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ORIGINAL RESEARCH

Double-blind, placebo-controlled, two-period, crossover trial to examine the pharmacokinetics of lisdexamfetamine dimesylate in healthy older adults

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Background: Pharmacokinetic and safety data on stimulants in older adults are limited. The objective of this study was to characterize the pharmacokinetics of lisdexamfetamine dimesylate (LDX), a d-amphetamine prodrug, in older adults.

Methods: In this two-period crossover trial, healthy adults (n = 47) stratified by age (55–64, 65–74, and ≥ 75 years) and gender received randomized, double-blind, single doses of LDX 50 mg or placebo. Baseline creatinine clearance, d-amphetamine and intact LDX pharmacokinetics, and safety were assessed.

Results: Mean (±standard deviation) baseline creatinine clearance in participants aged 55–64, 65–74, and ≥ 75 years was 102.5 ± 26.1, 105.3 ± 23.1, and 94.9 ± 27.3 mL per minute, respectively. In the groups aged 55–64, 65–74, and ≥ 75 years, the mean maximum plasma d-amphetamine concentration in men was 44.2 ± 11.1, 47.7 ± 7.0, and 53.4 ± 19.4 ng/mL, respectively; area under the concentration time curve from time 0 extrapolated to infinity (AUC_{0-inf}) was 915.0 ± 164.9, 1123.0 ± 227.0, and 1325.0 ± 464.4 ng · hour/mL; median time to reach peak plasma concentration was 4.5, 3.5, and 5.5 hours; in women, mean maximum plasma d-amphetamine concentration was 51.0 ± 6.7, 50.2 ± 6.8, and 64.3 ± 12.1 ng/mL, AUC_{0-inf} was 1034.5 ± 154.6, 988.4 ± 80.5, and 1347.8 ± 198.9 ng · hour/mL, and median time to reach peak plasma concentration was 3.5, 4.1, and 5.5 hours, respectively. d-Amphetamine clearance was unrelated to baseline creatinine clearance. Five participants aged 55–64 years reported treatment-emergent adverse events (versus one each aged 65–74 and ≥ 75 years), and as did six women (versus one man). No trends in blood pressure or pulse changes were seen with LDX according to age. In participants aged 55–64, 65–74, and ≥ 75 years, the mean change from time-matched baseline pulse ranged from –5.0 to 14.7, –4.3 to 9.5, and –3.0 to 14.7 beats per minute; for systolic blood pressure, from –3.9 to 18.5 mmHg, –2.1 to 14.5 mmHg, and –5.9 to 16.0 mmHg; for diastolic blood pressure from –2.5 to 8.3 mmHg, from –0.8 to 9.4 mmHg, and –0.6 to 9.5 mmHg. Vital sign changes were similar between men and women.

Conclusion: Clearance of d-amphetamine decreased with age and was unrelated to creatinine clearance. No trends in pulse or blood pressure changes with LDX were seen according to age. The safety profile of LDX was consistent with prior observations in younger adult study participants.

Keywords: lisdexamfetamine dimesylate, older adults, pharmacokinetics, attention-deficit/hyperactivity disorder, d-amphetamine

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Introduction

Lisdexamfetamine dimesylate (LDX) is a prodrug of dextro (d)-amphetamine and is approved in the United States for the treatment of attention-deficit/hyperactivity

disorder (ADHD) in children (6–12 years), adolescents (13–17 years), and adults.[1] After oral administration, LDX is biotransformed to L-lysine and its active component, d-amphetamine.[2] The pharmacokinetic profiles of intact LDX and LDX-derived d-amphetamine following LDX administration have been well characterized in school-aged children aged 6–12 years with ADHD[3,4] and in adults up to the age of 55 years.[5,6] The safety of LDX in children[7,8] and adults[9,10] with ADHD and in healthy adults[5,6] has also been extensively studied.

To date, the pharmacokinetics of LDX have been studied in adults aged 18–55 years,[5,6,9,10] as well as in children aged 6–12 years with ADHD.[3,4] In healthy adults, oral LDX in the dose range of 50–250 mg was associated with linear and dose-proportional plasma d-amphetamine pharmacokinetics.[6] On oral administration of 50-mg LDX capsules, a mean maximum plasma d-amphetamine concentration (C_{max}) of 44.6 ng/mL was reached 1.5 to 6.0 hours postdosing (time to C_{max} [T_{max}] median 4.0 hours).[6] Intersubject and intrasubject variability findings in d-amphetamine C_{max} and area under the plasma concentration versus time curve (AUC) parameters for doses of 50–150 mg were $< 20\%$, indicating predictable and consistent delivery of d-amphetamine, both within and between individual patients, following administration of the LDX prodrug. Other studies have shown that absorption, enzymatic conversion, and resulting d-amphetamine concentrations in healthy adults are neither affected by food nor according to whether LDX is given orally as a capsule or as a solution.[5] The pharmacokinetic profile of LDX is not affected by coadministration of omeprazole, suggesting that gastric pH does not alter LDX absorption.[11]

In the upcoming years, increasing numbers of older adults (aged $>$ 55 years) may be treated with stimulant medications. Some adults currently treated for ADHD may continue to require psychostimulant-based treatment throughout their lifetime. Data concerning the pharmacokinetics and safety profiles of psychostimulant drugs in older adult populations (aged $>$ 55 years) are limited.[12,13] Older adult patients may have an age-related decline in renal function,[12,14,15] which may affect the pharmacokinetic profile of psychostimulant medications. Because of this potential change in older adult patients, it was of interest to study stimulant treatment further in this group. The aim of the current investigation was to examine the pharmacokinetic and safety profiles of LDX and LDX-derived d-amphetamine in healthy older adults in relation to age and renal function.

Subjects and methods

Study design

This was a randomized, double-blind, placebo-controlled, two-period crossover, single-dose investigation of the pharmacokinetics and safety of LDX conducted in healthy, older adult volunteers (aged $\geq$ 55 years). The study consisted of a screening period, two treatment periods, and follow-up contact by telephone. Participants were stratified according to age (55–64, 65–74, and $\geq$ 75 years) and gender, then randomly assigned to one of two treatment sequences (LDX 50 mg followed by placebo or placebo followed by LDX 50 mg). Treatment periods within each sequence were separated by a 7–14-day washout period. After the cohorts aged 55–64 and 65–74 years completed the study, a blinded safety data review was conducted by the investigators before proceeding with enrolment of the cohort aged $\geq$ 75 years. Baseline creatinine clearance was determined based on a 24-hour urine collection, starting at predose day −1 of treatment period 1, with final urine collection obtained at predose day 1 of treatment period 1. For each of treatment periods 1 and 2, randomized participants were confined to the study center from day −2 through to completion of all study assessments on day 4.

The study was approved by the appropriate institutional review board and was conducted in accordance with current applicable regulations and local legal and ethical requirements, as well as International Conference on Harmonization guidance on pharmacokinetic testing in geriatric individuals.[16] All participants and informants provided their written consent. Randomization blinding was maintained throughout the study for participants and evaluating clinicians.

Participants

Healthy older male and postmenopausal females (aged $\geq$ 55 years) were enrolled. Key exclusion criteria included any current or recurrent disease that could affect the absorption, disposition, effect of the investigational product, or clinical or laboratory assessments; one or more cardiovascular disease risk factors at screening (body mass index $<$ 20 or $>$ 32.0 kg/m^2, history of type 1 or 2 diabetes or glycosylated hemoglobin $\geq$ 6.5%, total cholesterol $\geq$ 260 mg/dL or low density lipoprotein cholesterol $\geq$ 190 mg/dL, and history of uncontrolled hypertension or high blood pressure [systolic $>$ 160 mm Hg and/or diastolic $>$ 100 mmHg, taken at rest while sitting]).

Participants with a known cardiac structural abnormality or any other condition that may increase vulnerability to the effects of psychostimulants were excluded. Also excluded

were participants with a history of alcohol or other substance abuse, as were those having a positive screen for drugs of abuse during the screening visit or check-in or a positive screen for alcohol during check-in; and those with consumption of any alcohol, caffeine, or xanthine-containing products within 24 hours prior to and during admission to the study center.

Bioanalysis and pharmacokinetics

Serial blood samples were collected up to 72 hours after administration of the study medication on day 1 in treatment periods 1 and 2. Beginning on day 1 of each treatment period, samples were obtained predose at −0.5 hours and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 12, 24, 48, and 72 hours postdosing. Blood samples were kept on ice, and within 30 minutes of sampling were centrifuged at approximately 1500× g for 15 minutes at 4°C. The separated plasma was divided equally into primary and backup samples, and stored at −20°C until bioanalysis at the end of each treatment period. For participants dosed with LDX, plasma was analyzed for LDX and d-amphetamine using a liquid chromatography with tandem mass spectrometry method validated over the range of 1–100 ng/mL for LDX and 2–200 ng/mL for d-amphetamine based on 200 µL of human plasma. Human plasma samples containing LDX and d-amphetamine, and internal standards, ie, D8-LDX and D5-amphetamine, were extracted with ethyl acetate/toluene (1:1) in the presence of saturated sodium chloride/sodium hydroxide. Following centrifugation, the organic layer was transferred and evaporated. After addition of formic acid and reconstitution in mobile phase, an aliquot was injected into a SCIEX API 4000 (AB Sciex, Framingham, MA) tandem mass spectrometer equipped with a high-performance liquid chromatography column. The peak area of the m/z 264 → 84 LDX product ion was measured against the peak area of the m/z 272 → 92 D8-LDX internal standard product ion. The peak area of the m/z 136 → 91 amphetamine product ion was measured against the peak area of the m/z 141 → 96 D5-amphetamine internal standard product ion. Peak area integrations were performed using Analyst version 1.4.2 software from Applied Biosystems (Carlsbad, CA). Concentrations were calculated using eight-point curves in the range of 1–100 ng/mL for LDX and 2–200 ng/mL for d-amphetamine, with separate weighted linear regression. Based on a sample volume of 200 µL, the method had a lower limit of quantification of 1 ng/mL for LDX and 2 ng/mL for d-amphetamine. Values below the lower limit of quantification were reported as not quantifiable.

Pharmacokinetic parameters calculated from plasma concentrations of lisdexamfetamine and LDX-derived d-amphetamine using noncompartmental analysis included the following: C_{max}, T_{max}, area under the concentration time curve (AUC) from time 0 extrapolated to infinity (AUC_{0-inf}), AUC from time 0 to last measurable concentration at time t (AUC_{0-t}); apparent terminal disposition half-life ($t_{1/2}$); and apparent oral dose clearance corrected for body weight (CL/F; L/hour/kg). Variability was assessed as percent coefficient of variation.

All pharmacokinetic analyses were performed using the pharmacokinetic analysis set, ie, all participants who took at least one dose of study medication and had at least one postdose safety assessment, no major deviation related to study drug intake, and with sufficient and interpretable primary pharmacokinetic data.

Summary descriptive statistics were determined for all pharmacokinetic parameters, stratified by age and gender. Regression of LDX-derived d-amphetamine CL/F based on age was performed. Relationship of LDX-derived d-amphetamine CL/F based on creatinine clearance at baseline was examined by scatter diagram analysis.

Safety assessments

Safety was assessed based on reported adverse events obtained at regular intervals throughout the study and by evaluating the scheduled physical examination findings, vital signs (including heart rate, blood pressure, and pulse), clinical laboratory parameters, and electrocardiography. Treatment-emergent adverse events were categorized by organ system and class using the *Medical Dictionary for Regulatory Activities* version 11.1; frequency and intensity were summarized according to age and gender. Summary descriptive statistics for vital signs and clinical laboratory parameters were determined and stratified by age and gender for the 72-hour postdose period across treatment periods 1 and 2. Vital sign changes from baseline were calculated using time-matched baseline values, defined as the time-matched measurements on day −1 for each treatment period.

Results

Participant disposition and demographics

In this study, 138 individuals were screened and 47 participants were enrolled and randomized in each of three age groups (eight men and nine women aged 55–64 years; eight men and eight women aged 65–74 years; eight men and six women aged ≥ 75 years). Two participants

from the group aged 55–64 years (one man and one woman) withdrew their consent postdosing during pharmacokinetic observation. No participants withdrew because of adverse events. All 47 participants were included in the pharmacokinetics and safety analyses. Baseline creatinine clearance was lower in older adults (aged ≥ 75 years), but the mean creatinine clearance was in the normal range for all groups (Table 1). Other demographic characteristics were similar across age groups.

LDX and d-amphetamine pharmacokinetics

Intact LDX

With a single 50-mg dose of LDX, the pharmacokinetic parameters were generally similar among the age groups (Table 2). In all three age groups, and in both women and men, the median T_{max} and mean $t_{1/2}$ were < 2 hours and the mean (±standard deviation) CL/F rate ranged between 15.5 ± 7.7 and 25.3 ± 4.0 L/hour/kg. As illustrated by the LDX plasma concentration versus time profiles (Figure 1A and Table 2), women aged 55–64 years and ≥ 75 years tended to have higher values for intact LDX C_{max} and AUC_{0-inf} than men in all age groups.

d-Amphetamine

After a single 50-mg dose of LDX, men and women aged ≥ 75 years generally had greater mean d-amphetamine C_{max}, AUC_{0-inf}, median T_{max}, and mean $t_{1/2}$, and modestly lower CL/F compared with men and women aged 55–64 years and 65–74 years, respectively (Table 2). Within each age group, women had d-amphetamine pharmacokinetic parameters that were generally similar to men. Across all three age groups, with the exception of median T_{max}, which was higher for female and male participants aged ≥ 75 years than in younger adults (aged 55–64 years and 65–74 years), no trends were noted with increasing age between women and men.

Overall, LDX-derived d-amphetamine plasma concentration versus time profiles were similar between women and men across the three age groups (Figure 1B). Scatter plots of individual subject data were created to explore further the relationship between d-amphetamine CL/F (y axis), participant age, and baseline creatinine clearance (x axis). Older participants tended to have lower d-amphetamine CL/F (Figure 2A). No clear relationship between d-amphetamine CL/F and baseline creatinine clearance was discerned based on appearance of plot points (Figure 2B).

Safety

Two participants reported treatment-emergent adverse events during single-dose administration of placebo (somnolence and ecchymosis), and seven participants reported treatment-emergent adverse events during single-dose administration of LDX. For LDX, treatment-emergent adverse events were reported by five participants aged 55–64 years (versus one each in the age groups 65–74 years and ≥ 75 years) and six women (versus one man). Treatment-emergent adverse events reported by the five participants aged 55–64 years were constipation, nausea, vomiting, chills, headache, anxiety, and insomnia. Headache was reported as a treatment-emergent

Table 1 Demographic and baseline characteristics by age group

	55–64 years n = 17	65–74 years n = 16	≥ 75 years n = 14	Total n = 47
Age (years)				
Mean ± SD	57.7 ± 2.5	68.2 ± 3.0	78.9 ± 3.6	67.6 ± 9.2
Range	55–63	65–74	75–84	55–84
Gender, n (%)				
Male	8 (47.1)	8 (50.0)	8 (57.1)	24 (51.1)
Female	9 (52.9)	8 (50.0)	6 (42.9)	23 (48.9)
Race, n (%)				
White	16 (94.1)	15 (93.8)	13 (92.9)	44 (93.6)
Nonwhite	1 (5.9)	1 (6.3)	1 (7.1)	3 (6.4)
Black	1 (5.9)	1 (6.3)	1 (7.1)	3 (6.4)
Ethnicity, n (%)				
Hispanic or Latino	15 (88.2)	15 (93.8)	12 (85.7)	42 (89.4)
Not Hispanic or Latino	2 (11.8)	1 (6.3)	2 (14.3)	5 (10.6)
Weight, kg				
Mean ± SD	73.6 ± 9.8	71.6 ± 11.2	71.3 ± 10.4	72.2 ± 10.3
Creatinine clearance, mL per minute				
Mean ± SD	102.5 ± 26.1	105.3 ± 23.1	94.9 ± 27.3	101.2 ± 25.3

Abbreviation: SD, standard deviation.

Table 2 Mean lisdexamfetamine dimesylate and d-amphetamine pharmacokinetic parameters by age group and gender

	C_{max} (ng/mL)	AUC_{0-inf} (ng · hour/mL)	T_{max} (hours)[a]	$t_{1/2}$ (hours)	CL/F (L/hour/kg)
LDX					
55–64 years					
Females, n	9	9	9	9	9
Mean ± SD	41.3 ± 11.6	43.8 ± 10.4	1.0	0.5 ± 0.1	17.1 ± 3.5
Males, n	8	6	8	6	6
Mean ± SD	24.7 ± 9.8	35.3 ± 9.8	1.5	0.6 ± 0.2	19.8 ± 5.9
65–74 years					
Females, n	8	6	8	6	6
Mean ± SD	27.5 ± 13.0	28.5 ± 8.3	1.5	0.9 ± 1.1	25.3 ± 4.0
Males, n	8	6	8	6	6
Mean ± SD	33.6 ± 8.5	38.7 ± 14.2	1.0	0.6 ± 0.4	19.2 ± 4.4
≥ 75 years					
Females, n	6	5	6	5	5
Mean ± SD	43.0 ± 17.1	51.9 ± 18.9	1.8	0.7 ± 0.4	15.5 ± 7.7
Males, n	8	8	8	8	8
Mean ± SD	25.4 ± 14.0	37.6 ± 13.3	1.8	0.7 ± 0.2	20.0 ± 5.8
d-amphetamine					
55–64 years					
Females, n	9	9	9	9	9
Mean ± SD	51.0 ± 6.7	1034.5 ± 154.6	3.5	12.2 ± 1.9	0.7 ± 0.1
Males, n	8	7	8	7	7
Mean ± SD	44.2 ± 11.1	915.0 ± 164.9	4.5	12.8 ± 2.9	0.8 ± 0.2
65–74 years					
Females, n	8	8	8	8	8
Mean ± SD	50.2 ± 6.8	988.4 ± 80.5	4.1	12.8 ± 1.9	0.7 ± 0.1
Males, n	8	8	8	8	8
Mean ± SD	47.7 ± 7.0	1123.0 ± 227.0	3.5	15.0 ± 2.8	0.64 ± 0.1
≥ 75 years					
Females, n	6	6	6	6	6
Mean ± SD	64.3 ± 12.1	1347.8 ± 198.9	5.5	13.3 ± 2.5	0.57 ± 0.1
Males, n	8	8	8	8	8
Mean ± SD	53.4 ± 19.4	1325.0 ± 464.4	5.5	14.3 ± 3.4	0.6 ± 0.1

Note: [a]Median values are reported for T_{max}.

Abbreviations: AUC_{0-inf}, area under the plasma concentration versus time curve from time 0 extrapolated to infinity; CL/F, apparent oral dose clearance corrected for body weight; C_{max}, maximum plasma d-amphetamine concentration; LDX, lisdexamfetamine dimesylate; SD, standard deviation; T_{max}, time to C_{max}; $t_{1/2}$, apparent terminal disposition half-life.

adverse event by one participant in the age group 65–74 years and ventricular extrasystole was documented in one participant in the age group ≥ 75 years.

No consistent differences in change from baseline in vital signs (systolic or diastolic blood pressure and pulse) after a single 50-mg dose of LDX were observed between the age groups (Figure 3 and Table 3). All treatment groups had increases in vital signs (systolic or diastolic blood pressure and pulse) compared with placebo for most time points. For LDX, maximal mean increases in systolic and diastolic blood pressure in the groups aged 55–64 years and 65–74 years occurred between 1.5 and 4.5 hours postdose and, among those aged ≥ 75 years, at 5.5 hours.

For LDX, maximal mean increases in pulse among those aged 55–64 years and 65–74 years occurred at 12 hours postdose, and among those aged ≥ 75 years at 5.5 hours. Changes in vital signs were similar between men and women. No clinically significant changes in mean clinical laboratory or electrocardiographic parameters were noted during the study.

Across age and gender groups, electrocardiographic interval measurement showed that seven of 45 participants on placebo and four of 47 participants on LDX had QT interval values ≥ 450 msec but < 480 msec; none had QT interval values ≥ 480 msec. For QT corrected for heart rate by Fridericia's formula (QTcF), two of 45 participants on placebo and two of 47 participants on LDX had QTcF interval values ≥ 450 msec but < 480 msec; none had QTcF interval values ≥ 480 msec.

Discussion

In this pharmacokinetic study in older adults, a single oral 50-mg dose of LDX yielded d-amphetamine

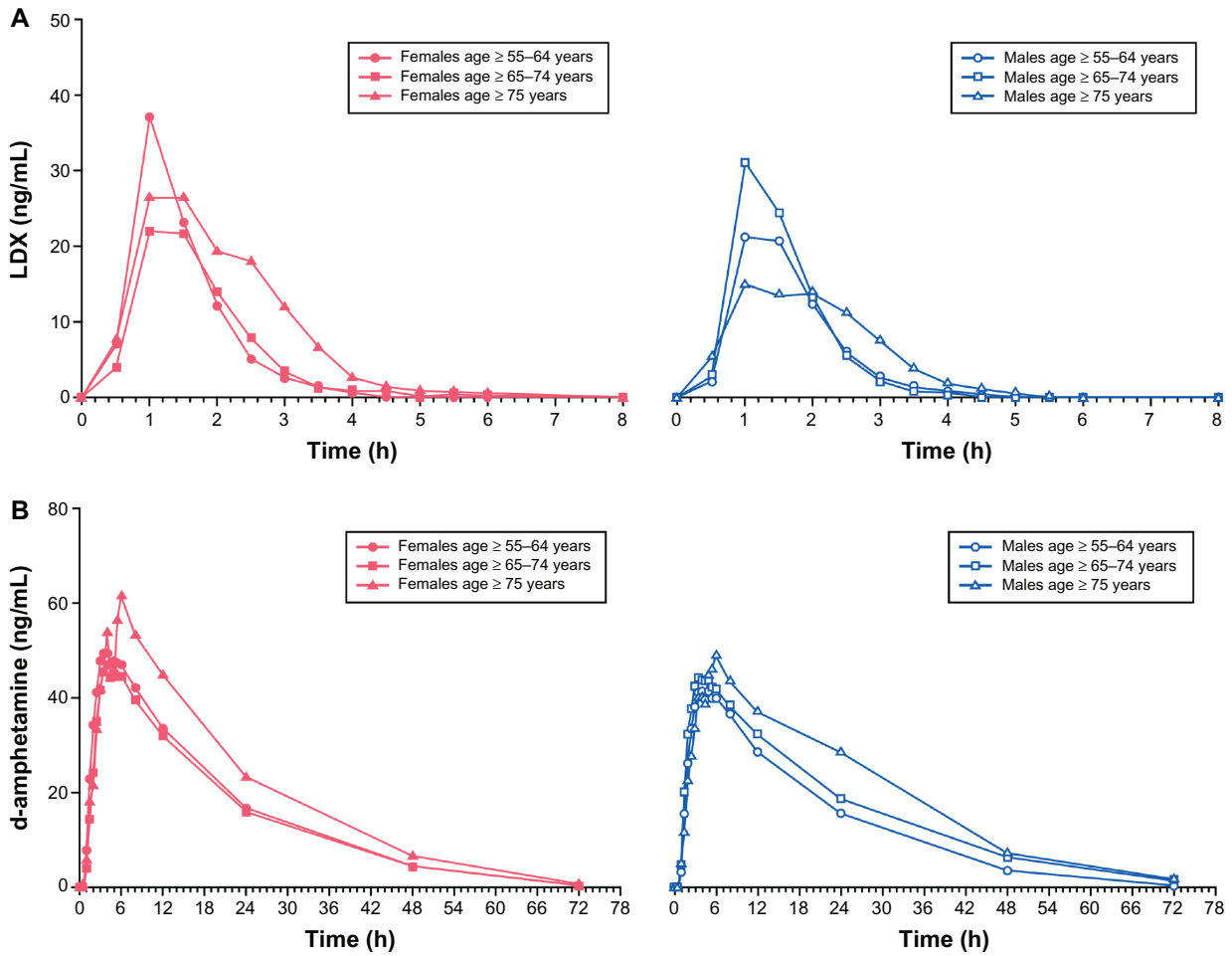

Figure 1 (**A**) LDX plasma concentration over time. (**B**) Mean ± standard deviation d-amphetamine plasma concentration over time.
Abbreviation: LDX, lisdexamfetamine dimesylate.

exposure (based on C_{max} and AUC_{0-inf}) that was modestly higher and clearance that was modestly slower in participants aged ≥ 75 years, compared with participants aged 55–64 years and 65–74 years. The d-amphetamine parameters were similar among women and men in each age group. Renal function, as assessed by baseline creatinine clearance, was lower in participants aged ≥ 75 years, compared with participants aged 55–64 years and 65–74 years, but the mean creatinine clearance was in the normal range for all groups and the slightly lower d-amphetamine creatinine clearance in the group aged ≥ 75 years was unrelated to renal function based on creatinine clearance at baseline.

The present findings in older adults are in line with results from previous pharmacokinetic investigations of LDX in younger adults aged ≤ 55 years.[5,6] In a study reported by Ermer et al,[6] administration of single oral LDX doses of 50–150 mg in 20 adults (mean age 33.3 years, mean body weight 75.0 kg) displayed linear d-amphetamine pharmacokinetic parameters and was associated with a CL/F of 0.9 L/hour/kg, with a mean C_{max} in the range of 44.6–126.6 ng/mL and a mean AUC_{0-inf} in the range of 818.1–2503.4 ng·hour/mL for LDX 50–150 mg.[6] In a report by Krishnan et al,[5] a 70-mg capsule of LDX given to fasted adult volunteers led to d-amphetamine C_{max} and AUC_{0-inf} values of 69.3 ng/mL and 1110 ng·hour/mL, respectively. Moreover, from the studies reported by Ermer et al[6] and Krishnan et al,[5] mean C_{max} values for LDX were 25.6 and 48.0 ng/mL, respectively, and AUC_{0-inf} values were 62.1 and 66.8 ng·hour/mL, respectively. The C_{max} and AUC_{0-inf} values for d-amphetamine observed among each of the age groups examined in the current investigation (44.2–51.0 ng/mL and 915.0–1347.8 ng·hour/mL, respectively) are generally similar to these previous data, as were C_{max} and AUC_{0-inf} values for LDX (24.7–43.0 ng/mL and 35.3–51.9 ng·hour/mL, respectively). The d-amphetamine parameters appeared comparable between women and men in each of the age groups. The current findings indicate that gender does not have a large effect on the disposition of d-amphetamine or LDX, and CL/F decreased with advancing age.

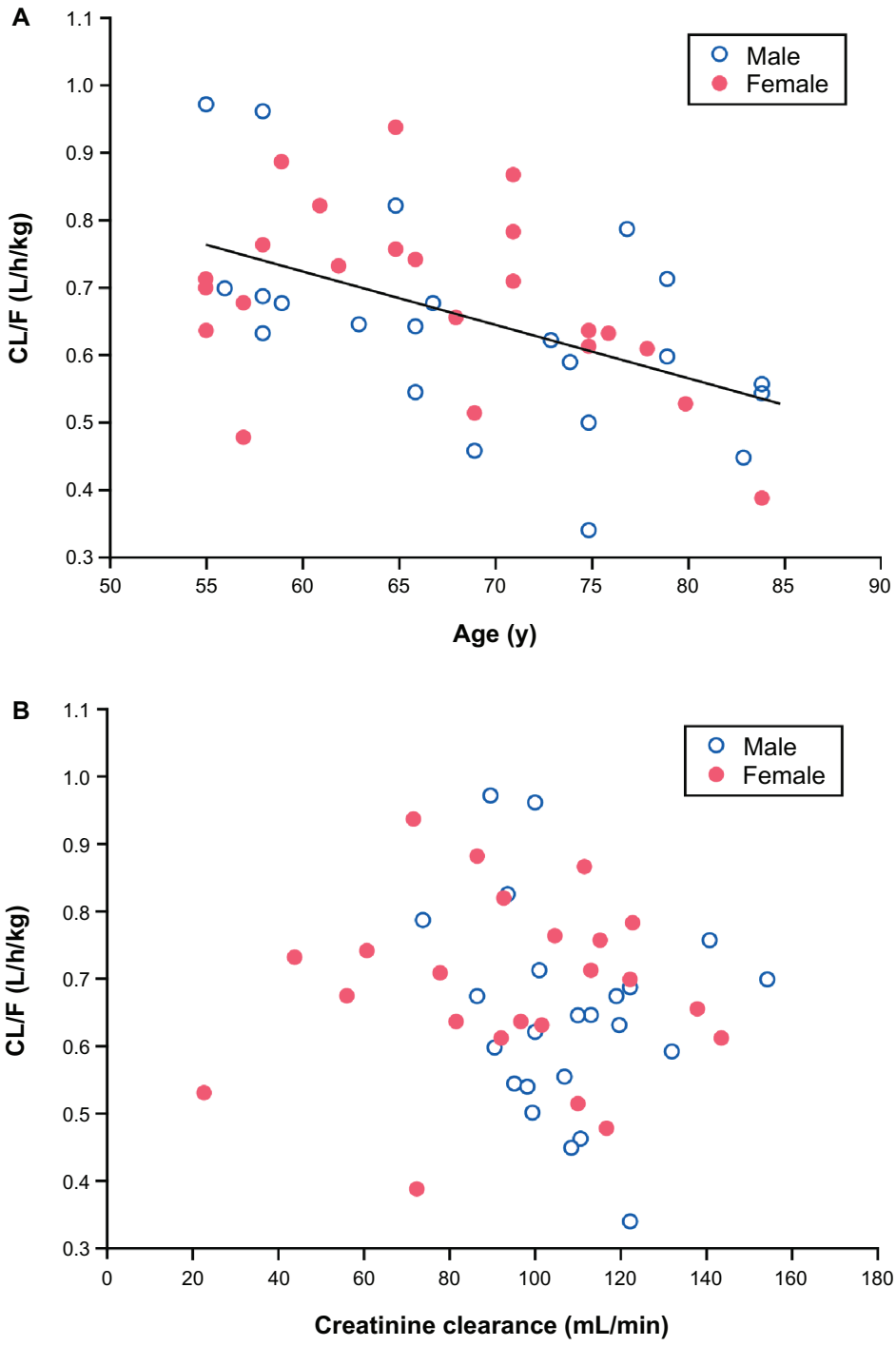

Figure 2 (**A**) d-Amphetamine clearance by participant age. Intercept of 1.1966 and slope (standard error) of –0.0079 (0.002); $R^2 = 0.2512$, predicted 95% confidence interval of the slope = –0.012, –0.004. (**B**) d-Amphetamine clearance by participant baseline creatinine clearance.
Abbreviation: CL/F, apparent oral dose clearance corrected for body weight.

Normal age-related decreases in renal function might have been expected to affect the pharmacokinetic characteristics of d-amphetamine in the current study. This is because a portion of administered d-amphetamine is excreted unchanged in the urine.[17] Although creatinine clearance and d-amphetamine clearance both tended to decrease with age among our older participants, no clear relationship was detected between these two factors in the current investigation. This is somewhat different from the findings of a prior investigation of the pharmacokinetics of amphetamine when given following stroke in older patients.[12] In that study, patients aged 66–70 years received

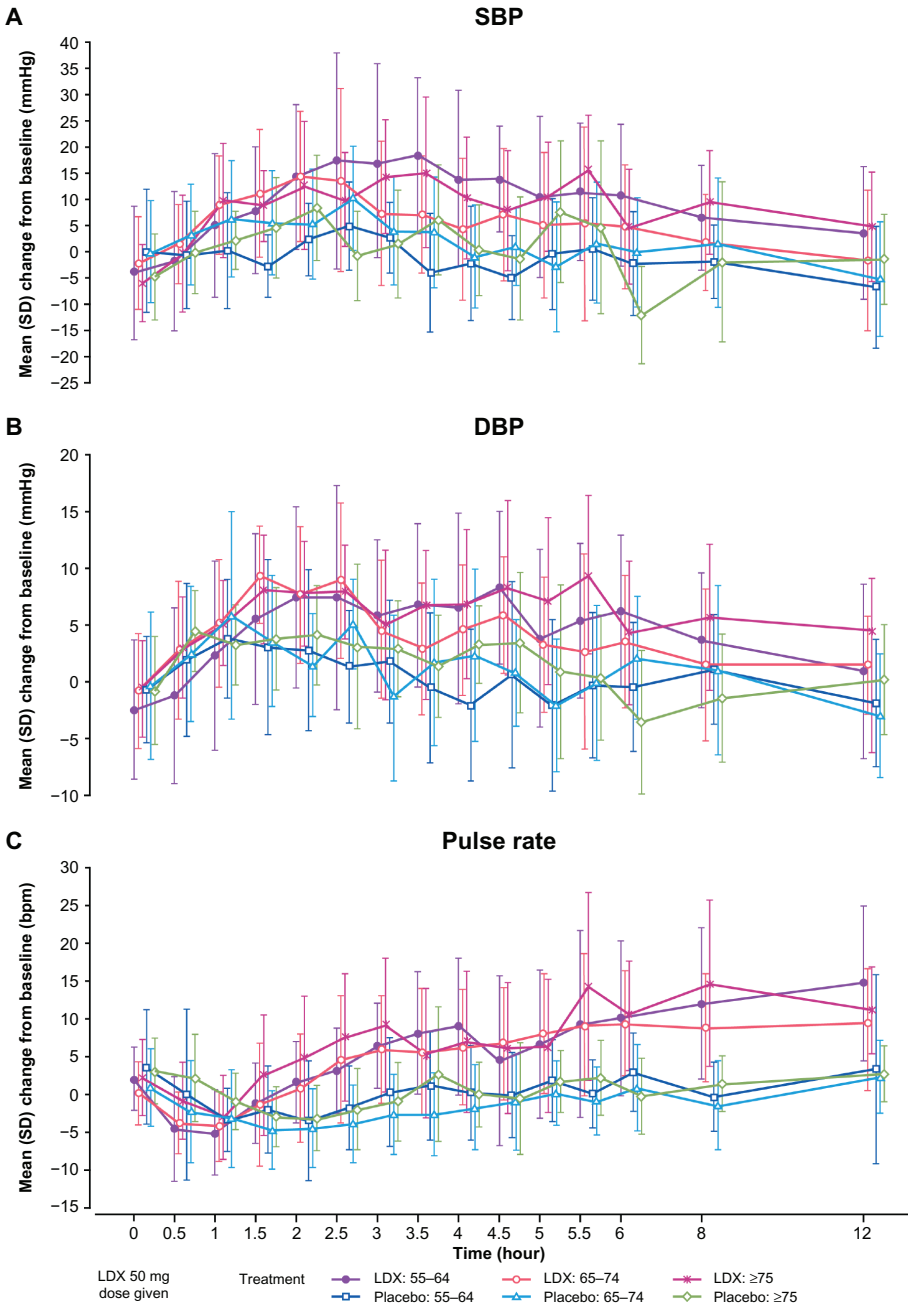

Figure 3 (**A–C**) Changes in vital signs from baseline by age group.
Abbreviations: bpm, beats per minute; DBP, diastolic blood pressure; SBP, systolic blood pressure; LDX, lisdexamfetamine dimesylate; SD, standard deviation.

Table 3 Range of mean changes from time-matched baseline[a] in vital signs over 12 hours postdose

Mean change from time-matched baseline	55–64 years		65–74 years		≥ 75 years	
	Placebo n = 15	LDX n = 17	Placebo n = 16	LDX n = 16	Placebo n = 14	LDX n = 14
Systolic blood pressure (mmHg)	–6.7 to 5.0	–3.9 to 18.5	–5.1 to 10.3	–2.1 to 14.5	–12.1 to 8.5	–5.9 to 16.0
Diastolic blood pressure (mmHg)	–2.1 to 3.8	–2.5 to 8.3	–3.0 to 5.9	–0.8 to 9.4	–3.6 to 4.5	–0.6 to 9.5
Pulse (beats per minute)	–3.5 to 3.6	–5.0 to 14.7	–4.7 to 2.3	–4.3 to 9.5	–3.1 to 3.0	–3.0 to 14.7

Note: [a]Baseline was defined as the time-matched measurement at day –1 for each treatment period.
Abbreviation: LDX, lisdexamfetamine dimesylate.

2.5 mg to 10 mg of immediate-release d-amphetamine twice daily for 5 days.[12] In contrast with the current findings, the pharmacokinetic analysis by Martinsson et al showed that creatinine clearance, but not patient age, was strongly correlated with d-amphetamine exposure, based on AUC_{0-inf}. It seems possible that such divergent findings may be due, in part, to sampling differences. The current trial enrolled a largely healthy sample of older volunteers; however, the patients in the report from Martinsson et al[12] were hospitalized following a stroke, likely had medical comorbidities, and were receiving a number of other medications that potentially may have altered renal function and/or disposition of d-amphetamine.[12] It may be of interest to examine more directly the effect of renal impairment on LDX and d-amphetamine pharmacokinetics in future investigations.

In the present trial, a single 50-mg dose of LDX did not result in any new or unexpected safety concerns. Overall, increases in blood pressure and pulse as well as in the incidence of treatment-emergent adverse events across all the age groups were consistent with those observed previously in healthy younger adults aged ≤ 55 years.[5,6] A similar profile of small mean increases in blood pressure and pulse has also been reported in adults with ADHD. In a 4-week, randomized, placebo-controlled trial of LDX in adults aged ≤ 55 years with ADHD,[9] small least squares mean changes from baseline to endpoint for placebo, and 30, 50, and 70 mg/day of LDX, respectively, in systolic blood pressure were −0.5, 0.8, 0.3, and 1.3 mmHg; in diastolic blood pressure were 1.1, 0.8, 1.1, and 1.6 mmHg; and in pulse were 0.0, 2.8, 4.2, and 5.2 beats per minute. The changes in pulse ($P = 0.0018$ versus placebo) but not blood pressure with LDX were statistically significant. In a post hoc analysis of that 4-week trial,[18] the proportion of participants who were pulse outliers (≥ 100 beats per minute, any one event) ranged from 3.3% to 8.5% in the LDX groups. Additionally, for the current study, it is important to note that although the absolute value of transient increases in pulse rate and blood pressure (in all age groups) may appear quite high relative to placebo, it is expected that, because of the rigorous monitoring procedures employed throughout the day, these results may overestimate the magnitude of pulse rate and blood pressure effects that would be noted using traditional vital sign monitoring procedures during typical outpatient use.

Although the number of participants was small, fewer older participants (aged ≥ 65 years) reported a treatment-emergent adverse event than those who were younger (aged 55–64 years). It is of interest that the safety profile of LDX among participants aged ≥ 75 years was not apparently compromised in this study, despite the slightly greater exposure to d-amphetamine seen in these participants. This is in line with normal age-related decreases in adrenergic sensitivity to sympathomimetic stimulation.[19,20] A larger proportion of female participants reported treatment-emergent adverse events compared with male participants. Safety analyses by gender in adults with ADHD have not been presented in previous reports; further, the number of participants in the current study is relatively small, so broad conclusions are not warranted. As with all psychostimulant medications, careful patient selection is key to maintaining adequate safety with LDX; regardless of age, patients with a history or evidence of cardiovascular disease or drug abuse should not be treated with LDX.[1]

The findings of this study should be interpreted while considering certain limitations. Participants received a single dose of LDX; this is not representative of clinical use of LDX. The current study enrolled older adults who were otherwise healthy, without significant hepatic or renal dysfunction. Pharmacokinetics and safety of LDX in medically or psychiatrically ill older patients is unknown. Thus, the current findings may not be applicable to a population of older adults with multiple health issues or compromised hepatic or renal function.

Only a single 50-mg dose of LDX was examined, so dose proportionality of the pharmacokinetic parameters cannot be determined from this study. However, dose proportionality has been established in both children[1] and younger adults aged ≤ 55 years.[6] Despite these limitations, the present study provides useful information to help consider appropriate procedures for LDX dosing in a diverse adult population.

Conclusion

In older adults, pharmacokinetic parameters for LDX-derived intact LDX and d-amphetamine, including C_{max}, T_{max}, and AUC_{0-inf}, were generally similar to those seen previously in younger adults aged 18–55 years.[5,6] d-Amphetamine exposure was modestly higher in participants aged ≥ 75 years than in those aged 55–64 years and 65–74 years. The increased d-amphetamine exposure did not appear related to decreased baseline creatinine clearance, which is an indication of kidney function. Safety of LDX among participants aged ≥ 75 years was not apparently compromised, despite their slightly greater exposure to d-amphetamine in this study. This may be accounted for by normal age-related decreases in adrenergic sensitivity to sympathomimetic stimulation.[19,20] No clear trends in blood pressure or pulse changes by age were seen with LDX. The safety profile

of LDX was consistent with prior data in healthy younger adults aged 18–55 years.

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