Short-Term Effects of Lisdexamfetamine Dimesylate on Cardiovascular Parameters in a 4-Week Clinical Trial in Adults With Attention-Deficit/Hyperactivity Disorder

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Objective: To evaluate the short-term impact of lisdexamfetamine dimesylate on cardiovascular parameters in adults with attention-deficit/hyperactivity disorder (ADHD).

Method: Medically healthy adults (18–55 years of age) with *DSM-IV-TR*–defined ADHD were randomly assigned to placebo or 30, 50, or 70 mg/d of lisdexamfetamine dimesylate for 4 weeks between May and November 2006. Electrocardiograms, systolic and diastolic blood pressure, and pulse were assessed pretreatment and weekly thereafter.

Results: There were no significant differences for mean systolic or diastolic blood pressure in any lisdexamfetamine dimesylate dose group versus placebo. Changes in pulse from baseline to endpoint were 0.0, 2.8, 4.2, and 5.2 bpm in the placebo and lisdexamfetamine dimesylate 30, 50, and 70 mg/d groups, respectively ($P < .05$, all lisdexamfetamine dimesylate groups vs placebo). Post hoc pulse outliers (pulse ≥ 100 bpm; any 1 event) ranged from 3.3% to 8.5% of subjects in the lisdexamfetamine dimesylate groups, and no subjects in the placebo group were pulse outliers ($P < .05$ for lisdexamfetamine dimesylate 50 mg vs placebo only). There were no clinically meaningful electrocardiogram abnormalities. Overall, 8.3% (35/420; safety population) of subjects had treatment-emergent cardiovascular adverse events, and 1.7% (7/420) withdrew from the study because of cardiovascular complaints. Cardiovascular adverse events with lisdexamfetamine dimesylate in these medically healthy adults were generally mild to moderate in severity.

Conclusions: Lisdexamfetamine dimesylate had limited short-term effects on heart rate, blood pressure, and electrocardiogram parameters that were of minimal clinical concern. These findings support the relative safety of lisdexamfetamine dimesylate. However, considering the potential of outliers, it is advisable to monitor cardiovascular parameters in stimulant-treated patients. Interpretation of these findings is limited to patients with no preexisting cardiac conditions who are taking their medication as prescribed.

Trial Registration: clinicaltrials.gov Identifier: NCT00334880

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Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent psychiatric disorders worldwide, affecting as many as 8% of children.[1,2] Once considered a pediatric condition, prominent ADHD symptoms are now recognized to persist into adolescence and adulthood in approximately half of childhood cases.[3,4] Recent data suggest that the prevalence of ADHD in adults is 4.4% in the United States.[5]

Stimulant treatment is among the established treatments for ADHD in adults.[6–12] In clinical practice, the majority of adults who are being treated pharmacologically for ADHD are treated with stimulants.[13] Among reported adverse effects (AEs) of stimulants, much attention has been paid to the potential cardiovascular effects of these agents.[14,15]

The stimulants currently used to treat ADHD are methylphenidate- and amphetamine-based products, sympathy omimetics known to increase blood pressure (BP) and pulse.[10,16–19] Stimulants are not recommended for use in patients with preexisting serious structural cardiac abnormalities, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of these agents.[20–23] Guidelines for monitoring cardiovascular parameters in children include general recommendations from the American Heart Association (AHA) for careful monitoring of risk factors and concomitant drug therapy in children receiving psychotropic agents.[16] These recommendations for screening and monitoring of children and adolescents receiving stimulants and other psychotropic agents (described more fully below) are well accepted. The AHA recently issued recommendations specifically on electrocardiogram (ECG) screening of children being considered for stimulant therapy for ADHD.[24] Additionally, a recent guideline from the American Academy of Pediatrics does not recommend routine ECG screening prior to treatment with stimulants, but as an option reserved for cases in which patient or family history or physical examination

suggests the potential for cardiac disease.[25] While pediatric recommendations are useful, risk factors for cardiovascular disease are different in adults. Currently, medical associations have not issued definitive recommendations for monitoring cardiovascular parameters in adults receiving stimulant medications.

The cardiovascular effects reported in otherwise healthy adults with ADHD receiving stimulants appear modest in magnitude, with changes noted in pulse and BP, but not ECG parameters. Previous studies of long-acting stimulants have noted small but statistically significant effects versus placebo on BP and pulse, and these findings have been interpreted as having limited clinical significance.[15,18,19,26] However, there are a limited number of studies that have examined the effects of stimulants on cardiovascular parameters in adults with ADHD.

Lisdexamfetamine dimesylate is a prodrug stimulant that is indicated for the treatment of ADHD in children 6 to 12 years of age and in adults. Lisdexamfetamine dimesylate is a prodrug that is therapeutically inactive. After oral ingestion, lisdexamfetamine dimesylate is converted to l-lysine and active *d*-amphetamine. While a small amount of lisdexamfetamine dimesylate is hydrolyzed to *d*-amphetamine in the gastrointestinal tract, it has recently been identified that the conversion of lisdexamfetamine dimesylate into active *d*-amphetamine occurs primarily in the blood.[27,28]

Lisdexamfetamine dimesylate reduced symptoms of ADHD in adults with generally good tolerability, with a safety profile consistent with long-acting stimulant use, in a large, randomized, placebo-controlled, multisite clinical trial.[29] Given the limited published information on cardiovascular tolerability of stimulants in adults with ADHD, this article focuses on the analyses of vital signs and ECG data that were ascertained as part of this study of lisdexamfetamine dimesylate in medically healthy adults with ADHD. We hypothesized that similar to what has been previously reported in this patient population,[18] compared with placebo, lisdexamfetamine dimesylate would be associated with significant increases in heart rate and BP, but not ECG indices.

METHOD

These analyses of cardiovascular data are from a large, multicenter, randomized, double-blind, placebo-controlled, parallel-group, forced-dose titration study conducted at 48 sites in the United States between May and November 2006.[29] Institutional review board approval was obtained for each study site, and all participants provided written informed consent after receiving a complete explanation of the study. This study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice according to the International Conference on Harmonization guidelines.

Inclusion/Exclusion Criteria

Subjects eligible for participation in the study were aged 18 to 55 years and satisfied *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision criteria for a primary diagnosis of ADHD. Subjects were diagnosed with ADHD via a comprehensive psychiatric evaluation using the Adult ADHD Clinical Diagnostic Scale (version 1.2),[30] with moderate-to-severe ADHD symptoms, as indicated by a baseline score of at least 28 on the ADHD Rating Scale (ADHD-RS). The ADHD-RS was administered to subjects by trained raters utilizing adult prompts developed at New York University and Massachusetts General Hospital.[30,31]

Additional inclusion criteria included a 12-lead ECG with QT/QTcF (Fridericia) intervals < 450 msec for men and < 470 msec for women, a resting heart rate between 40 and 100 beats per minute (bpm), a PR interval < 200 msec, and a QRS interval < 110 msec. ECG measurements were performed at screening and visits 2 to 6. At screening, 3 readings were taken at least 3 minutes apart after the subject rested supine for 10 minutes, ensuring accurate intervals were established to determine eligibility. At subsequent visits, ECG was recorded 1 or more times. Investigators made determinations regarding the clinical significance of ECG abnormalities with consultation of a cardiologist at the discretion of the investigator. Subjects were excluded from the study if they had a history of hypertension; a resting, sitting systolic BP (SBP) > 139 mm Hg or diastolic BP (DBP) > 89 mm Hg; any clinically significant abnormality on ECG; or a known cardiac structural abnormality/condition that might affect cardiac performance. Of note, if a participant had an SBP > 139 mm Hg or DBP > 89 mm Hg, the measurements were repeated twice more at 5-minute intervals, and the average of the measurements was used to determine the subject's eligibility for the trial.

Other exclusion criteria included any comorbid psychiatric diagnosis with significant symptoms that, in the opinion of the examining physician, would contraindicate treatment with lisdexamfetamine dimesylate or would confound efficacy and safety assessments; history of seizures (other than infantile febrile seizures); and current or recent history (within the last 6 months) of substance abuse (excluding nicotine). In addition, subjects were excluded if they were taking any prohibited medication (excluding ADHD medications, which were discontinued during a washout period) within 30 days of the screening visit. Excluded medications included, in addition to drugs with central nervous system effects, those known to affect BP, such as sympathomimetic and antihypertensive medications.

Study Design and Assessment Measures

The study had 3 phases: screening and washout, baseline, and double-blind treatment. Subjects underwent a screening period to ensure eligibility for participation in the study. Eligible subjects underwent a washout period during which

all ADHD medications were discontinued for at least 7 days (28 days if the subject was taking atomoxetine). Following the screening and washout periods, study participants underwent a baseline visit and were randomly assigned to treatment groups to receive placebo or once-daily oral doses of lisdexamfetamine dimesylate 30, 50, or 70 mg during the 4-week double-blind period. Randomization was achieved using a block-randomization schedule with a block size of 7 with a 2:2:2:1 allocation ratio of each of the 3 active doses versus placebo. Subjects randomly assigned to receive 50- or 70-mg/d doses of lisdexamfetamine dimesylate underwent a 1- and 2-week forced titration schedule, respectively. During the 4-week double-blind period, subjects attended weekly clinic visits for evaluation.

Safety assessments were conducted throughout the study and included the recording of AEs, vital signs (ie, SBP, DBP, and pulse), and ECGs, as well as clinical laboratory tests and physical examinations. Assessments of AEs were coded using the *Medical Dictionary for Regulatory Activities*, Version 9.1 (MedDRA: Maintenance and Support Service Organization, Reston, Virginia). Vital signs were recorded at all study visits. Blood pressure and pulse were determined after subjects were seated for 5 minutes. Blood pressure measurements were made using the subject's same arm for the duration of the study and were recorded using a manual or automated procedure (the same method was used throughout the study for individual subjects). Electrocardiograms were recorded 3 times during the screening visit but once per visit thereafter. Recordings were made after the subject rested supine for 10 minutes. Data collected included heart rate and interval parameters of QRS, QT, PR, and R-R.

Data Analysis

Data were analyzed using SAS Version 8.0 or higher (SAS Institute Inc., Cary, North Carolina). Efficacy was assessed in the intention-to-treat (ITT) population, defined as all subjects who were randomly assigned to treatment and had both a baseline and at least 1 postrandomization ADHD-RS total score available. Efficacy analyses and data were previously published.[29] Safety analyses were performed on the safety population, defined as all subjects who were enrolled, were randomized, and received the study drug.

For analyses assessing safety, the length of exposure to the study drug was calculated based on the dates of first dispensing and last dose of study medication and then dichotomized by week (ie, 1 week = 1–7 days, 2 weeks = 8–14 days, etc). Vital sign and ECG parameters were summarized by mean and standard deviation (SD). Changes in SBP, DBP, pulse, and ECG parameters from baseline were analyzed for differences among treatment groups using analysis of covariance (with Dunnett's test) at each postrandomization visit and at endpoint, using the baseline measurement as the covariate. For safety data, endpoint data were defined as the last nonmissing assessment obtained after the baseline visit, resulting in a last-observation-carried-forward analysis.

A priori (prespecified in the statistical plan) categorical analyses of cardiovascular parameters included analysis of vital signs (SBP, DBP, and pulse) and QT interval corrected using Fridericia method (QTcF). The Fridericia correction was chosen due to its resistance to the confounding effects of abnormally high or low heart rate.[32] Blood pressure assessments were categorized as outliers according to the following criteria: for SBP, as ≥ 150 mm Hg from a baseline of < 150 mm Hg; for DBP, as ≥ 95 mm Hg from a baseline of < 95 mm Hg; and for pulse, as ≥ (mean + [2 × SD]) from a baseline of < (mean + [2 × SD]). Categorical analyses of QTcF interval were prespecified by cutoff values of > 450 msec, > 480 msec, or > 500 msec for absolute values and as 30 to 59 msec and ≥ 60 msec change from baseline. These analyses were performed using shift tables for each postrandomization visit and at endpoint. Outlier criteria for QTcF were based on guidances from the US Food and Drug Administration[32] and from the European Agency for the Evaluation of Medicinal Products[33] and were used to investigate the potential for effects of lisdexamfetamine dimesylate on ventricular repolarization.

Post hoc outlier analyses of cardiovascular parameters (ie, SBP, DBP, pulse) were also performed using outlier criteria defined as SBP ≥ 140 mm Hg and ≥ 10% change in SBP from baseline to any time point during the study; DBP ≥ 90 mm Hg and ≥ 10% change in DBP from baseline to any time point during the study; or pulse ≥ 100 bpm at any time point during the study. Outlier criteria for BP were based on recommendations from the US Department of Health and Human Services (Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) for classification of high BP (ie, 140 mm Hg/90 mm Hg)[34] with inclusion of a minimum percentage change (ie, 10%) to account for normal variability of BP measurement.[35,36] Post hoc analyses are presented for outliers meeting criteria at any time point during the study and at a minimum of 2 time points during the study.

RESULTS

Subject Demographics and Disposition

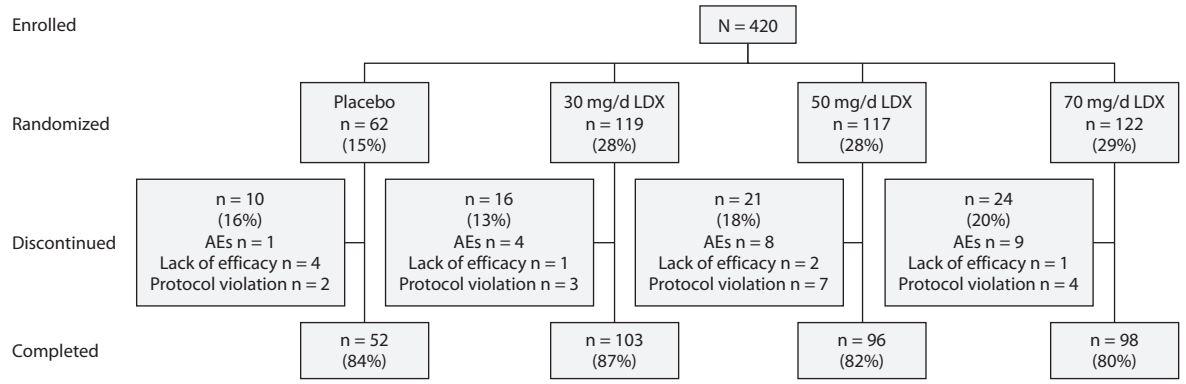
A total of 420 participants (lisdexamfetamine dimesylate 30 mg/d: n = 119; lisdexamfetamine dimesylate 50 mg/d: n = 117; lisdexamfetamine dimesylate 70 mg/d: n = 122; placebo: n = 62) were included in the present analysis and represent the safety population. All 4 treatment groups in the safety population were well matched at baseline and had no significant differences in baseline demographics, ADHD-RS total scores, or Clinical Global Impressions-Severity of Illness scale[37] scores. Baseline demographic characteristics of the participants are presented in Table 1.

Six subjects received treatment but did not have postrandomization ADHD-RS scores. Therefore, the ITT

Table 1. Baseline Demographic Characteristics (safety population)

Characteristic	Placebo (n = 62)	Lisdexamfetamine Dimesylate 30 mg/d (n = 119)	Lisdexamfetamine Dimesylate 50 mg/d (n = 117)	Lisdexamfetamine Dimesylate 70 mg/d (n = 122)
Age, mean ± SD, y	35.2 ± 10.9	35.3 ± 10.1	34.2 ± 10.0	35.8 ± 10.5
Male, n (%)	32 (51.6)	67 (56.3)	66 (56.4)	63 (51.6)
Caucasian, n (%)	48 (77.4)	94 (79.0)	99 (84.6)	108 (88.5)
Weight, mean ± SD, lb	181.3 ± 39.1	178.1 ± 38.9	173.1 ± 37.8	174.3 ± 37.3
Height, mean ± SD, in	67.9 ± 3.7	67.9 ± 3.9	67.6 ± 3.6	67.4 ± 3.7

Figure 1. Subject Disposition



Abbreviations: AE = adverse event, LDX = lisdexamfetamine dimesylate.

population consisted of 414 subjects. Of the 420 enrolled subjects, 349 (83%) completed the study; the remaining 71 (17%) discontinued prior to study completion (Figure 1). The rates of discontinuation in the lisdexamfetamine dimesylate treatment groups (13%–20%) were similar to that of the placebo group (16%).[29]

Concomitant medications used by subjects in this analysis were recorded at baseline, throughout the double-blind treatment period, and at follow-up. Approximately 39% of subjects in the study took concomitant medication, but, per protocol, few of these subjects used medications that would potentially impact cardiovascular parameters. Specifically, 1 subject in the 50 mg/d lisdexamfetamine dimesylate group took pseudoephedrine, 1 subject in the 30 mg/d lisdexamfetamine dimesylate group took albuterol, 1 subject in the 50 mg/d group and 1 subject in the placebo group took atomoxetine, 1 subject in the 50 mg/d group and 1 subject in the placebo group took methylphenidate, and 2 subjects in the 50 mg/d group, 1 in the 70 mg/d group, and 1 in the placebo group took Obetrol (similar to mixed amphetamine salts).

Cardiovascular Safety Analysis

At baseline, there were no statistically significant differences in least squares (LS) mean SBP or DBP between the groups randomly assigned to receive lisdexamfetamine dimesylate 30, 50, or 70 mg/d versus the placebo group. Treatment with lisdexamfetamine dimesylate was not associated with statistically significant changes in LS mean SBP or DBP from baseline at endpoint. Furthermore, the SBP and DBP LS mean changes from baseline at endpoint for each lisdexamfetamine dimesylate dose group were not statistically different than those of the group receiving placebo (Table 2).

Baseline LS mean (SE) pulse (obtained as part of vital signs assessment) was similar among treatment groups: 70.8 (0.87), 72.4 (0.87), 69.8 (0.86), and 70.9 (1.20) for the 30, 50, and 70 mg/d lisdexamfetamine dimesylate and placebo groups, respectively. Likewise, heart rates (measured by ECG) were similar among treatment groups: 65.4 (0.86), 66.4 (0.87), 65.1 (0.85), and 66.3 (1.20) for the 30, 50, and 70 mg/d lisdexamfetamine dimesylate and placebo groups, respectively. Overall analysis showed statistically significant treatment effects of lisdexamfetamine dimesylate versus placebo for pulse ($P < .05$) and heart rate ($P < .05$) at endpoint. All lisdexamfetamine dimesylate dose groups showed increases from baseline in pulse at endpoint, while the placebo group did not. Data for all 4 treatment groups are shown in Table 2. Significant differences in pulse were noted starting at week 2 and persisted through week 4. Significant increases in heart rate (ECG) were seen starting at week 2 and remained similarly elevated through week 4. Mean heart rate changes from baseline at endpoint are described in Table 2 for the 4 treatment groups. Analyses comparing the individual lisdexamfetamine dimesylate dose groups with placebo demonstrated that all the lisdexamfetamine

Table 2. Least Squares Mean Change (95% CI) in Vital Signs and Key ECG Parameters From Baseline at Endpoint in Patients Receiving Lisdexamfetamine Dimesylate or Placebo in a 4-Week Trial[a]

	Placebo	Lisdexamfetamine Dimesylate 30 mg/d	Lisdexamfetamine Dimesylate 50 mg/d	Lisdexamfetamine Dimesylate 70 mg/d
Vital signs				
Pulse, bpm	0.0 (−2.2 to 2.2)	2.8* (1.2 to 4.4)	4.2* (2.6 to 5.9)	5.2* (3.6 to 6.8)
SBP, mm Hg	−0.5 (−2.6 to 1.5)	0.8 (−0.7 to 2.3)	0.3 (−1.2 to 1.8)	1.3 (−0.2 to 2.7)
DBP, mm Hg	1.1 (−0.5 to 2.7)	0.8 (−0.4 to 2.0)	1.1 (−0.1 to 2.3)	1.6 (0.4 to 2.7)
Key ECG parameters				
Heart rate, bpm	1.1 (−1.2 to 3.3)	4.3* (2.6 to 5.9)	5.3* (3.6 to 6.9)	5.3* (3.7 to 6.9)
QRS interval, msec	0.0 (−1.2 to 1.3)	−0.1 (−1.1 to 0.8)	−0.1 (−1.0 to 0.9)	0.1 (−0.8 to 1.0)
QTcF interval, msec	−0.3 (−4.1 to 3.4)	4.0 (1.3 to 6.8)	−1.8 (−4.6 to 0.9)	2.7 (0.0 to 5.4)

[a]Endpoint defined as the last nonmissing assessment obtained after the baseline visit. *P* values are derived from pairwise comparisons with placebo using analysis of covariance. Placebo, n = 62; lisdexamfetamine dimesylate 30 mg/d, n = 119; lisdexamfetamine dimesylate 50 mg/d, n = 117; lisdexamfetamine dimesylate 70 mg/d, n = 122.
*$P < .05$ vs placebo.
Abbreviations: DBP = diastolic blood pressure, ECG = electrocardiogram, SBP = systolic blood pressure.

dimesylate groups were associated with significantly increased heart and pulse rates from baseline at endpoint relative to placebo.

Changes in PR interval from baseline to endpoint were statistically different compared with placebo for some dose groups. PR interval LS mean (95% CI) differences were −2.8 (−6.22 to 0.72), −4.4 (−7.87 to −0.94), and −4.9 (−8.38 to −1.47) msec for the 30, 50, and 70 mg/d groups ($P < .01$ for the 50 and 70 mg/d groups). RR interval LS mean (95% CI) differences were −40.3 (−80.74 to 0.08), −45.6 (−85.95 to −5.32), and −50.6 (−90.84 to −10.38) msec for the 30, 50, and 70 mg/d groups ($P < .05$ for the 50 and 70 mg/d groups). No significant changes in QRS intervals were associated with lisdexamfetamine dimesylate treatment or any specific lisdexamfetamine dimesylate dose groups at any time point over the course of the study or at endpoint (Table 2). The LS mean QT interval decreased from baseline across both the lisdexamfetamine dimesylate and placebo groups throughout the study. Analysis showed no significant treatment effect overall for lisdexamfetamine dimesylate versus placebo for mean change from baseline of QT interval at any time period throughout the study (ie, weeks 1 through 4 and endpoint). The 3 individual lisdexamfetamine dimesylate treatment groups showed no significant change in QTcF interval from baseline as compared with placebo at endpoint (Table 2) or at any of the 4 visits throughout the study.

A Priori Outlier Analyses

A priori outlier analyses for BP showed 1 event (30 mg/d lisdexamfetamine dimesylate group) and 2 events (70 mg/d lisdexamfetamine dimesylate group) of SBP ≥ 150 mm Hg from a baseline of < 150 mm Hg at any point in the study, along with 1 event (30 mg/d lisdexamfetamine dimesylate group), 5 events (50 mg/d lisdexamfetamine dimesylate group), and 9 events (70 mg/d lisdexamfetamine dimesylate group) of DBP ≥ 95 mm Hg from a baseline of < 95 mm Hg at any point during the study. Four events (placebo group), 31 events (30 mg/d lisdexamfetamine dimesylate group), 43 events (50 mg/d lisdexamfetamine dimesylate group), and 26 events (70 mg/d lisdexamfetamine dimesylate group) met the a priori criteria for pulse rate outliers [change ≥ (mean + 2 × SD)] at any time point during the study.

One subject had a QT interval > 500 msec at baseline visit and subsequent QT intervals either between 451 msec and 480 msec or ≤ 450 msec at weekly postbaseline visits and ≤ 450 msec at endpoint. At baseline, there were 15 QTcF interval readings between 451 msec and 480 msec, 5 in the placebo group and 10 in the 30 mg/d lisdexamfetamine dimesylate group. In all of these cases, subsequent QTcF readings at postbaseline visits were either between 451 msec and 480 msec or ≤ 450 msec. At postbaseline visits, 2 QTcF readings between 451 msec and 480 msec were observed in subjects receiving placebo, 1 at week 4 and 1 at endpoint. In subjects receiving 30 mg/d lisdexamfetamine dimesylate, 5 QTcF readings between 451 msec and 480 msec were recorded, 1 each at weeks 1 through 4 and at endpoint. In subjects receiving 50 mg/d lisdexamfetamine dimesylate, no postbaseline QTcF readings between 451 msec and 480 msec were recorded; 1 reading was recorded at week 1 in a subject receiving 70 mg/d lisdexamfetamine dimesylate. There were no QTcF interval readings of > 480 msec or > 500 msec across all postbaseline treatment weeks. There were no QTcF changes from baseline of ≥ 60 msec. At endpoint, the numbers of subjects with a QTcF interval change from baseline between 30 msec and 59 msec were 2 (3.2%), 5 (4.2%), 1 (0.9%), and 3 (2.5%) for the placebo, 30, 50, and 70 mg/d lisdexamfetamine dimesylate dose groups, respectively.

Post Hoc Outlier Analyses

A total of 9 subjects met the criteria for SBP outlier, defined as SBP ≥ 140 mm Hg and ≥ 10% change in SBP from baseline, at least once during the study (Table 3). These outliers—3 from the 30 mg/d group, 2 from the 50 mg/d group, and 4 from the 70 mg/d group—all received treatment with lisdexamfetamine dimesylate, but there was no apparent

Table 3. Vital Sign Outlier Analyses for Patients Receiving Lisdexamfetamine Dimesylate or Placebo in a 4-Week Trial[a]

Group	Placebo (n = 62)	Lisdexamfetamine Dimesylate 30 mg/d (n = 119)	Lisdexamfetamine Dimesylate 50 mg/d (n = 117)	Lisdexamfetamine Dimesylate 70 mg/d (n = 122)
Subjects with SBP ≥ 140 mm Hg and ≥ 10% change from baseline at any time point during the study				
Met criteria at any point	0 (0)	3 (2.5)	2 (1.7)	4 (3.3)
Met criteria at ≥ 2 time points	0 (0)	0 (0)	0 (0)	1 (0.8)
Subjects with DBP ≥ 90 mm Hg and ≥ 10% change from baseline at any time point during the study				
Met criteria at any point	2 (3.2)	3 (2.5)	7 (6.0)	7 (5.7)
Met criteria at ≥ 2 time points	0 (0)	0 (0)	2 (1.7)	2 (1.6)
Subjects with SBP ≥ 140 mm Hg and ≥ 10% change from baseline and DBP ≥ 90 mm Hg and ≥ 10% change from baseline at any time point during the study				
Met criteria at any point	0 (0)	2 (1.7)	0 (0)	3 (2.5)
Met criteria at ≥ 2 time points	0 (0)	0 (0)	0 (0)	0 (0)
Subjects with pulse ≥ 100 bpm at any time point during the study				
Met criteria at any point	0 (0)	7 (5.9)	10 (8.5)	4 (3.3)
Met criteria at ≥ 2 time points	0 (0)	2 (1.7)	2 (1.7)	0 (0)

[a]Data shown as n (%).
Abbreviations: DBP = diastolic blood pressure, SBP = systolic blood pressure.

Table 4. Cardiovascular-Related Treatment-Emergent Adverse Events With Subject Incidence ≥ 2% in Any Treatment Group in Patients Receiving Lisdexamfetamine Dimesylate or Placebo in a 4-Week Trial[a]

Body System Preferred Term (MedDRA 9.1)	Placebo (n = 62)	Lisdexamfetamine Dimesylate 30 mg/d (n = 119)	Lisdexamfetamine Dimesylate 50 mg/d (n = 117)	Lisdexamfetamine Dimesylate 70 mg/d (n = 122)	Active Doses (n = 358)
BP increased	0 (0)	1 (0.8)	4 (3.4)	5 (4.1)	10 (2.8)
Dyspnea	0 (0)	3 (2.5)	2 (1.7)	3 (2.5)	8 (2.2)
Heart rate increased	0 (0)	1 (0.8)	3 (2.6)	3 (2.5)	7 (2.0)
Palpitations	0 (0)	2 (1.7)	1 (0.9)	3 (2.5)	6 (1.7)
Tachycardia	0 (0)	1 (0.8)	3 (2.6)	0 (0)	4 (1.1)

[a]Data shown as n (%).
Abbreviation: BP = blood pressure.

dose relationship. Eight of the 9 SBP outliers met the criteria at only 1 time point during the study. The remaining subject met the outlier criteria at 2 time points, but the criteria were not sustained through endpoint.

DBP outlier criteria, DBP ≥ 90 mm Hg and ≥ 10% change in DBP from baseline, were met by 19 subjects (2 in the placebo group, 3 in the 30 mg/d lisdexamfetamine dimesylate group, and 7 each in the 50 mg/d and 70 mg/d lisdexamfetamine dimesylate groups) as described in Table 3. Thirteen of the 17 outliers in the lisdexamfetamine dimesylate treatment group had outlying values at only 1 time point, and of the 4 subjects that were outliers at more than 1 time point, none sustained the criteria through endpoint.

Five subjects met the outlier criteria for both SBP and DBP (30 mg/d lisdexamfetamine dimesylate: n = 2 and 70 mg/d lisdexamfetamine dimesylate: n = 3) at any time point during the study (Table 3). All 5 outliers described above met the criteria at only 1 point in the study, and none met the criteria at endpoint.

In this analysis, 21 subjects (30 mg/d lisdexamfetamine dimesylate: n = 7, 50 mg/d lisdexamfetamine dimesylate: n = 10, and 70 mg/d lisdexamfetamine dimesylate: n = 4) met outlier criteria for pulse, defined as pulse ≥ 100 bpm, at clinic visits at least once during the study (Table 3) ($P < .05$ vs placebo for lisdexamfetamine dimesylate 50 mg/d; P = NS for 30 mg/d and 70 mg/d). Of the 21 outliers, 17 met the criteria at only 1 point in the study, while 4 met the criteria during at least 2 weekly study visits. Of those with pulse ≥ 100 bpm on more than 1 occasion, 2 had such readings at endpoint: 1 at 30 mg/d and 1 at 50 mg/d.

Cardiovascular Adverse Events

Treatment with lisdexamfetamine dimesylate was not associated with any deaths or serious AEs. There were no cardiovascular-related AEs classified as occurring prerandomization. The cardiovascular-related treatment-emergent adverse events (TEAEs) reported at any time point during the study at an incidence ≥ 2% were increased BP, dyspnea, increased heart rate, palpitations, and tachycardia (Table 4). No cardiovascular-related TEAEs occurred in the group receiving placebo.

The majority of cardiovascular TEAEs were rated as mild or moderate in severity. Of the 6 reported AEs of palpitations, 4 were classified as mild and 2 were classified as moderate in severity. Sinus tachycardia was reported in 1 patient and classified as mild in severity and possibly/probably related to drug treatment. Tachycardia, which was reported in 4 subjects, was classified as mild in severity in 2 subjects, moderate in 1 subject, and severe in 1 subject, and as possibly/probably related to drug treatment in all cases. Six of the 8 dyspnea AEs were classified as mild, with 1 case each being reported as moderate or severe and as possibly/probably related to drug treatment in all but 1 case. Of the reports of dyspnea, 2 were associated with concomitant

Table 5. Cardiovascular-Related Treatment-Emergent Adverse Events at Any Time Point During the Study Leading to Discontinuation in Patients Receiving Lisdexamfetamine Dimesylate or Placebo in a 4-Week Trial[a]

Body System Preferred Term (MedDRA 9.1)	Placebo (n = 62)	Lisdexamfetamine Dimesylate 30 mg/d (n = 119)	Lisdexamfetamine Dimesylate 50 mg/d (n = 117)	Lisdexamfetamine Dimesylate 70 mg/d (n = 122)	Active Doses (n = 358)
Palpitations	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.3)
Sinus tachycardia	0 (0)	0 (0)	1 (0.9)	0 (0)	1 (0.3)
Tachycardia	0 (0)	1 (0.8)	1 (0.9)	0 (0)	2 (0.6)
BP increased	0 (0)	0 (0)	1 (0.9)	2 (1.6)	3 (0.8)
Hypertension	0 (0)	1 (0.8)	0 (0)	0 (0)	1 (0.3)
Dyspnea	0 (0)	1 (0.8)	1 (0.9)	1 (0.8)	3 (0.8)

[a]Data shown as n (%).
Abbreviation: BP = blood pressure.

tachycardia (1 of these was also associated with hypertension) and another with palpitations and left arm discomfort. Of the 10 reported events of elevated BP, 8 were mild and 2 were moderate in severity, and all events were considered possibly/probably related to drug treatment, while all of the increased heart rate TEAEs (n = 7) were mild in severity and deemed possibly/probably related to drug treatment in all cases. Of reports of elevated BP, 1 was associated with concurrent sinus tachycardia and drug discontinuation.

Overall, 7 subjects (1.7%) withdrew from the study because of cardiovascular adverse effects: 1 (0.8%) in the 30 mg/d lisdexamfetamine dimesylate group, 2 (1.7%) in the 50 mg/d lisdexamfetamine dimesylate group, and 4 (3.3%) in the 70 mg/d lisdexamfetamine dimesylate group. These 7 subjects reported a total of 11 cardiovascular TEAEs, which are described in Table 5. With the exception of 1 patient, all TEAEs resolved, with none of the events requiring ongoing treatment. One patient who was discontinued due to elevated BP was successfully treated with an angiotensin receptor antagonist/diuretic combination until study exit. It is not known whether treatment was continued beyond study exit.

DISCUSSION

The results of the current analyses of data from medically healthy adults with ADHD partially support our hypothesis of the effect of lisdexamfetamine dimesylate on cardiovascular indices. As hypothesized, lisdexamfetamine dimesylate was associated with predictable but modest increases in pulse and heart rate and with no meaningful effects on other ECG parameters such as PR, RR, and QT intervals. Of note, lisdexamfetamine dimesylate was not associated with statistically significant or clinically meaningful changes in SBP or DBP in this study with the exception of 1 subject, as noted above, who was treated for elevated BP.

Discontinuations related to abnormal cardiovascular measures were generally low (≤ 5%) in studies of stimulant therapy in otherwise healthy patients with ADHD.[15,38] As may be expected since BP increases with age, discontinuation rates associated with cardiovascular TEAEs are somewhat higher in studies of adults treated with long-acting stimulants for ADHD, ranging from ~ 2%–5%, and are in line with the findings of the current study.[15,19,38,39] These data highlight the limited cardiovascular AEs associated with lisdexamfetamine dimesylate in medically healthy adults but also underscore the need to assess baseline cardiovascular status and to monitor for cardiovascular symptoms that may emerge during treatment in this patient population. The importance of this monitoring is supported by a recent epidemiologic report that noted increasing prevalence of hypertension in all racial/ethnic and gender groups standardized by age.[40] In addition, patients may not be aware of their cardiovascular risk factors. It should be stressed that since subjects with a history or evidence of active cardiovascular diseases were excluded in this study of lisdexamfetamine dimesylate, no conclusions regarding its safety in such a population can be drawn.

In a placebo-controlled trial in adults with ADHD, pulse increases ranged from 4.2 to 6.2 bpm for 3 doses (20, 40, and 60 mg/d) of mixed amphetamine salts extended-release (MAS XR) compared with 1.9 bpm for placebo.[11] Heart rate increased by 4.5 bpm for all doses (mean [SD] dose = 80.9 [31.8] mg/d) of osmotic-release oral system methylphenidate (OROS-MPH) combined compared with −2.7 bpm for placebo[19] in one study that utilized an optimal dosing scheme, and in a recent placebo-controlled trial with fixed doses of OROS-MPH, pulse increases at endpoint were 2.7, 3.9, 5.2, and 9.8 bpm for placebo and 18, 36, and 72 mg/d of OROS-MPH, respectively.[41] In a recent placebo-controlled study of OROS-MPH with an expanded dose range (36, 54, 72, 90, 108 mg/d), pulse rate increased by 3.6 bpm for those receiving OROS-MPH versus −1.6 bpm for those receiving placebo.[42] In a fixed-dose, placebo-controlled study of *d*-methylphenidate extended release (dMPH-ER; 20, 30, 40 mg/d), a small, significant mean increase in pulse (4.4 bpm) was demonstrated for those receiving dMPH-ER, and an apparent dose trend was also noted, with increases ranging from 3.1 to 6.0 bpm.[43] When noted in these studies, tachycardia was reported as an AE in 5.6%[41] and 2.7%[42] of subjects receiving OROS-MPH and 1.2% of subjects receiving dMPH-ER.[43] Although not classified as a stimulant, atomoxetine is also associated with cardiovascular effects,[44] with increased pulse rates of 6.7,[45] 3.8,[45] and 4.5 bpm[46] being reported in three 10-week, placebo-controlled studies. While consistent mean increases in pulse were observed in

the current study, with a range across doses of 2.8 to 5.2 bpm, there was a low incidence (1.1%) of tachycardia reported as an AE and a relatively low incidence (5.0%) of pulse rate ≥ 100 bpm at any visit during the study, with < 1% having a pulse rate ≥ 100 bpm at 2 or more visits.

Although the finding that the great majority of subjects in this study experiencing DBP readings categorized as outliers had such readings on only 1 occasion is reassuring in terms of the low occurrence of sustained effects, these findings do suggest that careful observation of adult subjects receiving long-acting stimulants is warranted.

Our data, demonstrating no significant overall effects on BP given the relatively large size of the study, differ somewhat from the existing literature. Stimulants as a group have been reported as being associated with increases of 2 to 4 mm Hg in mean BP.[20–23,47,48] Of interest, studies of mixed amphetamine salts and methylphenidate showed statistically significant increases versus placebo or versus baseline of approximately 1 to 5 mm Hg in mean SBP or mean DBP with treatment.[10,18,19] Large studies that focused on short- and long-term cardiovascular effects of MAS XR demonstrated that mean changes in SBP, DBP, and pulse, while not judged to be clinically relevant, were statistically significant.[11,15] On the other hand, 2 recent placebo-controlled studies[41,42] with OROS-MPH have found small, nonsignificant changes in BP. Medori et al[41] found SBP changes at endpoint of 1.1, 0.1, 0.4, and 2.2 mm Hg and DBP changes of −1.8, −0.8, 1.7, and 1.6 mm Hg for placebo, 18, 36, and 72 mg/d of OROS-MPH, respectively. Adler et al[42] found a change at endpoint of −1.2 mm Hg in SBP and 0.4 mm Hg in DBP in subjects receiving OROS-MPH. Similarly, changes in SBP (−0.5 mm Hg) and DBP (1.0 mm Hg) in the placebo-controlled trial of dMPH-ER[43] were small and not different from placebo. Atomoxetine was associated with small changes in SBP (2.3 and 3.5 mm Hg, respectively) and DBP (2.3 and 1.2 mm Hg, respectively) in two 10-week studies that reported both parameters[45] and in DBP (1.7 mm Hg) in a third 10-week study.[46]

The current findings are consistent with recent studies in pediatric and adult subjects with ADHD treated with stimulants that showed a relative lack of significant effects of these drugs on ECG parameters.[14,15,49] More specifically, the current data, in aggregate with the literature, show consistency in a lack of clinically meaningful effect on atrioventricular (PR) or intraventricular conduction (QRS) or repolarization (QTc). While the lisdexamfetamine dimesylate data are generally reassuring, it is important to note that these studies have generally examined screened and medically healthy adults with ADHD without a history of cardiovascular disease.

Consensus guidelines for monitoring cardiovascular parameters in adults receiving stimulant medications have not yet been developed. However, in the absence of established guidelines, it seems consistent with good clinical practice to monitor BP and pulse (periodically and/or when clinically indicated) throughout treatment as well as to follow relevant labeling recommendations published in package inserts for these medications (see below).[20–23,47,48] A history of potential cardiovascular risk symptoms such as syncope, and, in particular, syncope on exertion; dizziness; palpitations; dyspnea; and/or chest discomfort, as well as current use of prescription and nonprescription medications and family history of cardiac disease, should be queried prior to beginning therapy, with this information guiding the choice of further evaluation. For the adult population, in particular, it is also important to consider that major cardiovascular risk factors increase with age.[50] As mentioned previously, the incidence of hypertension, in general, is increasing, and, therefore, review of previous BP and pulse readings and assessment of baseline BP and pulse will rule out preexisting hypertension prior to ADHD treatment. Monitoring occurrence of the above-mentioned symptoms at follow-up visits with attention to periods of dose adjustment are sensible as well. Similarly, clinical monitoring is clearly advisable when other medications with potential cardiovascular impacts are added or adjusted by clinicians or if other known cardiovascular risk factors such as increased weight or diabetes develop or worsen during treatment. Aggregate data to date in this patient population support that ECG monitoring is not mandatory but should be considered if indicated by history and physical examination.[24,25] Additionally, the reader should keep in mind that all stimulant medications in the United States, including lisdexamfetamine dimesylate, have guidance in the package insert, including sections on contraindications, warnings, precautions, and cardiovascular AEs associated with these agents, that should be reviewed prior to prescribing any stimulant medication.

The current study has several limitations. It was a short-term study with a 4-week, double-blind treatment period with cardiovascular parameters assessed only in the short-term, acute setting. Other studies are needed to evaluate the potential effects of lisdexamfetamine dimesylate on cardiovascular parameters over longer durations of treatment. Also, the cardiovascular measures reported and analyzed were obtained during the collection of safety data for a pivotal clinical trial[29] and were not part of a formal cardiovascular study on the effects of psychostimulants. As such, subjectively reported cardiovascular AEs were not systematically assessed with objective measurements. This study, as is generally true, did not limit or assess caffeine intake from food, drink, and nutritional supplements. Another limitation of this study is that it included forced-dose escalation, which might result in overestimation of AEs in the absence of a dose-optimization regimen. In addition, because older adults (> 55 years) and adults with comorbid psychiatric and cardiovascular diseases were systematically screened and excluded from the current study, it may not adequately represent the general adult population with ADHD. For this reason, it may not be appropriate to generalize the results of this study to the broader adult population with ADHD,

who may present with cardiovascular comorbidities such as preexisting hypertension or structural cardiac abnormalities. Ideally, large-scale observational studies would avoid the limitations described above as well as those of sampling error associated with the limited patient population and the limited number of subjects enrolled in placebo groups in such short-term efficacy trials. These large-scale trials would provide data from subjects treated in wide clinical use of these agents that are needed to fully assess the clinical impact of cardiovascular effects of stimulants.

Despite these limitations, the secondary analyses from this study supported previous conclusions that lisdexamfetamine dimesylate was generally well tolerated. We found effects on pulse and heart rate and no effect on ECG, similar to that previously reported with long-acting stimulants, but no significant effects on BP in this study. It should be noted that misuse or abuse of any stimulant medication may cause or contribute to sudden death or other serious cardiovascular/medical events.[20–23] Thus, lisdexamfetamine dimesylate and other approved stimulants are most safely used as prescribed in their approved product information. Careful attention to cardiovascular history, symptoms, and clinical findings in adults with ADHD prior to and during treatment with stimulants is advisable.

Drug names: albuterol (Proventil and others), atomoxetine (Strattera), *d*-methylphenidate extended release (Focalin XR), lisdexamfetamine dimesylate (Vyvanse), osmotic-release oral system methylphenidate (Concerta), pseudoephedrine (Semprex, Bromfed, and others).

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