

An Open-Label Investigation of the Pharmacokinetic Profiles of Lisdexamfetamine Dimesylate and Venlafaxine Extended-Release, Administered Alone and in Combination, in Healthy Adults

James Ermer · Mary B. Haffey · Cynthia Richards · Kenneth Lasseter · Benno Roesch · Jaideep Purkayastha · Mary Corcoran · Bree Harlin · Patrick Martin

Published online: 20 March 2013

© The Author(s) 2013. This article is published with open access at Springerlink.com

Abstract

Background Lisdexamfetamine dimesylate (LDX), a prodrug consisting of *d*-amphetamine and *l*-lysine, is being studied in clinical trials of major depressive disorder. Additional drug-drug interaction studies were warranted.

Objective This study aimed to describe the pharmacokinetics and safety of LDX and venlafaxine extended-release (VXR), alone or combined.

Study Design The study was an open-label, two-arm, single-sequence crossover investigation with randomization to treatment sequence.

Setting and Participants The study was conducted at two clinical study centres and included healthy adult males and females (18–45 years of age).

Intervention The study included two single-sequence crossover designs: LDX alone followed by LDX + VXR (Treatment Arm A); and VXR alone followed by VXR + LDX (Treatment Arm B). Drug treatment was initiated on day 1 with once-daily LDX or VXR alone with 15 days' titration to final dose (LDX 30, 50 and 70 mg for 5 days each; VXR 75, 150 and 225 mg for 5 days each).

On days 16–30, VXR, titrated to a final dose of 225 mg, or LDX, titrated to a final dose of 70 mg, was coadministered for participants in Treatment Arm A or B, respectively. On days 31–38, VXR doses were tapered.

Main Outcome Measures On days 1–2, 15–16 and 30–31, safety evaluations and blood samples were obtained pre-dose through 24 h post-dose for analysis of LDX, *d*-amphetamine, venlafaxine (VEN), and *O*-desmethylvenlafaxine (ODV). Combination treatment was considered bioequivalent to single treatment if 90 % confidence intervals (CIs) for geometric mean ratios (GMRs) of analytes fell within the interval 0.80–1.25 based on maximum plasma concentration (C_{\max}) and area under the plasma concentration-time curve (AUC) from time zero to time of last measurable concentration (AUC_{τ}). Safety assessments included treatment-emergent adverse events (TEAEs), pulse rate and blood pressure (BP), clinical laboratory assessments, and 12-lead electrocardiograms (ECG).

Results Among 80 enrolled subjects, 77 were included in pharmacokinetic and safety analyses. Combination LDX + VXR was bioequivalent to LDX alone, based on exposure to *d*-amphetamine (GMR [95 % CI], C_{\max} (ng/mL): 0.97 [0.82, 1.14], AUC_{τ} : 0.95 [0.81, 1.12]). Exposure to VEN with LDX + VXR (vs. VXR alone) was increased (C_{\max} : 1.10 [0.88, 1.38], AUC_{τ} : 1.13 [0.88, 1.45]) and ODV decreased (C_{\max} : 0.91 [0.77, 1.06], AUC_{τ} : 0.83 [0.71, 0.96]), whereas composite VEN + ODV was bioequivalent to VXR alone (C_{\max} : 0.96 [0.84, 1.09], AUC_{τ} : 0.98 [0.85, 1.13]). TEAEs with LDX or LDX + VXR were similar. Maximum mean increases from baseline were: pulse rate, +8.73 to 12.76 beats/min with either treatment alone and +17.67 to 20.85 beats/min with LDX + VXR; systolic BP, +4.32 to 6.56 mmHg with either treatment alone and +12.96 to 13.78 mmHg with LDX + VXR; diastolic BP, +5.39 to 5.74 mmHg with either treatment

M. B. Haffey is deceased.

Clinical Trial Registration Number: NCT01235338.

J. Ermer (✉) · M. B. Haffey · C. Richards · J. Purkayastha · M. Corcoran · B. Harlin · P. Martin
Shire Development LLC, 725 Chesterbrook Blvd,
Wayne, PA 19087, USA
e-mail: jaermer@shire.com

K. Lasseter
Clinical Pharmacology of Miami, Inc., Miami, FL, USA

B. Roesch
Advanced Biomedical Research, Inc., Hackensack, NJ, USA

alone and +12.09 to 12.46 mmHg with LDX + VXR. One participant was withdrawn due to a serious TEAE (pre-syncope). No unexpected, clinically meaningful trends or changes from baseline in mean laboratory or ECG parameters were observed during the trial.

Conclusion In healthy adults, combination LDX + VXR (vs. LDX alone) did not alter exposure to *d*-amphetamine. Although small changes in exposure to VEN (increased) and ODV (decreased) were seen with combination treatment, total VEN + ODV exposure showed no change (vs. VEN alone). LDX + VXR led to increases in BP and pulse rate, supporting existing recommendations for vital sign monitoring when using these medications.

1 Introduction

Lisdexamfetamine dimesylate (LDX) is a long-acting prodrug of dextroamphetamine (*d*-amphetamine) and is approved for the treatment of attention-deficit/hyperactivity disorder in children (6–12 years), adolescents (13–17 years) and adults [1]. After oral administration, active *d*-amphetamine is released via enzyme-mediated biotransformation [2]. The investigation of LDX in clinical trials for major depressive disorder [3, 4] indicated a need for additional information about pharmacokinetics and safety, including the potential for drug-drug interactions.

LDX does not inhibit any cytochrome P450 (CYP) isoenzyme tested to date [5], but its active component, *d*-amphetamine, weakly inhibits CYP2D6 activity [1]. In vitro studies suggest that exposure to amphetamine or its metabolites, as would follow LDX administration, might inhibit the CYP enzymes CYP2D6, CYP1A2 and CYP3A4 [1, 6], raising the possibility of drug-drug interactions. The CYP family of isoenzymes is also primarily responsible for the metabolism of several key medications used to treat patients with indications of interest in the LDX research programme [7, 8]. Coadministration of LDX with compounds for which these CYP enzymes play a metabolic role could potentially alter the pharmacokinetics of one or both drugs, marked by prolonged clearance, increased maximum plasma concentrations, and increased overall exposure.

Venlafaxine extended-release (VXR), a selective serotonin-norepinephrine reuptake inhibitor (SNRI), is indicated for treatment of major depressive disorder, as well as generalized and social anxiety disorders and panic disorder [9]. Venlafaxine (VEN), the active component of VXR, is metabolized to active *O*-desmethylvenlafaxine (ODV) by CYP2D6 [10], making it a useful substrate by which to test for potential interaction of LDX with the CYP2D6 system. Coadministration of VXR with LDX may lead to changes in VEN metabolism, potentially marked by increased exposure to VEN. Moreover, in adults, VEN exerts well-

characterized effects on cardiovascular functioning, marked by modest mean increases in blood pressure and heart rate. In a small number of individual patients (i.e., 0.7–1.3 %), larger sustained increases in blood pressure have led to treatment discontinuation [9, 11]. Mean increases in blood pressure and heart rate have also been observed in adults following administration of clinically optimized doses of LDX and other *d*-amphetamine- or methylphenidate-containing medications [1, 12–14], raising the possibility that combination LDX/VXR treatment may potentiate these cardiovascular effects. It is, therefore, of particular interest to carefully examine vital sign parameters during coadministration of these drugs.

The primary objective of the present investigation in healthy adults was to characterize the pharmacokinetics of the prodrug LDX and LDX-derived *d*-amphetamine and VEN and its active metabolite, ODV, when LDX and VXR were administered alone and in combination. A secondary objective was to examine the safety of combination LDX + VXR treatment, including pulse rate and blood pressure parameters.

2 Methods

2.1 Study Design

This study of LDX was an open-label, two-arm, single-sequence crossover investigation with randomization to treatment sequence investigation in healthy adults, consisting of a screening period, a 38-day treatment period, and safety telephone follow-up. There were two treatment arms: A (initial titration with LDX over 15 days followed by the addition of VXR, titrated over an additional 15 days) and B (initial titration with VXR over 15 days followed by the addition of LDX, titrated over an additional 15 days). During pre-dose baseline assessments, participant blood samples were obtained for CYP2D6 genotyping. To minimize the potential for adverse effects during initiation of treatment with either LDX (e.g., dizziness, palpitations) or VXR (e.g., nausea, vomiting), doses were gradually titrated upward at 5-day intervals to maximal doses of LDX 70 mg/day and VXR 225 mg/day; at the end of the study, VXR doses were also gradually decreased over a 1-week period. Figure 1 illustrates the dosing/titration schedule for each of the treatment arms and scheduled study assessments. On day –2 through day 2 and day 14 through day 31, participants remained at one of two clinical study centres (CSCs); on other days, participants made daily visits to the same CSC.

The study was approved by the Independent Investigational Review Board, Inc (Plantation, FL, USA) and was conducted in accordance with the principles of the

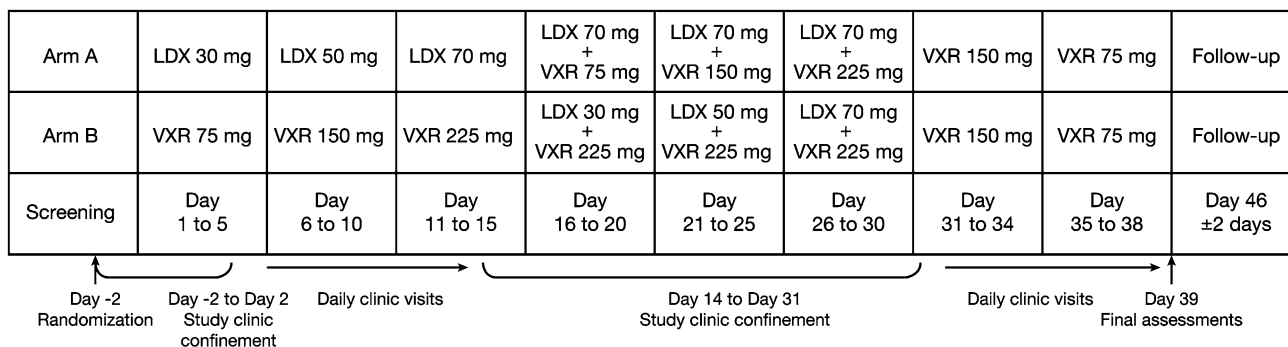


Fig. 1 Timing of study visits, and procedures. *LDX* lisdexamfetamine dimesylate, *VXR* venlafaxine extended-release

Declaration of Helsinki and its amendments, all local ethical and legal requirements, as well as US Food and Drug Administration (FDA) guidance on appropriate conduct of in vivo drug-drug interaction studies [15]. All participants were required to provide signed informed consent prior to performance of any study-related procedures and a separate consent for genotyping sampling.

2.2 Key Inclusion/Exclusion Criteria

This study enrolled healthy adult male and non-pregnant, non-lactating females (aged 18–45 years). Participants were excluded if they had any current or recurrent disease that could affect the absorption, disposition or effect of the investigational products, or clinical or laboratory assessments; medical or psychiatric illness that might require treatment, affect ability to comply with investigational protocol, or present undue risk; history of significant anxiety or agitation; current diagnosis or history of glaucoma; current diagnosis or history of a tic disorder, or personal/family history of Tourette's disorder; structural cardiac abnormality, transient ischaemic attack or stroke, or any other serious cardiac condition; history of hypertension, or high blood pressure at screening (systolic blood pressure [SBP] >139 mmHg and/or diastolic blood pressure [DBP] >89 mmHg, taken at rest while sitting); family history of sudden cardiac death or ventricular arrhythmia; history of alcohol or other substance abuse within the past year; a positive screen for drugs of abuse or alcohol during the screening visit or check-in; and consumption of alcohol within 7 days, or caffeine/xanthine-containing products within 24 h of the first study medication dose or during the study. Also excluded were individuals who had smoked or used nicotine-containing products within 30 days prior to the first dose of study medication or during the study, as well as those who had donated blood or blood products (e.g., plasma, platelets) within 60 days or had received another investigational product within 30 days prior to the first dose of study medication.

2.3 Study Medication Administration

Study medication was administered with 240 mL room temperature water; dosing occurred on the scheduled days at the study clinic throughout the investigation period. Capsules were swallowed whole, not cut, chewed or crushed. On days of serial blood sampling (days 1, 15 and 30), study medication was administered following a fast of approximately 10 h, and food was not given until 4 h post-dosing. Water intake was restricted for 4 h prior to dosing and 2 h following dosing.

2.4 Blood Sampling and Analysis

During baseline assessments, participant blood samples were obtained for CYP2D6 genotyping. For pharmacokinetic analysis, serial blood samples were collected up to 24 h after dose administration on days 1, 15 and 30; on these study days, samples were obtained pre-dose (at -0.5 h) and at the following times post-dose: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 9, 12 and at 0/24 h on days 2, 16, and 31. On days 14 and 29, a single blood sample was obtained at 0.5 h pre-dose. Plasma concentrations of LDX, *d*-amphetamine, VEN and ODV were measured using validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) methods. Samples from days on which participants were dosed with LDX alone were analysed for LDX and *d*-amphetamine only; samples from days on which participants were dosed with VXR alone were analysed for VEN and ODV only; and samples from days on which participants were dosed with both LDX and VXR were analysed for LDX, *d*-amphetamine, VEN and ODV. Briefly, LDX, *d*-amphetamine, VEN and ODV concentrations in human plasma were determined using a LC-MS/MS method validated over the range of 1–100 ng/mL for LDX and 2–200 ng/mL for *d*-amphetamine; over the range of 0.5–250 ng/mL for VEN and 1–500 ng/mL for ODV all based on 200 µL of human plasma. Human plasma containing LDX, *d*-amphetamine, VEN and ODV, and internal

standards, D8-LDX, D5-amphetamine or D6-VEN and D6-ODV, was extracted with ethyl acetate/toluene (1:1) in the presence of saturated sodium chloride/sodium hydroxide for LDX/*d*-amphetamine and with ethyl acetate in sodium phosphate buffer for VEN/ODV. Following centrifugation, the organic layer was transferred and evaporated. After the addition of formic acid for LDX/*d*-amphetamine and ethyl acetate for VEN/ODV and reconstitution in mobile phase, an aliquot was injected onto a AB SCIEX API™ 4000 LC-MS/MS (Framingham, MA, USA) 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. The peak area of the m/z 278 → 58 VEN product ion was measured against the peak area of the m/z 284 → 58 D6-VEN internal standard product ion. The peak area of the m/z 264 → 58 ODV product ion was measured against the peak area of the m/z 270 → 58 D6-ODV internal standard product ion. Peak area integrations were performed using Analyst software (version 1.4.2) from Applied Biosystems (Carlsbad, CA, USA). Concentrations were calculated using 8-point curves ranging from 1 to 100 ng/mL for LDX and 2 to 200 ng/mL for *d*-amphetamine with separate weighted linear regression; ranging from 0.5 to 250 ng/mL for VEN and 1 to 500 ng/mL for ODV 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; 0.5 ng/mL for VEN and 1 ng/mL for ODV. Values below this limit were reported as not quantifiable.

Pharmacokinetic parameters were determined from the plasma concentration-time data for LDX, *d*-amphetamine, VEN, ODV and composite (VEN + ODV) by non-compartmental analysis. The following pharmacokinetic parameters were calculated from plasma concentrations of *d*-amphetamine, LDX, VEN and ODV: maximum plasma concentration (C_{max}), time to reach C_{max} (t_{max}), area under the plasma concentration-time curve (AUC) from time zero to time of last measurable concentration (AUC_{τ}), elimination half-life ($t_{1/2}$) and relative bioavailability. Variability was assessed with percent coefficient of variation (% CV).

2.5 Safety Assessments

Safety was evaluated based on reported treatment-emergent adverse events (TEAEs), assessed at regular intervals throughout the study and coded using the *Medical Dictionary for Regulatory Activities* (MedDRA), version 11.1,

and by assessing the scheduled physical examination findings, vital signs (including pulse rate and blood pressure), clinical laboratory parameters and electrocardiograms (ECGs).

2.6 Statistical Analysis

To demonstrate bioequivalence (in each arm), 24 subjects were needed in each treatment arm to achieve 90 % power based on allowing for a 5 % difference in true means and the true within-subject SD (based on the higher of the AUC SDs between LDX and VXR) being ≥ 0.20 .

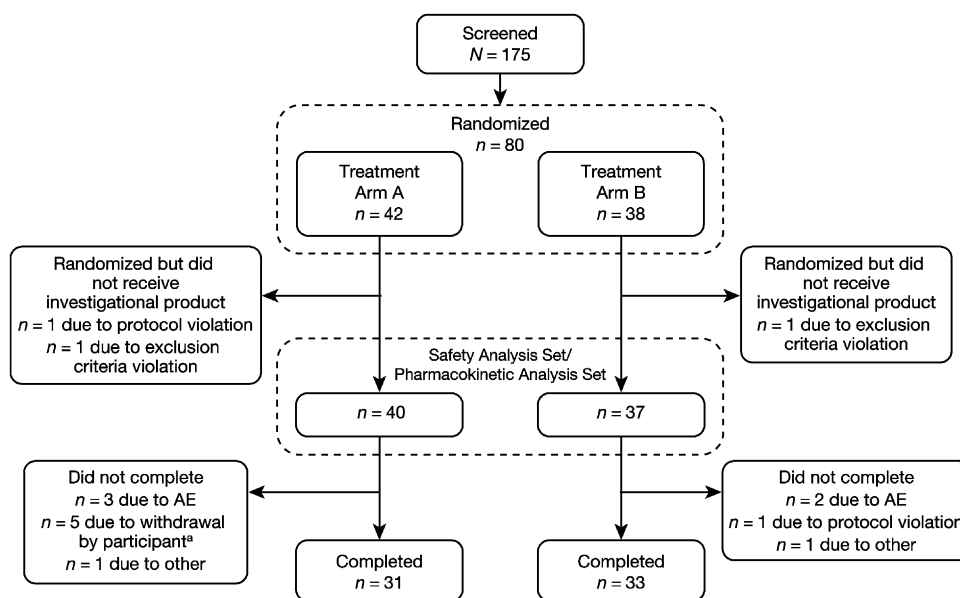
The safety analysis set was defined as all participants who received at least one dose of study medication and had at least one post-dose safety assessment. Pharmacokinetic parameters were analysed based on the pharmacokinetics analysis set, defined as all participants who received at least one dose of study medication, had at least one post-dose safety assessment, had no major protocol deviations related to intake of study medication (e.g., vomiting), and for whom the primary pharmacokinetic data were considered sufficient and interpretable. For each treatment arm, summary descriptive statistics were determined for all pharmacokinetic parameters as well as plasma concentrations of LDX, *d*-amphetamine, VEN and ODV at each scheduled sampling time. For each treatment arm, the means of log-transformed pharmacokinetic parameters were compared using mixed effects analysis of variance. To estimate the magnitude of difference in C_{max} and AUC_{τ} for LDX and *d*-amphetamine between LDX alone and LDX + VXR (Treatment Arm A) and for VEN, ODV and total VEN + ODV between VXR alone and LDX + VXR (Treatment Arm B), geometric mean ratios (GMRs) and their 90 % confidence intervals (CIs) were calculated. Combination LDX + VXR was considered not to have an interaction if the 90 % CIs for GMRs of analytes fell within the interval 0.80–1.25 based on C_{max} and AUC_{τ} .

3 Results

3.1 Disposition and Demographics

A total of 175 participants were screened; 80 healthy adults were randomized and enrolled ($n = 42$, Treatment Arm A; $n = 38$, Treatment Arm B) (Fig. 2) and 64 completed the study. Seventy-seven participants were included in the pharmacokinetic and safety analysis sets. Of the 16 participants who discontinued, 11 (26.2 %) discontinued from Treatment Arm A and 5 (13.2 %) discontinued from Treatment Arm B. The most common reasons for discontinuation were AEs ($n = 5$) and withdrawal of consent ($n = 5$).

Fig. 2 Participant disposition. *Treatment Arm A* initial LDX alone, followed by combination LDX + VXR; *Treatment Arm B* initial VXR alone, followed by combination LDX + VXR. *AE* adverse event, *LDX* lisdexamfetamine dimesylate, *VXR* venlafaxine extended-release



^aTwo participants in Treatment Arm A were experiencing treatment-emergent adverse events (palpitations and depressed mood, respectively; both moderate severity) when they withdrew consent to continue in the study

Table 1 Demographics and baseline characteristics

Characteristic	Treatment Arm A ^a (n = 40)	Treatment Arm B ^b (n = 37)	Total (n = 77)
Age, years [mean (SD)]	33.2 (7.01)	33.8 (7.29)	33.5 (7.10)
Male [n (%)]	28 (70.0)	27 (73.0)	55 (71.4)
Weight, kg [mean (SD)]	75.5 (12.09)	74.5 (11.64)	75.0 (11.81)
BMI, kg/m ² [mean (SD)]	25.5 (2.83)	25.5 (2.70)	25.5 (2.75)
Race [n (%)]			
White	31 (77.5)	25 (67.6)	56 (72.7)
Non-white	9 (22.5)	12 (32.4)	21 (27.3)

BMI body mass index, *LDX* lisdexamfetamine dimesylate, *VXR* venlafaxine extended-release

^a Treatment Arm A = initial LDX alone, followed by combination LDX 70 mg/day + VXR 225 mg/day

^b Treatment Arm B = initial VXR alone, followed by combination LDX 70 mg/day + VXR 225 mg/day

For participants in the safety analysis set, mean (SD) age at baseline was 33.5 (7.10) years, 55 (71.4 %) participants were men, and 56 (72.7 %) participants were white (Table 1). Mean (SD) weight was 75.0 kg (11.81), and mean (SD) body mass index was 25.5 kg/m² (2.75). Genotyping conducted at baseline revealed that most participants were extensive (n = 59) or intermediate (n = 16) CYP2D6 metabolizers; two participants were CYP2D6 poor metabolizers (both in Treatment Arm A).

3.2 LDX and *d*-Amphetamine Pharmacokinetic Analysis

The 24-h post-dose plasma concentration over time profiles for LDX and LDX-derived *d*-amphetamine on day 1 (beginning of titration), day 15 (end of titration), and day 30 (end of LDX + VXR coadministration) are shown in Fig. 3a, b, respectively. LDX and *d*-amphetamine pharmacokinetic parameters for days 15 and 30 are summarized in Table 2. LDX and *d*-amphetamine pharmacokinetic profiles were similar regardless of whether LDX was given alone (day 15) or combined with VXR (day 30) (Table 2). Standard bioequivalence criteria (interval 0.80–1.25) [16] confirmed that systemic exposure to *d*-amphetamine (based on C_{max} and AUC_τ) was similar for LDX given alone or in combination with VXR (Table 3).

3.3 Venlafaxine and ODV Pharmacokinetic Analysis

The 24-h post-dose plasma concentration over time profiles for VEN, ODV and total VEN + ODV on day 1 (beginning of titration), day 15 (end of titration) and day 30 (end of LDX + VXR coadministration) are shown in Fig. 4a–c, respectively. VEN, ODV and total VEN + ODV pharmacokinetic parameters for days 15 and 30 are summarized in Table 2. For combination LDX + VXR compared with VXR alone, VEN C_{max}, AUC_τ and t_{1/2} were slightly lower compared with VXR given alone for Treatment Arm A (LDX 70 mg/day + VXR 225 mg/day) and slightly higher for Treatment Arm B (VXR 225 mg/day + LDX 70 mg/day) (Table 2). ODV C_{max} and AUC_τ were lower for both

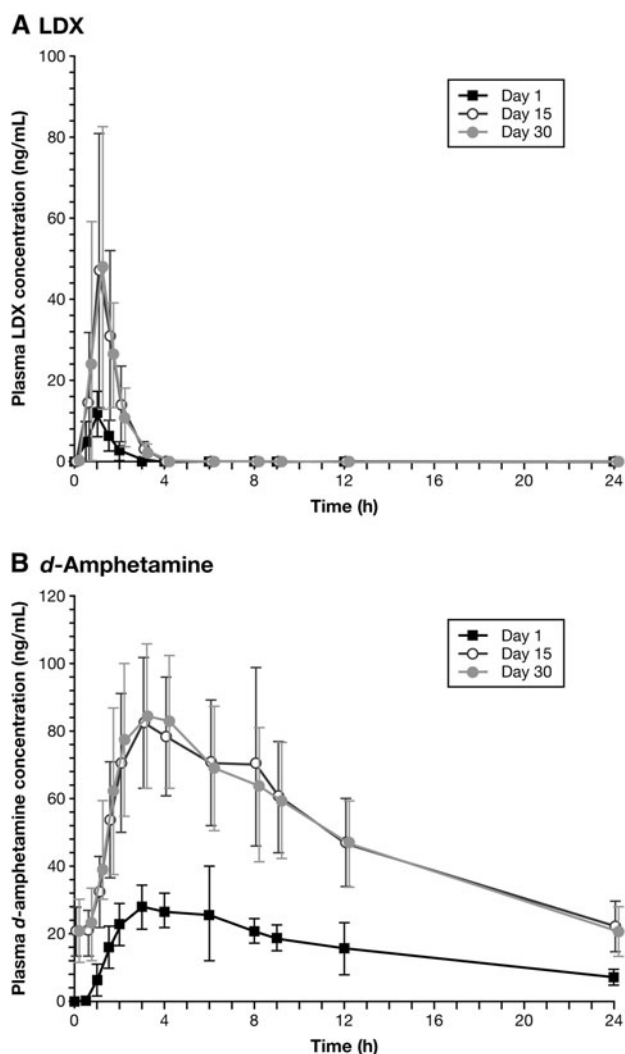


Fig. 3 Mean (SD) plasma concentration versus time plots for **a** LDX and **b** *d*-amphetamine, following administration of LDX 30 mg/day (day 1, beginning of titration), LDX 70 mg/day (day 15, end of titration), and LDX 70 mg/day + VXR 225 mg/day (day 30, end of coadministration). LDX lisdexamfetamine dimesylate, VXR venlafaxine extended-release

treatment arms, although $t_{1/2}$ was shorter for Treatment Arm A and longer for Treatment Arm B with combination LDX + VXR, compared with VXR alone (Table 2). Total VEN + ODV C_{max} and AUC_{τ} were slightly lower and $t_{1/2}$ was slightly longer with combination LDX + VXR compared with VXR alone. The results of bioequivalence testing, summarized in Table 3, showed that systemic exposure to VEN was increased, to ODV was decreased and to total VEN + ODV unaltered, given combination LDX + VXR, compared with VXR alone.

3.4 Pharmacokinetics in CYP2D6 Poor Metabolizers

One of two CYP2D6 poor metabolizers withdrew prematurely from the study (due to an AE of depressed mood)

and did not receive VXR. The remaining poor metabolizer completed the study and exhibited higher individual VEN plasma concentrations and lower ODV plasma concentrations at day 30 than all other participants at this time point. This participant's total VEN + ODV plasma concentrations were similar to those seen in other participants.

3.5 Safety

TEAEs with LDX or VXR treatment alone are summarized in Table 4. One participant (male, Treatment Arm A) had a serious AE (presyncope) on day 5 of the dose-titration period of the study (LDX 30 mg/day at time of TEAE onset); the event, considered related to study medication, resolved within 10 min. Prior to this event, the subject reported several TEAEs (somnolence, palpitations, erectile dysfunction, anorexia) during LDX titration; he was discontinued from the trial.

Changes from baseline blood pressure and pulse rate are shown in Table 5 and Fig. 5a–c. Maximum mean increases in pulse rate, SBP and DBP in Treatment Arm A (LDX alone) were approximately 13 beats/min, 7 mmHg and 6 mmHg, respectively. Maximum mean increases in pulse rate, SBP and DBP in Treatment Arm B (VXR alone) were approximately 9 beats/min, 4 mmHg and 5 mmHg, respectively. Maximum mean increases in pulse rate, SBP and DBP with combination treatment in Treatment Arm A (LDX + VXR) were approximately 18 beats/min, 13 mmHg and 12 mmHg, respectively, and with combination treatment in Treatment Arm B (VXR + LDX) were approximately 21 beats/min, 14 mmHg and 12 mmHg, respectively. No participant was discontinued due to a change in vital signs.

No clinically meaningful laboratory or ECG results or changes from baseline were observed during the trial among participants in either treatment arm, with the exception of a female participant aged 24 years in Treatment Arm B. At 2 h post-dose on days 15 (VXR 225 mg/day) and 30 (VXR 225 mg/day + LDX 70 mg/day) this participant exhibited what the investigator considered clinically abnormal ECG results for heart rate, PR interval, QRS duration, QT interval and corrected QT obtained using Bazett's formula (QTcB) interval. On both occasions, all ECG parameters returned to normal readings at 4 h.

4 Discussion

With LDX being studied in clinical trials with more medically diverse clinical populations, it was necessary to examine the safety and risk for drug-drug interactions of LDX coadministered with medications commonly used in

Table 2 Summary pharmacokinetic parameters after LDX alone, VXR alone (day 15) or combination LDX + VXR (day 30)

	C_{max} (ng/mL)	t_{max} (h)	AUC_{τ} (ng·h/mL)	$t_{1/2}$ (h)
LDX				
LDX alone	49.1 (32.25)	1.1 (0.3)	65.5 (44.0)	0.4 (0.1)
Combination ^a				
Arm A	49.8 (34.3)	1.1 (0.3)	63.9 (43.7)	0.4 (0.1)
Arm B	50.8 (19.68)	1.0 (0.3)	60.8 (19.2)	0.4 (0.2)
d-Amphetamine				
LDX alone	88.9 (26.9)	3.5 (1.5)	1,143.4 (292.8)	10.4 (1.8)
Combination ^a				
Arm A	88.9 (22.7)	3.2 (1.0)	1,135.4 (301.5)	9.8 (1.7)
Arm B	85.3 (20.6)	3.1 (1.3)	1,049.2 (268.7)	9.7 (2.1)
VEN				
VXR alone	211.0 (120.6)	6.4 (0.8)	2,900.0 (1,919.3)	10.8 (2.7)
Combination ^a				
Arm A	198.5 (105.48)	6.0 (1.3)	2,839.7 (1,706.8)	10.7 (2.4)
Arm B	228.9 (124.42)	5.9 (0.6)	3,202.6 (1,942.5)	11.2 (3.1)
ODV				
VXR alone	420.6 (139.67)	7.9 (1.2)	8,363.3 (2,168.1)	19.5 (6.0)
Combination ^a				
Arm A	413.7 (150.0)	8.5 (1.7)	8,061.3 (2,868.7)	18.3 (4.4)
Arm B	371.5 (104.9)	7.9 (1.3)	6,955.1 (1,962.8)	20.9 (6.7)
Total VEN + ODV				
VXR alone	624.6 (179.7)	7.3 (1.1)	10,738.0 (3,273.3)	16.9 (4.3)
Combination ^a				
Arm A	603.5 (181.3)	7.1 (1.4)	10,673.9 (3,035.7)	17.9 (4.9)
Arm B	588.7 (158.8)	7.0 (1.2)	10,342.2 (3,096.1)	18.4 (5.6)

Data are given as mean (SD)

Treatment Arm A = initial LDX alone, followed by combination LDX 70 mg/day + VXR 225 mg/day; Treatment Arm B = initial VXR alone, followed by combination LDX 70 mg/day + VXR 225 mg/day

AUC_{τ} area under the plasma concentration time curve from time zero to time of last measurable concentration, C_{max} maximum plasma concentration, **LDX** lisdexamfetamine dimesylate, **ODV** O-desmethylvenlafaxine, t_{max} time to reach C_{max} , $t_{1/2}$ elimination half-life, **VEN** venlafaxine, **VXR** venlafaxine extended-release

^a Combination VXR dose was 225 mg/day**Table 3** Bioequivalence test results

Analyte	Treatment arm	Geometric least squares means			Test/reference ratio [90 % CI]
		LDX alone Day 15	VXR alone Day 15	LDX + VXR Day 30	
d-Amphetamine	A	–			
AUC_{τ} (ng·h/mL)		1,112		1,057	0.95 [0.806, 1.121]
C_{max} (ng/mL)		85.87		83.03	0.967 [0.821, 1.139]
VEN	B	–			
AUC_{τ} (ng·h/mL)			2,407	2,719	1.129 [0.88, 1.45]
C_{max} (ng/mL)			180.7	199.2	1.103 [0.881, 1.38]
ODV	B	–			
AUC_{τ} (ng·h/mL)			8,083	6,676	0.826 [0.713, 0.956]
C_{max} (ng/mL)			391.5	354.9	0.907 [0.777, 1.058]
Total VEN + ODV	B	–			
AUC_{τ} (ng·h/mL)			10,128	9,894	0.977 [0.848, 1.126]
C_{max} (ng/mL)			593.1	567.4	0.957 [0.84, 1.089]

AUC_{τ} area under the plasma concentration time curve from time zero to time of last measurable concentration, *CI* confidence interval, C_{max} maximum plasma concentration, **LDX** lisdexamfetamine dimesylate, **ODV** O-desmethylvenlafaxine, **VEN** venlafaxine, **VXR** venlafaxine extended-release

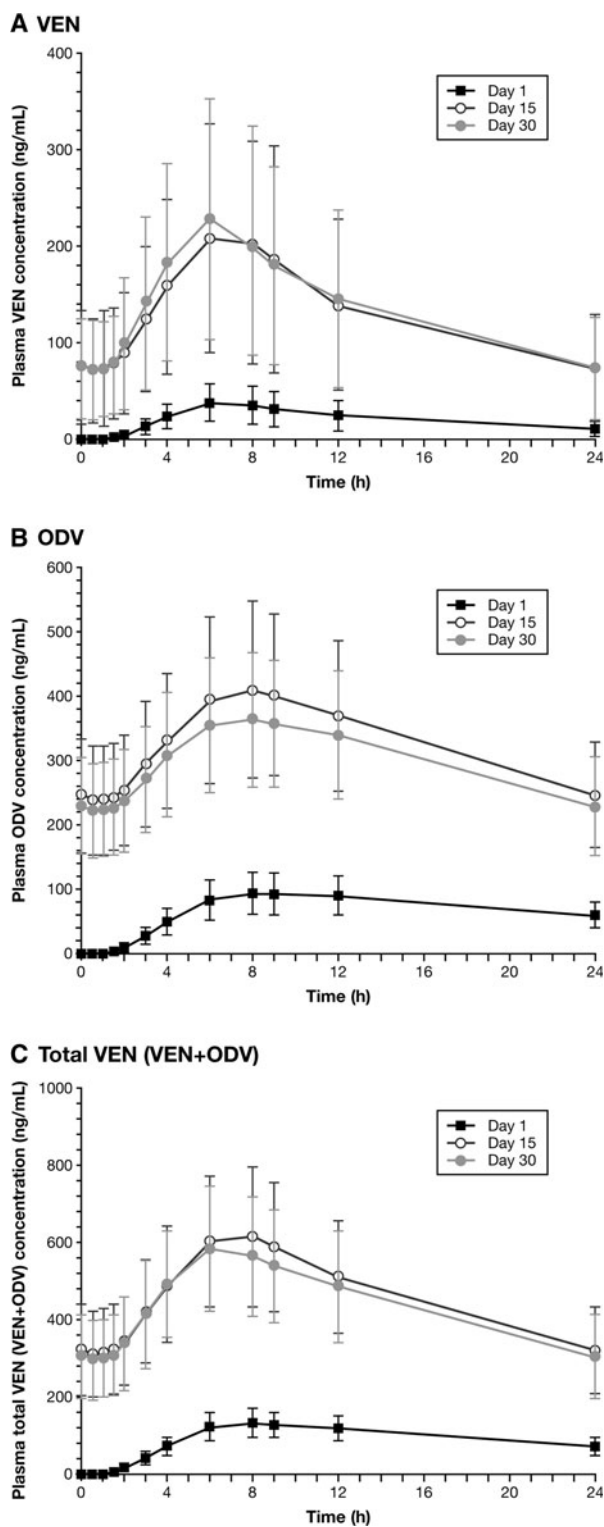


Fig. 4 Mean (SD) plasma concentration versus time plots for **a** VEN, **b** ODV and **c** composite VEN + ODV following administration of VXR 75 mg/day (day 1, beginning of titration), VXR 225 mg/day (day 15, end of titration), and LDX 70 mg/day + VXR 225 mg/day (day 30, end of coadministration). *LDX* lisdexamfetamine dimesylate, *ODV* *O*-desmethylvenlafaxine, *VEN* venlafaxine

Table 4 Frequency $\geq 5\%$ of TEAEs [*n* (%)] associated with study drug administration (treatment arms combined)

TEAE	LDX alone (<i>n</i> = 40) ^a	VXR alone (<i>n</i> = 37) ^a	LDX + VXR (<i>n</i> = 67) ^b
Any TEAE	33 (82.5)	25 (67.6)	46 (68.7)
Anorexia	12 (30.0)	9 (24.3)	0 (0.0)
Anxiety	5 (12.5)	0 (0.0)	2 (3.0)
Back pain	2 (5.0)	0 (0.0)	0 (0.0)
Chest pain	3 (7.5)	0 (0.0)	1 (1.5)
Constipation	3 (7.5)	3 (8.1)	11 (16.4)
Diarrhoea	2 (5.0)	3 (8.1)	2 (3.0)
Dizziness	3 (7.5)	4 (10.8)	7 (10.4)
Dry mouth	10 (25.0)	7 (18.9)	6 (9.0)
Dyspnoea	2 (5.0)	0 (0.0)	1 (1.5)
Epistaxis	0 (0.0)	0 (0.0)	5 (7.5)
Euphoric mood	3 (7.5)	0 (0.0)	0 (0.0)
Headache	7 (17.5)	6 (16.2)	13 (19.4)
Insomnia	7 (17.5)	3 (8.1)	5 (7.5)
Libido decreased	0 (0.0)	2 (5.4)	0 (0.0)
Nausea	6 (15.0)	7 (18.9)	4 (6.0)
Palpitations	8 (20.0)	0 (0.0)	2 (3.0)
Somnolence	7 (17.5)	7 (18.9)	0 (0.0)
Stomach discomfort	2 (5.0)	0 (0.0)	0 (0.0)
Testicular pain	0 (0.0)	0 (0.0)	5 (7.5)
Urinary hesitation	0 (0.0)	1 (2.7)	5 (7.5)
Vision blurred	2 (5.0)	0 (0.0)	0 (0.0)

LDX lisdexamfetamine dimesylate, *VXR* venlafaxine extended-release, *TEAE* treatment-emergent adverse event

^a Data for VXR alone and LDX alone = TEAEs reported during dose titration periods

^b The 67 participants in the combination group consisted of those receiving at least one dose of LDX + VXR in Treatment Arm A (32 participants) and VXR + LDX in Treatment Arm B (35 participants)

psychiatric practice. For this study, pharmacokinetic and safety profiles of LDX given alone and in combination with the antidepressant VXR were described in healthy adults. Combination LDX + VXR did not alter exposure to *d*-amphetamine (vs. LDX alone). Although small changes in exposure to VEN (increased) and ODV (decreased) were seen, total VEN + ODV exposure showed no change with combination treatment (vs. VXR alone) as demonstrated by bioequivalence testing. Changes from baseline in pulse rate and blood pressure were greater in magnitude during coadministration compared with either drug being administered alone. The TEAE profile with coadministration was similar to that when LDX was given alone.

LDX does not inhibit any CYP isoenzymes tested to date [5], but its active component, *d*-amphetamine, weakly inhibits CYP2D6 activity [1, 6]. CYP2D6 is the enzyme

Table 5 Range (1–2 h post-dose) of mean change from time-matched baseline^a in vital signs over 1–12 h post-dose

Vital signs	Treatment Arm A LDX alone	Treatment Arm B VXR alone	Combination LDX + VXR ^b
Pulse rate (beats/min)	−0.78 ^c to 12.76	−3.73 to 8.73	4.66–20.85
Systolic blood pressure (mmHg)	−0.77 ^c to 6.56	−0.52 to 4.32	4.44 ^c to 13.78
Diastolic blood pressure (mmHg)	0.57 ^c to 5.74	1.18–5.39	7.05–12.46

LDX lisdexamfetamine dimesylate, VXR venlafaxine extended-release

^a Baseline was defined as the time-matched measurement at day −1 for each treatment period

^b Includes subjects who received LDX + VXR in Treatment Arm A as well as those who received VXR + LDX in Treatment Arm B

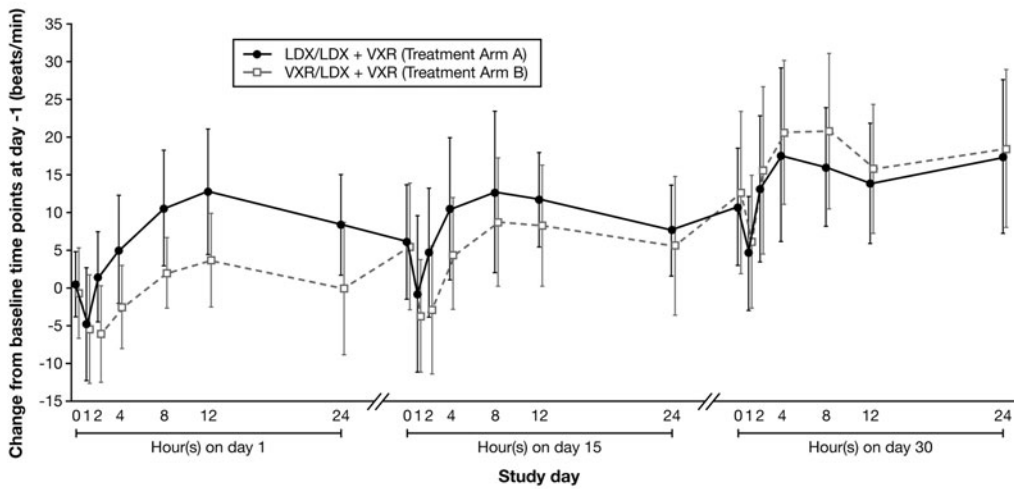
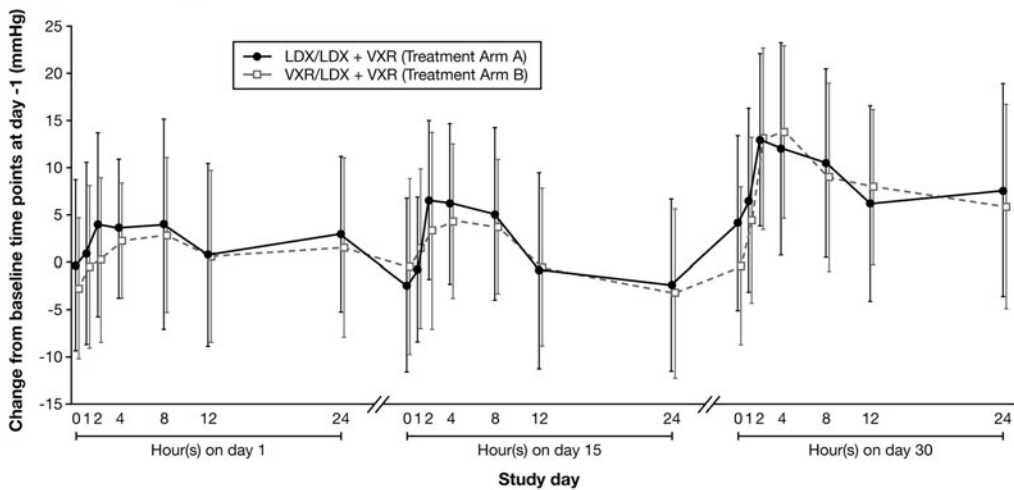
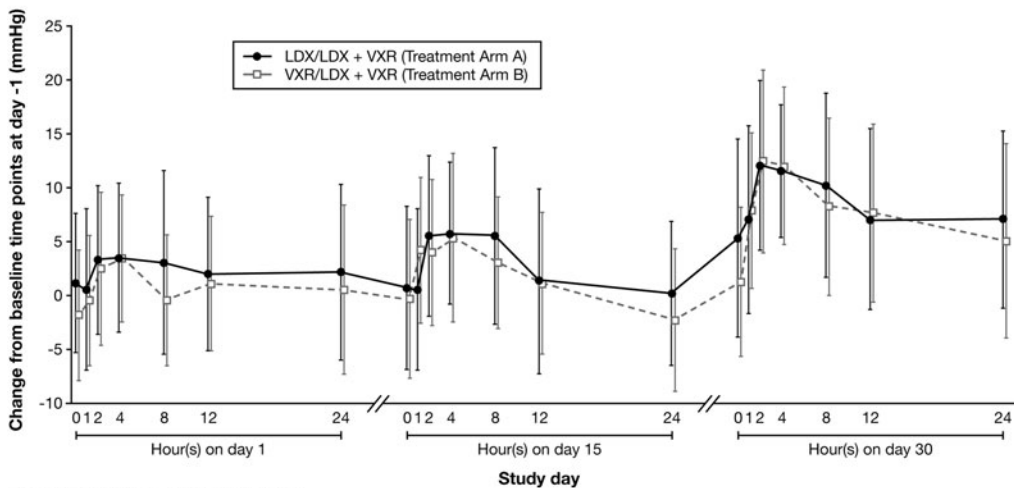
^c Value occurred at first post-dose measurement (1 h post-dose)

primarily responsible for the metabolism of various antidepressant and second-generation antipsychotic medications [7, 8]. Because VEN is primarily metabolized to active ODV via *O*-demethylation that is dependent on CYP2D6 isoenzyme activity (to a lesser degree, it is metabolized via CYP3A4-dependent *N*-demethylation [10]), VXR was chosen as a representative compound to test potential for interaction with LDX. The current pharmacokinetic findings confirm that *d*-amphetamine is a weak inhibitor of CYP2D6 activity. With LDX + VXR coadministration, slight but statistically significant increases in VEN exposure and slight decreases in ODV exposure were observed. The clinical impact of such changes is likely not significant. Both VEN and ODV are pharmacologically active, with similar neurotransmitter receptor affinity profiles [9]. Moreover, with LDX + VXR coadministration, exposure to the two active compounds (VEN + ODV) taken together was unchanged. Given these facts, the observed small changes in VEN and ODV pharmacokinetics are not expected to alter VXR-mediated clinical outcomes.

As expected, the single poor CYP2D6 metabolizer who completed the study exhibited higher levels of VEN and lower levels of ODV than were seen in the other participants who were extensive or intermediate metabolizers; total VEN + ODV exposure, however, was similar to the overall group mean. This finding highlights the potential clinical importance of *d*-amphetamine-mediated CYP2D6 inhibition for individuals receiving LDX in combination with other medications. The small pharmacokinetic changes currently observed with LDX + VXR coadministration do not rule out the possibility of clinically significant pharmacokinetic alterations when LDX is administered in combination with other compounds. Further research may be required to determine the potential for drug–drug interactions between LDX and other widely prescribed compounds that are metabolized predominantly via CYP2D6 activity [10] or which also inhibit CYP2D6 enzyme activity.

Safety observations with LDX + VXR coadministration were in line with expectations. The most common TEAEs reported with combination treatment were generally similar to those seen with LDX alone. As expected, common TEAEs with VXR alone included anorexia, dry mouth, nausea, somnolence and headache; with LDX alone, these included dry mouth, anorexia and palpitations. Also as expected, with either LDX alone or VXR alone, small mean increases in pulse rate and blood pressure occurred, and these increases were greater in magnitude when LDX and VXR were coadministered. As illustrated in Fig. 5a–c, these increases tended to emerge gradually over several days; no participant was discontinued due to an increase in pulse rate or blood pressure.

The present investigation had several limitations that warrant consideration. The sample comprised primarily healthy adult white men; thus, findings might not be generalizable to younger or older individuals, adults with medical or psychiatric co-morbidities, those of other racial or ethnic backgrounds, or women. LDX and VXR were coadministered at their maximum approved therapeutic doses (LDX 70 mg/day and VXR 225 mg/day); changes in VEN and ODV pharmacokinetics were not characterized using different (i.e., lower or higher) LDX and VXR doses. This study examined pharmacokinetics and safety during short-term coadministration of LDX + VXR; pharmacokinetics and safety with longer-term combination treatment are unknown. Comparison of data on vital signs to data gathered from previous outpatient clinical trials (summarized in the respective product information of LDX [1] and VXR [9]) should consider limitations due to several factors: (i) participants were housed for a relatively long time period in a CSC where normal routines of diet, activity and exercise were disrupted; (ii) LDX and VXR were tested in combination only at the highest recommended doses; and (iii) monitoring of vital signs in outpatient clinical trials occurs at various times of the day, whereas in the current trial vital signs were recorded according to a well-defined schedule, relative to time of dosing and time course of

A Pulse rate**B Systolic blood pressure****C Diastolic blood pressure**

*Plots staggered for illustrative purposes

Fig. 5 Mean (SD) change^a from baseline in **a** pulse rate, **b** systolic blood pressure and **c** diastolic blood pressure on day 1 (beginning of titration), day 15 (end of titration) and day 30 (end of coadministration). *LDX* lisdexamfetamine dimesylate, *VXR* venlafaxine extended-release

plasma drug levels. Despite these limitations, the current study provides useful information to help clinicians develop appropriate procedures for dosing and safety monitoring when LDX is coadministered with VXR in a diverse adult population. As with each agent alone, monitoring of vital signs (pulse rate, blood pressure) is recommended should LDX and VXR be coadministered.

5 Conclusion

In healthy adults, combination LDX + VXR (vs. LDX alone) did not alter exposure to *d*-amphetamine. Although small changes in exposure to VEN (increased) and ODV (decreased) were seen with combination treatment, supporting evidence that *d*-amphetamine is a weak inhibitor of CYP2D6 activity, total VXR + ODV exposure showed no change (vs. VEN alone). Increases in pulse rate and blood pressure observed when LDX and VEN were administered alone were consistent with previous studies [11, 13, 17]. Changes from baseline in vital signs were greater in magnitude during coadministration compared with when either LDX or VEN was administered alone. The TEAE profile with LDX + VXR coadministration was similar to that seen with LDX alone. This study provides useful information to help clinicians develop appropriate procedures for dosing and safety monitoring when LDX is used as combination therapy with VXR in an adult population. As with each agent alone, monitoring of vital signs (e.g., pulse rate, blood pressure) is recommended with combination therapy of LDX and VXR.

Acknowledgments With great sadness, the authors wish to acknowledge the passing of our colleague, Mary B. Haffey, RPh, and recognize her contributions to this article.

Funding Clinical research was funded by the sponsor, Shire Development LLC. Under the direction of the authors, Michael Pucci, PhD, an employee of SCI Scientific Communications & Information (SCI), and Karen Dougherty, PhD, a former employee of SCI, provided writing assistance for this publication. Editorial assistance in formatting, proofreading, copy editing, and fact checking was also provided by SCI. Brian Scheckner, PharmD, from Shire Development LLC also reviewed and edited the manuscript for scientific accuracy. Shire Development LLC provided funding to SCI for support in writing and editing this manuscript. Although the sponsor was involved in the design, collection, analysis, interpretation, and fact checking of information, the content of this manuscript, the ultimate interpretation, and the decision to submit it for publication in *Clinical Drug Investigation* were made by the authors independently.

Author Contributions All authors made substantial contributions to the conception and design or analysis and interpretation of data. All authors made substantial contributions to drafting the article or revising it critically for important intellectual content. All authors except Mary B. Haffey, RPh approved the final version to be published.

Disclosures James Ermer, MS, is a Shire employee and holds stock and/or stock options in Shire. Mary B. Haffey, RPh, was a Shire employee and held stock and/or stock options in Shire. Cynthia Richards, MD, is a Shire employee and holds stock and/or stock options in Shire. Kenneth Lasseter, MD, is a principal of Clinical Pharmacology of Miami, Inc. and does not hold stock and/or stock options in Shire. Benno Roesch, MD, is an employee of Advanced Biomedical Research, a subsidiary of Frontage Laboratories, LLC. Jaideep Purkayastha, MS, is a Shire employee and holds stock and/or stock options in Shire. Mary Corcoran, MS, is a Shire employee and holds stock and/or stock options in Shire. Bree Harlin, BS, is a contractor for Shire employed through DOCS Global. Patrick Martin, MD, is a Shire employee and holds stock and/or stock options in Shire.

Open Access This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and the source are credited.

References

1. Vyvanse[®] (lisdexamfetamine dimesylate) capsules [package insert]. Wayne: Shire US Inc.; 2012.
2. Pennick M. Absorption of lisdexamfetamine dimesylate and its enzymatic conversion to d-amphetamine. *Neuropsychiatr Dis Treat.* 2010;6(1):317–27.
3. Trivedi MH, Cutler A, Richards C, et al. Efficacy and safety of lisdexamfetamine dimesylate as augmentation therapy in adults with major depressive disorder treated with an antidepressant. Poster presented at: the 164th Annual Meeting of the American Psychiatric Association; May 14–18, 2011; Honolulu, HI.
4. Madhoo M, Keefe RSE, Roth RM, et al. Efficacy and safety of lisdexamfetamine dimesylate in adults with executive dysfunction and partial or full remission of major depressive disorder. Abstract presented at: College of Psychiatric and Neurologic Pharmacists' Annual Meeting; April 29–May 2, 2012; Tampa, FL.
5. Krishnan S, Moncrief S. An evaluation of the cytochrome p450 inhibition potential of lisdexamfetamine in human liver microsomes. *Drug Metab Dispos.* 2007;35(1):180–4.
6. Bach MV, Coutts RT, Baker GB. Involvement of CYP2D6 in the in vitro metabolism of amphetamine, two N-alkylamphetamines and their 4-methoxylated derivatives. *Xenobiotica.* 1999;29(7):719–32.
7. Hemeryck A, Belpaire FM. Selective serotonin reuptake inhibitors and cytochrome P-450 mediated drug-drug interactions: an update. *Curr Drug Metab.* 2002;3(1):13–37.
8. Sheehan JJ, Sliwa JK, Amatniek JC, et al. Atypical antipsychotic metabolism and excretion. *Curr Drug Metab.* 2010;11(6):516–25.
9. Effexor XR[®] (venlafaxine hydrochloride) extended-release capsules [package insert]. Philadelphia: Wyeth Pharmaceuticals Inc.; 2011.
10. Ball SE, Ahern D, Scatina J, et al. Venlafaxine: in vitro inhibition of CYP2D6 dependent imipramine and desipramine metabolism; comparative studies with selected SSRIs, and effects on human hepatic CYP3A4, CYP2C9 and CYP1A2. *Br J Clin Pharmacol.* 1997;43(6):619–26.
11. Perahia DG, Pritchett YL, Kajdasz DK, et al. A randomized, double-blind comparison of duloxetine and venlafaxine in the treatment of patients with major depressive disorder. *J Psychiatr Res.* 2008;42(1):22–34.
12. Adler LA, Goodman DW, Kollins SH, et al. 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(9):1364–73.
13. Adler LA, Weisler RH, Goodman DW, et al. Short-term effects of lisdexamfetamine dimesylate on cardiovascular parameters in a 4-week clinical trial in adults with attention-deficit/hyperactivity disorder. *J Clin Psychiatry*. 2009;70(12):1652–61.
 14. Adler LA, Lynch LR, Shaw DM, et al. Medication adherence and symptom reduction in adults treated with mixed amphetamine salts in a randomized crossover study. *Postgrad Med*. 2011; 123(5):71–9.
 15. US Department of Health and Human Services. Guidance for Industry: Drug interaction studies—study design, data analysis, implications for dosing, and labeling recommendations. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>. Accessed 24 May 2012.
 16. US Food and Drug Administration. Guidance for industry: bioavailability and bioequivalence studies for orally administered drug products—general considerations. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidelines/UCM070124.pdf>. Accessed 24 May 2012.
 17. Sir A, D'Souza RF, Uguz S, et al. Randomized trial of sertraline versus venlafaxine XR in major depression: efficacy and discontinuation symptoms. *J Clin Psychiatry*. 2005;66(10):1312–20.