EXPERT OPINION

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An update on lisdexamfetamine dimesylate for the treatment of attention deficit hyperactivity disorder

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Introduction: The efficacy and safety of stimulants for the pharmacologic management of attention deficit hyperactivity disorder (ADHD) is well documented. The US Food and Drug Administration approval of additional classes of medication even within stimulant treatments expands the prescribing options for practitioners. The focus of this paper is the prodrug amphetamine stimulant, lisdexamfetamine (LDX), which is an example of such an agent with a novel delivery system.

Areas covered: This review covers the proof-of-concept and later studies of LDX to describe its use to treat ADHD in pediatric and adult populations. A literature search and review of LDX were carried out using the PubMed database up to August 2012.

Expert opinion: Clinical studies of LDX in children and adults with ADHD demonstrate its tolerability and its efficacy in reducing ADHD symptoms. Future research should be less restrictive in order to address some of the unmet needs in ADHD treatment. The inclusion of patients with ADHD and co-occurring mental health disorders and/or medical conditions is typically not studied in clinical trials nor is the prior ADHD treatment exposure of study participants. The preschool age population also is understudied in recently approved ADHD treatments such as LDX. Finally, how to approach the treatment of participants or first-degree relatives with a medical history or presence of substance use disorder presents an ongoing clinical challenge.

Keywords: attention deficit hyperactivity disorder, lisdexamfetamine, prodrug

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1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder in children and adolescents [1]. Core symptoms of ADHD include developmentally inappropriate levels of inattention, hyperactivity and impulsivity with functional impairment in academic, family and social settings.

Management of ADHD symptoms consists of psychosocial and pharmacological treatment, which can be administered separately or in combination. In the United States, as of 2007, 66.3% of children with ADHD were reportedly taking medication for the disorder [2]. Prescribed agents for ADHD have varying degrees of efficacy and durations of effect to meet the needs of individual patients. Early treatment may decrease negative outcomes in life such as substance abuse, delinquency and greater incidence of personal injury and motor vehicle accidents, lower educational achievement, relationship difficulties, financial loss and diminished self esteem [3]. Thus, the development and investigation of new pharmacotherapies for ADHD may help reduce impairments in some of these outcome measures and domains.

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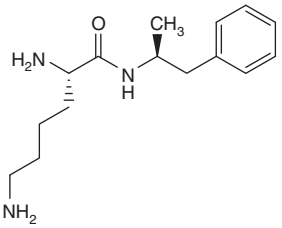
Box 1. Drug summary.

Drug name	Lisdexamfetamine (LDX)
Phase	Currently IV
Indication	ADHD
Pharmacology description/ mechanism of action	Prodrug; conversion to l-lysine and active d-amphetamine after ingestion/blocks reuptake of NE and DA in the presynaptic neuron to increase their availability into the extraneuronal space
Route of administration	Oral
Chemical structure	(2S)-2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl] hexanamide dimethanesulfonate 
Pivotal trial(s)	Phases I – IV

DA: Dopamine; d: Dextro; l: Levo; NE: Norepinephrine or noradrenaline.

Lisdexamfetamine dimesylate (LDX, Vyvanse®), is the first prodrug for managing ADHD symptoms – an amphetamine stimulant approved by the US Food and Drug Administration (FDA) for treating children, adolescents and adults with ADHD (see **Box 1**; [4]). As defined by the International Union of Pure and Applied Chemistry, a 'prodrug' is 'any compound that undergoes biotransformation before exhibiting its pharmacological effects' [5]. This indicates that a protective molecule is covalently bonded to the drug molecule, which renders it therapeutically inactive until ingestion. Levodopa is an example of an endobiotic and dopamine precursor commonly used in medical therapy; it is converted by 3,4-dihydroxyphenylalanine (DOPA) de-carboxylase to active dopamine for Parkinsonism which has led to Levodopa being called a prodrug [6]. Plavix (Clopidogrel) is an example of a prodrug given to patients with cardiovascular disease in order to reduce the risk of heart attack, unstable angina, stroke and cardiovascular death. Plavix is an inhibitor of the P2Y12 ADP receptor and works by decreasing platelet activation, decreasing the likelihood of clotting. Plavix is a prodrug that is metabolized by 2C19 enzyme to its active form, (S)2-oxo-clopidogrel [7]. LDX is hydrolyzed in the blood by endogenous enzymes to levo-lysine (l-lysine), a naturally occurring essential amino acid, and active dextro-amphetamine (d-amphetamine; see **Figure 1**), which provide its therapeutic effect [8].

2. Lisdexamfetamine

2.1 Overview of the market

Some of the unmet needs of currently available therapies for ADHD include the treatment of patients with (1) co-occurring or comorbid disorders along with ADHD symptoms; (2) co-occurring medical conditions including clinically significant cardiovascular abnormalities; (3) ADHD diagnosed in the pre-school years; (4) no prior experience versus previous experience with ADHD medications; and (5) a greater likelihood of substance abuse or dependency based on past and current substance use history.

2.1.1 *Comorbid conditions*

ADHD typically presents with co-occurring or comorbid psychiatric conditions, such as conduct disorder and oppositional defiant disorder (30 – 50%), depression and anxiety (25%), tic disorders (20%), bipolar (11%) and learning disorders (20 – 25%) such as reading disorder (RD), which may go unnoticed [2]. While stimulants are widely prescribed as treatments for ADHD, stimulant treatment may also alleviate comorbid conditions, such as depression, anxiety and learning disorders. Recent studies are beginning to address medication treatment in some of these areas. Findings of the NIMH Multimodal Treatment Study of Children with ADHD (MTA) demonstrated the importance of behavioral interventions administered as a component of combined therapy along with medication as an important tool for the treatment of children with ADHD with common comorbid conditions [9], although this work preceded the FDA approval of LDX and so it is not specific to LDX treatment. Children with ADHD and other disruptive behavior disorders displayed reduced academic and social impairment with combined therapy, as did those with comorbid anxiety. Children with comorbid learning disorders benefitted from stimulant treatment but required additional educational supportive services. For example, a single-blind, modified laboratory school study of children aged 6 – 12 years with 4 – 5 weeks of dose-optimization with LDX 30, 50 and 70 mg/day led to improvements in reading fluency. This study included children with a broad range of learning capabilities. Likewise, OROS methylphenidate hydrochloride is shown to improve a number of academic tasks thought to be related to reading performance in older elementary children in a laboratory school setting [10,11]. A larger, controlled clinic study of children and adolescents classified as ADHD only, ADHD with comorbid RD, or RD alone demonstrated improvements in a number of reading variables when treated with atomoxetine that could not be seen in subjects with ADHD symptoms alone [12]. It should be noted that LDX, OROS methylphenidate or atomoxetine are FDA approved to improve reading fluency.

2.1.2 *Coexisting medical conditions*

A number of medical conditions frequently occur with ADHD including urinary voiding dysfunction such as enuresis, with an odds ratio of 2.88 [13].

Other health conditions may naturally coexist such as hypertension or cardiac issues. However, it is only recently that studies have begun to address such medical conditions

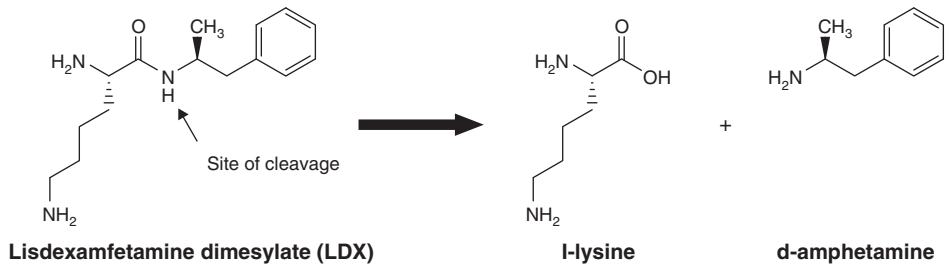


Figure 1. The chemical reaction of LDX after oral administration. L-lysine is covalently bound to d-amphetamine in a peptide bond. *In vitro* experiments for LDX used peptidases to catabolize LDX into l-lysine and d-amphetamine [8].

that may pre-exist or coexist to widen the inclusion and/or exclusion criteria of clinical trials to yield findings that are more generalizable to the larger population of individuals with ADHD.

2.1.3 *Younger (preschool-aged) children*

Behavior problems common to ADHD often are exhibited before elementary school resulting in their referral, assessment and treatment for ADHD in patient samples [14,15]. Lahey *et al.* published the first longitudinal study of young children with ADHD of which one-third were preschoolers and found that almost all of them continued to meet criteria for ADHD up to 3 years later [16]. The Preschool ADHD Treatment Study (PATS) and its follow-up study (PATS F/U) demonstrated the short-term efficacy and long-term safety of methylphenidate treatment in 3- to 5.5-year-olds rigorously diagnosed with ADHD following nonmedication interventions [17]. Overall, this study has shown that when stimulants are cautiously prescribed to preschoolers they are safe and effective; however, the safety and efficacy of LDX in pediatric patients below the age of 6 years has not been established. In a separate pharmacokinetic (PK) study of preschoolers at one of the six PATS sites, preschoolers were shown to have a slower clearance rate than school-aged children with ADHD even when body weight was controlled to account for a different volume of distribution (see **Table 1**; [18]). Results from the PATS, PATS F/U and PK study provided methodology for establishing multimodal interventions in these young children and their families and could be applied to the study of pharmacological treatments for ADHD besides methylphenidate in this young age group. While Vyvanse, like other amphetamines, is not recommended for children under 3 years of age, the safety and efficacy of amphetamines in children is also not well established [4].

2.1.4 *Prior exposure to medication for ADHD*

Previous medication history and the impact on treatment effects and adverse outcomes in treatment studies of ADHD have been little studied until recently [19,20]. In a study of 27 children (6 – 12 years) with ADHD, it was found that a greater incidence and greater severity but not longer duration of treatment-emergent adverse events (TEAEs) while taking LDX were associated with stimulant-naïve status than with previous stimulant exposure. Because ADHD symptom improvements were not related to previous stimulant treatments, LDX may be viewed as an efficacious treatment option for both previously treated and stimulant-naïve children with ADHD.

2.1.5 *Substance use*

There is a high comorbidity of substance abuse disorders among patients with ADHD, and it is hypothesized to relate to impaired brain dopamine activity [21]. The relationship between stimulant treatment and substance abuse still is not well understood, and it is yet uncertain if ADHD symptoms are exacerbated by chronic drug exposure [22]. It is yet to be seen if newer drug delivery systems, such as the prodrug LDX, may provide protective benefits. LDX has not been studied for drug abuse potential and is classified as a Schedule II controlled substance by the FDA with a high potential for abuse.

2.2 Introduction to LDX

LDX is manufactured by Shire Pharmaceuticals and received FDA approval for ADHD treatment in children in 2007, for adolescents in 2010 and for adults in 2008 [23]. Subsequently, Health Canada approved the use of LDX to treat children (6 – 12 years) with ADHD in 2010. It is administered once daily with an appropriate dose range of 20 to 70 mg as prescribed by physician. LDX is similar in its tolerability profile, adverse effects and contraindications to other long-acting amphetamine bead formulations. There are some intolerability aspects and contraindications that are different among the long-acting amphetamine formulations [24].

2.3 Chemistry

The chemical structure of LDX is (2S)-2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl] hexanamide dimethanesulfonate, belonging to the phenethylamine and amphetamine chemical classes (**Box 1**).

2.4 Pharmacodynamics

LDX, a single enantiomer (d-amphetamine), is therapeutically inactive and undergoes enzymatic hydrolysis *in vivo* after ingestion resulting in the amino acid l-lysine and

Table 1. PK parameters' comparison of methylphenidate in preschoolers and school-aged subjects.

	Preschoolers	School-aged	Difference in effect size	p-value
Age	5.33 ± 0.56	8.00 ± 0.56	4.77	< 0.001
Weight (kg)	19.2 ± 2.6	28.3 ± 5.8	2.22	< 0.001
Dose (mg)	5.89 ± 1.9	6.94 ± 3.3	0.42	0.33
Dose/weight (mg/kg)	0.311 ± 0.09	0.252 ± 0.13	-0.54	0.20
CL/F (L/h)	99.5 ± 44	232.6 ± 75	2.52	< 0.001
CL/F/weight (L/h/Kg)	5.12 ± 1.9	7.91 ± 1.6	1.52	0.01
$t_{1/2}$ (h)	3.82 ± 2.7	2.18 ± 0.3	-0.69	0.46
C_{max} (ng/mL)	10.2 ± 5.0	7.6 ± 4.2	-0.53	0.32
1000*C_{max}/D (1/L)	1.72 ± 0.5	1.10 ± 0.3	-1.44	0.003

*Adapted from [18].

d-amphetamine, which is the active drug used to treat ADHD symptoms (**Figure 1**). The exact mechanism of action of d-amphetamine in the body to treat ADHD symptoms is unknown. Prior research suggests that amphetamines increase norepinephrine and dopamine in the extraneuronal cleft [25]. Yet, LDX specifically is not shown to bind to presynaptic catecholamine reuptake sites *in vitro* [26].

2.5 PK and metabolism

After oral administration of LDX and enzymatic hydrolysis on erythrocytes, d-amphetamine is available for absorption. This biotransformation appears to be responsible for the rate of delivery of the active metabolite [8]. **Table 2** summarizes the PK parameters of LDX and mixed amphetamine salts extended release (MAS-XR or Adderall XR) [24,26]. It is important to note that due to LDX's formulation, the medication can be dissolved in water for those who find the capsule hard to swallow. In contrast, Adderall XR cannot be dissolved in water as the enteric-coated beads are insoluble until they enter the acidic environment of the stomach [27]. The capsule may be opened, and the entire contents sprinkled on applesauce. The sprinkled applesauce should be consumed immediately and not stored. The Adderall XR prescribing information explains that patients should take the sprinkled applesauce in its entirety without chewing. The dose of a single capsule should not be divided. With food, a lower peak of d-amphetamine level (lower T_{max}) is reached compared to an individual in the fasting state [28].

LDX is reported to show less inter-patient and intra-patient PK variability in PK parameters as it is independent of a bead formulation thereby reducing inter-individual differences in gastric acidity and gastrointestinal transit times [27,28]. In addition, substances altering the urinary pH can affect serum amphetamine levels. Urinary acidifying agents reduced the amount of plasma concentration of amphetamine by increasing urinary excretion, while urinary alkalinizing agents increase the plasma concentration of amphetamine [23].

2.5.1 Phase I studies

2.5.1.1 Children

An initial crossover study was conducted to examine the time delay needed to reach maximum plasma concentration (T_{max}) of LDX and d-amphetamine. A total of 18 school-aged children (6 – 12 years) with ADHD received three oral doses of 30, 50 and 70 mg of LDX after fasting overnight for 8 h. Mean values for LDX reached T_{max} by 1 h and d-amphetamine reached T_{max} by 3.5 h [30].

2.5.1.2 Healthy volunteers

A single dose crossover study with 18 healthy adult volunteers (18 – 55 years) was conducted to observe the PK parameters for LDX and d-amphetamine in three conditions: fasting, fed and oral solution. A single LDX dose of 70 mg was used to find the time needed to reach maximum plasma concentration (T_{max}), the maximum plasma concentration (C_{max}), area under the plasma drug concentration versus time curve (AUC), and plasma half life ($t_{½}$). Although significant differences among T_{max}, C_{max} and $t_{1/2}$ were recorded, the AUC values were equivalent for all three states. **Table 3** summarizes the mean values for the PK parameters after single oral administration of LDX with food to healthy participants. Thus, LDX can be taken with or without food or dissolved in water then ingested [28,29].

Another study with 12 healthy adults examined steady-state concentrations of d-amphetamine. The participants received one 70 mg capsule for 7 consecutive days. LDX levels were 0 at 5 h, and d-amphetamine levels approached 0 at 72 h. The $t_{1/2}$ values for LDX and d-amphetamine were 0.4 and 10.1 h [31].

2.6 Clinical efficacy

To date, there have been Phase II studies in school-aged children; Phase III studies in children, adolescents and adults and Phase IV studies in adults. **Table 4** reviews these studies by phase and age groups.

2.6.1 Phase II studies

2.6.1.1 Children

Biederman's study in 2007 considered the efficacy and safety of LDX in 52 children (6 – 12 years). The first 3 weeks were for dose optimization using MAS XR (doses: 10, 20 and 30 mg/day) followed by randomized crossover into three groups: LDX (doses: 30, 50, 70 mg), MAS XR (doses: 10,

Table 2. Summary of PK parameters of Vyvanse and Adderall XR.

	Vyvanse*‡	Adderall XR*§
In children (6 – 12 years)		
Elimination of prodrug	4 h	N/A
Onset of clinical effect (after oral ingestion)	1.5 h	Dependent on gastric transit time
d-amphetamine C_{max}	3.5 h	7 h
Biological half-life	9 h	11 h
In adults		
Elimination of prodrug	6 h	N/A
Onset of clinical effect (after oral ingestion)	2 h	Dependent on gastric transit time
d-amphetamine T_{max}	3.7 h	7 h
Biological half-life [adolescents (weight < 165 lbs)/adults]	10 h	13/13 – 14 h

*The values are obtained from FDA Product Labels [23,27,28].

‡The values are for d-amphetamine from LDX.

§The values are l- and d-amphetamine (l/d) for Adderall XR as applicable.

Table 3. Summary of PK parameters derived from a peer-reviewed study. Mean values after single oral administration of LDX (70 mg capsule) with a high fat meal to 18 healthy adult participants.

	T_{max}, h	$t_{1/2}$, h	C_{max}, ng/mL	AUC_{0-t}, (ng) (h)/mL	$AUC_{0-\infty}$, (ng) (h)/mL
LDX	2.08	0.63	26.2	53.68	58.81
d-amphetamine	4.72	9.59	65.3	972	1038

*Adapted from [28].

20, 30 mg) and placebo. Participants had been exposed to stimulant treatment and were diagnosed with ADHD (participants with comorbid disorders were excluded). The majority of the participants were male (64%). See **Table 2** for efficacy measures used and results. However, the study validated the safety and efficacy of LDX use in children [32].

2.6.2 *Phase III studies*

2.6.2.1 *Children*

A 4-week placebo-controlled study with 30, 50 and 70 mg of LDX showed significant improvement in symptoms of ADHD while treating ADHD in 290 children (6 – 12 years) across multiple centers in the United States. Participants receiving LDX were initiated on 30 mg for the first week of treatment. Those assigned to the 50 and 70 mg dose groups were titrated by 20 mg/week until they were receiving their assigned dose. As shown in **Table 4**, ADHD-RS-IV and Clinical Global Impression – Improvement Scale (CGI-I) were used as efficacy measures [33].

2.6.2.2 *Adults*

The efficacy and safety of LDX in adults (18 – 55 years) diagnosed with ADHD (excluding participants with comorbidities, hypertension or cardiovascular health problems) was examined in a 4-week optimization period with LDX (30, 50 and 70 mg/day), which was followed with 2 weeks of randomized crossover phase. The study design consisted of a modified analog classroom to simulate a workplace environment. The Permanent Product Measure of Performance (PERMP) was used as the measure of attention pre-dose (-0.5 h) and post-dose (2, 4, 8, 10, 12 and 14 h). Participants taking LDX performed significantly better than participants on placebo. Also, LDX participants averaged twice as well on PERMP-A (attempted) and PERMP-C (correct), thereby maintaining functionality throughout the day with LDX (**Table 4**; [34]).

A parallel group study for adults (18 – 55 years) with ADHD was conducted to test the efficacy and safety of LDX. During the 4 weeks of treatment, 420 participants were randomly selected to receive LDX capsules or placebo. All participants were initiated on 30 mg for the first week of treatment. Those assigned to the 50 and 70 mg dose groups were titrated by 20 mg/week until they were receiving their assigned dose. Efficacy was measured in terms of the change in total score of ADHD Rating Scale (ADHD-RS) from baseline to endpoint (**Table 4**). The study showed significantly improved symptoms of ADHD in participants using LDX as compared to placebo [23].

2.6.3 *Phase IV studies*

2.6.3.1 *Children*

A recent study addressed the use of stimulant medication in stimulant-naïve populations diagnosed with ADHD [20]. This was a single-blind, open-label, dose-optimization study with LDX doses 30,50 and 70 mg. Using two groups, stimulant-naïve and previous-exposure subjects, a total of

Table 4. LDX clinical trials.

Type	Participants	Dosage	Duration of treatment	Efficacy results
Phase II trials				
Prospective, randomized, double-blind, placebo-controlled, crossover trial, multicenter, open-label	Children (6 – 12 years); n = 52	LDX 30, 50, 70 mg vs MAS XR 10, 20, 30 mg vs Placebo	3-week open-label dose optimization with MAS XR followed with 3 weeks of randomized crossover	SKAMP-DS: LDX 0.8 vs Placebo 1.7 ($p < 0.0001$); MAS XR 0.8 vs Placebo 1.7 ($p < 0.0001$) | SKAMP-AS: LS mean LDX + MAS XR 1.2 vs Placebo 1.8 ($p < 0.0001$) | PERMP-A: LS LDX 133.3, MAS XR 133.6 vs Placebo 88 ($p < 0.0001$) | PERMP-C: LS LDX 129.6, MAS XR 129.4 vs Placebo 84.1 ($p < 0.0001$) | % very much improved or much improved: LDX 74%, MAS XR 72%, Placebo 18%
Phase III trials				
Prospective, randomized, double-blind, placebo-controlled, parallel-group study	Children (6 – 12 years); n = 290	LDX 30, 50, 70 mg vs Placebo	4 weeks	ADHD-RS-IV: -26.7 with 70 mg group; significant improvement with 30 and 50 mg ($p < 0.001$) compared with -6.2 in the placebo group | CGI-I – %very much improved or much improved: LDX 70% and higher, Placebo 18%
Prospective, single-blind, open label	Children (6 – 12 years); n = 28	LDX 30, 50, 70 mg	4 – 5 weeks	*Post hoc* subgroup analyses: Stimulant-naïve participants experienced severe adverse events compared to participants exposed to stimulants when taking LDX
Prospective, randomized, double-blind, placebo-controlled, workplace	Adults (18 – 55 years); n = 123	LDX 30, 50, 70 mg	4-week, open-label dose optimization followed with 2 weeks of randomized crossover	PERMP-A:Difference in post-dose LS Mean (95% CL) 12 (LDX 8.1, Placebo 15.8) | PERMP-C: Difference in post-dose LS Mean (95%CL) 11.5 (LDX 7.6, Placebo 15.4)
Randomized, double-blind, placebo-controlled, parallel-group study	Adults (18 – 55 years); n = 420	LDX 30, 50, 70 mg vs Placebo	4-week randomized trial	ADHD-RS: all groups receiving LDX had better changes in total score compared to the placebo group

ADHD-RS-IV: ADHD Rating Scale Version IV; CGI-I:Clinical Global Impression – Improvement Scale; CL: Confidence level; LDX: Lisdexamfetamine; LS: Least Squares; n: Sample size; PERMP-A: Permanent Product Measure of Performance (Attempted); PERMP-C: Permanent Product Measure of Performance (Correct); SKAMP-AS: Swanson, Kotkin, Agler, M-Flynn and Pelham (Attention); SKAMP-DS: Swanson, Kotkin, Agler, M-Flynn and Pelham (Deportment).

28 participants were monitored for TEAEs for LDX. All individuals initially received 30 mg of LDX followed by dose optimization where 20 mg increments of LDX were given to participants. The stimulant-naïve group experienced insomnia, abdominal pain and hyperfocus, while previous-exposure subjects experienced decreased appetite, dizziness and less lip sucking. Thus, stimulant-naïve subjects experience severed TEAEs in comparison to previous-exposure subjects; however, LDX reduced the core symptoms of ADHD [20].

2.6.3.2 *Ongoing studies*

Phase IV trials are currently recruiting or implementing study designs to examine LDX's optimal use, benefits, and risks in children and adults with ADHD. For instance, an in-depth cardiovascular study of LDX is being undertaken in healthy and hypertensive adults with ADHD per clinicaltrials.gov.

2.7 Safety and tolerability

In a study examining the dose range of 50 – 250 mg LDX, there was no apparent saturation of enzymes that cleave active d-amphetamine from the prodrug. The dose-proportionality observed in blood levels of d-amphetamine with doses of up to 250 mg suggests that there is no overdose protection at supratherapeutic doses of LDX [35]. However, the maximum recommended dose of LDX is 70 mg/day in children aged 6 – 12 years [4].

2.8 Regulatory affairs

The approved dosage strengths of LDX in the United States are 20, 30, 40, 50, 60 and 70 mg for ages 6 – 12, 13 – 17 and adults [36]. Vyvanse has been approved in Canada in the dosage strengths 20, 60, 40, 50 and 60 mg for ages 6 – 12, 13 – 17 and adults. LDX is approved in Brazil for ages 6 – 12 with the dosage strengths 30, 50 and 70 mg under the trade name Venvanse®. It is also being reviewed by health authorities in several European Union countries as well.

3. Conclusion

LDX is a stimulant prodrug clinically approved by the FDA for treatment of ADHD in children, adolescents and adults. The primary goal for stimulant use is to reduce symptoms of ADHD and to increase everyday functionality (e.g., school/job performance, quality of life and peer relationships) in individuals with ADHD. Additional research may help refine any unique properties of this agent for treating particular patient subgroups as described in this paper.

4. Expert opinion

The recent expansion of the guidelines for pediatricians on the evaluation, diagnosis and treatment of ADHD is very relevant to this topic [37]. Recommendations include the directive to primary care clinicians to assess for behavioral, developmental and physical coexisting conditions with ADHD. An important consideration for patients receiving pharmacotherapy for other medical or psychiatric conditions is that amphetamine is a P450 2D6 substrate. Therefore, concentration-dependent inhibition of P450 isoforms does not occur with LDX treatment, and there are no *in vivo* studies of P450 enzyme inhibition. The practice guidelines also changed from covering the school aged group of 6- to 12-year-olds to now included preschoolers and adolescents (4- to 18-year-olds). For the preschool aged group, evidence-based behavioral therapy is recommended as the first-line therapy for youth with ADHD. However, balancing putative risks in medication treatment at young ages, with the potential benefit of not delaying diagnosis and treatment, must be carefully weighed by practitioners. One might also speculate whether early treatment could prevent further development of primary effects of ADHD and/or secondary psychiatric illnesses.

A practical aspect of ADHD symptom management with LDX is that it offers ease in oral administration. The LDX capsule may be opened and its contents dissolved in plain water [31]. Its long duration of effect, which is presumably related to its prodrug properties may be an advantage for individuals desiring a greater time course of ADHD symptom control across the day.

The study of prior medication status in controlled trials would be helpful for practitioners and patients to further understand the role of medication history on perceived clinical effects on the core symptoms of ADHD and management of physiological risks and adverse events.

Measures of abuse liability were included in the initial development and approval of LDX. Even though the findings of these studies showed attenuated responses, they were not sufficient to classify LDX as a non-controlled substance. Equally yoked comparator trials could provide unbiased liability data. Such future studies would increase the appeal of prescribing LDX to certain patients by enhancing our understanding of oral LDX administration and its abuse liability and safety in individuals with a history of stimulant abuse [38]. Until then, conservative practitioners may continue to be promoters of nonstimulant medications for households with suspected substance abusers.

The risks of stimulant use for treating ADHD symptoms are clear. Yet, there are important and valid reasons for using pharmacotherapy. Left untreated, both primary (impulsivity, inattention and hyperactivity) and secondary (agitation, depression and anxiety) aspects of ADHD can severely impact daily quality of life and relationships of children and adults. The inclusion of both naturalistic, clinical studies and research in more standardized settings for consistency of evaluation as in the laboratory classroom environment [39] for evaluating newer treatments such as LDX provides practitioners a better sense of treatment strategies and drug usefulness for current as well as newly diagnosed patients.

Declaration of interest

The collection, analysis and interpretation of data were made by the independent authors as was the writing of this article and the decision to submit this article for publication in this journal. Dr S Wigal is a consultant for, on the speaker or advisory boards for and/or has received grant/research support from Eli Lilly, Forest, NextWave Pharmaceuticals, NuTec, Rhodes, Shionogi Pharm and Shire. The remaining authors have no competing interests to declare.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th edition. Text Revision (DSM-IV-TR). Am Psychiatry Assoc; Washington, DC: 2000
2. Centers for Disease Control and Prevention. Increasing prevalence of parent-reported attention-deficit/ hyperactivity disorder among children - United States, 2003 and 2007. Morb Mortal Wkly Rep 2010;59(44):1439-43
3. Pliszka SR. Practice Parameter for the assessment and treatment of children and adolescents with attention-deficit/ hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2007;46:894-921
4. FDA: Approval Letter. Drug Approval Package: Vyvanse (Lisdex- amfetamine dimesylate) NDA #021977. U.S. Food and Drug Administration. 2007.Available from: www.accessdata.fda.gov/drugsatfda_ docs/nda/2007/021977s000TOC.cfm [Accessed 29 May 2009]
5. Stanczak A, Ferra A. Prodrugs and soft drugs. Pharmacol Rep 2006;58:599-613
6. Da Prada M, Keller HH, Kettler PL, et al. The pharmacology of Parkinson's disease: basic aspects and recent advances. Experientia 1984;40:1165-72
7. Pereillo JM, Maftouh M, Andrieu A, et al. Structure and stereochemistry of the active metabolite clopidogrel. Drug Metab Dispos 2002;30(11):1288-95
8. Pennick M. Absorption of lisdexamfetamine dimesylate and its enzymatic conversion to d-amphetamine. Neuropsychiatr Dis Treat 2010;6:317-27

•• **An original study demonstrating LDX hydrolysis by RBCs.**

9. Jensen PS, Hinshaw SP, Kraemer HC, et al. ADHD comorbidity findings from the MTA study: comparing comorbid subgroups. J Am Acad Child Adolesc Psychiatry 2001;40(2):147-58
10. Wigal SB, Maltas S, Crinella F, et al. Reading Performance as a Function of Treatment With Lisdexamfetamine Dimesylate in Elementary School Children Diagnosed With ADHD. J Atten Disord 2012;16(1):23-33
11. Wigal SB, Wigal T, Schuck S, et al. Academic, behavioral and cognitive effects of OROS® methylphenidate on older children with attention-deficit/ hyperactivity disorder. J Child Adolesc Psychopharmacol 2011;21(2):121-31
12. Shaywitz S, Shaywitz B, Wietecha L, et al. Effect of atomoxetine on reading and phonological skills in children and adolescents with dyslexia or attention deficit/hyperactivity disorder and comorbid dyslexia. Poster presented at the 59th Annual Meeting of the American Academy of Child & Adolescent; October2012; San Francisco, CA
13. Shreeram S, He JP, Kalaydilian A, et al. Prevalence of enuresis and its association with attention-deficit/hyperactivity disorder among U.S. children: results from a nationally representative study. J Am Acad Child Adolesc Psychiatry 2009;48(1):35-41
14. Zito JM, Safer DJ, dosReis S, et al. Trends in the prescribing of psychotropic medications to preschoolers. JAMA 2000;283(8):1025-30
15. Zuvekas S, Vitiello B. Stimulant medication use in children: a 12-year perspective. Am J Psychiatry 2012;169(2):160-6
16. Lahey BB, Pelham WE, Loney J, et al. Three-year predictive validity of DS-IV attention deficit hyperactivity disorder in children diagnosed at 4-6 years of age. Am J Psychiatry 2004;161(11):2014-20
17. Greenhill L, Kollins S, Abikoff H, et al. Efficacy and safety of immediate-release methylphenidate treatment for preschoolers with ADHD. J Am Acad Child Adolesc Psychiatry 2006;45:1284-93
18. Wigal SB, Gupta S, Greenhill L, et al. Pharmacokinetics of methylphenidate in preschoolers with Attention-Deficit/ Hyperactivity Disorder. J Child Adolesc Psychopharmacol 2007;17(2):153-64

•• **An original study demonstrating differences in clearance for MPH PK in preschool versus school-aged children.**

19. Wigal SB, Jun A, Wong AA, et al. Does prior exposure to stimulants in children with ADHD impact physiological effects from lisdexamfetamine dimesylate? Postgraduate Med 2010;122(5):27-34
20. Wigal SB, Wong AA, Jun A, et al. Adverse events in medication treatment-naive children with attention-Deficit/Hyperactivity disorder: results from a small, controlled trial of lisdexamfetamine dimesylate. J Child Adolesc Psychopharmacol 2012;22(2):149-56
21. Volkow ND, Wang GJ, Newcorn J, et al. Brain dopamine transporter levels in treatment and drug naive adults with ADHD. Neuroimage 2007;34(3):1182-90
22. Volkow ND, Swanson JM. Does childhood treatment of ADHD with stimulant medication affect substance abuse in adulthood? Am J Psychiatry 2008;165(5):553-5
23. Shire US, Inc. Vyvanse® (lisdexamfetamine dimesylate) C-II Prescribing Information. 2012. [Accessed June 2012
24. Elbe D, Macbride A, Reddy D. Focus on Lisdexamfetamine: a Review of its use in Child and Adolescent Psychiatry. J Can Acad Child Adolesc Psychiatry 2010;19(4):303-14
25. Solanto MV. Neuropsychopharmacological mechanisms of stimulant drug action in attention-deficit hyperactivity disorder: a review and integration. Behav Brain Res 2010;19(4):303-14
26. Najib J. The efficacy and safety profile of lisdexamfetamine dimesylate, a prodrug of d-amphetamine, for the treatment of attention-deficit/hyperactivity disorder in children and adults. Clin Ther 2009;31(1):142-76
27. Shire US, Inc. ADDERALL XR® Medication Guide. C-II. 2011. [Accessed June 2012
28. Krishnan S, Zhang Y. Relative bioavailability of lisdexamfetamine 70-mg capsules in fasted and fed healthy adult volunteers and in solution: a single dose, crossover pharmacokinetic study. J Clin Pharmacol 2008;48(3):293-302
29. Haffey MB, Buckwalter M, Zhang P, et al. Effects of omeprazole on the pharmacokinetic profiles of LDX and Mixed amphetamine salts extended release in adults. Clin Pharmacol 2009;121(5):11-29

30. Vyanse(lisdexamfetamine dimesylate). Wayne, PA:Shire US Inc. 2008.Available from: http://www.vyvanse.comindexchild.aspWT.srch=1&src=1&mid=V000803&tid=1489731&KEYWORD=vyvanse&gelid-CIH_96fMvpcCFQObFQodCXofS [Accessed 29 July 2012]

31. Krishnan SM, Stark JG. Multiple daily dose pharmacokinetics of lisdexamfetamine dimesylate in healthy adult volunteers. Curr Med Res Opin 2008;24:33-40

32. Biederman J, Boellner SW, Childress A, et al. Lisexamfetamine dimesylate and mixed amphetamines salts extended-release in children with ADHD: a double-blind, placebo-controlled, crossover analog classroom study. Biol Psychiatry 2007;62:970-6

33. Biederman J, Krishnan S, Zhang Y, et al. Efficacy and tolerability of lisdesamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: a phase III, multicenter, randomized, double blind, forced dose, parallel group study. Clin Ther 2007;29:450-63

34. Wigal T, Brams M, Gasior M, et al. Randomized, double-blind, placebo-controlled, crossover study of the efficacy and safety of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder: novel findings using a simulated adult workplace environment design. Behav Brain Funct 2010;6:34

35. Ermer J, Homolka R, Martin P, et al. Lisdexamfetamine dimesylate: linear dose-proportionality, low intersubject and intrasubject variability, and safety in an open-label single-dose pharmacokinetic study in healthy adult volunteers. J Clin Pharmacol 2010;50:1001-11

36. Shire Canada Inc. Vyvanse® Product Monograph. Saint-Laurent, QC: Shire Canada Inc.; 2011

37. Subcommittee on Attention-Deficit/hyperactivity Disorder, Steering Committee on Quality Improvement and Management. ADHD: Clinical practice guideline for the diagnosis, evaluation, and treatment of Attention-Deficit/hyperactivity Disorder in children and adolescents. Pediatrics 2011;128(5):1-16

38. Jasinski DR, Krishnan S. Abuse liability and safety of oral lisdexamfetamine dimesylate in individuals with a history of stimulant abuse. J Psychopharmacol 2009;23(4):419-27

39. Wigal SB, Wigal TL. The laboratory school protocol: its origin, use, and new applications. J Atten Disord 2006;10:92-111

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