, LDX, unlike atomoxetine, is not metabolized by CYP450 enzymes, thus has a low potential for interacting with other drug affected by the isoenzymes.

A recent systemic review and meta-analysis estimated the efficacy of LDX in adult patients with ADHD to be 1.07 (95% confidence interval [CI]: 0.74-1.40) in European patients compared with 0.83 (95% CI: 0.58-1.08) in US patients.[53] Both effect sizes were larger than the 0.8 threshold for large effect sizes; however, the effect sizes noted for osmotic-release oral system methylphenidate (OROS-MPH) and atomoxetine, 2 other alternative therapies for ADHD, were also reported higher in adult patients in European vs US studies: 0.627 vs 0.384 and 0.616 vs 0.372, respectively. The pooled European location effect size was larger compared with the United States which may explain the higher effect size, as can changes in study design regarding placebo, and clinical and methodological diversity among studies which may influence estimated effect sizes.

Conclusions

Lisdexamfetamine dimesylate is a stimulant prodrug which has consistently demonstrated improvement in ADHD symptoms throughout the day by increasing functionality in adults with ADHD. The long duration lasting up to 14 hours after ingestion gives patients on LDX the advantage of avoiding supplemental doses of short-acting stimulants in the afternoon or early evening. Participants who were switched to placebo from a previous stable dose of LDX exhibited a return of ADHD symptoms. Commonly reported adverse effects are consistent with those reported with other stimulants and include a decrease in appetite, dry mouth, and insomnia. Due to the increase in noradrenergic and dopaminergic neurotransmission, sympathomimetic effects including increases in blood pressure and pulse may occur, changes in vital signs are usually small, and changes in ECG are not clinically relevant. However, the drug carries a warning that misuse of amphetamines may cause sudden death and serious cardiovascular adverse events, and caution is indicated in treating patients with preexisting hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia.

Author Contributions

JN coordinated and retrieved the computerized searches for data analysis, analyzed studies, drafted the initial manuscript, and approved the final manuscript as submitted. DW coordinated and retrieved the computerized searches for data analysis, analyzed studies, critically reviewed the manuscript, and approved the final manuscript as submitted. JZ, KWL, NR, EPM, and AT analyzed studies; reviewed the manuscript; and approved the final manuscript as submitted.

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