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Long-Term Safety and Effectiveness of Lisdexamfetamine Dimesylate in Adults With Attention-Deficit/Hyperactivity Disorder

Richard Weisler, MD, Joel Young, MD, Greg Mattingly, MD, Joseph Gao, PhD, Liza Squires, MD, and Lenard Adler, MD, on behalf of the 304 Study Group

ABSTRACT

Objective: To evaluate the long-term safety and effectiveness of lisdexamfetamine dimesylate (LDX) in the treatment of adults with attention-deficit/hyperactivity disorder (ADHD).

Methods: Following a 4-week, placebo-controlled, double-blind trial, 349 adults with ADHD were enrolled into an open-label, single-arm study for up to 12 months. Treatment was initiated at 30 mg/day and titrated up to 70 mg/day at subsequent visits to achieve optimal effectiveness and tolerability. Safety assessments included adverse events inquiries, vital signs, and electrocardiograms while the primary effectiveness assessment was the ADHD Rating Scale (ADHD-RS) total score.

Results: A total of 191 (54.7%) subjects completed the study. The most common treatment-emergent adverse events (TEAEs) were upper respiratory tract infection (21.8%), insomnia (19.5%), headache (17.2%), dry mouth (16.6%), decreased appetite (14.3%), and irritability (11.2%). Most TEAEs were mild to moderate in severity. At endpoint, small but statistically sig-

FOCUS POINTS

- Attention-deficit/hyperactivity disorder (ADHD) is a chronic neurobehavioral disorder that often persists into adulthood and psychostimulants are an important first-line treatment for management of ADHD symptoms in adults.
- The stimulant prodrug, lisdexamfetamine dimesylate (30, 50, and 70 mg/day) given for up to 1 year was found to be safe and effective in adults with ADHD.
- The flexible dosing strategy, similar to clinical practice, used here likely contributed to achieving optimal dosing and may have contributed to the relatively low rates of adverse events and discontinuations.

nificant increases in pulse and blood pressure were noted. Significant improvements in mean ADHD-RS total scores were observed at week 1 and sustained throughout the study ($P < .0001$ at all postbaseline visits). At endpoint, the mean improvement from baseline ADHD-RS total score was 24.8 ($P < .0001$).

Conclusions: LDX demonstrated a safety profile consistent with long-acting stimulant use and provided continued effectiveness in adults with ADHD for up to 12 months.

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Affiliation and Disclosure Information: Please see page 585.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD), one of the most common psychiatric disorders, is estimated to have a worldwide prevalence among children of ~5.3%.^{1,2} Nearly two-thirds of children with ADHD experience symptoms into adolescence and adulthood.³⁻⁵ Overall, ADHD is estimated to affect 4.4% of adults in the United States.⁶ Adults with ADHD experience significant impairment^{6,7} in multiple domains of daily living, including the workplace, home, school, and various social settings.⁸ In fact, current diagnostic criteria for ADHD set out in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision require that impairment be present in at least two settings.²

Stimulants represent the most frequently prescribed ADHD treatment⁹⁻¹¹ and have demonstrated efficacy in alleviating symptoms in adults with ADHD.^{9,12-15} In otherwise healthy adults with ADHD, stimulants have been found to cause modest increases in systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse.¹⁶⁻¹⁹ There has also been concern that stimulants might prolong sleep onset or cause insomnia.^{9,20} These effects, however, may be difficult to differentiate from preexisting sleep problems that are frequently reported by both children and adult patients with ADHD.^{9,21-25} Lisdexamfetamine dimesylate (LDX) is the first long-acting prodrug stimulant, and is approved for the treatment of ADHD in children 6–12 years of age and adults. LDX is a prodrug that is therapeutically inactive. After oral ingestion, LDX is converted to l-lysine and active d-amphetamine. Recent *in vivo* studies in anesthetized rats demonstrated that a high proportion of LDX is absorbed intact from the gastrointestinal (GI) tract.²⁷ Parallel studies in isolated rat and human tissues and blood elements showed that conversion occurs primarily in red blood cells.^{26,27} The conversion of LDX to d-amphetamine is unlikely to be affected by GI pH and variations in normal GI transit times.^{28,29}

In a clinical trial with healthy adults, LDX demonstrated consistent d-amphetamine delivery within and between patients.³⁰ In this pharmacokinetic study of LDX in healthy adult subjects receiving escalating doses (up to 3–8 times recommended therapeutic doses), systemic exposure to LDX demonstrated dose-proportionality and low intra- and interpatient variability.³⁰

LDX has demonstrated safety and efficacy versus placebo in children and adults with ADHD.

Children treated with LDX demonstrated significant (vs. placebo) improvements in ADHD Rating Scale IV (ADHD-RS-IV), Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP), Permanent Product Measure of Performance (PERMP), and Clinical Global Impressions (CGI) scores.^{31,32} In pediatric clinical trials, LDX has demonstrated sustained efficacy versus placebo after dosing throughout a 12-hour and a 13-hour trial.^{32,33}

In a recent 4-week, double-blind, placebo-controlled trial in adults with ADHD, treatment with LDX was associated with significant improvements (vs. placebo) in ADHD-RS total score.³⁴ LDX treatment demonstrated efficacy versus placebo for the 30, 50, and 70 mg/day doses. Superiority over placebo was also demonstrated by CGI-Improvement (CGI-I) scores. In that trial, the most common LDX-emergent adverse events (AEs) were decreased appetite, dry mouth, insomnia, nausea, diarrhea, and anxiety. Treatment with LDX was not associated with clinically meaningful changes in SBP, DBP, or electrocardiogram (ECG) parameters. Because ADHD is a chronic disorder often requiring long-term therapy, data regarding the long-term safety and effectiveness of ADHD treatments are vital. While long-term use of LDX in children has been shown to be safe and effective,³⁵ the present study evaluated the long-term safety, effectiveness, and tolerability of LDX in adults with ADHD.

METHODS

Subjects and Study Design

This open-label, multicenter, single-arm study was conducted at 44 sites in the US between July 2006 and November 2007. All subjects participating in this study had participated in a previous randomized, double-blind, placebo-controlled, parallel-group, 4-week study with forced-dose titration.³⁴ Inclusion criteria for the prior study included 18–55 years of age, a primary diagnosis of ADHD by *DSM-IV-TR* criteria and moderate-to-severe disease as assessed by a baseline ADHD-RS score of at least 28 using adult prompts for the ADHD-RS scale developed at New York University and Massachusetts General Hospital (NYU/MGH prompts).^{36,37} During the conduct of the study, subjects, investigators, and study staff were aware of the treatment and daily dose of LDX that subjects were receiving. This study was conducted in accordance with the Declaration of

Helsinki and Good Clinical Practice according to the International Conference on Harmonisation guidelines. The study protocol was approved by each center's institutional review board and all subjects provided written informed consent.

Subjects were excluded from enrollment for any disorder or condition that, in the opinion of the examining physician, would contraindicate treatment or confound effectiveness or safety assessments. These included comorbid psychiatric diagnosis with significant symptoms such as any severe comorbid Axis II disorders or severe Axis I disorders including posttraumatic stress disorder, psychosis, bipolar illness, severe obsessive-compulsive disorder, severe depressive, or severe anxiety disorder. However, subjects who had mild to moderate forms of Axis I disorders, including social phobia and dysthymia, could be included while subjects with a lifetime history of psychosis or bipolar disorder would be excluded from participation. Also excluded were those subjects with a history of seizures or hypertension and those with a clinically significant ECG abnormality or cardiac structural abnormality. Subjects were excluded if they had a resting SBP >139 mm Hg or DBP >89 mm Hg or were taking medications that affect the central nervous system or BP (excluding ADHD medications, which were washed out).³⁴ Medications prohibited during the trial included tricyclic antidepressants, selective serotonin or norepinephrine reuptake inhibitors, antipsychotics, anxiolytics, benzodiazepines, psychostimulants, nonstimulant ADHD medications, anticonvulsants, sedatives and hypnotics, and antihypertensive, herbal, or investigational medications.

Other exclusion criteria included pregnancy or a positive urine drug screen at screening (except for stimulant therapy).³⁴ Females of childbearing potential had to comply with contraceptive restrictions including abstinence or the use of adequate and reliable contraception throughout study. Subjects also had to have completed at least 2 weeks of the short-term, placebo-controlled trial and experienced no AEs that would preclude continued exposure to LDX.

The screening and baseline procedures for participants in this study were dependent on whether subjects enrolled within 7 days of finishing the prior short-term, double-blind trial or later. To provide continuity of safety and tolerability assessments, subjects who enrolled

within 7 days and had not taken any excluded medications during that period had their safety data (eg, ECG and vital signs) and clinical assessments (lab data, physical exam, height, and weight, etc) from the final study visit transferred and used as baseline for this study. Subjects who enrolled after 7 days underwent a full screening and, if needed, a week-long wash-out of all psychoactive medications, and new baseline demographic and safety data were recorded. Alternatively, to facilitate comparison of effectiveness measures with pretreatment values, baseline data for assessment of effectiveness (ADHD-RS and CGI scores), as well as demographic data, for all subjects were carried over from the baseline visit of the prior short-term, double-blind trial.

Irrespective of prior exposure to LDX, all subjects began a 4-week dose-titration period at the minimum study dose of 30 mg/day dispensed at visit 1. At 4 subsequent weekly visits, the daily dose of LDX could be increased or decreased in 20 mg increments to a maximum daily dose of 70 mg as deemed appropriate by the investigator to achieve a balance of optimal effectiveness and tolerability for each subject. Following dose titration, subjects began a long-term maintenance period for up to 11 months and visited the study site monthly at which time their daily dose could be increased or decreased in 20 mg increments if deemed appropriate by the investigator. Follow-up interviews by telephone or direct contact to collect information on any serious AEs that may have occurred during that period or AEs that were unresolved at final study visit and were deemed related to study drug were conducted ~30 days after the final LDX dose. At each visit, subjects were dispensed the number of capsules appropriate for the subsequent dosing period and treatment compliance was assessed by capsule counts.

Safety Measures

Safety was assessed through inquiries with nonleading questions and observation by investigators regarding AEs at every study visit. Treatment-emergent AEs (TEAEs) were defined as those AEs occurring after dispensing of study medication. AE intensity was based on the worst intensity of the AE experienced by the subject during the course of the event. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 9.1).

The Pittsburgh Sleep Quality Index (PSQI) assessed the impact of treatment with LDX on parameters of sleep. The measure consists of 19 self-rated items that generate 7 component scores (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction) with each component score ranging from 0–3 (3 reflects severe difficulty). The component scores are added to generate a global score ranging from 0–21. Higher score indicates worse sleep quality and a score >5 indicates poor sleep quality.³⁸ The baseline PSQI from the double-blind trial was used as the baseline score for this study and the measure was reassessed every 3 months.

Vital signs (ie, BP, pulse, and temperature) were recorded at baseline, as previously described, and at each subsequent visit. Resting BP and pulse were determined after subjects were in a sitting position for 5 minutes using an appropriately sized cuff. While manual or automated BP measurement was permitted, the method and arm used for each subject remained consistent throughout the study. ECGs were recorded every 3 months and parameters of interest included heart rate as well as RR, PR, QRS, QT, and QTcF/B (Fridericia and Bazett corrections) intervals. Additional postbaseline safety assessments included physical exam and clinical laboratory tests (eg, hematology, chemistry, and urinalysis) performed at month 6 and the end of study visit or at the time of any early termination when possible. Subjects' height was recorded at the final visit of the prior study and of the current study, and weight was recorded monthly using the same scales, measures, and circumstances at all assessments.

Effectiveness Measures

The primary effectiveness measure was the total score of the ADHD-RS. The ADHD-RS for adults contains 18 items each scored between 0 (no symptoms) and 3 (severe symptoms). The clinician-rated scale was administered at all postbaseline study visits by trained raters utilizing adult NYU/MGH prompts.^{36,37}

The CGI scale was a secondary measure of the long-term effectiveness of LDX. The CGI-Severity of Illness (CGI-S) scale is a 7-point scale that ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill subjects) providing a global assessment of each subject's baseline dis-

ease severity. At each postbaseline study visit, symptom improvement relative to baseline was assessed by investigators using the CGI-I scale. The CGI-I is also a 7-point scale that ranges from 1 (very much improved) to 7 (very much worse).

Statistical Analyses

Subjects in the present study were required to have participated in a prior short-term, double-blind study, which enrolled 420 subjects.³⁴ Planned enrollment for this long-term trial was 300 subjects, estimated to provide 12-month data for 100 subjects.

Safety was assessed in the safety population, defined as all enrolled subjects who received at least 1 dose of LDX, while effectiveness was assessed in the intention-to-treat (ITT) population, defined as all subjects who were treated and had both baseline and at least 1 postbaseline ADHD-RS total score. In addition, to analyze the occurrence of AEs and cardiovascular responses in relation to prior exposure to LDX for some analyses, subjects were dichotomized based on their assignment in the prior study: those who received LDX and those who received placebo (ie, LDX naive).

For safety analyses, length of exposure was calculated based on the dates of first dispensing (for the present study) and the last dose of LDX. Length of exposure was categorized based on the following: 1–4 weeks, 5–8 weeks, 9–12 weeks, 13–16 weeks, 17–20 weeks, 21–24 weeks, 25–48 weeks, and ≥49 weeks. AEs were treated as treatment-emergent if the start date was missing and as possibly related if the relatedness was missing.

Vital signs were summarized for baseline and each postbaseline visit and ECG parameters every 3 months, using descriptive statistics. Changes in parameters from baseline were analyzed using the paired t-test for each applicable postbaseline visit and endpoint. Endpoint was defined as the last postbaseline assessment available for each subject, which was equivalent to the last-observation-carried-forward (LOCF) approach. Outlier analyses with cutoff values were performed using shift tables for each postbaseline visit and endpoint. The QT interval cutoff values, defined a priori, were >450 msec, >480 msec, or >500 msec for QT, QTcF, and QTcB, respectively. Increases in QT or QTcF from baseline were categorized as ≥60 msec, 30–59 msec, and ≤29 msec for each postbaseline visit and endpoint. The outlier criteria for vital signs were

defined, a priori, as SBP ≥ 150 mm Hg, DBP ≥ 95 mm Hg, and pulse greater than or equal to baseline mean + 2 x SD or less than or equal to baseline mean - 2 x SD. Additional outlier criteria for vital signs were developed for post hoc analyses: SBP ≥ 140 mm Hg and $\geq 10\%$ change from baseline, DBP ≥ 90 mm Hg and $\geq 10\%$ change from baseline, and pulse ≥ 100 bpm.

The primary effectiveness analysis was performed on the mean change from baseline of the ADHD-RS total score at endpoint using a paired t-test; the type I error rate for rejecting a null hypothesis being an alpha level of .05. Effectiveness analyses were also performed on the mean change from baseline of the ADHD-RS total score at each study visit using a paired t-test. A post hoc analysis of percent change from baseline to endpoint in ADHD-RS total scores was performed using a 1-sample t-test. CGI-I scores were summarized for each treatment visit and at endpoint. For analysis, the CGI-I was dichotomized into 2 categories with 1 (very much improved) and 2 (much improved) representing improved and the remaining items (3 to 7) representing not improved. The proportion of treatment responders as assessed by dichotomized CGI-I scores was reported at the endpoint and each study visit.

RESULTS

Subject Disposition and Demographics

A total of 349 subjects enrolled in the present study and all were included in the safety population. Of those, 337 (96.6%) enrolled within 7 days of ending the prior clinical trial. Of the 12 subjects who enrolled after 7 days of ending the prior study, 1 subject underwent a week-long washout period. Overall, 297 subjects received LDX and 52 received placebo in the prior study. A total of 191 (54.7%) subjects completed the study (Figure 1). The ITT population consisted of 345 participants. The demographic characteristics of the overall safety population are summarized in Table 1. The mean (SD) age of study participants was 35.8 (10.1) years of age. Men comprised 54.4% (n=190) of the safety population.

Drug Exposure

At the start of the treatment period, all subjects began treatment at a 30-mg/day dose of LDX. The last daily dose of LDX was 70 mg/day for 50.1% (n=175) of subjects while 32.4%

(n=113) and 17.5% (n=61) of subjects received 50 and 30 mg/day, respectively. The starting dose of 30 mg/day had a mean (SD) exposure of 40.4 (84.0) days compared with 93.2 (119.2) and 205.0 (132.2) days for the 50 and 70 mg/day doses, respectively. Overall, subjects were exposed to LDX for a mean (SD) of 266.4 (124.0) days and 195 subjects (55.9%) were exposed to LDX for at least 49 weeks.

Adverse Events

Overall, 306 subjects (87.7%) experienced AEs with similar percentages reported between those subjects who were LDX naive and those who had received LDX previously (84.6% vs. 88.2%). Except for 6 subjects who reported a total of 7 AEs prior to beginning treatment, all AEs were considered TEAEs. The most common TEAEs included upper respiratory tract infection (URI), insomnia, headache, dry mouth, decreased appetite, and irritability (Table 2). During the first 4 weeks of treatment, 68.5% of subjects reported

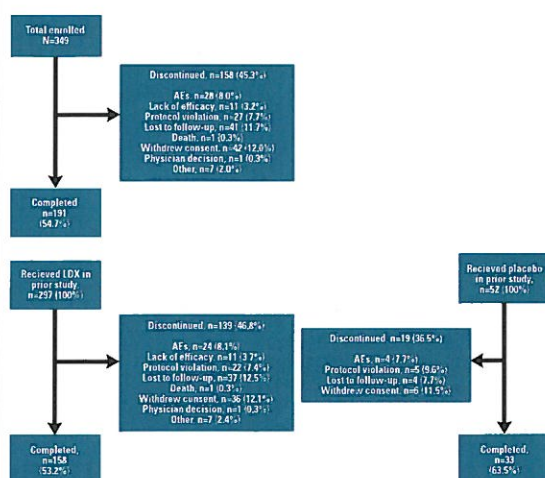
TABLE 1.
Subject Demographics at Baseline
(Safety Population)

	<i>All Subjects</i>
<i>Number of subjects</i>	349
Gender, n (%)	
Male	190 (54.4)
Female	159 (45.6)
Race, n (%)	
Caucasian	310 (88.8)
African American	14 (4.0)
Asian	3 (0.9)
Native American	1 (0.3)
Other	21 (6.1)
Ethnicity	
Hispanic	36 (10.3%)
Non-Hispanic	313 (89.7%)
Age (years), mean (SD)	35.8 (10.1)
Age group (years), n (%)	
18-29	111 (31.8)
30-39	101 (28.9)
40-49	100 (28.7)
50+	37 (10.6)
Height (inches), mean (SD)	67.6 (3.6)
Weight (lbs), mean (SD)	174.9 (38.2)

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a TEAE and, thereafter, the percentage of subjects reporting new TEAE occurrences during each sub-

FIGURE 1.
Subject disposition



AEs=adverse events.

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sequent treatment interval was <53%. After weeks 1–4, the only TEAEs with an onset (or worsening) reported by >5% during any of the treatment intervals were URI (weeks 9–16: 7.1%; weeks 17–24: 6.0%; weeks 25–36: 8.4%; weeks 37–48: 5.0%) and headache (weeks 9–16: 5.2%). Post hoc analysis of the incidence of TEAEs during the first 8 weeks of treatment revealed that during weeks 1–4, LDX-naïve subjects had a greater incidence of TEAEs than those who received LDX in the prior trial (Table 3). Overall, for the 5 most common TEAEs other than URI, the percentage of subjects reporting ≥1 new or ongoing AEs in the first month and at months 3, 6, 9, and 12 decreased from highs in the first month and continued to present in some subjects (Figure 2).

Of all 1,673 TEAEs, fewer than half (45.1%) were determined by the investigator to be “probably” or “possibly” related to treatment; these events were higher in the LDX-naïve (58.5% of events) than in the cohort that had previously received LDX (41.6% of events). Most AEs reported were mild or moderate in intensity. Severe AEs occurred in 12.0% (n=42) of the safety population and all were treatment-emergent. Severe TEAEs “possibly” or

TABLE 2.
TEAEs With Overall Incidence >5%

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

Dose level represents dosage of LDX being received by subjects at TEAE onset. The starting dose of 30 mg/day had a mean (SD) exposure of 40.4 (84.0) days compared with 93.2 (119.2) for the 50 mg/day and 205.0 (132.2) days for the 70 mg/day doses.

TEAEs=treatment emergent adverse events; MedDRA=Medical Dictionary for Regulatory Activities; LDX=lisdexamfetamine; SD=standard deviation.

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"probably" related to treatment were experienced by 10 subjects (12 events) and included 1 event each of dry mouth, dysphagia, irritability, muscle spasms (muscle strain), anxiety, depressive symptom, tension, and sexual dysfunction, as well as 2 events each of initial insomnia and insomnia.

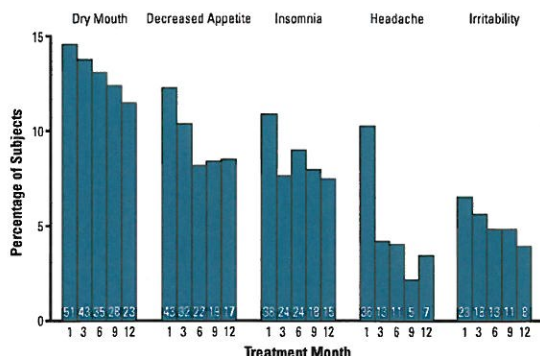
Eight (2.3%) subjects experienced a total of 10 serious AEs during the trial; all were judged unrelated to LDX treatment. One death occurred during the study: a 22-year-old male died from cocaine and alcohol toxicity. In the preceding study, the subject had a negative drug screen at screening and had been randomized to receive 30 mg/day LDX. The subject had been enrolled in the present study for approximately 10.5 months at the time of his death. His dose of LDX had been titrated to 70 mg/day at week 5 then reduced to 50 mg/day at week 6 secondary to palpitations and tachycardia. The subject's drug screen at autopsy was positive for cocaine and ethanol and negative for amphetamines. No cardiac abnormalities were found. The medical examiner's autopsy report specified cocaine and ethanol toxicity as the cause of death; the study investigator judged the death as unrelated to LDX.

Of the 158 (45.3%) subjects who discontinued from the study, 28 (8.0%) did so secondary to AEs.

The 28 subjects in the safety population who discontinued due to AEs did so at a rate of <1% per month over the course of the study. Excluding 1

FIGURE 2.

Percentage of subjects reporting ≥ 1 AEs (new or ongoing) at months 1, 3, 6, 9, and 12*†



* Number within each bar indicates the number of subjects entering that visit with an AE occurring or ongoing.

† Total number of subjects entering each visit interval was 349 at month 1, 312 at month 3, 268 at month 6, 225 at month 9, and 199 at month 12.

AEs=adverse events.

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TABLE 3.

TEAEs With Initial Incidences >5% During Weeks 1–4 or 5–8 by Prior Treatment Exposure to LDX

<u>Preferred Terminology (MedDRA 9.1)</u>	N (%) of Subjects Reporting			
	Weeks 1 to 4		Weeks 5 to 8	
	<u>Prior LDX (n=297)</u>	<u>Prior Placebo (n=52)</u>	<u>Prior LDX (n=279)</u>	<u>Prior Placebo (n=47)</u>
Any events	200 (67.3)	39 (75.0)	91 (32.6)	14 (29.8)
Agitation	4 (1.3)	3 (5.8)	0	1 (2.1)
Bruxism	2 (0.7)	3 (5.8)	1 (0.4)	0
Decreased appetite	29 (9.8)	13 (25.0)	1 (0.4)	2 (4.3)
Dry mouth	33 (11.1)	18 (34.6)	2 (0.7)	2 (4.3)
Feeling jittery	2 (0.7)	3 (5.8)	0	0
Headache	27 (9.1)	8 (15.4)	7 (2.5)	1 (2.1)
Initial insomnia	7 (2.4)	4 (7.7)	1 (0.4)	2 (4.3)
Insomnia	27 (9.1)	8 (15.4)	7 (2.5)	2 (4.3)
Irritability	17 (5.7)	6 (11.5)	4 (1.4)	1 (2.1)
Myalgia	3 (1.0)	3 (5.8)	1 (0.4)	0

TEAEs=treatment emergent adverse events; LDX=lisdexamfetamine; MedDRA=Medical Dictionary for Regulatory Activities.

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subject who discontinued because of AEs that were not treatment-emergent, 27 subjects discontinued secondary to a total of 35 TEAEs: 5 events had a dose at onset of 30 mg/day, 9 at 50 mg/day, and 21 at 70 mg/day. Overall, 28 events that contributed to discontinuations were listed as "probably" or "possibly" related to LDX. The TEAEs leading to discontinuation that occurred more than once were insomnia (3 events) as well as anxiety, dizziness, and dysphoria (2 events each)—all "possibly" or "probably" related to LDX treatment. There was 1 case each of palpitations, decreased appetite, initial insomnia, central nervous system stimulation, and mania/manic-like symptoms leading to discontinuation, each "probably" related to LDX treatment.

Cardiac-related TEAEs reported by subjects included angina pectoris reported by 1 subject (50 mg/day) and palpitations reported by 7 subjects (30 mg/day [$n=1$]; 50 mg/day [$n=3$]; 70 mg/day [$n=3$]). Angina pectoris, reported by a 23-year-old female receiving 50 mg/day LDX, was mild in intensity and possibly related to LDX. Study dose was decreased to 30 mg/day but, due to concurrent dizziness, the subject discontinued from the study. The subject's ECG at study end demonstrated no abnormal findings. Eight events of tachycardia were reported for 7 subjects (50 mg/day [$n=4$] and 70 mg/day [$n=4$]) and extrasystoles were reported for 3 subjects (50 mg/day [$n=1$] and 70 mg/day [$n=2$]). Other cardiovascular-related

TEAEs included hypertension (3 subjects), elevated BP (8 subjects), increased heart rate (10 subjects), and dyspnea (4 subjects).

Vital Signs

For the safety population, the mean (SD) pulse at baseline was 74.1 (10.3) bpm. Statistically significant changes from baseline were seen from week 1 through endpoint for the safety population ($P \leq .024$). The mean (SD) increase in pulse from baseline at endpoint for the safety population was 3.2 (11.6) bpm ($P < .0001$). The mean (SD) increases were ~3x greater for LDX-naïve subjects than for subjects who received LDX previously (7.6 [10.1] vs. 2.4 [11.7] bpm; $P < .0001$ and $P = .0004$ vs. baseline, respectively). By post hoc analysis, the mean (SD) increase in pulse from baseline to endpoint by final dose group was 5.1 (11.0), 0.6 (11.0), and 4.3 (11.9) bpm for the 30, 50, and 70 mg/day dose groups.

The mean (SD) baseline SBP for the overall safety population was 117.3 (10.0) mm Hg. Small statistically significant mean elevations from baseline were seen in the overall safety population at week 2 (1.3 [9.0] mm Hg; $P = .006$), week 4 (1.4 [9.7] mm Hg; $P = .008$), and continuing at visits through endpoint (Table 4). At endpoint, a mean (SD) increase in SBP of 3.1 (10.7) mm Hg was observed for the safety population ($P < .0001$). By post hoc analysis, the mean (SD) increase in SBP from baseline to endpoint by final dose group was 1.8 (11.1), 3.2 (10.9), and

TABLE 4.
Mean Change From Baseline in SBP, DBP, and Pulse at 3-Month Intervals (Safety Population)

	SBP (mm Hg)		DBP (mm Hg)		Pulse (bpm)	
	<i>Mean (SD)</i>	<i>Mean (SD) Change From Baseline</i>	<i>Mean (SD)</i>	<i>Mean (SD) Change From Baseline</i>	<i>Mean (SD)</i>	<i>Mean (SD) Change From Baseline</i>
Baseline	117.3 (10.0)		75.4 (8.0)		74.1 (10.3)	
Month 3	119.7 (10.9)	2.4 (10.1)*	76.4 (8.2)	1.1 (7.8)*	78.0 (9.9)	4.1 (9.8)*
Month 6	119.7 (11.4)	2.5 (10.5)*	76.2 (8.4)	0.8 (8.3)	78.3 (10.2)	4.4 (11.0)*
Month 9	119.5 (11.1)	2.2 (10.7)*	76.8 (8.6)	1.6 (8.5)*	78.7 (10.9)	4.5 (11.2)*
Month 12	121.9 (11.8)	4.9 (10.6)*	77.6 (8.0)	2.4 (7.1)*	77.9 (10.3)	3.5 (11.8)*
Endpoint	120.5 (11.7)	3.1 (10.7)*	76.8 (8.2)	1.3 (7.6)*	77.1 (10.4)	3.2 (11.6)*

* $P < .05$.

P -value determined by t-test vs baseline.

SBP=systolic blood pressure; DBP=diastolic blood pressure; SD=standard deviation.

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3.4 (10.6) mm Hg for the 30, 50, and 70 mg/day dose groups. The mean (SD) baseline DBP for the overall safety population was 75.4 (8.0) mm Hg. At endpoint, the mean (SD) change in DBP for the safety population was 1.3 (7.6) mm Hg ($P=.001$), but changes in DBP were not consistent throughout the study (Table 4). By post hoc analysis, the mean (SD) increase in DBP from baseline to endpoint by final dose group was 0.4 (7.8), 0.7 (8.4), and 2.0 (7.0) mm Hg for the 30, 50, and 70 mg/day dose groups.

Outlier criteria were more frequently met for pulse than for SBP or DBP. At endpoint, 20 subjects met the a priori outlier criteria for pulse (ie, \geq baseline mean + 2•SD). Outlier criteria for SBP (ie, ≥ 150 mm Hg) and DBP (ie, ≥ 95 mm Hg) were each met by 2 subjects at endpoint. Additional post hoc analyses of outlier data, using different criteria, demonstrated that 32 subjects experienced a SBP ≥ 140 mm Hg and $\geq 10\%$ change from baseline or DBP ≥ 90 mm Hg and $\geq 10\%$ change from baseline at only 1 time point during the study. Fifteen subjects met these criteria at 2 points during the study, while 4 subjects met the criteria at 2 or more consecutive time points. Using post hoc cutoff values for pulse (ie, ≥ 100 bpm), 34 subjects met the criteria for pulse at only 1 time point during the study, while 8 subjects met the criteria at 2 points during the study.

Electrocardiograms

The mean (SD) baseline heart rate for the safety population was 69.9 (11.4). At months 3, 6, 9, and 12, and at endpoint, the mean (SD) changes from baseline in heart rate of the safety population were 4.5 (10.8), 4.9 (10.9), 4.4 (12.1), 4.1 (11.1), and 3.4 (10.8) bpm, respectively (all visits and at endpoint $P<.0001$). At endpoint, the mean (SD) heart rate for the overall safety population was 73.3 (11.3) bpm. The mean (SD) prolongation of the QTcF interval from baseline at endpoint was 6.2 (18.1) msec for the safety population. At endpoint, the mean (SD) QTcF was 409.6 (18.9) msec for the safety population. At endpoint, 3 subjects (0.9%) were assessed to have a QT interval that was ≥ 60 msec longer than their baseline measurement and 1 subject's QTcF interval increased ≥ 60 msec from baseline. No subject was assessed as having a QTcF of >480 msec at any visit during the trial.

Two clinically significant abnormal ECG findings were documented by the investigators during the trial. One subject was found to have clinically significant QT interval prolongation (QT:

405 msec; QTcB: 511 msec; QTcF: 473 msec) at month 6 that resolved (QT: 407 msec; QTcB: 441 msec; QTcF: 429 msec) with continued treatment when a repeat ECG was performed 11 days later. The subject's baseline ECG was normal (QT: 409 msec; QTcB: 432 msec; QTcF: 424 msec). The subject was subsequently discontinued from the study at the request of the investigator. A second subject was found to exhibit premature ventricular contraction (PVC) at month 9. At a follow-up ECG 3 days later with continued treatment, PVCs were not recorded and the subject was subsequently lost to follow-up.

Other Safety Assessments

The mean (SD) global PSQI score at the baseline visit of the prior study was 6.5 (3.2); scores ranged from 1.0 to 18.0 at baseline. At endpoint, scores were significantly reduced from baseline, indicating a mean improvement in overall sleep efficiency. The overall mean (SD) change from baseline to endpoint was -1.3 (2.8) ($P<.0001$) such that, at endpoint, the mean (SD) global PSQI score for subjects in the safety population was 5.1 (2.9); scores ranged from 0.0 to 16.0 at endpoint.

The mean (SD) baseline weight for the safety population was 174.9 (38.2) lbs. The mean (SD) change in body weight from baseline at endpoint was -4.0 (10.5) lb ($P<.0001$) for the safety population. For the overall safety population, mean (SD) changes in body weight from baseline were greatest at month 10 (-6.8 [11.4] lb). Post hoc analyses evaluating changes in body mass index (BMI) demonstrated that of 105 subjects with a normal BMI (ie, >18 to ≤ 24) at baseline, one subject ended the study as underweight (BMI=19.2 at baseline and 17.5 at endpoint) and 6 ended the study as overweight (BMI ranged from 23.2–23.9 at baseline and 24.0–25.1 at end of study). Categorical increases in BMI were observed in 100% ($n=1$) of subjects classified as underweight at baseline, 5.7% ($n=6$) of those with a normal BMI at baseline, and 3.6% ($n=5$) of subjects overweight at baseline. Of subjects with baseline BMIs classified as overweight, obese, and extremely obese, categorical decreases in BMI status were observed in 20.7% ($n=29$), 19.8% ($n=17$), and 25.0% ($n=2$) of subjects, respectively.

Over the course of the present study, 3 subjects became pregnant and were subsequently withdrawn from the study. One subject gave birth to a full-term normal female and is estimated to have been on LDX for ~6 weeks after conception.

One subject voluntarily terminated the pregnancy without any complications. A third subject, believed to be on LDX for ~11 weeks of her pregnancy, delivered a female at ~37–38 weeks' gestation. The neonate developed jaundice within her first week of life that resolved without treatment and she was subsequently found to be physically normal.

One subject experienced elevated blood glucose levels, considered unrelated to LDX treatment, that resulted in discontinuation from the study. Otherwise, any changes in laboratory values were not considered clinically meaningful.

Effectiveness

Subjects in the ITT population had a mean (SD) baseline ADHD-RS total score of 40.6 (6.6), taken from the baseline assessment in the prior short-term study. Significant changes from baseline in ADHD-RS total scores were observed at every postbaseline visit (Figure 3). The mean (SD) change in ADHD-RS total score was -24.8 (11.7) ($P<.0001$), which was shown in a post hoc analysis as corresponding to a 60.7% (26.3) ($P<.0001$) mean (SD) relative improvement from baseline. For those who did ($n=296$) or did not ($n=49$) previously receive LDX, mean (SD) improvements in ADHD-RS total scores were 61.6% (25.1) and 55.1% (32.0), respectively. The mean (SD) ADHD-RS total score at endpoint for the ITT population was 15.8 (10.7).

At baseline, all subjects in the ITT population were rated as being at least moderately ill (ie, CGI-S score ≥ 4). The mean (SD) CGI-S score

for the ITT population was 4.8 (0.7). At endpoint, the mean (SD) CGI-I score was 1.7 (0.9). At weeks 1, 2, 3, and 4, the proportion of the ITT population rated as improved on the CGI-I was 43.9%, 68.3%, 83.4%, and 89.1%, respectively. At month 12, 92.6% were assessed as being improved as measured by the CGI-I. At endpoint, 84.1% of the ITT population improved from baseline as measured by the CGI-I with similar percentages observed in both the LDX-naïve population (79.6%) and the prior LDX-treated population (84.8%).

DISCUSSION

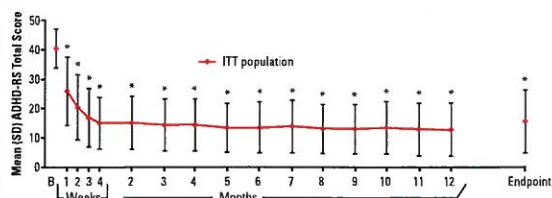
The safety and efficacy of LDX versus placebo for treating adults with ADHD have been previously demonstrated in a large, short-term, randomized, placebo-controlled, double-blind trial.³⁴ The results of this study demonstrate the continued safety and effectiveness of LDX for up to 1 year.

The AE profile seen with long-term use of LDX is similar to that seen with short-term use.³⁴ The high incidence of URI, which was generally considered unrelated to LDX treatment, is not unexpected during a long-term study. The other frequent TEAEs (ie, insomnia, headache, dry mouth, decreased appetite, and irritability) are known effects of amphetamines.^{13,39}

Only 8.0% of enrolled subjects discontinued as a result of AEs. While most subjects had previously been treated with LDX, and, therefore, had already demonstrated good tolerability of LDX, a subset was LDX naïve. Of subjects who had not previously been treated with LDX, only 7.7% ($n=4$) discontinued from the study due to AEs; this was comparable to the 3.0% (30 mg/day) to 7.0% (50 and 70 mg/day) of subjects receiving LDX in the prior short-term study who discontinued as a result of AEs.³⁴ TEAEs were generally mild to moderate in severity and were more common at the beginning of treatment. Serious AEs were uncommon in the present study and none was determined to be related to treatment with LDX. The death of 1 subject as a result of cocaine and alcohol toxicity was determined to be unrelated to LDX treatment, but stresses the importance of initial and ongoing assessment to minimize the potential impact of substance abuse in subjects with ADHD, two conditions that demonstrate high rates of comorbidity.⁶

Consistent with the known effects of stimulants,^{40–42} subjects demonstrated small but statistically significant mean increases from

FIGURE 3.
Mean ADHD-RS total score by each treatment visit in the ITT population



Baseline ADHD-RS assessment was obtained at baseline of short-term, double-blind trial. Results at endpoint are LOCF results for the ITT population.

* $P<.0001$ versus baseline (paired t-test).

ADHD-RS=attention deficit/hyperactivity disorder rating scale; ITT=intent to treat; LOCF=last observation carried forward.

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baseline in DBP (1.3 mm Hg), SBP (3.1 mm Hg), and pulse (3.2 bpm) at endpoint. These changes were generally greater in LDX-naïve subjects compared with those who received LDX in the prior trial. These differences may be attributed to differences in prior exposure to LDX, as evidenced by the higher baseline pulse observed in subjects previously treated with LDX. At endpoint, both groups of subjects had similar pulse and BP measurements. Significant increases in BP and pulse are commonly seen in clinical studies of medications used to treat ADHD.^{13,14,16-18,43} No subject discontinued from the present trial secondary to increases in pulse or BP. While LDX increased mean heart rate and QTc intervals, these changes were not considered clinically meaningful.

Although no clinically significant long-term changes were evident in various cardiovascular parameters, clinicians should use good clinical judgment and evaluate subjects for the presence of cardiovascular disease prior to prescribing stimulants to treat adults with ADHD, as the class labeling for these agents warns of potentially serious cardiovascular AEs.^{40,41,44} Patients should be asked about the presence of cardiovascular risk symptoms such as syncope, dizziness, palpitations, dyspnea, and/or chest discomfort after the initiation of therapy or dose adjustment. While no consensus guidelines have been established regarding monitoring the cardiovascular status of adults receiving stimulants, clinicians are encouraged to perform routine monitoring of BP and heart rate in these patients. Additional investigations should be performed if indicated by history and physical examination.

At baseline, the adults in this study were poor sleepers as evidenced by mean global PSQI scores >5. Insomnia, which occurred in <20% of subjects, was generally mild to moderate in severity for most subjects and led to few discontinuations. As assessed by the PSQI global score, sleep quality was not negatively impacted by LDX treatment and in fact, improved on average by 1.3 points (from a mean baseline score of 6.5) throughout the study. While patients should be monitored for signs and symptoms of poor sleep quality and insomnia, these results suggest that LDX is generally tolerable in patients with poor sleep quality at baseline.

Decreases in weight are expected with stimulant therapy and were observed at magnitudes consistent with other long-acting stimulants.³⁹

Mean weight loss peaked at month 10 and appeared to be decreasing during months 11 and 12. Moreover, when analyzed by BMI category, decreases were more common in overweight or obese subjects than in subjects with normal starting BMIs.

The present study demonstrated the long-term effectiveness of LDX at reducing ADHD symptoms as assessed by both the ADHD-RS and CGI-I. Significant improvements from baseline of ADHD-RS total scores were noted at all study visits for the overall ITT populations as well as both subgroups of subjects. LDX was also associated with improvements early in treatment as evidenced by CGI-I scores, with more than 89% of subjects being improved at week 4. These improvements were sustained through endpoint when more than 84% of subjects were rated as improved.

Approximately half (50.1%) of the subjects in the present study were optimized to receive 70 mg/day LDX. The average exposure time to 70 mg/day LDX was more than 200 days suggesting that most dosage increases occurred relatively early in treatment. Despite many subjects being maintained on treatment with 70 mg/day LDX for extended periods of time, improvements in ADHD-RS total scores were maintained throughout the study suggesting that subjects did not develop tachyphylaxis to LDX over time. During the trial, only 11 subjects (3.2%), none of which were in the LDX-naïve group, withdrew citing lack of effectiveness.

The findings of this trial should be viewed in light of several methodologic limitations. The open-label nature of the study and absence of a control arm present the possibility of bias. Additionally, subjects who demonstrated poor tolerability to LDX or experienced AEs that would preclude continued exposure to LDX in a prior trial were not enrolled in the present study. Subjects with comorbid psychiatric disease, unstable medical conditions, and significant cardiovascular disease were also excluded from this study. Therefore, these results may not be able to be generalized to the broader adult population that may present with comorbidities, nor provide information regarding the safety of LDX in adults with preexisting hypertension or other cardiovascular disease. Information on occurrence of AEs was gathered by open-ended, nonleading inquiry; structured rating scales for AE incidence and severity were not employed.

CONCLUSION

This study is the first to demonstrate that long-term treatment with LDX (30–70 mg/day) for up to 1 year was generally well tolerated and efficacious in adults with ADHD. This study employed a flexible dosing strategy, similar to that employed in clinical practice. It is likely that the flexibility of multiple dose levels contributed to achieving optimal dosing for the subjects in this study and may have contributed to the relatively low rate of AEs and discontinuations secondary to AEs. It is also likely that individually optimized dosing contributed positively to sustained effectiveness over a year-long study. Overall, the results are consistent with a prior short-term, double-blind trial of LDX in adults with ADHD. Treatment was associated with increases in BP and pulse that were small and not clinically significant, and decreases in body weight, which are to be expected with stimulant use. However, as with all stimulants, the use of LDX should be avoided in patients with any history or evidence of structural cardiac disease and/or significant or poorly controlled cardiovascular disease, including hypertension or arrhythmias. Misuse or abuse of any stimulant medication may cause or contribute to sudden death and/or other serious cardiovascular AEs.^{40–42,44} Thus, LDX and the other approved stimulants are most safely used as prescribed according to the approved product information. Appropriate monitoring, as clinically indicated, of BP and pulse is suggested for all adults treated with LDX. Insomnia, a recognized AE of stimulants, was commonly reported at the beginning of LDX treatment; however, sleep quality was generally not adversely affected by LDX treatment. These results support the use of once-daily LDX in otherwise healthy adults with ADHD. *CNS*

REFERENCES

- Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and meta-regression analysis. *Am J Psychiatry*. 2007;164:942–948.
- Diagnostic and Statistical Manual of Mental Disorders*. Fourth Edition. Text Revision. Washington, DC: American Psychiatric Association; 2000.
- Barkley RA, Fischer M, Edelbrock CS, Smallish L. The adolescent outcome of hyperactive children diagnosed by research criteria: I. An 8-year prospective follow-up study. *J Am Acad Child Adolesc Psychiatry*. 1990;29:546–557.
- Barkley RA, Fischer M, Smallish L, Fletcher K. The persistence of attention-deficit/hyperactivity disorder into young adulthood as a function of reporting source and definition of disorder. *J Abnorm Psychol*. 2002;111:279–289.
- Biederman J, Mick E, Faraone SV. Age-dependent decline of symptoms of attention deficit hyperactivity disorder: impact of remission definition and symptom type. *Am J Psychiatry*. 2000;157:816–818.
- Kessler RC, Adler L, Barkley R, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. *Am J Psychiatry*. 2006;163:716–723.
- Biederman J, Faraone SV, Spencer TJ, Mick E, Monuteaux MC, Aleardi M. Functional impairments in adults with self-reports of diagnosed ADHD: a controlled study of 1001 adults in the community. *J Clin Psychiatry*. 2006;67:524–540.
- Biederman J, Mick E, Fried R, Aleardi M, Potter A, Herzog K. A simulated workplace experience for nonmedicated adults with and without ADHD. *Psychiatr Serv*. 2005;56:1617–1620.
- Greenhill LL, Pliszka S, Dulcan MK, et al. Practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. *J Am Acad Child Adolesc Psychiatry*. 2002;41(2 suppl):26S–49S.
- Wilens TE, Dodson W. A clinical perspective of attention-deficit/hyperactivity disorder into adulthood. *J Clin Psychiatry*. 2004;65:1301–1313.
- Faraone SV, Spencer TJ, Montano CB, Biederman J. Attention-deficit/hyperactivity disorder in adults: a survey of current practice in psychiatry and primary care. *Arch Intern Med*. 2004;164:1221–1226.
- Spencer T, Wilens T, Biederman J, Faraone SV, Ablon JS, Lapey K. A double-blind, crossover comparison of methylphenidate and placebo in adults with childhood-onset attention-deficit hyperactivity disorder. *Arch Gen Psychiatry*. 1995;52:434–443.
- Spencer T, Biederman J, Wilens T, et al. Efficacy of a mixed amphetamine salts compound in adults with attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry*. 2001;58:775–782.
- Weisler RH, Biederman J, Spencer TJ, et al, on behalf of the SLI381.303 Study Group. Mixed amphetamine salts extended-release in the treatment of adult ADHD: a randomized, controlled trial. *CNS Spectr*. 2006;11:625–639.
- Fallu A, Richard C, Prinzo R, Binder C. Does OROS-methylphenidate improve core symptoms and deficits in executive function? Results of an open-label trial in adults with attention deficit hyperactivity disorder. *Curr Med Res Opin*. 2006;22:2557–2566.
- Biederman J, Mick E, Surman C, et al. A randomized, placebo-controlled trial of OROS methylphenidate in adults with attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2006;59:829–835.
- Weisler RH, Biederman J, Spencer TJ, Wilens TE. Long-term cardiovascular effects of mixed amphetamine salts extended release in adults with ADHD. *CNS Spectr*. 2005;10(12 suppl 20):35–43.
- Wilens TE, Hammerness PG, Biederman J, et al. Blood pressure changes associated with medication treatment of adults with attention-deficit/hyperactivity disorder. *J Clin Psychiatry*. 2005;66:253–259.
- Nutt DJ, Fone K, Asherson P, et al. Evidence-based guidelines for management of attention-deficit/hyperactivity disorder in adolescents in transition to adult services and in adults: recommendations from the British Association for Psychopharmacology. *J Psychopharmacol*. 2007;21:10–41.
- Adler LA, Reingold LS, Morrill MS, Wilens TE. Combination pharmacotherapy for adult ADHD. *Curr Psychiatry Rep*. 2006;8:409–415.
- Philipsen A, Hornyak M, Riemann D. Sleep and sleep disorders in adults with attention deficit/hyperactivity disorder. *Sleep Med Rev*. 2006;10:399–405.
- Mick E, Biederman J, Jetton J, Faraone SV. Sleep disturbances associated with attention deficit hyperactivity disorder: the impact of psychiatric comorbidity and pharmacotherapy. *J Child Adolesc Psychopharmacol*. 2000;10:223–231.
- Owens JA. The ADHD and sleep conundrum: a review. *J Dev Behav Pediatr*. 2005;26:312–322.
- Carlson GA, Kelly KL. Stimulant rebound: how common is it and what does it mean? *J Child Adolesc Psychopharmacol*. 2003;13:137–142.
- Mattingly GW. ADHD, psychostimulants and sleep disorders: is there a link? *The Year in ADHD*. 2008; 2009;1:32–37.
- Pennick M. Absorption of lisdexamfetamine dimesylate and hydrolysis to form the active moiety, d-amphetamine. Poster presented at: New Clinical Drug Evaluation Unit 49th Annual Meeting; June 29–July 2, 2009; Hollywood, FL.
- Pennick M. Hydrolytic conversion of lisdexamfetamine dimesylate to the active moiety, d-amphetamine. Poster presented at: Society of Biological Psychiatry's 64th Annual Scientific Convention and Meeting; May 14–16, 2009; Vancouver, British Columbia, Canada.
- Shojaei A, Ermer JC, Krishnan S. Lisdexamfetamine dimesylate as a treatment for ADHD: dosage formulation and pH effects. Poster presented at: 160th Annual Meeting of the American Psychiatric Association; May 19–24, 2007; San Diego, CA. Poster NR 740.
- Krishnan S, Zhang Y. Relative bioavailability of lisdexamfetamine 70-mg capsules in fasted and fed healthy adult volunteers and in solution: a single-dose, crossover pharmacokinetic study. *J Clin Pharmacol*. 2008;48:293–302.
- Ermer J, Homolka R, Martin P, Buckwalter M, Purkayastha J, Roesch BG. Linear dose proportionality, low inter- and intraindividual variability, and safety of lisdexamfetamine dimesylate in an open-label single-dose pharmacokinetic study in healthy adult volunteers. Poster presented at: 37th Annual Meeting of the American College of Clinical Pharmacy Annual Meeting; October 19–22, 2008; Louisville, KY. Poster 201.

31. Biederman J, Krishnan S, Zhang Y, McGough JJ, Findling RL. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: a phase III, multicenter, randomized, double-blind, forced-dose, parallel-group study. *Clin Ther*. 2007;29:450-463.
32. Biederman J, Boellner SW, Childress A, Lopez FA, Krishnan S, Zhang Y. Lisdexamfetamine dimesylate and mixed amphetamine salts extended-release in children with ADHD: a double-blind, placebo-controlled, crossover analog classroom study. *Biol Psychiatry*. 2007;62:970-976.
33. Wigal SB, Kollins SH, Childress AC, Squires L, for the 311 Study Group. A 13-hour laboratory school study of lisdexamfetamine dimesylate in school-aged children with attention-deficit/hyperactivity disorder. *Child Adolesc Psychiatry Ment Health*. 2009;3:17.
34. Adler LA, Goodman DW, Kollins SH, et al, on behalf of the 303 Study Group. Double-blind, placebo-controlled study of the efficacy and safety of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder. *J Clin Psychiatry*. 2008;69:1364-1373.
35. Findling RL, Childress AC, Krishnan S, McGough JJ. Long-term effectiveness and safety of lisdexamfetamine dimesylate in school-aged children with attention-deficit/hyperactivity disorder. *CNS Spectr*. 2008;13:614-620.
36. Adler L, Cohen J. Diagnosis and evaluation of adults with attention-deficit/hyperactivity disorder. *Psychiatr Clin North Am*. 2004;27:187-201.
37. ADHD-RS Initial Evaluation. Available at: <http://www.askdrjones.com/wp-content/uploads/patientforms/ADHD%20Screening-Initial%20Eval.pdf>. Accessed August 12, 2009.
38. Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28:193-213.
39. Biederman J, Spencer TJ, Wilens TE, Weisler RH, Read SC, Tulloch SJ, on behalf of the SLI 381.304 Study Group. Long-term safety and effectiveness of mixed amphetamine salts extended release in adults with ADHD. *CNS Spectr*. 2005;10(12 Suppl 20):16-25.
40. Adderall XR [package insert]. Wayne, PA: Shire US Inc; 2009.
41. Concerta [package insert]. Titusville, NJ: McNeil Pediatrics; 2009.
42. Focalin XR [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2009.
43. Adler LA, Spencer TJ, Williams DW, Moore RJ, Michelson D. Long-term, open-label safety and efficacy of atomoxetine in adults with ADHD: final report of a 4-year study. *J Atten Disord*. 2008;12:248-253.
44. Vyvanse [package insert]. Wayne, PA: Shire US Inc; 2009.

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