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

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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Levodopa being called a prodrug[6]. Plavix (Clopidogrel) is an
enzyme to active dopamine for Parkinsonism which has led to
converted by 3,4-dihydroxyphenylalanine (DOPA) de-carboxyl-
and dopamine precursor commonly used in medical therapy; it is
inactive until ingestion. Levodopa is an example of an endobiotic
bonded to the drug molecule, which renders it therapeutically
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Some of the unmet needs of currently available therapies for
ADHD typically presents with co-occurring or comorbid psy-
chiatric 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 treat-
ments 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 interven-
tions administered as a component of combined therapy
along with medication as an important tool for the treatment of
children with ADHD with common comorbid condi-
tions[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 dis-
played reduced academic and social impairment with com-
bined 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 chil-
ren 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 chil-
ren 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 methylpheni-
date or atomoxetine are FDA approved to improve
reading fluency.

2.1.1 Coexisting medical conditions
A number of medical conditions frequently occur with
ADHD including urinary voiding dysfunction such as
euresis, 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

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

<table>
<thead>
<tr>
<th>Box 1. Drug summary.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug name</td>
</tr>
<tr>
<td>Phase</td>
</tr>
<tr>
<td>Indication</td>
</tr>
<tr>
<td>Pharmacology description/mechanism</td>
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<tr>
<td>Route of administration</td>
</tr>
<tr>
<td>Chemical structure</td>
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<tr>
<td>Pivotal trial(s)</td>
</tr>
</tbody>
</table>

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 under-
goes 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-carboxyl-
ase 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].

2.1.2 Coexisting medical conditions
A number of medical conditions frequently occur with
ADHD including urinary voiding dysfunction such as
euresis, 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

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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 d-amphetamine.
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 Tmax) is reached compared to an empty stomach [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 may affect serum amphetamine levels. Urinary acidifying agents reduced the amount of plasma concentration of amphetamine by increasing urinary excretion, while urinary alkalizing agents increase the plasma concentration of amphetamine [23].

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

<table>
<thead>
<tr>
<th></th>
<th>Preschoolers</th>
<th>School-aged</th>
<th>Difference in effect size</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>5.33 ± 0.56</td>
<td>8.00 ± 0.56</td>
<td>4.77</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>19.2 ± 2.6</td>
<td>28.3 ± 5.8</td>
<td>2.22</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Dose (mg)</td>
<td>5.89 ± 1.9</td>
<td>6.94 ± 3.3</td>
<td>0.42</td>
<td>0.33</td>
</tr>
<tr>
<td>Dose/weight (mg/kg)</td>
<td>0.311 ± 0.09</td>
<td>0.252 ± 0.13</td>
<td>-0.54</td>
<td>0.20</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>10.2 ± 5.0</td>
<td>7.6 ± 4.2</td>
<td>-0.53</td>
<td>0.32</td>
</tr>
<tr>
<td>1000*Cmax/D (1/L)</td>
<td>1.72 ± 0.5</td>
<td>1.10 ± 0.3</td>
<td>-1.44</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*Adapted from [18].

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 (Tmax) 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 Tmax by 1 h and d-amphetamine reached Tmax 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 (Tmax), the maximum plasma concentration (Cmax), area under the plasma drug concentration versus time curve (AUC), and plasma half life (t½). Although significant differences among Tmax, Cmax and t½ 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 t½ 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.

<table>
<thead>
<tr>
<th></th>
<th>Vyvanse*‡</th>
<th>Adderall XR*§</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In children (6 – 12 years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elimination of prodrug</td>
<td>4 h</td>
<td>N/A</td>
</tr>
<tr>
<td>Onset of clinical effect (after oral ingestion)</td>
<td>1.5 h</td>
<td>Dependent on gastric transit time</td>
</tr>
<tr>
<td>d-amphetamine Cmax</td>
<td>3.5 h</td>
<td>7 h</td>
</tr>
<tr>
<td>Biological half-life</td>
<td>9 h</td>
<td>11 h</td>
</tr>
<tr>
<td><strong>In adults</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elimination of prodrug</td>
<td>6 h</td>
<td>N/A</td>
</tr>
<tr>
<td>Onset of clinical effect (after oral ingestion)</td>
<td>2 h</td>
<td>Dependent on gastric transit time</td>
</tr>
<tr>
<td>d-amphetamine Tmax</td>
<td>3.7 h</td>
<td>7 h</td>
</tr>
<tr>
<td>Biological half-life [adolescents (weight &lt; 165 lbs)/adults]</td>
<td>10 h</td>
<td>13/13 – 14 h</td>
</tr>
</tbody>
</table>

*The values are obtained from FDA Product Labels [23,27,28].
1The values are for d-amphetamine from LDX.
2The 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.

<table>
<thead>
<tr>
<th></th>
<th>Tmax, h</th>
<th>t1/2, h</th>
<th>Cmax, ng/mL</th>
<th>AUCl – t, (ng) (h)/mL</th>
<th>AUCl – ∞, (ng) (h)/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDX</td>
<td>2.08</td>
<td>0.63</td>
<td>26.2</td>
<td>53.68</td>
<td>58.81</td>
</tr>
<tr>
<td>d-amphetamine</td>
<td>4.72</td>
<td>9.59</td>
<td>65.3</td>
<td>972</td>
<td>1038</td>
</tr>
</tbody>
</table>

*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
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 severe 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.

### Table 4. LDX clinical trials.

<table>
<thead>
<tr>
<th>Type</th>
<th>Participants</th>
<th>Dosage</th>
<th>Duration of treatment</th>
<th>Efficacy results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase II trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prospective, randomized, double-blind, placebo-controlled, crossover trial, multicenter, open-label</td>
<td>Children (6 – 12 years); n = 52</td>
<td>LDX 30, 50, 70 mg vs MAS XR 10, 20, 30 mg vs Placebo</td>
<td>3-week open-label dose optimization with MAS XR followed with 3 weeks of randomized crossover</td>
<td>SKAMP-DS: LDX 0.8 vs Placebo 1.7 (p &lt; 0.0001); MAS XR 0.8 vs Placebo 1.7 (p &lt; 0.0001)</td>
</tr>
<tr>
<td><strong>Phase III trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prospective, randomized, double-blind, placebo-controlled, parallel-group study</td>
<td>Children (6 – 12 years); n = 290</td>
<td>LDX 30, 50, 70 mg vs Placebo</td>
<td>4 weeks</td>
<td>ADHD-RS-IV: -26.7 with 70 mg group; significant improvement with 30 and 50 mg (p &lt; 0.001) compared with -6.2 in the placebo group</td>
</tr>
<tr>
<td>Prospective, single-blind, open label</td>
<td>Children (6 – 12 years); n = 28</td>
<td>LDX 30, 50, 70 mg</td>
<td>4 – 5 weeks</td>
<td>Post hoc subgroup analyses: Stimulant-naïve participants experienced severe adverse events compared to participants exposed to stimulants when taking LDX</td>
</tr>
<tr>
<td>Prospective, randomized, double-blind, placebo-controlled, workplace</td>
<td>Adults (18 – 55 years); n = 123</td>
<td>LDX 30, 50, 70 mg</td>
<td>4-week, open-label dose optimization followed with 2 weeks of randomized crossover</td>
<td>PERMP-A: Difference in post-dose LS Mean (95% CL) 12 (LDX 8.1, Placebo 15.8)</td>
</tr>
<tr>
<td>Randomized, double-blind, placebo-controlled, parallel-group study</td>
<td>Adults (18 – 55 years); n = 420</td>
<td>LDX 30, 50, 70 mg vs Placebo</td>
<td>4-week randomized trial</td>
<td>ADHD-RS: all groups receiving LDX had better changes in total score compared to the placebo group</td>
</tr>
</tbody>
</table>

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 severe TEAEs in comparison to previous-exposure subjects; however, LDX reduced the core symptoms of ADHD [20].

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

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Bibliography

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


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