

Lisdexamfetamine Dimesylate: Prodrug Delivery, Amphetamine Exposure and Duration of Efficacy

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Published online: 28 March 2016

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Abstract Lisdexamfetamine dimesylate (LDX) is a long-acting *d*-amphetamine prodrug used to treat attention-deficit/hyperactivity disorder (ADHD) in children, adolescents and adults. LDX is hydrolysed in the blood to yield *d*-amphetamine, and the pharmacokinetic profile of *d*-amphetamine following oral administration of LDX has a lower maximum plasma concentration (C_{\max}), extended time to C_{\max} (T_{\max}) and lower inter- and intra-individual variability in exposure compared with the pharmacokinetic profile of an equivalent dose of immediate-release (IR) *d*-amphetamine. The therapeutic action of LDX extends to at least 13 h post-dose in children and 14 h post-dose in adults, longer than that reported for any other long-acting formulation. Drug-liking scores for LDX are lower than for an equivalent dose of IR *d*-amphetamine, which may result from the reduced euphorogenic potential associated with its pharmacokinetic profile. These pharmacokinetic and pharmacodynamic characteristics of LDX may be

beneficial in the management of symptoms in children, adolescents and adults with ADHD.

Key Points

Lisdexamfetamine dimesylate (LDX) is the first, and so far the only, long-acting stimulant in which the active drug is released biochemically in the blood rather than mechanically in the gastrointestinal tract.

The duration of therapeutic action of LDX is longer than that reported for any other long-acting stimulant medication, and extends to at least 13 h post-dose in children and 14 h post-dose in adults with ADHD.

The pharmacokinetic and pharmacodynamic characteristics of LDX may be beneficial in the management of symptoms in children, adolescents and adults with ADHD.

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1 Introduction

The stimulants amphetamine and methylphenidate (MPH) are long-established and effective treatments for attention-deficit/hyperactivity disorder (ADHD) in children, adolescents and adults [1]. The therapeutic effects of immediate-release (IR) formulations, however, wear off within 4–6 h, necessitating repeated dosing to achieve symptom control throughout the day [2–5]. To extend the efficacy of stimulants throughout the day and into the evening following a single morning dose, long-acting stimulants have been

developed [6]. These rely on the gradual and phased release of amphetamine or MPH in the gastrointestinal (GI) tract and, for certain formulations, the duration of action has been reported to extend for up to 12 h post-dose [7].

Lisdexamfetamine dimesylate (LDX) is the first stimulant prodrug [8], and is approved for the treatment of children, adolescents and adults with ADHD in the USA, Canada, Brazil and Australia. In Europe, it is the only available long-acting amphetamine and is approved in selected countries for the treatment of children and adolescents with a clinically inadequate response to MPH. In Denmark, Sweden and the UK, it is also approved for the treatment of adults with ADHD. LDX has also received approval in the USA for the treatment of moderate to severe binge eating disorder in adults [9].

Unlike other long-acting stimulants, the active drug is not released in the GI tract following oral administration. Instead, the pharmacologically inactive parent molecule, consisting of *d*-amphetamine covalently linked to L-lysine (Fig. 1), is rapidly and actively taken up from the small intestine by carrier-mediated active transport [10], probably via the oligopeptide transporter peptide transporter 1

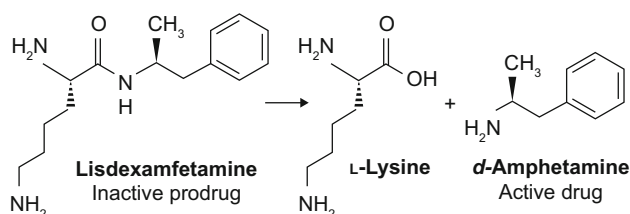
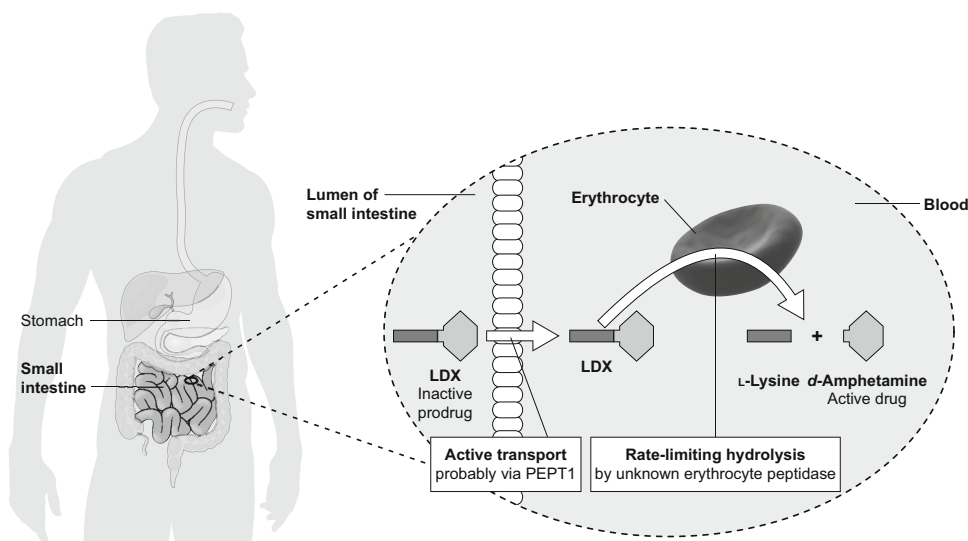


Fig. 1 Chemical structure of LDX and immediate metabolites. In the inactive prodrug LDX, a peptide bond links the amino group of *d*-amphetamine to the carboxyl group of L-lysine. Enzymatic hydrolysis of this bond releases active *d*-amphetamine, and also yields L-lysine as a byproduct. *LDX* lisdexamfetamine dimesylate

Fig. 2 Systemic delivery of *d*-amphetamine by hydrolysis of LDX in the blood. *LDX* lisdexamfetamine dimesylate, *PEPT1* peptide transporter 1



(PEPT1) [11]. Once in the blood, LDX is hydrolysed in erythrocyte cytosol by an unknown aminopeptidase, yielding pharmacologically active *d*-amphetamine (Fig. 2) [11, 12]. The *d*-amphetamine generated from LDX crosses the blood-brain barrier to access binding sites in the central nervous system [13] and to exert therapeutic effects by increasing noradrenergic and dopaminergic neurotransmission. Here, we discuss the relevance of this distinctive mode of action to clinicians and patients by reviewing the pharmacokinetics and pharmacodynamics of *d*-amphetamine delivered by hydrolysis of LDX. Relevant journal articles and clinical studies were identified by searching PubMed and ClinicalTrials.gov for 'lisdexamfetamine' or 'SPD489'.

2 Pharmacokinetics of *d*-Amphetamine Delivered by Hydrolysis of Lisdexamfetamine Dimesylate (LDX)

2.1 Plasma Concentration–Time Profiles for *d*-Amphetamine Following Oral LDX Administration

The pharmacokinetic parameters that describe blood plasma concentration–time profiles and thereby quantify an individual's exposure to LDX or *d*-amphetamine are defined in Table 1.

Figure 3, panels a and b, show the observed blood plasma concentration–time profiles for intact LDX and *d*-amphetamine following oral administration of LDX in children with ADHD ($N = 17$) [14] and healthy adults ($N = 11$) [15], respectively. Tables 2 and 3 summarise published pharmacokinetic parameters for *d*-amphetamine and LDX, respectively, following administration of LDX in

the therapeutic range (30, 50 or 70 mg/day) to children with ADHD, healthy adults and healthy older adults. The mean time to maximum plasma concentration (T_{\max}) is longer for *d*-amphetamine (3.0–4.7 h) than for LDX (1.0–2.1 h), because of the rate-limited hydrolysis of the parent drug. After peaking, plasma LDX concentrations declined rapidly (mean elimination half-life [$t_{1/2}$], 0.4–0.9 h), whereas *d*-amphetamine was cleared more slowly (mean $t_{1/2}$, 8.6–15.0 h). Exposure to *d*-amphetamine (maximum plasma concentration [C_{\max}] and area under the plasma concentration-time curve from zero to infinity [$AUC_{0-\infty}$]) were linearly proportional to LDX dose in children with ADHD within the therapeutic dose range (Table 2; Fig. 3a) [14] and in healthy adults at therapeutic and supratherapeutic doses ($N = 20$) [16].

2.2 Comparison of *d*-Amphetamine Pharmacokinetics Following Oral LDX or Immediate-Release *d*-Amphetamine

Data directly comparing *d*-amphetamine pharmacokinetic profiles following oral administration of LDX or an IR *d*-amphetamine formulation are limited to a single-blind study involving a supratherapeutic dose of LDX in three cohorts of adults with histories of stimulant abuse ($N = 12$). The mean plasma *d*-amphetamine T_{\max} in each cohort occurred 1 h later following administration of LDX 100 mg (range 3.78–4.25 h) than for an equivalent dose of *d*-amphetamine sulfate (40 mg; 1.88–2.74 h) [17], suggesting that the systemic delivery of *d*-amphetamine from LDX is dependent upon the rate-limiting conversion of the parent molecule.

2.3 Consistency of Exposure to *d*-Amphetamine Following LDX Administration

Reliable symptom control by LDX is dependent on predictable and consistent exposure to *d*-amphetamine. Table 2 shows that *d*-amphetamine exposure was generally consistent across studies for a given LDX dose and age group, but that some age-related variability in *d*-amphetamine exposure was apparent. In children with ADHD, both *d*-amphetamine C_{\max} and $AUC_{0-\infty}$ for given doses of LDX were higher than in healthy adults, presumably reflecting differences in body size. Also, in healthy adults aged 55–74 years and 75 years and older, *d*-amphetamine

exposure was higher and $t_{1/2}$ longer than in younger adults. This observation may be explained by a decrease in *d*-amphetamine clearance with age due to reduced renal function [18].

Within-study variability in *d*-amphetamine exposure may be expressed as the percentage coefficient of variation (% CV = [parameter standard deviation/parameter mean] \times 100) for C_{\max} , AUC_{0-t} and $AUC_{0-\infty}$. Percent CVs below 30 are considered to represent low variability [19]. Table 2 shows that % CVs for *d*-amphetamine exposure following doses of LDX were generally low (in the range 12.1–35.7), irrespective of age. In a single-dose study in healthy adults, both intra- and inter-individual % CVs for *d*-amphetamine exposure (log C_{\max} and log $AUC_{0-\infty}$) were low following administration of a wide range of doses of LDX (50–250 mg); all but the 50 mg dose were supratherapeutic [16]. These data indicate that *d*-amphetamine is delivered consistently and predictably following LDX administration. In contrast, within-study inter-individual % CVs for intact LDX exposure were nearly always higher than the equivalent values for *d*-amphetamine (Table 3).

2.4 Gastrointestinal Factors Influencing *d*-Amphetamine Pharmacokinetics Following LDX Administration

Factors that influence a drug's rate of transit through, and uptake from, the GI tract include the presence of food and pH [20–22]. In a single-dose crossover study, Krishnan and Zhang [23] reported that *d*-amphetamine T_{\max} was delayed by approximately 1 h in healthy adults ($N = 18$) administered LDX 70 mg following a high-fat meal compared with those who fasted; there were no significant differences in C_{\max} , $AUC_{0-\infty}$ or $t_{1/2}$ (Table 2; high-fat meal defined in legend). In contrast, while T_{\max} for intact LDX also exhibited a significant delay of approximately 1 h, C_{\max} was significantly lower and $t_{1/2}$ significantly longer in the fed than in the fasted state, although $AUC_{0-\infty}$ was unaffected ($N = 8$) (Table 3) [24]. Following orally administered extended-release mixed amphetamine salts (MAS XR), however, the mean T_{\max} of plasma *d*-amphetamine was reported as approximately 2.5 h longer in fed than in fasted individuals, with C_{\max} and $AUC_{0-\infty}$ modestly lower [21, 22]. These results suggest that LDX hydrolysis, rather than GI transit and uptake, is the dominant factor in

Table 1 Interpreting pharmacokinetic parameters

C_{\max}	Maximum plasma concentration: provides a measure of peak drug exposure
AUC_{0-t}	Area under the plasma concentration–time curve from time zero to another specified time (t): provides a measure of overall drug exposure
T_{\max}	Time to C_{\max} : relevant to speed of onset
$t_{1/2}$	Elimination half-life: relevant to duration of efficacy

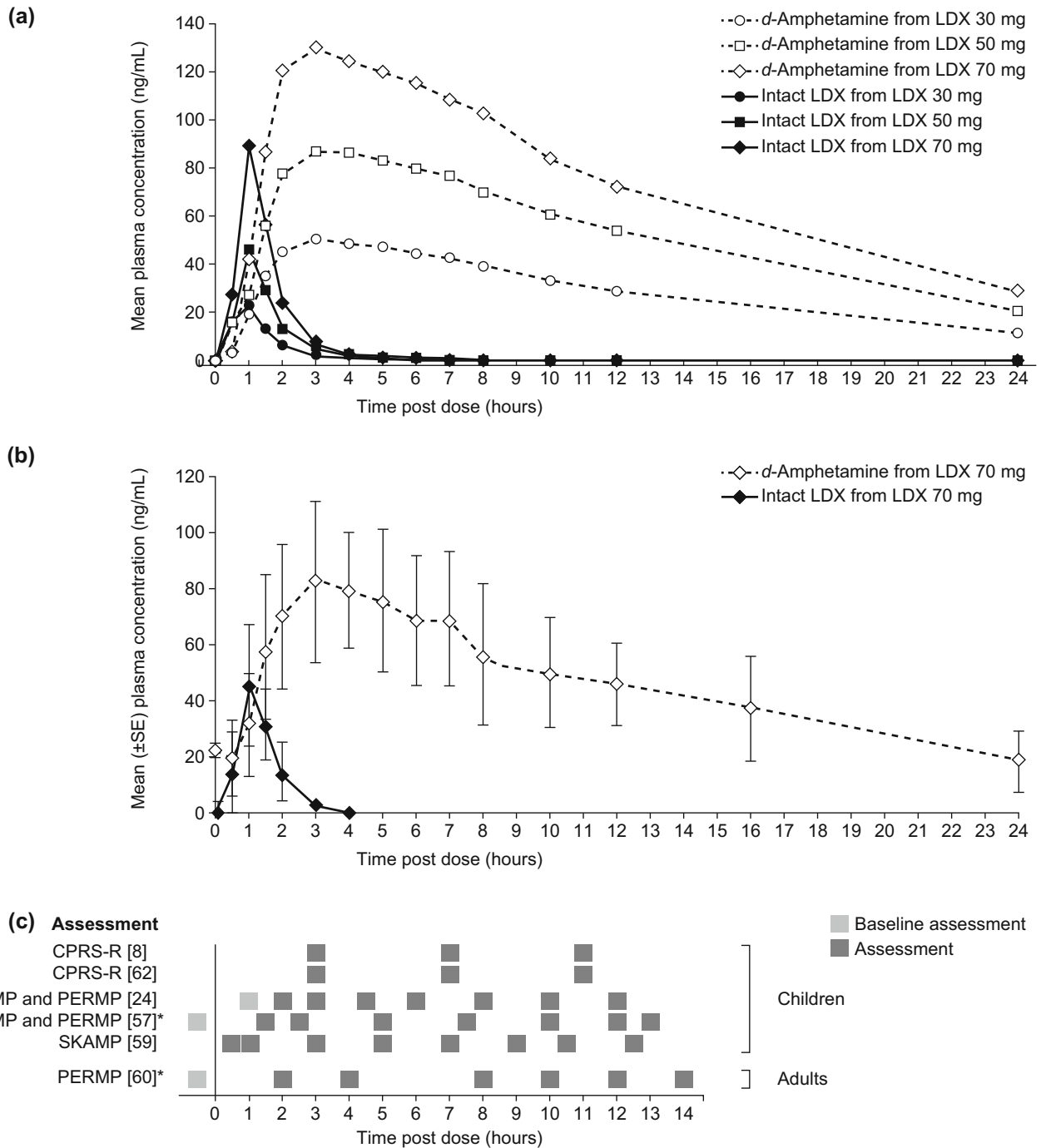


Fig. 3 Pharmacokinetic profiles of plasma LDX and *d*-amphetamine **a** after a single oral dose of LDX in children with ADHD ($N = 17$) [14] (Reproduced from ‘Pharmacokinetics of lisdexamphetamine dimesylate and its active metabolite, *d*-amphetamine, with increasing oral doses of lisdexamphetamine dimesylate in children with attention-deficit/hyperactivity disorder: a single-dose, randomized, open-label, crossover study’, Boellner SW et al. *Clinical Therapeutics* 2010;32:252–64. ©2010 Excerpta Medica Inc. Reproduced with permission from Elsevier), **b** on day 7 of daily oral LDX dosing in healthy adults ($N = 11$) [15] (Krishnan SM and Stark JG, *Current Medical Research and Opinion* 2008;24:33–40, copyright ©2008

Informa Healthcare. Adapted with permission of Informa Healthcare), and **c** timings of symptomatological (SKAMP, CPRS-R) or functional (PERMP) assessments in studies of the efficacy of LDX throughout the day [8, 24, 57, 59, 60, 62]. *Asterisk* Effect sizes for LDX versus placebo in these studies are presented in Fig. 4. Biederman et al. [24] used a post-dose time point as baseline. *ADHD* attention-deficit/hyperactivity disorder, *CPRS-R* Connors’ Parent Rating Scale-Revised, *LDX* lisdexamphetamine dimesylate, *PERMP* Permanent Product Measure of Performance, *SKAMP* Swanson, Kotkin, Agler, M-Flynn, and Pelham

Table 2 Pharmacokinetic parameters of *l*-amphetamine after oral administration of LDX in the therapeutic range

	Alimentation	LDX dose, mg	N	C _{max} , ng/mL			T _{max} , h			AUC ₀₋₄ , ng·h/mL			AUC _{0-∞} , ng·h/mL			t _{1/2} , h		
				Mean (SD)	%	CV	Mean (SD)	%	CV	Mean (SD)	%	CV	Mean (SD)	%	CV	Mean (SD)	%	CV
Children with ADHD (aged 6–12 years), single dose																		
Boellner et al. [14]	Fasted	30	17	53.2 (9.62)	18.1	3.41 (1.09)	31.9	NR	745.3 (129.3)	17.4	48	844.6 (116.7)	13.8	8.90 (1.33)	15			
	Fasted	50	17	93.3 (18.2)	19.5	3.58 (1.18)	33.0	NR	1448.0 (246.7)	17.0	48	1510.0 (241.6)	16.0	8.61 (1.04)	12.1			
	Fasted	70	17	134 (26.1)	19.4	3.46 (1.34)	38.6	NR	2088.0 (394.0)	18.9	48	2157.0 (383.3)	17.8	8.64 (1.32)	15.3			
Biederman et al. [24]	NR	70	8	155 (31.4)	20.3	NR	15.3	4.5 (4.5–6.0)	1326 (285.8)	21.6	12	NR	–	NR	–			
Healthy adults (aged 18–55 years), single dose																		
Ermer et al. [16]	Fasted	50	20	44.6 (9.31)	20.9	NR	NR	4 (1.5–6.0)	763.1 (190.4)	24.9	96	818.1 (194.6)	23.8	11.3 (2.4)	21.0			
Ermer et al. [10, 33]	Fasted	50	18	37.6 (4.54)	12.1	4.4 (0.8)	17.7	5	719.1 (157.05)	21.8	72	776.9 (167.69)	21.6	11.6 (2.8)	24.1			
Haffey et al. [26]	Fasted	50	24	45.0 (13.97)	NR	3.5 (1.14) ^a	NR	3	626.3 (198.98) ^a	NR	96	713.0 (134.75)	NR	9.7 (1.55)	NR			
	Fasted	50 ^b	21	46.3 (9.71)	NR	3.5 (0.97) ^a	NR	3	687.0 (196.91) ^a	NR	96	761.6 (191.13)	NR	10.4 (1.65)	NR			
Roesch et al. [43]	NR	50	41	36.48 (7.13)	NR	4.2 (1.1)	26.2	4 (3–6)	NR	–	–	686.9 (159.8)	NR	11.2 (1.6)	NR			
Krishnan and Zhang [23]	Fasted	70	18	69.3 (14.3)	NR	3.78 (1.01)	26.7	NR	1020 (319.8)	NR	72	1110 (314.2)	NR	9.69 (1.96)	NR			
	Fed ^c	70	18	65.3 (13.4)	NR	4.72 (1.07)	22.7	NR	972 (228.3)	NR	72	1038 (238.6)	NR	9.59 (1.89)	NR			
	Fasted	70 ^d	18	68.4 (14.6)	NR	3.33 (1.19)	35.7	NR	1007 (223.5)	NR	72	1074 (220.8)	NR	9.37 (2.06)	NR			
Krishnan et al. [87]	Fasted	70 ^e	6	80.3 (11.8)	14.6	NR	41.0	3 (2–6)	1260 (219.7)	17.4	120	1342 (216.9)	16.16	10.39 (1.90)	18.3			
Ermer et al. [40]	Fasted	70 ^f	29	74.60 (14.00)	NR	4.4 (1.2)	NR	NR	NR	–	72	1310.3 (191.8)	NR	11.09 (1.68)	NR			
Healthy adults (aged 18–55 years), multiple doses																		
Ermer et al. [28]	Fasted	70 ^g	40	88.9 (26.9)	30.3	3.5 (1.5)	42.9	NR	1143.4 (292.8)	25.6	24	NR	–	10.4 (1.8)	17.3			
Krishnan and Stark [15]	Fasted	70 ^h	11	90.1 (29.6)	32.8	3.0 (1.4)	38.5	3.0 (1.5–7.0)	1110 (397)	35.7	24	NR	–	10.1 (NR)	NR			
Healthy older adults (aged ≥55 years), single dose; Ermer et al. [18]																		
55–64 years, women	NR	50	9	51.0 (6.7)	NR	NR	–	3.5	NR	–	–	1034.5 (154.6)	NR	12.2 (1.9)	NR			
55–64 years, men	NR	50	8	44.2 (11.1)	NR	NR	–	4.5	NR	–	–	915.0 (164.9)	NR	12.8 (2.9)	NR			
65–74 years, women	NR	50	8	50.2 (6.8)	NR	NR	–	4.1	NR	–	–	988.4 (80.5)	NR	12.8 (1.9)	NR			
65–74 years, men	NR	50	8	47.7 (7.0)	NR	NR	–	3.5	NR	–	–	1123.0 (227.0)	NR	15.0 (2.8)	NR			
≥75 years, women	NR	50	6	64.3 (12.1)	NR	NR	–	5.5	NR	–	–	1347.8 (198.9)	NR	13.3 (2.5)	NR			

Table 2 continued

Alimentation	LDX dose, mg	N	C _{max} , ng/mL		T _{max} , h		AUC _{0-t} , ng·h/mL		AUC _{0-∞} , ng·h/mL		t _{1/2} , h		
			Mean (SD)	% CV	Mean (SD)	% CV	Mean (SD)	% CV	Mean (SD)	% CV	Mean (SD)	% CV	
≥75 years, men	NR	8	53.4 (19.4)	NR	NR	5.5	NR	NR	NR	1325.0 (464.4)	NR	14.3 (3.4)	NR

ADHD attention-deficit/hyperactivity disorder, AUC_{0-∞} area under the plasma concentration-time curve from time 0 to infinity, AUC_{0-t} area under the plasma concentration-time curve from time 0 to the last sampling time at which the analyte was measurable, C_{max} maximum plasma concentration, CV coefficient of variation, LDX lisdexamfetamine dimesylate, NR not reported, SD standard deviation, t last sampling time in the study, t_{1/2} elimination half-life, T_{max} time to C_{max}

^a Data from ClinicalTrials.gov, NLM identifier: NCT00746733 [88]

^b Co-administered with oral omeprazole 40 mg

^c The high-fat meal used in this study consisted of 1 English muffin with butter, 1 fried egg, 1 slice of American cheese, 1 slice of Canadian bacon, 2 oz (57 g) of hash brown potatoes, and 8 fl oz (240 mL) of whole milk

^d Oral solution

^e Radiolabelled oral solution

^f Co-administered with oral Cooperstown cocktail: caffeine 200 mg, dextromethorphan 30 mg, omeprazole 40 mg, midazolam 0.025 mg/kg

^g Fifth day of administration

^h Seventh day of administration

determining the *d*-amphetamine exposure profile following oral administration of LDX.

GI disorders, including ulcers and dyspepsia, are commonly treated using proton pump inhibitors, such as omeprazole, to suppress acid secretion by the stomach mucosa and thereby increase the pH. The inhibition of gastric acid secretion may, however, interfere with the absorption of drugs for which pH is an important determinant of bioavailability [25], such as MAS XR which uses pH-sensitive beaded technology to achieve phased release. Haffey et al. [26] reported that the median T_{max} for total amphetamine was approximately 2 h shorter in healthy adults when MAS XR was co-administered with omeprazole (T_{max}, 2.75 h) than when administered alone (T_{max}, 5 h) (N = 24). In the same study, *d*-amphetamine pharmacokinetic parameters remained largely unaltered when LDX was co-administered with oral omeprazole (Table 2). Thus, these results indicate that, unlike MAS XR, LDX provided an amphetamine exposure profile that was unaffected by administration of a proton pump inhibitor.

LDX is soluble in water [9] and can, therefore, be administered as a solution or mixed into food to individuals who experience difficulty in swallowing capsules, or in circumstances when the monitoring of drug consumption is a requirement. This differs from other long-acting stimulant formulations which rely on mechanical phased release of the active drug from a capsule. In another study (NCT01890785), similar values of *d*-amphetamine C_{max} and AUC_{0-96h} were seen when oral LDX 70 mg was administered to healthy adults as capsules, or capsule contents were dissolved in orange juice or mixed into vanilla yogurt [27]; in addition administration with yogurt delayed T_{max} by only 0.4 h compared with the fasted state [9].

To summarise, the above LDX single-dose studies suggest that the hydrolysis of LDX to *d*-amphetamine in the blood is the rate-limiting step, rather than the uptake of the parent drug from the GI tract. This leads to consistent intra- and inter-individual *d*-amphetamine exposure profiles.

2.5 Multiple Once-Daily Dosing of LDX

In a study of multiple once-daily dosing of LDX 70 mg in healthy adults, Krishnan and Stark [15] observed that steady-state plasma *d*-amphetamine concentrations were achieved by day five [15, 28]. At steady state, pre-dose plasma *d*-amphetamine concentrations were approximately 20 ng/mL, and C_{max} following each daily dose was approximately 90 ng/mL (Fig. 3b), moderately higher than following a single 70 mg dose in adults (Table 2) [15]. The values for *d*-amphetamine T_{max}, t_{1/2} and AUC_{0-∞} were similar following a single dose of LDX, regardless of

Table 3 Pharmacokinetic parameters of intact LDX after oral administration of LDX in the therapeutic range

	Alimentation	LDX dose, mg	N	C _{max} , ng/mL		T _{max} , h		AUC _{0-t} , ng·h/mL		AUC _{0-∞} , ng·h/mL		t _{1/2} , h			
				Mean (SD)	% CV	Mean (SD)	% CV	Mean (SD)	% CV	Mean (SD)	% CV	Mean (SD)	% CV		
Children with ADHD (aged 6–12 years), single dose															
Boellner et al. [14]	Fasted	30	17	21.9 (5.97)	27.3	0.97 (0.14)	14.4	NR	25.54 (8.37)	32.8	48	27.88 (9.29)	33.3	0.50 (0.19)	37.9
	Fasted	50	17	46.0 (20.7)	44.9	0.98 (0.06)	6.2	NR	56.20 (21.51)	38.3	48	57.90 (21.03)	36.3	0.60 (0.44)	72.8
	Fasted	70	17	89.5 (38.5)	43.0	1.07 (0.17)	16.3	NR	107.4 (50.25)	46.8	48	108.90 (50.46)	46.3	0.51 (0.19)	37.6
Biederman et al. [24]	NR	70	8	NR	-	NR	-	NR	NR	-	-	NR	-	NR	-
Healthy adults (aged 18–55 years), single dose															
Ermer et al. [16]	Fasted	50	20	25.6 (13.16)	51.4	NR	-	1 (1–2)	28.1 (16.1)	57.3	96	62.1 (31.4)	NR	0.6 (0.1)	16.7
Ermer et al. [10, 33]	Fasted	50	18	19.8 (5.6)	28.3	1.2 (0.4)	28.9	1.0	23.4 (7.46)	31.8	72	25.2 (7.21)	28.6	NR	-
Haffey et al. [26]	Fasted	50	24	NR	-	NR	-	NR	NR	-	-	NR	-	NR	-
Roesch et al. [43]	NR	50	41	NR	-	NR	-	NR	NR	-	-	NR	-	NR	-
Krishnan and Zhang [23]	Fasted	70	18	48.0 (23.8)	NR	1.15 (0.28)	24.3	NR	59.47 (24.85)	NR	72	66.84	NR	0.41 (0.07)	NR
	Fed ^a	70	18	26.2 (11.9)	NR	2.08 (0.65)	31.3	NR	53.68 (17.72)	NR	72	58.81	NR	0.63 (0.20)	NR
	Fasted	70 ^b	18	46.5 (17.0)	NR	0.97 (0.27)	27.8	NR	53.07 (16.56)	NR	72	55.10	NR	0.44 (0.10)	NR
Krishnan et al. [87]	Fasted	70 ^c	6	58.2 (28.1)	48.36	NR	99.69	1.0 (0.5–4.0)	70.21 (19.80)	28.19	120	67.04 (18.94)	28.26	0.47 (0.16)	34.58
Ermer et al. [40]	Fasted	70 ^d	29	43.88 (17.96)	NR	1.5 (0.7)	NR	NR	NR	-	72	62.0 (21.4) ^e	NR	0.56 (0.26) ^e	NR
Healthy adults (aged 18–55 years), multiple doses															
Ermer et al. [28]	Fasted	70 ^f	40	49.1 (32.25)	65.7	1.1 (0.3)	27.3	NR	65.5 (44.0)	67.2	24	NR	-	0.4 (0.1)	25.0
Krishnan and Stark [15]	Fasted	70 ^g	11	47.9 (18.6)	38.8	1.0 (0.3)	28.5	1 (1–2)	60.7 (21.0)	34.6	24	NR	-	0.4 (NR)	NR
Healthy older adults (aged ≥55 years), single dose; Ermer et al. [18]															
55–64 years, women	NR	50	9	41.3 (11.6)	NR	NR	-	1.0	NR	-	-	43.8 (10.4)	NR	0.5 (0.1)	NR
55–64 years, men	NR	50	8	24.7 (9.8)	NR	NR	-	1.5	NR	-	-	35.3 (9.8)	NR	0.6 (0.2)	NR
65–74 years, women	NR	50	8	27.5 (13.0)	NR	NR	-	1.5	NR	-	-	28.5 (8.3)	NR	0.9 (1.1)	NR
65–74 years, men	NR	50	8	33.6 (8.5)	NR	NR	-	1.0	NR	-	-	38.7 (14.2)	NR	0.6 (0.4)	NR
≥75 years, women	NR	50	6	43.0 (17.1)	NR	NR	-	1.8	NR	-	-	51.9 (18.9)	NR	0.7 (0.4)	NR

Table 3 continued

Alimentation	LDX dose, mg	N	C_{\max} , ng/mL		T_{\max} , h		AUC_{0-t} , ng·h/mL		$AUC_{0-\infty}$, ng·h/mL		$t_{1/2}$, h	
			Mean (SD)	% CV	Mean (SD)	% CV	Mean (SD)	% CV	Mean (SD)	% CV	Mean (SD)	% CV
NR	50	8	25.4 (14.0)	NR	NR	1.8	NR	NR	37.6 (13.3)	NR	0.7 (0.2)	NR

ADHD attention-deficit/hyperactivity disorder, $AUC_{0-\infty}$ area under the plasma concentration-time curve from time 0 to infinity, AUC_{0-t} area under the plasma concentration-time curve from time 0 to the last sampling time at which the analyte was measurable, C_{\max} maximum plasma concentration, CV coefficient of variation, LDX lisdexamfetamine dimesylate, *NR* not reported, *SD* standard deviation, t last sampling time in the study, $t_{1/2}$ elimination half-life, T_{\max} time to C_{\max}

^a The high-fat meal used in this study consisted of 1 English muffin with butter, 1 fried egg, 1 slice of American cheese, 1 slice of Canadian bacon, 2 oz (57 g) of hash brown potatoes, and 8 fl oz (240 mL) of whole milk

^b Oral solution

^c Radiolabelled oral solution

^d Co-administered with oral Cooperstown cocktail: caffeine 200 mg, dextromethorphan 30 mg, omeprazole 40 mg, midazolam 0.025 mg/kg

^e $N = 16$

^f Fifth day of administration

^g Seventh day of administration

whether steady state had previously been reached (Table 2). These results suggest that *d*-amphetamine exposure reaches therapeutic levels after a single dose of LDX and that systemic concentrations of *d*-amphetamine do not markedly increase with multiple once-daily dosing.

2.6 Effect of Route of Administration of LDX or Immediate-Release *d*-Amphetamine on Plasma *d*-Amphetamine Pharmacokinetics

The abuse of stimulants often involves intranasal or intravenous administration to shorten stimulant blood plasma T_{\max} and increase C_{\max} , thereby enhancing the euphoric potential [29–31]. The pharmacokinetics of intravenous LDX compared with intravenous *d*-amphetamine were evaluated in a single-dose, crossover study in adults with a history of stimulant abuse ($N = 9$). Mean (SD) *d*-amphetamine T_{\max} was shorter and C_{\max} higher following intravenous IR *d*-amphetamine (20 mg; T_{\max} , 0.8 h [1.3]; C_{\max} , 105 ng/mL [91.4]) than after an equivalent dose of intravenous LDX (50 mg; T_{\max} , 2.5 h [1.5]; C_{\max} , 38.9 ng/mL [8.1]) [32]. This more gradual approach to a lower peak plasma *d*-amphetamine concentration for LDX compared with IR *d*-amphetamine presumably resulted from rate-limited hydrolysis of the prodrug in the blood. The impact of the route of administration was further explored in a single-dose, crossover study in healthy adults, which found no difference in *d*-amphetamine pharmacokinetics following oral and intranasal administration of LDX 50 mg ($N = 18$) (Table 4) [33].

2.7 Impact of Compromised Erythrocytes and Haematocrit Level on the Generation of *d*-Amphetamine from LDX

The effects on LDX metabolism of moderately compromised erythrocytes and low haematocrit have been investigated in vitro. The rate of LDX hydrolysis was similar in blood from donors with or without sickle cell disease [34]. Furthermore, the rate of LDX hydrolysis was haematocrit-dependent, but substantial *d*-amphetamine production was still observed at 10 % of normal haematocrit [11]. These results suggest that LDX biotransformation is unaffected by clinically relevant variations in erythrocyte viability and levels [11, 34].

2.8 Potential for Drug–Drug Interactions

In vitro evidence indicates that LDX itself does not interact with the major cytochrome P450 (CYP) isoforms commonly inhibited or induced by therapeutic drugs (CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 3A4/5 [35] and 2C8 [36]), and does not inhibit or act as a substrate for human

Table 4 Pharmacokinetic parameters of *d*-amphetamine and intact LDX in studies using parenteral routes of LDX administration

	Route	Dose, mg	N	C _{max} , ng/mL		T _{max} , h		AUC _{0-t} , ng·h/mL		AUC _{0-∞} , ng·h/mL		t _{1/2} , h			
				Mean (SD)	% CV	Mean (SD)	% CV	Mean (SD)	Median	Mean (SD)	t, h	Mean (SD)	% CV	Mean (SD)	% CV
<i>d</i> -Amphetamine															
Jasinski and Krishnan [32]	Intravenous	50	9	38.9 (8.1)	20.8	2.5 (1.5)	58.6	NR	562.7 (115.5)	20.5	24	NR	-	NR	-
Ermer et al. [33]	Intranasal	50	18	35.9 (6.49)	18.1	4.8 (1.2)	24.3	5	690.5 (157.05)	22.7	72	746.2 (171.58)	23.0	11.3 (1.8)	15.9
	Oral ^a	50	18	37.6 (4.54)	12.1	4.4 (0.8)	17.7	4	719.1 (157.05)	21.8	72	776.9 (167.69)	21.6	11.6 (2.8)	24.1
LDX															
Jasinski and Krishnan [32]	Intravenous	50	9	NR	-	NR	-	NR	NR	-	-	NR	-	NR	-
Ermer et al. [33]	Intranasal	50	18	50.4 (34.65)	68.8	0.5 (0.5)	116.1	0.2	48.3 (16.39)	33.9	72	49.3 (16.40)	33.3	NR	-
	Oral ^a	50	18	19.8 (5.6)	28.3	1.2 (0.4)	28.9	1	23.4 (7.46)	31.8	72	25.2 (7.21)	28.6	NR	-

AUC_{0-∞} area under the plasma concentration-time curve from time 0 to infinity, AUC_{0-t} area under the plasma concentration-time curve from time 0 to the last sampling time at which the analyte was measurable, C_{max} maximum plasma concentration, CV coefficient of variation, LDX lisdexamfetamine dimesylate, NR not reported, SD standard deviation, t last sampling time in the study, t_{1/2} elimination half-life, T_{max} time to C_{max}

^a Data are also presented in Tables 2 and 3

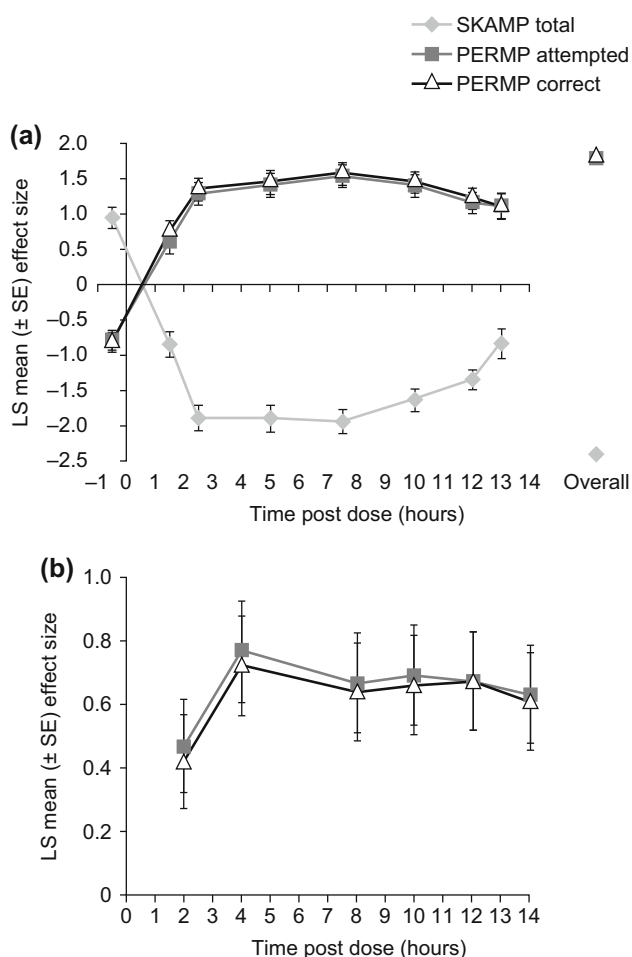


Fig. 4 Analyses of the effect sizes of LDX versus placebo in **a** children with ADHD in an analogue classroom study (post-hoc) [58] and **b** adults with ADHD in a model workplace study [61] (Effect size of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder, Wigal T et al. Postgraduate Medicine 2011 123:169–76, Informa Healthcare. Reprinted by permission of the publisher Informa healthcare <http://informahealthcare.com/>) LDX demonstrated significant improvement versus placebo, by effect size, at all post-dose time points in both studies. For PERMP, positive effect sizes indicate superiority over placebo; for SKAMP, negative effect sizes indicate superiority over placebo. ADHD attention-deficit/hyperactivity disorder, LS least-squares, SE standard error, SEM standard error of the mean, SKAMP Swanson, Kotkin, Agler, M-Flynn, and Pelham, PERMP Permanent Product Measure of Performance

P-glycoprotein [36]. Other in vitro studies suggest that amphetamine weakly inhibits CYP2D6 [37] and 2A6 [38], and that its metabolites weakly inhibit CYP2D6, 1A2 and 3A4 [39].

In an in vivo study designed to investigate whether LDX affects the activity of CYP isoforms, the following drugs were administered to healthy individuals in the form of a Cooperstown cocktail with or without LDX: caffeine (a CYP1A2 substrate), dextromethorphan (a CYP2D6 substrate), midazolam (a CYP3A substrate) and omeprazole

(the proton pump inhibitor described in the ‘gastrointestinal factors’ section and a CYP2C19 substrate). The pharmacokinetic profiles of *d*-amphetamine and LDX were similar to those observed in other studies (Tables 2, 3). Furthermore, LDX had no effect on the activity of CYP1A2, 2D6 or 3A as determined by the C_{max} and $AUC_{0-\infty}$ of their respective substrates. For omeprazole a small decrease in C_{max} was observed, possibly indicating that LDX may have an effect either on CYP2C19 activity or on omeprazole absorption [40].

In vivo, co-administration of LDX with extended-release guanfacine, an α_2 -adrenoreceptor agonist that is approved in the USA [41] and Canada [42] for treatment of ADHD in combination with psychostimulants (and is a CYP3A4 substrate), led to no clinically meaningful difference in *d*-amphetamine or guanfacine pharmacokinetic profiles [43]. When LDX was co-administered with venlafaxine, a serotonin-noradrenaline reuptake inhibitor that is predominantly metabolised by CYP2D6 [44], there was no change in *d*-amphetamine pharmacokinetics. Although a small decrease in exposure to *O*-desmethylvenlafaxine (the active metabolite of venlafaxine) was observed, total exposure to venlafaxine plus *O*-desmethylvenlafaxine was unaffected [28].

3 Pharmacodynamics of *d*-Amphetamine Delivered by Hydrolysis of LDX

3.1 Efficacy Throughout the Day Following an Early-Morning Dose of LDX

The pharmacokinetics of *d*-amphetamine delivered by hydrolysis of LDX are reflected in the duration of the therapeutic action following an early-morning dose of LDX. Although the shorter *d*-amphetamine T_{max} for IR amphetamine compared with LDX leads to more rapid initial symptom control, the therapeutic effects of IR amphetamine and IR MAS do not extend beyond 4–6 h in children with ADHD [2–5, 45] or hyperkinetic disorder [46, 47]. This necessitates multiple daily doses of IR amphetamine or IR MAS to extend symptom control into the afternoon and evening [2].

Extended-release formulations have been developed to provide prolonged drug delivery [3, 48–55]. To date, LDX is the only prodrug ADHD medication, the only long-acting stimulant that does not rely on mechanical phased release, and the only stimulant for which efficacy in treating the symptoms of ADHD has been demonstrated beyond 12 h post-dose [56]. The duration of action of LDX following an early-morning dose has been evaluated in a series of model environment studies and phase III clinical trials conducted in children, adolescents and adults with

ADHD. Figure 3 illustrates how the timings of efficacy assessments in these studies (Fig. 3c) relate to the pharmacokinetic profiles of intact LDX and *d*-amphetamine following a single dose of LDX 30, 50 and 70 mg (Fig. 3a) or after the last of seven daily doses of LDX 70 mg (Fig. 3b).

Two randomised, double-blind, placebo-controlled, crossover analogue classroom studies in children (aged 6–12 years) with ADHD have studied changes in scores on the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) and Permanent Product Measure of Performance (PERMP) scales. In the first study ($N = 117$), dose-optimised LDX led to marked, sustained and statistically significant ($p < .005$) improvements in the SKAMP Department and Attention subscale scores and PERMP scale scores from 1.5 h to at least 13 h post-dose (last assessment) compared with placebo [57]. Post hoc analyses showed that effect sizes in favour of LDX over placebo remained large from 2.5 h until at least 13 h post-dose (range 0.84–1.11) for SKAMP total and PERMP Attempted and Correct scores (Fig. 4a) [58]. In the second classroom study ($N = 52$), significant ($p < .001$) improvements compared with placebo in SKAMP Department and Attention subscale scores and PERMP Attempted and Correct scores were maintained for 12 h (last assessment) after an optimised dose of LDX [24]. Additionally, a summer camp study in children with ADHD ($N = 25$) investigated the relative effectiveness of dose-optimised LDX, intensive behavioural intervention and a combination of both treatments. Compared with intensive behavioural intervention alone, the overall magnitude of changes in SKAMP scores were large for both LDX alone (effect size, 1.16) and combined treatment (effect size, 1.14), and the benefits were maintained until the last assessment (12.5 h post-dose) [59].

The duration of action of LDX in adults with ADHD was evaluated in a randomised, double-blind, placebo-controlled, crossover study in a simulated workplace environment ($N = 127$). Compared with placebo, both absolute ($p \leq .0017$) and change from baseline ($p < .001$) PERMP total scores were significantly improved at all post-dose assessments from 2 to 14 h [60]. Medium-to-large least-squares mean model-based effect sizes for PERMP Attention and Correct scores were maintained for up to 14 h after LDX administration (Fig. 4b) [61].

Two randomised, double-blind, phase III clinical trials have used the Conners' Parent Rating Scale-Revised (CPRS-R) to assess the duration of therapeutic response in children and adolescents (6–17 years) with ADHD. Although the range of post-dose assessment time points was not as extensive as in the model environment studies and the outcomes relied on parent/caregiver reports rather than direct observations, these phase III clinical trials

enrolled large patient numbers and provide robust data. At endpoint in a 7-week, dose-optimised, European trial in children and adolescents with ADHD ($N = 336$), differences between LDX and placebo in least-squares mean change from baseline in CPRS-R total score were statistically significant ($p < .001$) at 10 am, 2 pm and 6 pm following an early-morning dose (approximately 7 am), with effect sizes maintained in the range 1.30–1.42 [62]. Similarly, in a 4-week, fixed-dose, US trial in children (6–12 years) with ADHD ($N = 290$), the reductions in CPRS-R scores were significantly greater for LDX 30, 50 and 70 mg than for placebo at all three assessment times ($p < .001$) [8].

3.2 Safety

The safety profile of LDX, including treatment-emergent adverse events (TEAEs), vital sign changes and laboratory signs is consistent with the known safety profile of stimulants used in the treatment of ADHD, and has been recently reviewed [63]. Here we further review in greater detail two safety concerns associated with stimulants that are particularly pertinent to the pharmacokinetic and pharmacodynamic characteristics of LDX: effects on sleep and the potential for abuse, misuse and diversion as determined by drug-liking scores.

3.2.1 Effect of LDX on Sleep

Sleep-related TEAEs are a consistent finding in clinical trials of stimulant medications in individuals of all ages with ADHD [64, 65]. With the duration of efficacy of LDX extending at least into the evening, the effect on sleep-related TEAEs is of clinical interest, although the proportion of patients who experience TEAEs during a clinical study does not provide information about the time of onset or the duration of the TEAE. The incidence of insomnia as a TEAE in short-term, randomised, double-blind, parallel-group, phase III clinical trials of LDX ranges from 11.2 to 18.8 % in children and/or adolescents [8, 66–68], and from 12.7 to 19.3 % in adults [69, 70], compared with rates of 4.8 % or below in individuals receiving placebo. In longer-term safety and efficacy extension studies of at least 6 months' duration, the incidence of insomnia as a TEAE in individuals with ADHD who were receiving LDX was similar to that in the short-term trials: 17.3 % in children [71], 12.1 % in adolescents [72], 14.1 % in children and adolescents [73], and 19.5 % in adults [74].

The relationships between stimulant treatment, the incidence of sleep-related TEAEs, and sleep disturbance are not, however, straightforward because ADHD itself is associated with disturbance of sleep [75–77], which may be exacerbated in the evening if the efficacy of medication

wanes [64, 65, 78]. In a short-term, phase III trial in adults with ADHD, despite sleep-related TEAEs being reported by a higher proportion of individuals receiving LDX (109/358, 30.4 %) than by those taking placebo (9/62, 14.5 %), there was no difference at endpoint in the mean global Pittsburgh Sleep Quality Instrument (PSQI) score, a subjective assessment of sleep quality, among those reporting sleep-related TEAEs. Indeed, significant improvements were observed in the LDX group compared with the placebo group in one of the PSQI components (daytime functioning, $p = .0001$), leading the authors to caution against relying on self-reported TEAEs alone as an indication of the effect of stimulant medications on sleep [79]. In a post hoc analysis of this study, a greater proportion of individuals in the LDX group (20.9 %) than in the placebo group (8.2 %) demonstrated better sleep at endpoint than at baseline, and the relationship between treatment group and endpoint PSQI score was statistically significant ($p = .03$) [80]. Furthermore, the relationship between clinically meaningful improvements in the symptoms of ADHD (defined as Clinical Global Impressions-Improvement [CGI-I] scores of 1 or 2) and improved sleep (i.e. decreased PSQI scores) was statistically significant ($p = .0008$) [80]. In a laboratory sleep study [81], children (6–12 years) with ADHD ($N = 24$) were randomised (2:1) to receive an optimal dose of LDX (30, 50 or 70 mg based on therapeutic response during a 3-week open-label dose-optimisation period) or placebo. This study found no difference between individuals treated with LDX and those who received placebo in the polysomnographic assessments of latency to persistent sleep, wake time after sleep onset or total sleep time, but the number of awakenings after sleep was significantly decreased in those receiving LDX compared with participants who received placebo ($p < .0001$) [81].

3.2.2 Drug-Liking Scores for LDX Compared with Immediate-Release Amphetamine

Drug-liking scores for LDX and IR *d*-amphetamine have been compared following oral and intravenous administration. On the primary measure of abuse liability in a double-blind, randomised, placebo-controlled, crossover study in individuals with a history of stimulant abuse ($N = 36$), the maximum change of the Drug Rating Questionnaire-Subject (DRQS) Liking scale score was not significantly different from placebo for oral LDX 50 and 100 mg, but was significant ($p < .001$) at the supratherapeutic dose of 150 mg. In addition, participants significantly favoured oral IR *d*-amphetamine 40 mg over an equivalent oral dose of LDX (100 mg, $p < .05$) but not LDX 150 mg. Furthermore, mean peak DRQS Liking scale scores for LDX were observed approximately 3 h (LDX 50

and 100 mg) or 4 h (LDX 150 mg) post-dose compared with 1.5–2 h post-dose for *d*-amphetamine 40 mg [82].

In a second double-blind, randomised, placebo-controlled, crossover study conducted in individuals with a history of intravenous drug abuse ($N = 9$), maximum mean change in DRQS Liking scale scores for intravenous *d*-amphetamine 20 mg (5.6 [standard error, 1.3]) was significantly ($p = .01$) different from placebo (0.0 [1.3]), whereas scores for an equivalent intravenous dose of LDX 50 mg (2.1 [1.3]) did not differ from those for placebo ($p = .290$) [32].

A post hoc analysis of these two drug-liking studies revealed that the subjective effects of LDX were not statistically significantly different when the drug was administered orally versus intravenously, in keeping with the broadly similar *d*-amphetamine pharmacokinetic profiles generated by LDX following oral and intravenous administration. In contrast, the subjective effects of IR amphetamine are both larger and more rapid in onset when administered intravenously than when administered orally [30]. These results, presumably reflecting the delayed T_{\max} and lower C_{\max} of the *d*-amphetamine pharmacokinetic profile, suggest that LDX may have a lower abuse potential than IR *d*-amphetamine.

Real-world data from a retrospective, observational case series of single-substance exposures to LDX (7,113 cases), dextroamphetamine/amphetamine IR (10,195 cases) or dextroamphetamine/amphetamine XR (6245 cases) is suggestive of a lower potential for abuse/misuse of LDX [83]. The study reports the odds of abuse/misuse was 2.3 (95 % confidence interval [CI] 2.0–2.4) times higher for dextroamphetamine/amphetamine IR than that for LDX and dextroamphetamine/amphetamine XR combined. The odds of abuse/misuse of dextroamphetamine/amphetamine XR was 1.9 (95 % CI 1.7–2.2) times higher than lisdexamfetamine.

3.3 Why Might the Daily Duration of Efficacy of LDX Exceed that of Immediate-Release Amphetamine?

Regardless of whether *d*-amphetamine is delivered via oral LDX or an IR formulation, the plasma *d*-amphetamine $t_{1/2}$ is approximately 10 h, and the $AUC_{0-\infty}$ is roughly similar for equivalent doses [2, 21, 26, 39, 84]. This raises the question of why the daily therapeutic duration of action of LDX is at least threefold that of IR amphetamine. The explanation may lie in the fact that the rate of increase in plasma *d*-amphetamine concentration is less steep (i.e. T_{\max} is longer) and C_{\max} is lower following oral administration of LDX compared with IR amphetamine [85], which suggests that acute tolerance (tachyphylaxis) could be a factor.

Acute tolerance may be defined as a reduction in response to a drug over the course of a single exposure. In other words, for a given drug plasma concentration, therapeutic effects (and side effects) are greater when the drug plasma concentration is rising than when it subsequently declines. In terms of ADHD medication, acute tolerance to MPH has been observed, and understanding this phenomenon has led to improvements in long-acting formulations to treat ADHD [48–51, 54, 55]. Specifically, Swanson et al. [48] reported that a second bolus of MPH was less effective when given in the declining phase of plasma MPH concentration than in the ascending phase following an initial dose. This finding led to the discovery that a long-acting formulation delivering an ascending (rather than flat) profile of plasma MPH concentration was as effective in providing relief of ADHD symptoms through the day as three equally spaced doses of IR MPH per day [53].

Acute tolerance to the subjective effects of oral *d*-amphetamine 20 mg has been observed in healthy adults [29], and the potential for LDX and IR *d*-amphetamine to cause acute tolerance has been investigated in rats by measuring plasma *d*-amphetamine concentrations, striatal extracellular concentrations of the neurochemical mediator dopamine and locomotor activity (as a behavioural outcome). The overall *d*-amphetamine exposure was similar for equivalent doses of both drugs, but delivery of the active drug via rate-limited hydrolysis resulted in a lower *d*-amphetamine C_{\max} and delayed T_{\max} for LDX than for IR *d*-amphetamine. Compared with IR *d*-amphetamine, the pharmacokinetic profile of plasma *d*-amphetamine produced by LDX led to behavioural activation that was less pronounced as extracellular striatal dopamine concentrations increased, but was maintained for longer as extracellular striatal dopamine concentrations decreased [86]. One potential explanation for these observations may be lower acute tolerance to *d*-amphetamine when generated from the prodrug than for IR *d*-amphetamine which, in turn, may be responsible for the extended daily duration of therapeutic action and reduced drug-liking effects of LDX compared with IR amphetamine formulations.

4 Conclusions

The hydrolysis of LDX produces a plasma *d*-amphetamine pharmacokinetic profile with lower C_{\max} , extended T_{\max} and lower inter- and intra-individual variability than that produced by an equivalent dose of IR *d*-amphetamine. The therapeutic duration of action of LDX is considerably longer than that of an equivalent dose of IR *d*-amphetamine, possibly because reduced acute tolerance means that behavioural effects of LDX are maintained into

the declining phase of the plasma *d*-amphetamine concentration-time curve. The safety profile of LDX is typical of the stimulant class of ADHD medications. The reduced drug-liking profile of LDX compared with IR *d*-amphetamine formulations at equivalent doses may reflect the lower plasma *d*-amphetamine C_{\max} and delayed T_{\max} of the prodrug that therefore reduce the euphorogenic potential. These pharmacokinetic and pharmacodynamic characteristics of LDX may be beneficial in the management of symptoms in patients with ADHD.

Acknowledgments Dr. M. Cottingham and Dr. H. Lang of Oxford PharmaGenesis Ltd provided writing assistance under the direction of the authors. Editorial assistance in editing, fact-checking, formatting, proofreading and submission was also provided by Oxford PharmaGenesis Ltd.

Compliance with Ethical Standards

Shire International GmbH provided funding to Oxford PharmaGenesis Ltd for writing and editorial support for this publication. J. C. Ermer and G. Frick are employees of Shire, and own stock and/or stock options. M. Pennick is a former employee of Shire and owns stocks and/or stock options. Shire develops and markets drugs to treat psychiatric disorders, including ADHD.

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