Focus on Lisdexamfetamine: A Review of its use in Child and Adolescent Psychiatry

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Abstract

Objective: To summarize and review published literature regarding lisdexamfetamine and its use in child and adolescent psychiatry. **Method:** A literature review was conducted using the PubMed search term: 'lisdexamfetamine' with limits: Human trials, English language, All Child (aged 0-18 years). Additional articles were identified from reference information and poster presentation data. **Results:** Lisdexamfetamine (Vyvanse®) is a prodrug formulation of dextroamphetamine used for the treatment of Attention Deficit/Hyperactivity Disorder (ADHD). Conversion of lisdexamfetamine to active dextroamphetamine occurs via hydrolytic enzymes located on erythrocytes, and leads to an onset of action within 1-2 hours post-dose, and duration of up to 13 hours. Administration of lisdexamfetamine via nasal or intravenous routes did not result in significant elevation of drug liking scores in known stimulant abusers, suggesting low potential for abuse. Lisdexamfetamine has been available in the United States since 2007, but was only recently approved by Health Canada for use in children 6 to 12 years of age. There are five randomized controlled trials with lisdexamfetamine in children and adolescents showing efficacy for treatment of ADHD. In addition, several open-label trials and case reports were identified. The adverse effect profile of lisdexamfetamine is similar to that observed with other long-acting amphetamine formulations. **Conclusion:** Lisdexamfetamine is a novel long-acting stimulant formulation with efficacy for treatment of ADHD and low abuse potential due to its prodrug formulation.

Key words: *lisdexamfetamine, ADHD, amphetamine, stimulants, attention deficit, hyperactivity, substance abuse*

Introduction

Lisdexamfetamine (Vyvanse®, LDX) is a novel prodrug formulation of the commonly used stimulant medication dextroamphetamine. It was released in Canada in February 2010, but has been available in the United States since 2007. LDX has received approval from Health Canada for use in children aged 6-12 years of age, and in the US, is FDA approved for use in this age group, as well as for treatment of adults with ADHD. This article will focus on helping the clinician understand the implications of the prodrug pharmacology employed in this product and review the available evidence regarding the use of LDX for the treatment of Attention Deficit/Hyperactivity Disorder (ADHD) in child and adolescent psychiatry.

ADHD is a common condition, with an estimated prevalence of 3-7% (American Psychiatric Association [*DSM-IV-TR*], 2000), though prevalence has been reported elsewhere at rates of 4-12% (Brown et al., 2001). Stimulant medications including methylphenidate and amphetamine derivatives in various long-acting formulations are established as first-line therapies for treatment of ADHD (Plizska et al., 2006, CADDRA 2008). However, misuse/abuse liability for stimulant medications, particularly of the short-acting formulations is an ongoing concern. In a 2009 report on youth risk behavior (Department of Health & Human Services Centre for Disease Control and Prevention, 2010), over 20% of US youths report having taken a prescription drug without a doctor's prescription at least once in their lifetime. Rates of non-prescribed stimulant use ranged from 5-35% in college-age individuals in one systematic review (Wilens et al., 2008). The primary source of supply of inappropriately used stimulants such as methylphenidate appears to be from patients who are prescribed this medication legitimately, making efforts directed at preventing stimulant diversion worthwhile (Barrett, Darredeau, Bordy & Pihl, 2005). A Canadian law

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enforcement officer, author and expert in street drug enforcement matters who has managed over 780 undercover drug transactions stated anecdotally that short-acting stimulant formulations are commonly abused, but long-acting stimulant formulations are almost never recovered in busts of drug trafficking operations (S. Walton, personal communication, June 15, 2010).

Long-acting methylphenidate and amphetamine-based formulations and non-stimulant drugs such as atomoxetine have been developed in recent years in an effort to combat the problem of stimulant diversion. Similarly, LDX was developed to have similar efficacy to currently available long-acting stimulants, with reduced toxicity in overdosage, and reduced liability for misuse/abuse via inhalation or injection.

Pharmacology

LDX is available in 20, 30, 40, 50 and 60 mg capsules. A 70 mg capsule is marketed in the US, but is not available in Canada. The commercial preparation consists of drug powder and excipients inside a plain capsule shell. The capsule may be opened and the contents dissolved in plain water prior to oral administration (Shire Canada Inc., 2010). Dilution of LDX in fluids other than plain water has not been studied, and no specific recommendations can be made (A. Kotsoros, (Shire Canada), personal communication, May 5, 2010).

Following oral administration, LDX is absorbed via peptide transport proteins in the small intestines (Pennick, 2010), but not the colon. Peak d-amphetamine levels are slightly but non-significantly lowered when LDX is taken with food compared to when taken in the fasting state (Krishnan & Zhang, 2008). Time to achieve peak level is delayed by approximately one hour when LDX is taken with food compared to when taken in the fasting state. Available long-acting stimulant formulations which rely on breakdown of bead coating to delay drug release may be susceptible to significant variation in time to onset and duration of action due to inter-individual variations in gastric acidity. In a single-dose study in adults, LDX absorption was not significantly affected by differences in gastric pH associated with administration of the gastric proton-pump inhibitor omeprazole (Haffey et al., 2009).

LDX is a therapeutically inactive prodrug. Each LDX molecule consists of a molecule of dextroamphetamine attached via covalent bond to a molecule of the naturally occurring essential amino acid lysine. Following oral ingestion, LDX undergoes enzymatic hydrolysis into its component molecules. The site where LDX hydrolysis occurs was the subject of some controversy. Initially, this was reported to occur via digestive enzymes in the gastrointestinal tract (Krishnan & Moncrief, 2007). More recently, it was shown that LDX hydrolysis takes place on the erythrocyte (Pennick, 2010) as demonstrated by rapid conversion of LDX to dextroamphetamine when incubated with human erythrocytes, and negligible conversion to dextroamphetamine when incubated with human leucocytes, platelets, colon tissue or liver microsomes. The enzymatic process appears to be high-capacity, with saturation unlikely to occur at therapeutic LDX dosages.

Peak levels of (intact inactive pro-drug) LDX occur at 1 hour, and complete elimination of intact pro-drug occur by 4 hours post-dose following a single LDX dose in children (Boellner et al., 2010) and by 6 hours post-dose following multiple daily dosing in adults (Krishnan & Stark, 2008). Peak levels of d-amphetamine are achieved at a mean of 3.7 hrs following LDX administration. Despite this longer time to achieving peak levels compared to other immediate and extended-release amphetamine formulations, onset of clinical effect was noted by 2 hours following LDX administration and was comparable to the clinical effect seen with administration of mixed amphetamine salts extended-release (MAS-XR) (Biederman, Boellner, Childress, Lopez & Zhang, 2007b). Peak d-amphetamine levels are dosage-proportional at recommended dosages (Ermer, Homolka, Martin, Buckwalter, Purkayastha & Roesch, 2010, Boellner, Stark, Krishnan & Zhang, 2010) but are attenuated at dosages above 130-150 mg, suggesting saturation of the enzymatic hydrolysis, and reduced potential for toxicity in overdose (Ermer et al., 2010). LDX and d-amphetamine levels have low inter- and intra-subject variability (Ermer et al., 2008, Boellner et al., 2010).

Levels of d-amphetamine achieved following LDX administration did not differ by gender or age group (6-9 years of age compared to 10-12 years of age) when LDX dose was normalized by weight (Boellner et al., 2010). Serum elimination half-life of d-amphetamine following LDX administration ranged from 8.6 to 10.4 hours (Boellner et al., 2010), and is comparable to the half-life previously reported for d-amphetamine (DrugDex Evaluations, 2010, LexiComp™ Online, 2010). Once ingested, the pharmacodynamic profile of LDX is similar to that of d-amphetamine.

LDX did not demonstrate concentration dependent inhibition of any of seven common cytochrome p450 isoforms in an *in vitro* study, and appears to have a low potential for drug-drug interactions (Krishnan & Moncrief, 2007).

Abuse potential

The pharmacokinetics of active dextroamphetamine following LDX administration via both the oral and intranasal routes are virtually identical (Ermer et al., 2009). When compared to

placebo, twelve male intravenous substance abusers showed elevated Drug Rating Questionnaire (DRQS) 'liking' scores following intravenous injection of dextroamphetamine 20 mg, but not following intravenous injection of LDX 50 mg (Jasinski & Krishnan, 2009a). Oral administration of LDX at doses of 50 mg and 100 mg to 36 known adult stimulant abusers did not result in significantly elevated DRQS scores, compared to placebo, though LDX 150 mg (over twice the recommended maximum oral dosage, and representing approximately 60 mg of dextroamphetamine base) did result in elevated DRQS scores, similar to those achieved with administration of dextroamphetamine 40 mg. (Jasinski & Krishnan, 2009b). Surveillance data from the three years following market availability in the US revealed a low number of reports of non-medical use of LDX (Varughese, Rosen, Ertischek, Sembower, St. Jean & Schnoll, 2010).

Efficacy Data

A review of the literature was conducted using the MEDLine search term: 'lisdexamfetamine' with limits: Human trials, English language, All Child (aged 0-18 years). Additional articles were identified from reference information and poster presentation data. Table 1 summarizes the published pediatric literature on LDX. The studies are ranked by Level of Evidence (Centre for Evidence Based Medicine, 2009). There have been 5 prospective, randomized control trials (RCT) of LDX in children or adolescents and 2 prospective open-label dose optimization trials.

Biederman, Krishnan, Zhang, McGough & Findling (2007a) showed a significant treatment difference favoring LDX compared to placebo on the ADHD Rating Scale Version IV (ADHD-RS-IV), Conner's Parent Rating Scale—Revised (CPRS-R) and the Clinical Global Impression—Improvement Scale (CGI-I) in a 4 week placebo-controlled trial with LDX (30mg, 50mg or 70 mg). Earlier, Biederman et al. (2007b) had shown significant improvements for LDX (30 mg, 50 mg or 70 mg) and MAS-XR (10 mg, 20 mg or 30 mg) versus placebo using the Swanson, Kotkin, Agler, M-Flynn, and Pelham deportment scale (SKAMP-DS), Swanson, Kotkin, Agler, M-Flynn, and Pelham attention scale (SKAMP-AS), Permanent Product Measure of Performance (attempted) (PERMP-A), Permanent Product Measure of Performance (correct) (PERMP-C) and CGI-I. This study involved a 3 week open-label dose-optimization period followed by a 3 week randomization period. Comparing LDX and MAS-XR, no significant differences in primary or secondary outcome measures were observed between the two treatment groups.

Wigal, Kollins, Childress & Squires (2009) conducted a 4 week dose optimization followed by a 2 week double-blind randomized crossover trial of LDX versus placebo. Beginning with the primary endpoint of SKAMP-DS scores measured 1.5 hours post-dose and the key secondary endpoint of clinically significant separation ($p<0.005$) of LDX versus placebo at all time points. In addition, for the secondary endpoint of ADHD-RS-IV scores, LDX (all doses) were superior to placebo ($p< 0.0001$). Changes in PERMP-A and PERMP-C scores in the LDX groups compared to those receiving placebo were statistically significant as well.

Childress et al. (2010) using the ADHD-RS-IV, CGI-I, and the Youth Quality of Life—Research Version (YQOL-R), found statistically significant improvement in a 4 week randomized controlled trial of 314 adolescents with ADHD comparing LDX (30 mg, 50 mg or 70 mg) to placebo. However, there was not statistically significant improvement in quality of life scores for LDX compared to placebo.

In a 3 week open-label dose optimization followed by a 4 week randomization comparing LDX (30 mg, 50 mg or 70 mg) to placebo, Giblin & Strobel (2010) noted a significant improvement with LDX compared to placebo on the ADHD-RS-IV, Conner's Parent Rating Scale—Revised: Short (CPRS-R-S) and the CGI-I. However, there was no significant benefit of LDX on sleep-related behaviours.

Two prospective open-label LDX dose optimization trials were completed (Findling, Childress, Krishnan & McGough 2008, Findling, Ginsberg, Jain & Gao, 2009). In the earlier trial (Findling et al., 2008), ADHD-RS-IV scores were reduced by over 60% from baseline with LDX and 81% were rated improved or better on the CGI-I at trial endpoint. In the later study (Findling et al., 2009), there was statistically significant improvement in the ADHD-RS-IV, Expression and Emotion Scale for Children (EESC) and Behaviour Rating Inventory of Executive Function (BRIEF) compared to baseline, and 90% were rated improved or better on the CGI-I and 85% rated improved on the Parental Global Assessment scale (PGA) respectively.

Safety Data

Since LDX is ultimately converted to d-amphetamine, intuitively, the adverse effect profile of LDX may be expected to be similar to that observed with other long-acting amphetamine formulations. Safety data were reviewed from a Pharmacokinetic Single-dose Randomized Open-Label Cross-Over Trial, a Randomized Double-Blind Placebo Controlled Safety Trial, a head-to-head comparison of LDX and MAS-XR, and 2 case reports.

Table 1. Summary of lisdexamfetamine evidence in children and adolescents

Report type & level of evidence	Year/Lead Author/Journal	# of pts (n), % males	Pt age (mean (SD) and range) (years)	Dosage	Duration of treatment	Efficacy Rating Scales (Bold = 1° Endpoint)	Efficacy results	Adverse effects (AE)
Prospective Double-Blind Randomized Trial **(Level 1b)**	2010; Giblin; J Atten Disord	n = 24 (40.7% male)	LDX group 10.5 (2.2) PI group 8.8 (2.2) (range: 6-12)	LDX 30mg, 50mg, or 70mg vs PI	3 week open-label dose-optimization followed by 4 weeks randomization	**ADHD-RS-IV** CGI-I CPRS-R:S CSHQ	**ADHD-RS-IV: mean improvement of 28.7 (p<0.0001)** CPRS-R:S: (p<0.0001) comparing LDX group to PI from baseline to endpoint CGI-I: (p<0.0001) comparing LDX group to PI from baseline to endpoint CSHQ: no effect of LDX on sleep-related behaviours	non-significant (P=0.35) increase in LPS in LDX vs PI WASO,TST&actigraphy: no statistically significant change in LDX vs PI AE % above placebo: increased pulse (20.8%), headache (16.6%), increased blood pressure (4.2%)
Prospective Double-Blind Randomized Placebo-Controlled Trial (Level 1b)	2010; Childress; APA poster presentation/ clinicaltrials.gov NCT 00735371	n = 314 (70.9% male)	14.5 (1.39) (range: 13-17)	LDX 30mg, 50mg, or 70mg vs PI	4 weeks	**ADHD-RS-IV** CGI-I YQOL-R	**ADHD-RS-IV: LDX 30mg vs PI p<0.0056; LDX 50mg vs PI (p<0.0001); LDX 70mg vs PI (p<0.0001)** CGI-I: LDX 30mg vs PI (p=0.0235); LDX 50mg vs PI (p<0.0001); LDX 70mg vs PI (p<0.0001) YQOL-R: no statistically significant change compared to PI	AE % above placebo: decreased appetite (31.3%), decreased weight (9.4%), insomnia (7.3%), dry mouth (5.2%), irritability (3%), nasal congestion (2.5%), nasopharnygitis (1.7%), fatigue (1.7%), headache (1.6%), nausea (1.3%), dizziness (0.4%)
Prospective Double-Blind Randomized Placebo-Controlled Dose-Optimization Crossover Trial (Level 1b)	2009; Wigal; Child Adolesc Psychiatry Ment Health	n = 117 (76% male)	10.1 (1.5) (range: 6-12)	LDX 30mg, 50mg, or 70mg vs PI	4 week dose-optimization then 2 weeks double-blind crossover	**SKAMP-DS** SKAMP-AS PERMP-A PERMP-C CGI-I ADHD-RS-IV	**SKAMP-DS: 1º endpoint 1.5hrs post-dose; key secondary endpoint; p<0.005 separation of LDX vs PI at all time points; mean score difference LS means (95% CI) of LDX vs PI was 0.74 (-0.85, -0.63) (p<0.0001)** SKAMP-AS: LDX vs PI p≤0.001 @ all time points PERMP-A: differences in LS means (95% CI) of LDX vs PI @ 1.5hrs=16.97 @ 13hrs=28.28 (p<0.0001) PERMP-C: differences in LS means (95% CI) of LDX vs PI @ 1.5hrs=19.1 @ 13hrs=28.14 (p<0.0001) CGI-I: dose-optimization phase = 100% "improved"; crossover phase = LDX 82.3% "improved" vs PI 19.5% "improved" ADHD-RS-IV: LDX (all doses) vs PI (p<0.0001)	Dose-optimization phase AE >10%: decreased appetite (47.3%), insomnia (27.1%), irritability (16.3%), headache (17.1%), upper abdominal pain (15.5%), affect lability (10.1%) Crossover phase (% above placebo): decreased appetite (5.2%), insomnia (4.3%), headache (3.5%) Pts withdrawn due to AE = 7%
Prospective Randomized Double-Blind Placebo-Controlled Crossover Trial (Level 1b)	2007b; Biederman; Biol Psychiatry	n = 52 (64% male)	9.1 (1.7) (range: 6-12)	LDX 30mg, 50mg or 70mg vs MAS XR 10mg, 20mg, or 30mg vs PI	3 week open-label dose-optimization followed by 3 weeks randomization	**SKAMP-DS** SKAMP-AS PERMP-A PERMP-C CGI-I	**SKAMP-DS: LDX 0.8 ±0.1 vs PI 1.7 ±0.1 (P<0.0001)** **MAS XR 0.8 ±0.1 vs PI 1.7 ±0.1 (P<0.0001)** SKAMP-AS: LS mean LDX + MAS XR 1.2 vs PI 1.8 (P<0.0001) PERMP-A: LS LDX 133.3 vs MAS XR 133.6 vs PI 88 (P<0.0001) PERMP-C: LS LDX 129.6 vs MAS XR 129.4 vs PI 84.1 (P<0.0001) CGI-I: LDX 2.2 vs MAS XR 2.3 vs PI 4.2 (P<0.0001); LDX 74% rated as very much improved or much improved vs MAS XR 72% vs PI 18%	(LDX % above placebo) insomnia (6%), decreased appetite (6%), anorexia (4%) (MAS XR % above placebo) decreased appetite (4%), upper abdominal pain (2%), abdominal pain (4%) Pts withdrawn due to AE = 2%
Prospective Randomized Double-Blind Trial (Level 1b)	2007a; Biederman; Clin Ther	n = 290 (69% male)	9 (1.8) (range: 6-12)	LDX 30mg, 50mg, or 70mg vs PI	4 weeks	**ADHD-RS-IV** CPRS-R CGI-I	**ADHD-RS-IV: treatment difference vs PI (negative score denotes improvement) - 20.5 with 70mg group; all doses significant improvement (p<0.001)** CPRS-R : all doses vs PI (p<0.001) CGI-I: all doses ≥70% rated as very much improved or much improved vs 18% for PI	AE % above placebo: decreased appetite (35%), insomnia (16%), irritability (10%), weight loss (8%), upper abdominal pain (6%), vomiting (5%), nausea (3%), headache (2%) Pts withdrawn due to AE = 7%

continued

Table 1. Summary of lisdexamfetamine evidence in children and adolescents (continued)

Report type & level of evidence	Year/Lead Author/Journal	# of pts (n), % males	Pt age (mean (SD) and range) (years)	Dosage	Duration of treatment	Efficacy Rating Scales (Bold = 1° Endpoint)	Efficacy results	Adverse effects (AE)
Secondary analysis of Biederman 2007a trial (Level 1b)	2008; Lopez; Postgraduate Medicine	n = 290 (69% male)	9 (1.8) (range: 6-12)	LDX 30mg, 50mg, or 70mg vs Pl	4 weeks	CPRS-R:S CPRS-R:S ADHD Index CPRS-R:S Hyperactivity CPRS-R:S Cognition CPRS-R:S Oppositional	CPRS-R:S = all doses vs Pl (p<0.0001) CPRS-R:S ADHD Index = improvement from baseline for all doses vs Pl (p<0.0001) CPRS-R:S Hyperactivity = improvement from baseline for all doses vs Pl (p<0.0001) CPRS-R:S Cognition = improvement from baseline for all doses vs Pl (p<0.0001) CPRS-R:S Oppositional = improvement from baseline for all doses vs Pl @ 1000 & 1400 (p<0.01) but not significant for 1800 assessment time	AE % above placebo: decreased appetite (35%), insomnia (16%), irritability (10%), weight loss (8%), upper abdominal pain (6%), vomiting (5%), nausea (3%), headache (2%) Pts withdrawn due to AE = 7%
Prospective Open-Label Dose-Optimization Trial (Level 2b)	2009; Findling; J Child Adolesc Psychopharmacol	n = 318 (70.7% male)	9.1 (1.9) (range: 6-12)	Flexible Dose (range: LDX 20-70mg)	7 weeks	**ADHD-RS-IV** CGI-I PGA EESC BRIEF	**ADHD-RS-IV: mean (SD) improvement of -28.6 (10.9) compared to baseline (p<0.0001)** CGI-I: 89.9% of pts were classified as improved PGA: 85% of pts classified as improved EESC: mean (SD) improvement of -7.5 (0.3) (p<0.0002) BRIEF: mean (SD) improvement of -17.9 (3.1)	decreased appetite (43.2%), decreased weight (17%), irritability (16.1%), insomnia (16.1%), headache (13.9%), upper abdominal pain (13.2%), initial insomnia (11.4%) AE were noted to be highest at the 20mg dose and lowest at the 70mg dose Pts withdrawn due to AE = 4.1%
Prospective Open-Label Trial (Level 2b)	2008; Findling; CNS Spectr	n = 272 (69.5% male)	9.2 (range: 6-12)	LDX 30mg, 50mg or 70mg	12 months	**ADHD-RS** CGI-I	**ADHD-RS: improved by 27.2 (±13.0) points over baseline (p<0.0001); score reduced by >60% from baseline** CGI-I: 81.1% at endpoint rated "improved"	AE 5%: decreased appetite (33%), headache (18%), decreased weight (18%), insomnia (17%), upper abdominal pain (11%), upper respiratory tract infection (11%), irritability (10%), nasopharyngitis (10%), vomitting (9%), cough (7%), influenza (6%) Pts withdrawn due to AE = 9.2%
Randomized Double-Blind Placebo Controlled Safety Trial (Level 2c)	2010; Goodman; APA poster presentation	n = 290 (69% male) (children) n = 310 (70% male) (adolescents) n = 420 (54% male) (adults)	children = 6-12 adolescents = 12-17 adults = 18-55	LDX 30mg, 50mg, or 70mg vs Pl	4 weeks	n/a	Not Reported	AE above placebo: Children = decreased appetite (34.8%), insomnia (16%), upper abdominal pain (6.3%), dry mouth (4.6%), headache (2.2%) Adolescents = decreased appetite (31.3%), insomnia (7.3%), dry mouth (3%), headache (1.6%) Adults = decreased appetite (24.9%), dry mouth (22.5%), insomnia (14.5%), headache (7.8%), upper abdominal pain (7.8%)
Case Report (Level 4)	2010; Hood; Pediatrics	n = 1 (male)	14	LDX 30mg	5 months	n/a	Not Reported	Eosinophilic hepatitis developed after 5 months treatment with LDX 30mg; pt required hospitilization; other causes of hepatitis ruled out; Hepatitis resolved completely 2 months after discontinuation of LDX
Case Report (Level 4)	2009; Brahm; Prim Care Companion J Clin Psychiatry	n = 1 (female)	5	LDX 30mg	5 days	n/a	Not Reported	Generalized alopecia noted after 5 days of treatment with LDX. Resolved 2 days after discontinuation of LDX
Exploratory Uncontrolled (Level 4)	2010; Faraone; J Am Acad Child Adolesc Psychiatry	n = 281 (69% male)	10.4 (1.8) (range: 6-13)	LDX 30mg, 50mg, or 70mg	up to 15 months mean (SD) 265 (149) days	n/a	weight: mean loss in expected weight = 3.7kg (compared to CDC norms) Height: average loss in expected height = 0.9cm BMI: mean raw BMI scores decreased significantly from baseline to endpoint (t_{276} = 10.15; (p<0.0001))	Cumulative LDX dose predicted decreases in expected weight, height, and BMI during treatment

continued

Table 1. Summary of lisdexamfetamine evidence in children and adolescents (continued)

Report type & level of evidence	Year/Lead Author/Journal	# of pts (n), % males	Pt age (mean (SD) and range) (years)	Dosage	Duration of treatment	Efficacy Rating Scales (Bold = 1° Endpoint)	Efficacy results	Adverse effects (AE)
Pharmacokinetic Single-dose Randomized Open-Label Cross-Over Trial (level N/A)	2010; Boellner; Clin Ther	n = 18 (56% male)	9.6 (1.9) (range: 6-12)	LDX 30mg, 50mg, or 70mg single dose	3 weeks (6 day washouts in between doses)	n/a	Pharmacokinetic: C_{max} (%CV) of d-amphetamine with LDX 30mg = 53.2(18.1), 50mg = 93.3(19.5), 70mg = 134.0(19.4) suggesting a linear dose-proportional increase C_{max} of intact LDX was not dose-proportional For all 3 doses of LDX, C_{max} was reached @ ~3.5hrs and remained >LLOQ @ 48hrs No statistically signficant change in mean $t_{1/2}$ or T_{max}	% average of all 3 doses: anorexia (36.7%); increased blood pressure (11.7%); abdominal pain (11.7%)
Pharmacokinetic Open-Label Randomized Crossover (Level N/A)	2009; Haffey; Postgraduate Medicine	n = 24 (75% male)	37.7 (6.54) (range: 18-45)	LDX 50mg MAS XR 20mg omeprazole 20mg	23 days	n/a	Pharmacokinetic: LDX = C_{max}, AUC_{inf} & T_{max} unchanged with administration with omeprazole MAS XR = C_{max} & AUC_{inf} unchanged with administration with omeprazole; T_{max} reduced from 5hrs without omeprazole to 2.75hrs with omeprazole Showed unpredictable release of the delayed release bead of MAS XR likely due to reduced stomach acid while taking omeprazole	For LDX (≥5%) = anxiety; vasospasm; headache; dizziness; palpitations; tachycardia For MAS XR (≥ 5%) = vasospasm; anxiety All reports of vasospasm occurred during treatment with stimulants in combination with omeprazole Blood pressure and pulse increased after LDX and MAS XR but was considered non-clinically significant
Pharmacokinetic Single-dose (Level N/A)	2010; Ermer; J Clin Pharmacol	n = 20 (75% male)	33.3 (8.14) (range: 18-55)	LDX 50mg, 100mg, 150mg, 200mg, and 250mg single dose	5 dosing periods of 5 days	n/a	Pharmacokinetic: Mean d-amphetamine C_{max} and $AUC_{0-\infty}$ increased in a linear dose-dependent manner Median T_{max} ranged between 4-6hrs Median $t_{1/2}$ ranged from 10.6-11.7hrs Low inter & intrasubject variability (<20%) in doses of 50-150mg	AE >15%: nausea; dizziness; headache; psychomotor hyperactivity; dysuria Dose-dependent increases in mean blood pressure & pulse peaked @ 2hrs and 8-12hrs respectively
Pharmacokinetic partially-randomized single-blind (Level N/A)	2006; Jasinski; Poster presentation at US Psychiatric & Mental Health Congress	n = 12 (100% male)	43 (range: 29-52)	LDX 30mg, 50mg, 70mg, 100mg, 130mg, 150mg, d-AS 40mg, and Pl	2 months	n/a	Pharmacokinetic: C_{max} & AUC increased with doses of 30mg-130mg of LDX then attenuated between 130mg & 150mg amphetamine AUC over first 4 hrs was substantially lower with LDX than with d-AS (comparible doses) $t_{1/2}$ of LDX was 0.44-0.76 hrs indicating rapid clearance of the prodrug	For LDX: most frequent by frequency counts were headache (8 counts); most frequent by subject incidence was headache (50%) Effects of LDX 30-100mg on blood pressure and pulse appeared to be less intensive as compared to d-AS 40mg (effects of 130-150mg LDX were similar to d-AS with a delayed peak of ~ 1hr)

Abbreviations

ACCP = American College of Clinical Pharmacy; AUC = area under the curve;
BMI = Body Mass Index;
CDC = Center for Disease Control; CI = confidence interval; C_{max} = maximum concentration; CV = coefficient of variation; d-AS = d-amphetamine sulfate;
LDX = lisdexamfetamine; LLOQ = lower limit of quantitation; LS = least squares; LPS = latency to persistent sleep;
MAS XR = mixed amphetamine salts extended-release;
Pl = placebo;
SD = standard deviation;
T_{max} = time to maximum concentration; TST = total sleep time; $t_{1/2}$ = half-life;
WASO = wake time after sleep onset

Abbreviatiosn of rating scales used

ADHD-RS-IV = ADHD Rating Scale Version IV
BRIEF = Behaviour Rating Inventory of Executive Function
CGI-I = Clinical Global Impression - Improvement Scale
CPRS-R = Conner's Parent Rating Scale - Revised
CPRS-R:S = Conner's Parent Rating Scale - Revised: Short
CSHQ = Child's Sleep Habits Questionnaire
EESC = Expression and Emotion Scale for Children
PERMP-A = Permanent Product Measure of Performance (attempted)
PERMP-C = Permanent Product Measure of Performance (correct)
PGA = Parental Global Assessment
SKAMP-AS = Swanson, Kotkin, Agler, M-Flynn, and Pelham (attention)
SKAMP-DS = Swanson, Kotkin, Agler, M-Flynn, and Pelham (deportment)
YQOL-R = Youth Quality of Life - Research Version

In a pharmacokinetic single-dose randomized open-label crossover trial, Boellner, Stark, Krishnan & Zhang (2010) conducted a 3 week study evaluating LDX 30 mg, 50 mg and 70 mg doses (with 6 day washouts periods in between study days). Taken as an average of all 3 dose levels, 36.7% of patients experienced anorexia, 11.7% experienced abdominal pain, and 11.7% had blood pressure increases. All adverse effects were classed as mild or moderate, and no serious adverse effects were reported.

Goodman et al., (2010), reported adverse effects in a Randomized Double-Blind Placebo Controlled Safety trial in children and adolescents (6 to 17 years of age) and adults aged 18-65 years of age respectively. Children experienced decreased appetite (34.8%), insomnia (16%), upper abdominal pain (6.3%), dry mouth (4.6%) and headache (2.2%). Adolescents experienced adverse effects in similar proportions (decreased appetite (31.3%), insomnia (7.3%), dry mouth (3%) and headache (1.6%)) with the exception of upper abdominal pain. Adults had similar adverse effects as children and adolescents, with the rate of decreased appetite (24.9%) and insomnia (14.5%) less than in children but a greater rate of dry mouth (22.5%), headache (7.8%) and upper abdominal pain (7.8%). Despite significant rates of decreased appetite and anorexia in this trial, mean z-scores for weight in children and adolescents remained above means for age- and sex-matched general populations.

In the LDX and MAS-XR head-to-head trial (Biederman, 2007b) insomnia was reported more often with LDX (8%) compared to MAS-XR (2%) and placebo (2%), while upper abdominal pain and vomiting was reported rarely with MAS-XR and placebo, but not with LDX. MAS-XR includes l-amphetamine (as d-/l-racemates of both the aspartate and sulfate salts), which has greater norepinephrine release compared to d-amphetamine (Easton, Steward, Marshall, Fone & Marsden 2007). There was speculation that due to this property, MAS-XR may be more likely to induce anxiety compared to LDX, which is ultimately converted to "pure" d-amphetamine. However, anxiety was not documented as an adverse effect in either treatment group during this trial.

Hood & Nowicki (2010) reported a case of eosinophilic hepatitis requiring hospitalization that developed in a 14 year old male following 5 months treatment with LDX 30 mg. The hepatitis resolved completely within 2 months after LDX discontinuation.

Brahm & Hamilton (2009) described a case of generalized alopecia (diffuse thinning of hair) following 5 days of treatment with LDX 30 mg in a 5 year old female. Alopecia was less marked 2 days after LDX discontinuation.

Faraone, Spencer, Kollins & Glatt (2010) noted mean loss in expected weight (compared to Center for Disease Control (CDC) norms) was 3.7 kg following a mean of 265 days of LDX treatment in children 6-13 years of age. The average loss in expected height was 0.9 cm and mean raw BMI scores decreased significantly from baseline to endpoint.

Haffey et al. (2009) compared the pharmacokinetics of LDX 50 mg and MAS-XR 20 mg when co-administered with placebo or the proton pump inhibitor, omeprazole. Time to peak d-amphetamine level from LDX administration was not affected by omeprazole, but was reduced from 5 hours to 2.75 hours when MAS-XR was co-administered with omeprazole, indicating unpredictable breakdown of delayed release beads due to reduced stomach acid. Despite this difference, both treatment groups experienced similar rates of adverse effects, with anxiety and vasospasm occurring in greater than 5% of patients. Headache, dizziness, palpitations, and tachycardia also occurred at rates of greater than 5% in the LDX group. All reports of vasospasm occurred during treatment with stimulant/omeprazole combination. Blood pressure and pulse increases were noted with both LDX and MAS-XR but were considered clinically insignificant.

Ermer et al. (2010) reported that for adults who received single doses of LDX 50 mg, 100 mg, 150 mg, 200 mg or 250 mg, greater than 15% of participants experienced nausea, dizziness, headache, psychomotor hyperactivity and dysuria. Dose-dependent increases in mean blood pressure and heart rate were observed, which peaked at 2 hours and 8-12 hours post-dose respectively. No subjects had vital sign measurements judged to be of clinical concern, and no adverse events were related to vital signs.

Jasinski & Krishnan (2006) reported adverse effects of 12 adult stimulant abusers receiving LDX 30 mg, 50 mg, 70 mg, 100 mg, 130 mg, 150 mg, d-amphetamine 40 mg, and placebo in random order. The most frequently reported adverse effect was headache (8 reports, in 6 patients). Effects of LDX 30-100 mg on blood pressure and pulse appeared to be less intensive compared to d-amphetamine 40 mg, while effects of LDX 130-150 mg were similar to d-amphetamine with a time to peak effect occurring approximately one hour later with LDX).

Discussion and Recommendations

LDX is a novel prodrug formulation which requires metabolism by erythrocytes to active d-amphetamine. This feature is very helpful in treating patients with ADHD who are likely to, or currently abuse prescription drugs including stimulants. Once ingested, the pharmacodynamic profile of LDX is similar to that of d-amphetamine. Surveillance data from the three

years following market availability in the US revealed a low number of reports of non-medical use of LDX.

The RCT evidence reviewed thus far are positive for LDX, which appears as clinically effective in reducing symptoms of hyperactivity, inattention and impulsivity, as other available stimulants. Although peak d-amphetamine are achieved at a mean of 3.7 hours following LDX administration, the onset of clinical effect was seen as early as 2 hours following LDX administration, which was similar to the onset following MAS-XR administration. In terms of duration, LDX appears to last as long as, or longer than other extended release stimulants.

The adverse effect profile of LDX is similar to other available stimulants. LDX did not demonstrate concentration dependent inhibition of any of seven common cytochrome p450 isoforms and appears to have a low potential for causing pharmacokinetic drug interactions, which is an important consideration if a patient is receiving pharmacotherapy for other medical or psychiatric conditions.

Use of LDX in patients in age groups outside the Health Canada approved range of 6-12 years is likely to be considered by clinicians. As mentioned above, the US FDA has already granted approval for use of LDX in adults. An application for FDA approval in adolescents has been submitted based on the results of the LDX trial (Childress, 2010) conducted in adolescents and recently announced at the 2010 American Psychiatric Association annual meeting. Systematic study of LDX has not been undertaken in children under the age of 6. There is a single case report of LDX use in a 5 year old female (Brahm, 2009) documenting an adverse reaction of moderate severity.

The price range of the available LDX dosage forms is somewhat higher than other long-acting stimulant formulations available in Canada (e.g. Adderall XR®, Concerta® and Biphentin®). This may pose a barrier to widespread use and provincial formulary uptake of LDX and ultimately, reduction of the rate of stimulant abuse. Conversely, the long duration of action of LDX observed in clinical trials (up to 13 hours in one analog classroom study (Wigal, 2009)) may prevent the hidden cost of administration of a supplementary short-acting stimulant in the late afternoon (as sometimes required with other long-acting stimulants).

In summary, LDX is an effective treatment for ADHD with a tolerability profile similar to other long-acting amphetamine based products. LDX does not appear to be susceptible to variations in gastric acidity, and has a low potential for drug-drug interactions. The prodrug formulation of LDX is novel, and significantly reduces the likelihood that LDX will be abused by stimulant-seeking prescription drug abusers.

Acknowledgements/Conflicts of Interest

Dean Elbe has presented educational sessions pertaining to lisdexamfetamine on behalf of Shire Canada. Angela MacBride has no conflicts to disclose. Dorothy Reddy is the principal investigator of a lisdexamfetamine clinical trial currently underway at BC Children's Hospital.

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