

Human pharmacology of intravenous lisdexamfetamine dimesylate: abuse liability in adult stimulant abusers

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Abstract

The objective of this study is to determine the safety, tolerability and abuse liability of single intravenous (i.v.) doses of lisdexamfetamine dimesylate (LDX) and immediate-release d-amphetamine sulphate in adult stimulant abusers compared with placebo. Adult substance abusers were enrolled in this phase I, randomized, single-centre, double-blind study. An initial cohort of three subjects was enrolled to assess safety followed by a primary cohort that consisted of nine subjects. Single i.v. doses of LDX (25 or 50 mg), immediate-release d-amphetamine sulphate (10 or 20 mg) or placebo were administered at a minimum of 48-h intervals in a single-dose, three-way crossover design. 20 mg of d-amphetamine showed significantly increased abuse-related liking scores compared with placebo ($P < 0.05$), whereas the liking effects of 50 mg LDX did not significantly

differ from placebo. The mean C_{\max} of d-amphetamine was 38.9 ± 8.1 and 105 ± 91.4 ng/ml after the administration of 50 mg LDX and 20 mg d-amphetamine respectively. The mean T_{\max} of d-amphetamine was 2.51 h after the administration of 50 mg LDX and 0.82 h after the administration of 20 mg d-amphetamine. LDX was well tolerated in this population. In contrast to d-amphetamine, LDX administered intravenously did not produce significant subjective abuse-related liking scores at assessed doses.

Key words

abuse; ADHD; LDX; stimulant; Vyvanse

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common psychiatric disorder characterized by significant impairments in occupational functioning, academic achievement and interpersonal relationships (Biederman and Faraone, 2005; Goldman, *et al.*, 1998). Pharmacotherapy for ADHD relies heavily on stimulants with amphetamine salts and methylphenidate as first-line agents (American Academy of Child and Adolescent Psychiatry, 2007; American Academy of Pediatrics Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement, 2001; Pliszka, *et al.*, 2006). However, the use of stimulants is coupled with concerns about misuse, abuse and diversion (Jasinski, *et al.*, 2007; Jasinski, *et al.*, 1974; Jasinski, 2000; Jasinski and Henningfield, 1982; Jasinski and Kovacevic-Ristanovic, 2000; Wilens, *et al.*, 1997; Wilens, *et al.*, 2006). Due to their aqueous solubility, stimulants may be abused through multiple routes including orally, intravenously and intranasally. To reduce the potential for stimulant abuse, attention has focussed on developing abuse-resistant products to treat ADHD.

One such product, lisdexamfetamine dimesylate (LDX; Vyvanse™, Shire US Inc, Wayne, PA, USA) is the first pro-drug stimulant that is FDA-approved for the treatment of ADHD. Multiple clinical trials have established the efficacy and safety of LDX in improving ADHD symptoms in children (Biederman, *et al.*, 2007a,b; Findling, *et al.*, 2007). LDX administered orally was found in a clinical trial to have onset of efficacy within 2 h that lasted through the duration of the 12-h testing period (Biederman, *et al.*, 2007a). LDX is a biologically inactive molecule. In the body, LDX is converted by a rate-limited process (e.g. enzymatic hydrolysis) to L-lysine, a naturally occurring essential amino acid, and d-amphetamine, which is responsible for the drug's activity. It has been proposed that this rate-limited conversion process may contribute to the extended duration of effect that is seen throughout the day and a reduced abuse-related drug liking effect.

The current study was undertaken to characterize the pharmacokinetic and pharmacodynamic profiles of intravenously administered LDX and d-amphetamine, a prototypical drug of abuse, compared with placebo in adults with a history of stimulant abuse. The goal of the present study was to evaluate the abuse liability profile, safety and tolerability of these treatments.

Materials and methods

Participants

This was a phase I, randomized, single-centre, double-blind study conducted at the Johns Hopkins Bayview Medical Center (Baltimore, Maryland, USA) between 27 September and 4 November 2005. The protocol and informed consent form (ICF) were submitted to the Institutional Review Board for review and approval prior to the start of the study. All prospective subjects signed the ICF after receiving written information and an explanation of what the study involved before initiation, and received a copy of the ICF. All subjects were paid volunteers, who were required to reside in an inpatient clinic for the duration of the study. All subjects were discharged 48 h after administration of the last dose.

Inclusion and exclusion criteria

Male or nonpregnant, nonlactating female subjects who met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria for stimulant abuse with a history of intravenous (i.v.) drug abuse were recruited and enrolled in this study. All had a minimum reading level of grade 6, were administered the Hopkins Mini-Mental State Exam to rule out organic brain disease and were between 18 and 55 years of age (inclusive). Exclusion criteria included dependence on benzodiazepines, opiates, alcohol or a history of disorders that could, in the opinion of the investigator, affect the validity of results or prevent completion of the study. Subjects were required to have no other medical or psychiatric disorders that precluded participation, as judged from the medical and psychiatric histories, physical examinations or laboratory or electrocardiogram (ECG) findings. The absences of serious suicidal risk, severe learning difficulty or mental retardation were specifically documented.

Study procedures

Eligible subjects participated in single-dose and three-way crossover drug administration in two cohorts of three and nine subjects respectively. Single doses of 25 mg LDX, 10 mg d-amphetamine sulphate or placebo were given to the safety cohort of three subjects at a minimum of 48-h intervals in a three-way crossover design to evaluate the safety, tolerability and abuse potential of LDX. The results of each study treatment administration were reviewed by the investigator at the completion of the crossover in the three subjects of the safety cohort. The decision to proceed to the next research phase, using the next higher dose level for the two active treatments in the primary cohort of nine subjects, was made by the investigator. This was based on acceptable safety and tolerability data from the safety cohort. The primary cohort, therefore, received 50 mg LDX, 20 mg d-amphetamine and placebo interspersed in the same three-way crossover design as the safety cohort.

For each cohort, vital sign measures, and subjective and behavioural effects [with the exception of the Treatment Enjoyment Assessment Questionnaire (TEAQ)] were assessed on each dosing day before dosing and again at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 16 and 24 h after i.v. administration. TEAQ was assessed 24 h after the last dose was administered.

A 5-ml sample of blood was taken for analyses of LDX and d-amphetamine levels before dosing and at 5, 10 and 20 min, and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 16 and 24 h after dosing. Immediately after each collection, the Vacutainer tube was centrifuged at 4 °C, approximately 600 g, for 10 min. Within approximately 60 min of collection, samples were stored in a polypropylene container labelled with the protocol number, day number, subject randomization number, collection date and time-point. All plasma samples were stored at approximately -20 °C or below. Plasma samples were assayed by CEDRA Corporation, Austin, Texas, using liquid chromatography/mass spectrometry/mass spectrometry method with a lower limit of quantification of 2.00 ng/ml for d-amphetamine and 1.00 ng/ml for intact LDX.

Plasma concentration–time data were summarized by treatment for each cohort, using descriptive statistics at each scheduled time-point. Mean concentration–time profiles for each treatment within cohort and individual concentration–time profiles were generated. Concentration–time data for individual subjects were analysed by noncompartmental methods using actual elapsed times by means of WinNonlin Enterprise Edition (Version 4.0; Pharsight Corporation, Pharsight®, Mountain View, CA, USA).

The following parameters were calculated using noncompartmental analysis for d-amphetamine: C_{\max} , T_{\max} , AUC_{0-24} . These parameters were defined as follows: C_{\max} , maximum observed drug concentration during 0 h and 24 h postdose; T_{\max} , time at which C_{\max} occurs and AUC_{0-24} , area under the drug concentration–time curve at the last time-point assessed, which was 24 h postdose.

The respective LDX and d-amphetamine doses were selected because on a mole-weight basis, the d-amphetamine free-base content in 25 and 50 mg LDX is equivalent to the d-amphetamine free-base content of a 10-mg and a 20-mg dose of d-amphetamine sulphate respectively.

Abuse liability assessments

The primary measure of abuse liability was the Drug Rating Questionnaire–Subject (DRQS); it includes three visual analogue scales (VAS), each being a 1-to-29 scale, with 1 being ‘not at all’ and 29 ‘an awful lot’. This VAS is widely used in clinical trials when the abuse liability of stimulants is being addressed (Jasinski, *et al.*, 2007; Jasinski, 2000; Jasinski and Kovacevic-Ristanovic, 2000). The DRQS Scale asks three questions, one of which is, ‘How much do you like the effects you are feeling now?’ and the score for this question (Liking Scale) was the primary measure of abuse liability. Secondary abuse liability measures included the other two questions on the DRQS: ‘How much do you feel the drug now?’ and

'Do you dislike the drug effect you are feeling now?' The Drug Rating Questionnaire–Observer (DRQO) included three VAS items similar to the items of the DRQS, but was completed by the investigator rating the subject. Effect on all measures was assessed by the maximum change and time to maximum change from baseline, defined as 30 min predose. An increase in the liking score may be associated with greater abuse liability, whereas an increase drug disliking score may be associated with a decrease in abuse liability (Jasinski, *et al.*, 1974; Jasinski, 2000; Jasinski and Kovacevic-Ristanovic, 2000).

The Addiction Research Center Inventory (ARCI) short form was also utilized in this study as a secondary outcome measure. ARCI is a 49-item true/false questionnaire that contains the following five subscales: (a) Morphine–Benzedrine Group Scale (the MBG or 'euphoria' scale; a measure of euphoria); (b) Benzedrine Group Scale (the BG or 'stimulant' scale; a measure of stimulant effects relating to intellectual efficacy and energy); (c) Amphetamine Scale (AS; a measure of specific amphetamine-like effects); (d) Lysergic Acid Diethylamide Scale (the LSD or 'dysphoria' scale; a measure of somatic discomfort and dysphoria) and (e) Phenobarbital–Chlorpromazine–Alcohol Group Scale (the PCAG or 'sedation' scale; a measure of apathetic sedation) (Martin, *et al.*, 1971).

TEAQ was additionally used as a secondary measure to assess the subject's ratings on the drug treatment experienced during the study and which treatment he/she would enjoy taking again. Other pharmacodynamic measures included systolic and diastolic blood pressure and pulse rate changes from baseline.

Randomization Following screening, eligible subjects were admitted to the inpatient research unit. At admission time, subjects were assigned to a randomization number and received treatment accordingly. Randomization schedule was based on a 3×3 Latin square. The randomization schedule had six blocks with three randomization numbers per block and randomization numbers ranged from 001 to 018. At the time of randomization, the schedule was used by the research pharmacist in ascending order to allocate subjects to a treatment sequence with LDX, d-amphetamine and placebo. To preserve blinding, all i.v. solutions were produced by assigned personnel, who then provided the drugs to the study co-ordinator for administration to subjects according to the blinded treatment sequence.

Safety measures Vital signs were assessed before dosing and again at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 16 and 24 h after dosing. During the course of the study, spontaneous reports of adverse events (AEs) were solicited before and after drug administrations. At these times, heart rate, blood pressure and behaviour were also assessed. Laboratory tests, physical examinations and ECGs were performed at the time of admission and discharge (or withdrawal from study).

If the subjective and cardiovascular effects produced by 25 mg LDX in the safety cohort of three subjects were equal

to those produced by the 10-mg dose of d-amphetamine sulphate, or were no different than placebo, then the primary cohort of nine subjects were to be given 50 mg LDX, placebo and 20 mg d-amphetamine sulphate interspersed in the same three-way crossover design according to 3×3 balanced Latin squares.

Statistical methods Twelve subjects in two cohorts of three and nine subjects, respectively, were to participate in this study. No formal sample-size estimation was performed, and subjects who did not complete all three treatments were to be replaced.

The maximum change from baseline was determined for each pharmacodynamic measure. For the safety cohort of the initial three subjects, descriptive statistics were provided for each treatment condition. For the primary cohort of nine subjects, the responses of 50 mg LDX vs. placebo and 20 mg d-amphetamine vs. placebo were analysed based on a general linear model for the 3×3 balanced Latin squares. This model included the period, treatment, subject and dose day as main effects. Following the analysis of variance (ANOVA), the estimated marginal mean and standard error values, as well as the 95% confidence interval of the marginal mean values, were reported for each treatment of the pharmacodynamic population, and linear contrast was performed to compare each of the active treatments to placebo on these measures. This study did not directly compare the effects of LDX to d-amphetamine.

For safety parameters, incidence and frequency of AEs were calculated in total and for each treatment group. Mean values, standard deviation values, minimum, maximum, and median values were calculated for vital signs.

Results

Twelve male subjects with a history of i.v. substance abuse were enrolled in the study. Eleven of the subjects (92%) were African American and one was Caucasian. The demographics of the subjects are described in Table 1. According to randomization dates, subjects were grouped into two cohorts, consisting of the

Table 1 Demographic and baseline characteristics of the randomized population

Characteristic	Category/parameter	Total (<i>N</i> = 12)
Race	Caucasian, <i>n</i> (%)	1 (8)
	African American, <i>n</i> (%)	11 (92)
Gender	Male, <i>n</i> (%)	12 (100)
Height (cm)	Mean	176.0
	SD	7.1
Weight (kg)	Mean	69.5
	SD	10.3
Age (years)	Mean	45.9
	SD	3.3

Abbreviation: SD, standard deviation.

Table 2 Pharmacokinetic parameters for d-amphetamine in the safety cohort

Parameter	25 mg LDX				10 mg d-amphetamine			
	N	Mean	SD	CV%	N	Mean	SD	CV%
C_{\max} (ng/ml)	3	20.7	1.5	7.4	3	74.2	58.7	79.1
T_{\max} (h)	3	2.5	1.3	53.8	3	0.2	0.2	99.2
AUC_{0-24} (h·ng/ml)	3	319.5	26.3	8.3	3	355.8	8.3	2.3

Abbreviations: LDX, lisdexamfetamine dimesylate; C_{\max} , maximum drug concentration; T_{\max} , time to maximum concentration; AUC_{0-24} , area under the concentration–time curve from time 0 to 24 h; SD, standard deviation; CV%, percent coefficient of variation.

initial three subjects in the safety cohort, followed by nine subjects in the primary cohort.

Pharmacokinetic measures

In the safety cohort ($n = 3$), the T_{\max} and C_{\max} of d-amphetamine after i.v. administration of 10 mg d-amphetamine sulphate were 0.2 h and 74.2 ng/ml respectively (Table 2). In contrast, the T_{\max} and C_{\max} of d-amphetamine after i.v. administration of 25 mg LDX, with an equivalent content of d-amphetamine as 10 mg d-amphetamine sulphate, were 2.5 h and 20.7 ng/ml respectively.

Concentration–time data for d-amphetamine and LDX for the primary cohort are summarized in Figure 1(A,B). In the primary cohort ($n = 9$), the T_{\max} and C_{\max} of d-amphetamine after i.v. administration of 20 mg d-amphetamine sulphate were 0.8 h and 105 ng/ml respectively (Table 3). In contrast, the T_{\max} and C_{\max} of d-amphetamine after i.v. administration of 50 mg LDX, with an equivalent content of d-amphetamine as 20 mg d-amphetamine sulphate, were 2.5 h and 38.9 ng/ml respectively. Overall, similar to the findings in the safety cohort, the mean T_{\max} of d-amphetamine was longer and the mean C_{\max} was lower following the administration of LDX compared with d-amphetamine alone. Percent coefficients of

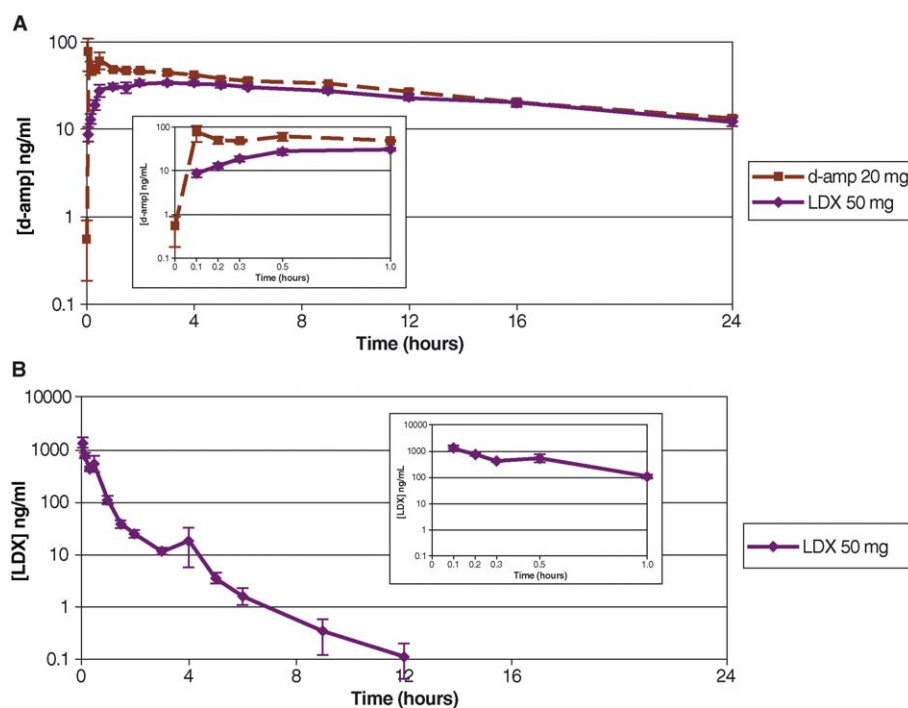


Figure 1 (A) Mean d-amphetamine blood plasma levels over time. (B) Mean lisdexamfetamine dimesylate (LDX) blood plasma levels over time. Panels 1A and B represent the mean d-amphetamine and LDX blood plasma levels over time. A 5-ml sample of blood was taken for analyses of LDX and d-amphetamine levels before dosing and at 5, 10 and 20 min, and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 16 and 24 h after dosing. Plasma samples were assayed using liquid chromatography/mass spectrometry/mass spectrometry method with a lower limit of quantification of 2.00 ng/ml for d-amphetamine and 1.00 ng/ml for intact LDX.

Table 3 Pharmacokinetic parameters for d-amphetamine in the primary cohort

Parameter	50 mg LDX				20 mg d-amphetamine			
	N	Mean	SD	CV%	N	Mean	SD	CV%
C_{\max} (ng/ml)	9	38.9	8.1	20.8	9	105	91.4	86.6
T_{\max} (h)	9	2.5	1.5	58.6	9	0.8	1.3	155.6
AUC_{0-24} (h·ng/ml)	9	562.7	115.5	20.5	9	681.4	96.69	14.2

Abbreviations: LDX, lisdexamfetamine dimesylate; C_{\max} , maximum drug concentration; T_{\max} , time to maximum concentration; AUC_{0-24} , area under the concentration–time curve from time 0 to 24 h; SD, standard deviation; CV%, percent coefficient of variation.

variation of both C_{\max} and T_{\max} were lower for LDX (20.8 and 58.6 respectively) than for d-amphetamine (86.6 and 155.6 respectively).

Overall exposures (AUC_{0-24}) to d-amphetamine were 355.8 and 681.4 h·ng/ml after the administration of 10 and 20 mg d-amphetamine respectively. Following i.v. administration of 25 and 50 mg LDX, the overall exposures (AUC_{0-24}) to d-amphetamine were 319.5 and 562.7 h·ng/ml respectively.

Pharmacodynamic measures

Drug Rating Questionnaire The primary pharmacodynamic outcome measure was the maximum change in DQRS liking scores. Compared with placebo, i.v. d-amphetamine 20 mg produced significant maximum mean change in abuse-related liking scores ($P = 0.01$). Intravenous LDX 50 mg, compared with placebo, produced no significant maximum mean abuse-related liking scores ($P = 0.290$) (Table 4). Time to maximum mean abuse-related liking effects for LDX was similar to that observed for immediate release d-amphetamine (Figure 2).

Secondary measures included the DRQS disliking and feel scores. Neither d-amphetamine nor LDX produced significant maximum mean changes in disliking scores ($P = 0.630$, $P = 0.197$ respectively) or feel drug scores compared with placebo (Table 4). Secondary measures also included DRQO scores. d-amphetamine produced significant change in investigator-rated liking scores ($P < 0.05$) compared with placebo. LDX, however, produced no significant change in mean maximum scores on investigator-rated liking scores ($P = 0.850$). Neither d-amphetamine nor LDX produced significant changes in investigator-rated disliking scores ($P = 1.000$, $P = 0.241$ respectively) compared with placebo.

ARCI Compared with placebo, i.v. d-amphetamine 20 mg produced significant maximum mean change in scores on the MBG Scale ($P < 0.05$), BG Scale ($P < 0.05$) and Amphetamine Scale ($P < 0.05$) (Table 5). All effects peaked 15 min after the administration of d-amphetamine. Intravenous LDX 50 mg showed no significant change compared with placebo on any of the five ARCI subscales: the MBG Scale ($P = 0.090$), BG Scale ($P = 0.080$), Amphetamine Scale ($P = 0.140$), LSD Scale ($P = 0.229$) and PCAG Scale ($P = 0.198$).

TEAQ d-Amphetamine was uniformly favoured by all three subjects in the safety cohort. In the primary cohort, six subjects chose 20 mg d-amphetamine, two subjects chose neither of the two treatments and one selected 50 mg LDX.

Cardiovascular responses Systolic blood pressure in the safety cohort changed little following placebo administration. Administration of 10 mg d-amphetamine resulted in an initial increase that peaked at 15 min postadministration, followed by decreasing effects that dissipated in 3–4 h. With 25 mg LDX, there was a lesser initial increase, which peaked between 1 and 3 h after administration.

In the primary cohort, there was little change in systolic blood pressure following placebo administration. Administration of 20 mg d-amphetamine resulted in an initial increase that peaked at 15 min postadministration, followed by decreasing effects that dissipated in 4–5 h. With 50 mg LDX, there was a lesser initial increase, which peaked 2–3 h postadministration (Figure 3).

Diastolic blood pressure in the safety cohort also showed little initial change following placebo administration. Administration of 10 mg d-amphetamine resulted in an initial increase that peaked at 15 min postadministration, followed by decreasing effects. With 25 mg LDX, there was a lesser initial increase, which peaked between 1 and 3 h after administration.

In the primary cohort, there was no change in diastolic blood pressure following placebo administration. Administration of 20 mg d-amphetamine resulted in an initial increase that peaked at 15 min postadministration, followed by decreasing effects that dissipated in 4–5 h. With 50 mg LDX, there was a lesser initial increase, which peaked 2–3 h postadministration.

In both cohorts, placebo caused little initial change in heart rate, but there was a diurnal increase later in the day. Administration of d-amphetamine induced an initial decrease in heart rate followed by a greater increase later in the day, which peaked approximately 13–14 h after dosing. LDX administration caused little initial change in heart rate, similar to placebo, and a pattern similar to d-amphetamine as the day progressed. The magnitude of the change was also similar between d-amphetamine and LDX.

Safety measures No subjects discontinued due to AEs. Five (42%) subjects reported one or more AE; 11 events were judged

Table 4 Maximum mean change in DRQ measures from predose following d-amphetamine and LDX administration (primary cohort, $N = 9$)

Drug	Mean	Standard error	95% CI (LB, UB)
1) Do you like the drug effect you are feeling now? (Liking – Subject)			
Placebo	0.0	1.3	(–2.9, 2.9)
d-Amphetamine 20 mg	5.6*	1.3	(2.7, 8.1)
LDX 50 mg	2.1	1.3	(–0.8, 5.0)
2) Do you dislike the drug effect you are feeling now? (Disliking – Subject)			
Placebo	0.0	1.3	(–2.7, 2.7)
d-Amphetamine 20 mg	0.9	1.3	(–1.8, 3.6)
LDX 50 mg	2.4	1.3	(–0.3, 5.2)
3) Do you feel a drug effect now? (Feel drug – Subject)			
Placebo	0.0	1.4	(–2.9, 2.9)
d-Amphetamine 20 mg	4.4	1.4	(1.5, 7.4)
LDX 50 mg	2.6	1.4	(–0.4, 5.5)
4) Does the subject like the drug? (Liking – Observer)			
Placebo	0.4	0.8	(–1.3, 2.2)
d-Amphetamine 20 mg	3.9*	0.8	(2.1, 5.6)
LDX 50 mg	0.7	0.8	(–1.1, 2.4)
5) Does the subject dislike the drug? (Disliking – Observer)			
Placebo	0.0	1.2	(–2.5, 2.5)
d-Amphetamine 20 mg	0.0	1.2	(–2.5, 2.5)
LDX 50 mg	2.0	1.2	(–0.5, 4.5)
6) Does the subject feel a drug effect now? (Feel drug – Observer)			
Placebo	0.8	1.0	(–1.4, 2.9)
d-Amphetamine 20 mg	3.8	1.0	(1.6, 5.9)
LDX 50 mg	0.9	1.0	(–1.3, 3.0)

* $P < 0.05$ compared with placebo.

Bold text indicates primary efficacy variables.

Abbreviations: LB, lower bound; UB, upper bound; LDX, lisdexamfetamine dimesylate; DRQ, Drug Rating Questionnaire.

as treatment-emergent. All events were mild-to-moderate in nature and judged to be unrelated to the treatment by the investigator. There were no reported serious AEs. The major treatment-emergent AEs were eye redness, venipuncture site reaction, tinnitus, dyspepsia and muscle cramp.

At discharge, no treatment-emergent laboratory abnormalities were determined by the investigator to be AEs. In addition, physical examinations revealed no abnormalities that emerged during the course of the study. Finally, no clinically significant abnormal ECGs were reported.

Discussion

The abuse potential of a new drug may be assessed by comparing it with a pharmacologically comparable prototypical drug of abuse. The present study was designed to compare the abuse-related and cardiovascular pharmacodynamic and pharmacokinetic effects of LDX and immediate-release d-amphetamine sulphate compared with placebo in subjects with a history of substance abuse. In primary measures of abuse liability, i.v. d-amphetamine produced significant liking and euphoric effects. In contrast, equivalent mole-weight doses of LDX did not produce abuse-related liking or euphoric effects that

differed significantly from placebo. Disliking scores, which indicate the subjects' displeasure for the drug, were numerically, but not statistically larger for LDX compared with placebo. Although numerically larger, the disliking score may be predicted due to its pharmacokinetic profile. TEAQ scores show that, when given a choice, most patients choose d-amphetamine again indicating a clear liking of that molecule.

Furthermore, the pharmacokinetic profile of d-amphetamine after i.v. administration of LDX showed a delayed time to maximum concentration in contrast to i.v. administration of d-amphetamine. Peak concentrations of d-amphetamine were also lower for all doses of LDX relative to equivalent doses of immediate-release d-amphetamine. The pharmacokinetic findings with LDX may be a consequence of the rate-limited conversion of the prodrug to active d-amphetamine.

A relationship could be observed between the peak plasma d-amphetamine levels and maximum change in abuse-related liking measures for d-amphetamine sulphate with peaks for both plasma amphetamine concentrations and pharmacodynamic effects 15 min after drug administration. These included significant euphoric responses (Liking Scales and MBG Scales), amphetamine-like subjective effects (AS and BG Scales) and cardiovascular effects (systolic blood pressure increase). In comparison, the changes in systolic blood pressure

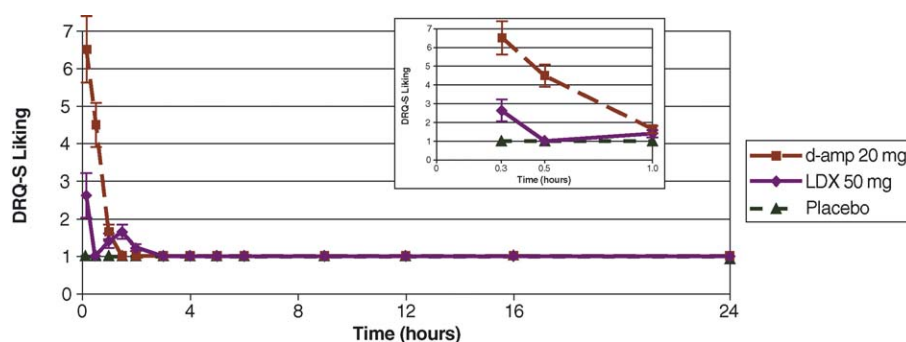


Figure 2 Mean peak liking effects over time. The primary measure of abuse liability was the Drug Rating Questionnaire–Subject (DRQS) Liking scale, which is a visual analogue scale (1-to-29 scale, with 1 being ‘not at all’ and 29 ‘an awful lot’). DRQS Liking was assessed before dosing and again at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 16 and 24 h after intravenous administration.

with LDX are not only attenuated (have a less initial increase), but the time to peak effect was approximately 2–3 h postadministration when compared with the effects of d-amphetamine (Figure 3). Therefore, the relationship between peak plasma d-amphetamine levels and maximum change in pharmacodynamic effects for LDX may be related to the unique prodrug nature of LDX.

In contrast to extended-release stimulants, which commonly contain immediate-release stimulant in their formulations,

LDX does not. LDX is a prodrug consisting of lisdexamfetamine and inert excipients. No d-amphetamine exists in LDX capsules, and d-amphetamine will not become available through mechanical manipulation, such as crushing. A relatively sophisticated biochemical process is needed to obtain d-amphetamine from LDX.

The human pharmacology findings from this study suggest that LDX, when administered intravenously to doses as high as 50 mg, lacked the dose-related reinforcing and euphoric effects

Table 5 Maximum mean change in ARCI measures from predose (primary cohort, $N = 9$)

Drug	Mean	Standard error	95% CI (LB, UB)
1) Morphine Benzidine Group Scale			
Placebo	0.0	1.2	(–2.5, 2.5)
d-Amphetamine 20 mg	3.9*	1.2	(1.4, 6.4)
LDX 50 mg	3.0	1.2	(0.5, 5.5)
2) Benzidine Group Scale			
Placebo	4.0	0.6	(2.7, 5.3)
d-Amphetamine 20 mg	6.6*	0.6	(5.2, 7.9)
LDX 50 mg	5.7	0.6	(4.3, 7.0)
3) Amphetamine Scale			
Placebo	0.0	0.8	(–1.7, 1.7)
d-Amphetamine 20 mg	2.9*	0.8	(1.2, 4.6)
LDX 50 mg	1.8	0.8	(0.1, 3.5)
4) LSD Scale			
Placebo	4.0	0.7	(2.5, 5.5)
d-Amphetamine 20 mg	4.8	0.7	(3.3, 6.3)
LDX 50 mg	5.2	0.7	(3.7, 6.7)
5) PCAG Scale			
Placebo	4.0	0.6	(2.6, 5.4)
d-Amphetamine 20 mg	4.1	0.6	(2.7, 5.5)
LDX 50 mg	5.2	0.6	(3.9, 6.6)

* $P < 0.05$ compared with placebo.

Abbreviations: ARCI, Addiction Research Center Inventory; LB, lower bound; UB, upper bound; LDX, lisdexamfetamine dimesylate; LSD, Lysergic Acid Diethylamide; PCAG, Phenobarbital-Chlorpromazine-Alcohol Group.

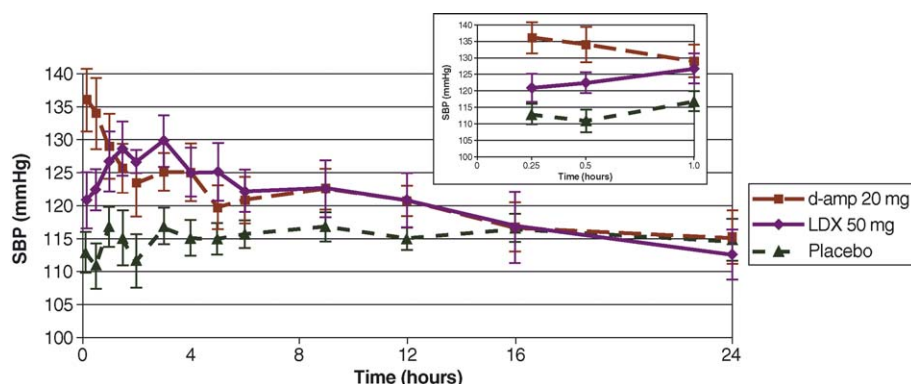


Figure 3 Change in systolic blood pressure over time. Vital signs were assessed before dosing and again at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 16 and 24 h after dosing.

observed with d-amphetamine. This finding, coupled with the difficulty of extracting d-amphetamine from the product, suggests that LDX may have less potential for abuse through i.v. routes compared with other stimulants currently available.

The limitations of this study include enrolment of men only. Additionally, because LDX dissolved in unbuffered solution has an acidic pH (Shojaei, *et al.*, 2007), it is possible that subjects may have detected the administration of LDX, compromising the blinding of the study. This may also have been responsible for the effects of placebo.

In conclusion, LDX administered intravenously did not produce significant subjective abuse-related liking scores at assessed doses, which was the primary measure of abuse liability in this study. In contrast, d-amphetamine did produce significant abuse-related liability when compared with placebo. These findings may be related specifically to the prodrug nature and the unique pharmacokinetic profile of LDX.

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