Evaluation of the Efficacy and Tolerability of Vyvanse (Lisdexamfetamine Dimesylate) in Treating Children Age 6-12 with Attention Deficit Hyperactivity Disorder

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Abstract

Background: Lisdexamfetamine Dimesylate (LDX) is a therapeutically inactive amphetamine prodrug. Pharmacologically active d-amphetamine is released from Lisdexamfetamine following oral ingestion. It is indicated in the treatment of children ages 6-12 with Attention Deficit Hyperactivity Disorder (ADHD). The goal of LDX is to provide a one dose, extended release medication throughout the day as well as a reduced potential for abuse, overdose toxicity and drug misuse.

Hypothesis: Evaluation of the Efficacy and Tolerability of Lisdexamfetamine Dimesylate (Vyvanse) in Treating Children Age 6-12 with Attention Deficit Hyperactivity Disorder

Study Design: Extensive search of available medical literature and review regarding LDX efficacy and tolerability in children ages 6-12 with ADHD.

Methods: Exhaustive literature search using the following search engines: MEDLINE, Evidence Based Medicine Reviews Multifile, CINAHL, Pub Med, MD Consult, And PsycINFO. The main inclusion criteria were: children age 6-12, patients taking single therapy Lisdexamfetamine dimesylate, primary diagnosis of ADHD based on a psychiatric evaluation that reviews DSM-IV criteria. The exclusion criteria for the study were: comorbid psychiatric diagnoses (such as psychosis, bipolar illness, pervasive developmental disorder, severe obsessive compulsive disorder, and severe depressive or severe anxiety disorder), adolescent or adults and patients currently taking alternative amphetamines.

Results: Biederman et al, Study A: Significant improvements in ADHD-RS-IV scores were seen with all doses of LDX compared with placebo (all, P<0.0001), and in CPRS scores with all LDX doses versus placebo throughout the day (all, P<0.0001 for all comparisons). Efficacy was observed by the first week of treatment and improvements were observed throughout the day up to 6pm. Biederman et al, Study B: LDX treatment significantly improved scores on SKAMP-Depportment, and Attention, PERMP attempted and correct and CGI improvement from baseline. Adverse events were similar for both active treatments. Wigal et al, Study C: Compared with placebo, LDX demonstrated significantly greater efficacy at each post-dose time point (1.5 hours to 13 hours), as measured by SKAMP-Deportment and attention scale and PERMP (P < 0.005). The most common adverse effects during dose optimization were: decreased appetite, insomnia, headache, irritability, upper abdominal pain and affect lability, which were less frequent in the crossover phase. Findling et al, Study D: From baseline to endpoints, mean ADHD-RS score improved 27.2 points (P <0.0001). Improvements occurred during each of the first 4 weeks, and were maintained throughout. Based on CGI improvement scale scores, >80% of subjects at endpoint and >95% of completers at 12 months were rated “improved”. Most adverse events were mild to moderate and occurred during the first 4 weeks. There were no clinically meaningful changes in blood pressure or ECG.

Conclusion: In school aged children ages 6-12 with ADHD, LDX a long acting prodrug of D-amphetamine, has been reported to be effective in improving ADHD symptoms throughout the school day and into the early evening with a once daily dose. Additional long term, non bias and comparison studies are needed to evaluate the efficacy and tolerability with prolonged use.
Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

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Keywords
Attention Deficit Hyperactivity Disorder, Children, Lisdexamfetamine Dimesylate, Vyvanse, NRP-104

Subject Categories
Medicine and Health Sciences

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Evaluation of the Efficacy and Tolerability of Vyvanse (Lisdexamfetamine Dimesylate) in Treating Children Age 6-12 with Attention Deficit Hyperactivity Disorder

McKenzie Thurman

A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University
Hillsboro, OR
For the Masters of Science Degree, August 15, 2009

Faculty Advisor: Dr. Mark Pedemonte MD
Clinical Graduate Project Coordinators: Rob Rosenow PharmD, OD & Annjanette Sommers MS, PAC
Biography

McKenzie Thurman is a native Oregonian; she grew up in rural Oregon where she majored in General Science with minors in Chemistry and Psychology at Oregon State University. Throughout college McKenzie had the benefit of working in a drug and alcohol rehabilitation center for teenagers and also in the homes of adults with developmental disorders. This was a very influential time in her life. She spent 6 months as an exchange student in Bangor, Wales and discovered the love of traveling. After completion of her undergraduate degree, she worked for a rural ambulance company as an EMT-Basic on the Oregon Coast. She soon met the love of her life and moved back to Corvallis, Oregon where she worked as a Medical Assistant for an Internist and later an OB/GYN Physician Assistant. McKenzie has been driven to become a Physician Assistant since High School and has fully enjoyed the experiences that lead her to this lifelong dream.
Abstract

Background: Lisdexamfetamine Dimesylate (LDX) is a therapeutically inactive amphetamine prodrug. Pharmacologically active d-amphetamine is released from Lisdexamfetamine following oral ingestion. It is indicated in the treatment of children ages 6-12 with Attention Deficit Hyperactivity Disorder (ADHD). The goal of LDX is to provide a one dose, extended release medication throughout the day as well as a reduced potential for abuse, overdose toxicity and drug misuse.

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Results: Biederman et al, Study A: Significant improvements in ADHD-RS-IV scores were seen with all doses of LDX compared with placebo (all, P<0.0001), and in CPRS scores with all LDX doses versus placebo throughout the day (all, P<0.0001 for all comparisons). Efficacy was observed by the first week of treatment and improvements were observed throughout the day up to 6pm. 1 Biederman et al, Study B: LDX treatment significantly improved scores on SKAMP-Deportment, and Attention, PERMP attempted and correct and CGI improvement from baseline. Adverse events were similar for both active treatments. 2 Wigal et al, Study C: Compared with placebo, LDX demonstrated significantly greater efficacy at each post-dose time point (1.5 hours to 13 hours), as measured by SKAMP-Deportment and attention scale and PERMP (P < 0.005). The most common adverse effects during dose optimization were: decreased appetite, insomnia, headache, irritability, upper abdominal pain and affect lability, which were less frequent in the crossover phase. 3 Findling et al, Study D: From baseline to endpoints, mean ADHD-RS score improved 27.2 points (P <0.0001). Improvements occurred during each of the first 4 weeks, and were maintained throughout. Based on CGI improvement scale scores, >80% of subjects at endpoint and >95% of completers at 12 months were rated “improved”. Most adverse events were mild to moderate and occurred during the first 4 weeks. There were no clinically meaningful changes in blood pressure or ECG. 4
**Conclusion:** In school aged children ages 6-12 with ADHD, LDX a long acting prodrug of D-amphetamine, has been reported to be effective in improving ADHD symptoms throughout the school day and into the early evening with a once daily dose. Additional long term, non bias and comparison studies are needed to evaluate the efficacy and tolerability with prolonged use.

**Keywords:** Attention Deficit Hyperactivity Disorder, Children, Lisdexamfetamine Dimesylate, Vyvanse, NRP-104, stimulant, and amphetamine.
Acknowledgements

To my ever supportive husband. We have been through plenty over the last two years. You married me in-between terms, put up with my late night studying and stressing, you were always an unwilling participant when I was practicing my physical exams, you drove me to and from school when the 8 blocks was “just too far”, you were always there at the airport, and were there to answer my late night calls of me laughing or crying. We survived missed birthdays, holidays, your graduation and our first anniversary, (you are a saint for going to my families functions without me). Most importantly you have “held down the fort” by yourself for over a year and never stopped loving me. I can’t describe the gratitude, love and deep friendship I have for you. Thank you for your understanding, flexibility and being the rock in our relationship. You have helped me develop into the woman and professional that I am today. I am honored to call you my husband.

To my family:

“What a long strange trip it’s been”
~Jerry Garcia
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List of Abbreviations

ADHD…………………………………………Attention Deficit Hyperactivity Disorder
ADHD-RS-IV…………………………………………ADHD Rating Scale Version IV
CPRS…………………………………………Conners Parent Rating Scale
CGI…………………………………..Clinical Global Impression of Improvement Scale
DSM-IV……….Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
LDX…………………………………………………...…Lisdexamfetamine Dimesylate
MAS-XR……………………………………Mixed Amphetamine Salts Extended Release
PERMP…………………………………….Permanent Product Measure of Performance
SKAMP…. ......Swanson, Kotkin, Agler, M-Flynn, and Pelham Deportment Rating Scale
Evaluation of the Efficacy and Tolerability of Vyvanse (Lisdexamfetamine Dimesylate) in Treating Children Age 6-12 with Attention Deficit Hyperactivity Disorder

Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurobehavioral disorders of childhood and adolescence. It is estimated to affect 8%-12% of children worldwide.\(^1\) Typically it is first diagnosed in childhood and the symptoms often persist into adolescence and adulthood. According to the American Psychiatric Association’s *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Test Revision* (DSM-IV-TR) (Table I), ADHD is characterized by inattention, hyperactivity and impulsivity developing before the age of 7 that are both, more severe and more frequent, than commonly observed in children at a similar developmental level.\(^{15}\) The symptoms of ADHD can cause significant impairments throughout one’s life if left untreated. A comorbid condition is present in as many as two thirds of clinically referred children with ADHD, this makes diagnosis and treatment very difficult\(^6\). The origin and risk factors for ADHD are unknown, but researchers are finding that genetics play a key role.

Medications to treat ADHD historically included stimulants, most commonly, methylphenidate (MPH) and amphetamines (AMP).\(^7\) MPH and AMP, both stimulant medications, have the most evidence for efficacy and safety in the treatment of ADHD and remain the first line pharmacological intervention for ADHD.\(^8\) In 2002, a non-stimulant option, Amoxetine was approved by the FDA.\(^7\) Medications used to treat ADHD are most successful when combined with psychotherapy, behavioral management,
classroom and home strategies that support children with ADHD.\textsuperscript{76} The stimulant class of medications helps reduce hyperactivity and impulsivity while improving the ability to focus, work and learn.\textsuperscript{9} They come in various forms ranging from: short-acting, long-acting, extended release capsules, pills, liquid and skin patch. The efficacies of these various forms of stimulants have been well studied and established in improving ADHD symptoms. Stimulants are considered to be the most researched medication in children and have been shown to expand children’s academic performance over the years.\textsuperscript{6}

Nevertheless, there continue to be areas regarding the effectiveness of the current stimulants that are problematic. For example, adverse effects of stimulants: decreased appetite, sleep disturbances, headache and upper abdominal pain. Another area of concern around stimulants is multi-dosing throughout the day, inadequate control of the duration of action, and potential for abuse. These problematic areas motivate researchers to develop a more tolerated form of medication to help treat ADHD. There is no cure for ADHD, but these medications can help individuals become more successful in school and manage a productive life. Effective treatment of ADHD that will achieve an optimal therapeutic response and an appropriate duration of action, along with patient satisfaction and compliance are difficult. This fine balance involves taking into consideration the specific needs of the patient, the characteristics of the individual patient, the formulation of the stimulant or non-stimulant and their delivery method.

Lisdexamfetamine Dimesylate (LDX) is a prodrug of dextroamphetamine, a stimulant that was approved by the FDA in February 2007 for the treatment of attention deficit hyperactivity disorder (ADHD).\textsuperscript{9} LDX is the first prodrug stimulant to be developed. It is a therapeutically inactive prodrug made up of \textit{l}-lysine amino acid
covalently bonded to $d$-amphetamine (dextroamphetamine). After oral ingestion it is activated by being converted into dextroamphetamine in the gastrointestinal tract. Thus it is not converted to the active form if injected or inhaled, thereby limiting the potential for abuse. It has been developed to have similar efficacy to that of current extended-release central stimulants with reduced potential for abuse, overdose toxicity, and drug tampering.

**Objective**

This article reviews the literature regarding the development and use of Lisdexamfetamine Dimesylate (LDX, Vyvanse) in treating children age 6-12 with attention deficit hyperactivity disorder (ADHD). The results of the literature search appear in Table II.

**Methods**

An exhaustive literature search using the following search engines was performed: MEDLINE, Evidence Based Medicine Reviews Multifile, CINAHL, Pub Med, MD Consult, and PsycINFO. The literature search was performed using the following search terms. Attention deficit hyperactivity disorder, Children, Lisdexamfetamine Dimesylate, Vyvanse, NRP-104, and stimulant.

The criteria for inclusion of a study were children ages 6-12, diagnoses of ADHD defined by DSM-IV, and patients taking single therapy Lisdexamfetamine to treat their ADHD. The criteria for exclusion of a study were comorbid psychiatric diagnoses, adolescents, adults, combination therapy.
Results

Study A

Biederman et al (study A), a phase III, multicenter, randomized, double blinded, forced-dose, parallel-group study was supported by New River Pharmaceuticals Inc. and Shire Development Inc. (Table II) This study has a calculated Jadad score five. The study randomized 290 patients in a 1:1:1:1 ratio, using a computer generated randomization schedule to receive double-blind, oral capsules of LDX 30mg for 4 weeks, 50mg (30mg/d for week 1, with forced dose escalation to 50mg/d for weeks 2-3), or 70mg (30mg/d for week 1, with forced dose escalation to 50mg/d for week 2 and 70mg/d for weeks 3 and 4), or placebo capsules for 4 weeks. Of the participants’ 201 were boys, 89 were girls, the mean age was 9 years and they all have a DSM-IV diagnosis of ADHD.1

ADHD symptoms were assessed using parent and investigator completed rating scales. (Table III) The efficacy of LDX was assessed using the ADHD Rating Scale Version IV (ADHD-RS-IV), the Conners [SIC] Parent Rating Scale (CPRS) and the Clinical Global Impression of Improvement Scale (GCI). Tolerability was assessed throughout this study by evaluating adverse events, ECG, physical examination and clinical laboratory tests.1

Out of the 297 children enrolled seven children discontinued before randomization, 290 received the randomized and blinded treatment, 285 were included in the Intent to treat (ITT) population, 230 completed the study (LDX 30mg n = 56; LDX 50mg n = 60; LDX 70mg n = 60 and placebo n = 54). 60 participants were withdrawn
before the study completion most commonly due to lack of drug efficacy (LDX 30mg =1%, LDX 50mg = 0%, LDX 70mg = 1% and placebo = 17%) and adverse events (LDX 30mg = 9%, LDX 50mg = 5%, LDX 70mg = 14% and placebo = 1%). Treatment compliance was 84% in the randomized population for all 4 treatment weeks.

Primary Efficacy

Primary efficacy was measured by the change from baseline to end point by the attention deficit hyperactivity disorder-rating scale-fourth edition (ADHD-RS-IV) total score. The ADHD-RS-IV total score was significantly greater with each of the 3 Lisdexamfetamine (LDX) doses compared with placebo (P<0.001). The largest mean reduction in ADHD-RS-IV score was in the 70mg group. During the first week after all treated patients received LDX 30mg, ADHD-RS-IV scores were significantly improved compared with placebo and continued to improve over the 4 week period. All LDX groups compared with placebo showed greater improvement in both the ADHD-RS-IV Inattention and Hyperactivity subscales from baseline to end point (all, P < 0.001). Dose comparisons showed the difference in least squares (LS) mean ADHD-RS-IV change from baseline scores between the 30 and 70mg groups was – 4.91 (P < 0.05).

Secondary Efficacy

The Conners Parent Rating Scale-Revised: short form (CPRS-Revised), is a parent rated scale designed to assess the symptomatic behaviors of ADHD. (Table II) This scale was used to evaluate participants at 10am, 2pm and 6pm. The CPRS comprised of 27 questions grouped into 4 subscales: Oppositional, Cognitive Problems,
Hyperactivity and ADHD index. Based on CPRS-Revised scores, beginning after appropriate dose titration and continuing throughout the study (P < 0.01), parents/guardians of patients in each LDX dose group reported significantly greater improvement in symptom control throughout the day. The CPRS-Revised was used to assess symptoms in the morning (10 AM), afternoon (2 PM) and evening (6 PM) compared with placebo (P < 0.01). Again those taking the 70mg LDX dose showed the most improvement of the CPRS-Revised scores compared with placebo.¹

_Clinical Global Impressions_

Clinical Global Impressions (CGI) scale scores are used to measure symptom severity, treatment response and the efficacy of treatments in therapy studies. (Table III) The scale is used by clinicians and has a seven point rating scale (1= very much improved, 7= very much worse). ADHD symptom severity was measured by the CGI scale at baseline and then was reassessed as following visits. In this study the GCI-improvement scale showed a considerably greater improvement from starting to finishing treatment for all active treatment groups compared with placebo (all, P <0.001). CGI-Improvement scale ratings which clinicians rate the illnesses development compared to base line. A score of 1 is very much improved and 7 are very much worse. Participants CGI-Improvement rate were “very much improved” (CGI-I score 1) or “much improved” (CGI-I score 2) in ≥ 70% of treatment group patients, compared to 18% of placebo patients.¹
Adverse Events

Adverse events were experienced by each of the treatment groups (LDX 30mg = 72%, LDX 50mg = 68%, LDX = 84% and placebo = 47%). (Table IV) The adverse events experienced while talking LDX are commonly seen with amphetamine use. More than 95% of adverse effects requiring treatment were considered mild to moderate in intensity. The adverse effects were commonly noticed during the first week and then slowly disappeared. No serious adverse effects were demonstrated. Adverse effects observed with LDX and placebo use were: decreased appetite (39% with LDX vs. 4% with placebo; P ≤ 0.05), insomnia (19% vs. 3%; P ≤ 0.05), upper abdominal pain (12% vs. 6%; P=NS), headache (12% vs. 10% P = NS), irritability (10% vs. 0%; P ≤ 0.05), vomiting (9% vs. 4%, P = NS), weight loss (9% vs. 1%; P ≤ 0.05), and nausea (6% vs. 3%; P = NS). ¹

Study B

Biederman et al (study B) was an additional study evaluating the efficacy, safety and pharmacokinetic properties of LDX compared with placebo in the treatment of ADHD in children ages 6-12 with DSM-IV diagnosed ADHD (Table II). This was a phase II, randomized, multicenter, double-blinded, placebo and active controlled, crossover study with mixed amphetamine salts extended release (MAS XR) included as a reference arm. This study has a calculated Jadad score four. The study was supported by New River Pharmaceuticals Inc. and Shire Development Inc. ²
The efficacy portion was conducted in an analog classroom environment with 52 participants (33 male, 19 female, mean ages 9.1) in 3 phases over 4 weeks at 4 study sites. Efficacy was measured by Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) Department Rating Scale, Permanent Product Measure of Performance Attempted and Corrected (PERMP) and Clinical Global Impressions – Improvement (CGI-I) Scales. (Table III) SKAMP is scored on a seven point impairment scale ranging from zero to six, with higher scores indicating more severe ADHD symptoms. The SKAMP scores were completed by classroom evaluators for each subject during the classroom session of the assessment day. The PERMP, a validated 10 minute math test was developed to evaluate response to stimulant medications. It contains 400 age appropriate math problems and is scored to obtain an objective measure of academic performance by grading the number of attempted and completed problems. Both SKAMP and PERMP have been shown to be sensitive to dosage and time effects of stimulant medications. 2

The study design comprised a 1) screening period (visit 1), 2) dose titration period (visits 2-5), 3) double blind crossover period (visits 6-4), 4) final study visit (visit 9) and 5) 30-day telephone follow up. The school laboratory portion included an analog classroom and lasted for 13 hours. After screening and the washout period participants entered the dose titration period with open label administration of MAS XR for 3 weeks. The final dose of MAS XR at the end of the third titration week was considered the optimal daily dose and was used in the double blind phase to determine the dose of LDX subjects received. The participants were randomized by identical block-randomization schedules for all 3 cohorts after an open label dose adjustment period with MAS-XR,
which determined the optimal dose of LDX. Participants received all three treatments during this phase and the order of treatments was randomized. Cohort A (n = 10) received MAS-XR 10mg, LDX 30mg or Placebo for 1 week each, Cohort B (n = 17) received MAS-XR 20mg, LDX 50mg or Placebo for 1 week each and lastly Cohort C (n = 25) received MAS-XR 30mg, LDX 70mg or placebo for 1 week each (total of 3 weeks). At the end of each week evaluation of behavioral and safety parameters were assessed in a laboratory classroom.  

Pharmacokinetics

At the last visit of the study pharmacokinetics were measured. Cohort C was the largest group (n = 25) thus, making it the best measurement of pharmacokinetics. In Cohort C d-amphetamine from LDX reached median peak plasma levels in 4.5 hours and MAS XR at 6 hours. The mean $C_{\text{max}}$ value for d-amphetamine following MAS XR 30mg administration was 119 ± 52.5ng/ml. The mean $C_{\text{max}}$ value for d-amphetamine following LDX 70mg was 155 ± 31.4ng/ml.  

Primary Efficacy

Of the study participants treated with LDX, the mean SKAMP-Deportment score (primary efficacy measure) showed 0.8 ± 0.1 compared to placebo 1.7 ± 0.1 (P < 0.0001). The least squares (LS) mean SKAMP-Attention score for LDX was 1.2, compared to placebo of 1.8 (P < 0.0001).
Secondary Efficacy

PERMP-Attempted scores (response to stimulant) for LDX were 133.3 compared to placebo 88.2 (P < 0.0001). The LS mean PERMP-Correct scores for LDX were 129.6 and 84.1 for placebo (P < 0.0001). In an analysis of PERMP ratings, this showed the duration of action of LDX (measured by the change in score at each hour beginning from 1 hour after first dose) was favored in the population intended to treat at all time points (1, 2, 3, 4.5, 6, 8, 10 and 12 hours). The onset was observed to begin 2 hours after first dose compared to placebo.²

Clinical Global Impressions

On the CGI-Improvement scales LDX scores (2.2) indicated significant improvement compared with placebo (4.2) (P < 0.0001). Investigators rated 32% very much improved (CGI-I 1) and 42% much improved (CGI-I 2) of those LDX treated subjects compared to placebo at 18%.²

Adverse Effects

56% of participants complained of adverse effects, ranging from mild to moderate during the study, 16% of those were from LDX, 18% MAS-XR and 15% placebo. (Table IV) Adverse effects occurring at an incidence of > 2% while taking LDX during the double blinded treatment period were: insomnia (8%), decreased appetite (6%), and anorexia (4%). They claim that no serious adverse effects or deaths were reported in this study.²
**Study C**

Wigal et al, a multicenter study was published in 2009 that assessed the initial onset and duration of efficacy of LDX compared with placebo (Table II). This study has a calculated Jadad score four. Grants for research were supported by Addrenex, Eli Lilly, McNeil, Psychogenics, Shire and NIMH. This study was comprised of 129 subjects, 98 male, 91 female, mean ages 10.1, across 7 study sites over 10 weeks. The study design followed an open-label, dose-optimization of LDX (30, 50, 70mg daily for 4 weeks) followed by a randomized, placebo controlled, 2 way crossover phase (1 week each). Primary efficacy is measured by the SKAMP-Deportment scale and secondary efficacy is measured by the SKAMP-Attention and the PERMP attempted/corrected scales. These scales to measure efficacy were used before the first dose and at 1.5, 2.5, 5, 7.5, 10, 12 and 13 hours after the first dose.3

*Primary Efficacy*

At 1.5 hours after the first dose and continuing through the measured time points including the 13 hour, LDX showed significant improvement on the SKAMP-Deportment scale compared with placebo. At 12 and 13 hour after the first dose, SKAMP-Deportment scores were numerically worse but not statistically different from the predose levels. In the placebo group SKAMP-Deportment scores were worse than predose scores at all time points. There was significant separation in SKAMP-Deportment scales of LDX from placebo at all post dose time points (P < 0.005 for all time points).3
Secondary Efficacy

The results for PERMP-Attempted and PERMP-Correct were consistent with the results of SKAMP-Deportment. PERMP-Attempted and PERMP-Corrected scores were improved when evaluated at each post dose time (1.5-13 hours). LDX also showed separation in PERMP-Attempted and Completed scores from placebo at these post dose times (P < 0.0001 for all points). At predose assessments least squares (LS) mean (SE) PERMP-Attempted and PERMP-Correct scores for LDX groups were [85.54 (4.88) and 81.86 (4.84) respectively] compared to placebo [102.43 (4.880 and 99.17 (4.840) respectively; P < 0.005]. The differences in LS means (95% CI) of LDX vs. placebo in PERMP-Attempted at 1.5 hours and 13 hours were 16.97 (9.39, 24.56) and 28.28 (21.51, 3.04), respectively (both P < 0.001). The differences in LS means (95% CI) of LDX vs. placebo in PERMP-Correct at 1.5 hours and 13 hours were 19.10 (12.25, 25.94) and 28.14 (21.46, 34.83), respectively (both P < 0.001). The differences in LS means (95% CI) of LDX vs. placebo in SKAMP-Attention at 1.5 hours and 13 hours were –0.43(-0.62, -0.23) and -0.47 (-0.62, -0.31), respectively (both P < 0.001).³

Clinical Global Impressions

The CGI-Improvement score in the dose optimization phase for all subjects was rated as improved (64.6%) or much improved (35.4%). During the crossover period 93 (82.3%) of participants were improved on LDX (58.4% very much improved and 23.9% much improved) vs. 22 (19.5%) with placebo. Of those subjects, 81 (71.7%) were improved while receiving LDX but not placebo, while 10 subjects (8.8%) were improved
on placebo but not on LDX. In the end the difference between LDX and placebo treatment was statistically significant (P < 0.0001).³

Adverse Effects

During the dose optimization phase that included 129 participants, 110 (85.3%) of participants had an adverse event: affected lability 13 (10.1%), decreased appetite 61 (47.3%), headache 22 (17.1%), insomnia 35 (27.1%), irritability 21 (16.3%) and upper abdominal pain 20 (15.5%). While in the crossover phase of 115 subjects 38 (33%) had an adverse effect. These included: affected lability 0 (0.0%), decreased appetite 7 (6.1%), headache 6 (5.2%), insomnia 5 (4.3%), irritability 1 (0.9%) and upper abdominal pain 2 (1.7%). Compared to placebo in the crossover phase 22 (19.1%) had adverse effects including: affected lability 1 (0.9%), decreased appetite 1 (0.9%), headache 2 (1.7%), insomnia 0 (0.0%), irritability 1 (0.9%) and upper abdominal pain 3 (2.6%). (Table IV)³

Study D

Findling et al, conducted the first long term, open label, multicenter, single arm study to evaluate children on maintenance doses of LDX for 11 months (Table II). Funding and support of this study was provided by shire development Inc. 272 participants were titrated to LDX 30, 50 or 70mg a day over 4 weeks and then put on a maintenance dose based on titration. Of these 272 participants, 271 had participated in previous double-blinded trials of LDX within the past 7 days. Over time, the effectiveness of the dose was evaluated once monthly by the ADHD Rating Scale (ADHD-RS).
Primary Efficacy

The mean ADHD-RS total score change from baseline was -27.2 ± 13.0 points in the population intended to treat a greater than 60% change from baseline (P < 0.0001). The mean ADHD-RS inattentive subscale score at endpoint changed -13.4 ± 7.0 points, again a 60% change from baseline (P < 0.0001). Lastly the ADHD-RS hyperactivity score at endpoint changed -13.8 ± 7.0 points a 66% change from baseline (P < 0.0001).

Secondary Efficacy

The CGI Improvement scale rated 81.1% of subjects in the population intended to treat were rated as improved at the end of the study. The percentage of subjects who improved increased weekly during the 4-week dose titration period (51.5% at week 1, 75.7% at week 2, 84.6% at week 3); to 90.0% by the time of dose stabilization at week 4. Thereafter, the percentage of subjects who improved remained at 90% for each monthly assessment and was 95.9% for subjects completing 12 months of treatment.

Adverse Effects

Over the course of the study 213 (78%) of the 272 participants experienced adverse effects, 97.5% of which were mild to moderate. (Table IV) The majority of these occurred in the first 4 weeks in >5% of the study population. These adverse events were reported as: decreased appetite 90 (33%), headache 48 (18), weight decrease 48 (18%), insomnia 47 (17%), upper abdominal pain 29 (11%), upper respiratory tract infection 29 (11%), irritability 28 (10%), nasopharyngitis 26 (10%), vomiting 23 (9%), cough 19 (7%) and influenza 16 (6%). The most common reasons given for discontinuation (>1%) were
aggression, irritability and decreased appetite (n = 3 each; 1.1%). Insomnia (70mg/day = 17%, 50mg/day = 9% and 30mg/day = 4%) and vomiting (70mg/day = 6%, 50mg/day = 4% and 30mg/day = 3%) occurred more often in the patients receiving higher doses. Height increased an average 1.5 inches (P<0.05) and subject weight increased an average 0.6 pounds (P = NS vs. baseline). When height and weight was normalized using z-scores, which took expected growth into consideration, the average changes in z-scores for height and weight at endpoint were -0.08 (P<0.05 vs. baseline) and -0.40 (P = NS vs. baseline). The age and sex normalized mean change in weight from baseline in percentile was -13.4 over 1 year (average percentile at baseline and 12 months were 60.6 and 47.2, respectively). There were no clinically significant changes observed in laboratory values or finding from physical examinations. 4

Discussion

Lisdexamfetamine Dimesylate (LDX) is the latest medication approved by the FDA for the treatment of ADHD in children ages 6-12. As with any new ground breaking medication there continues to be a need for further evaluation and long term assessment. The initial studies have shown results positive for primary and secondary efficacy throughout the day with once daily dosing. The clinical trials revealed areas of study design that need improvement and concepts that require further evaluation. In a clinical trial, children are a very difficult population to study, especially long term. There are many concerns in studies involving children. They are more difficult to follow long term, parents don’t want their children to be treated with placebo and be consequently uncontrolled and there are ethical considerations.
Pharmaceutical Bias

All of these research articles were sponsored by pharmaceutical companies which can lead to a major bias in how the literature is compiled, presented and marketed. Dr. Biederman’s research (Study A and B) was supported by New River Pharmaceuticals INC., and Shire Development Inc. He received research support from various pharmaceutical companies including, Abbott Laboratories, AstraZeneca Pharmaceuticals and Eli Lilly and company. Dr. Biederman is a member of Cephalon Inc., Eli Lilly and Company, McNeil, Novartis Pharmaceuticals Corporation, Shire and UCB Pharma, Inc. speaker’s bureaus. He is also a member of the advisory boards of the following pharmaceutical companies: Cephalon Inc., Eli Lilly and Company, Janssen Pharmaceutica Products LP, McNeil, Novartis Pharmaceuticals Corporation and Shire. Dr. Findling (Study A and D) is also a member of similar pharmaceutical advisory boards. For Study D he received research support from Shire Development Inc. Study C was again funded by Shire Development Inc and statistical support was provided by a former Shire Development Inc. employee.

This weakens the credibility of these studies because they would be less likely to be critical of their employers and would have personal benefit in the outcomes. Therefore, all results should be reviewed with skepticism and the benefit of the pharmaceutical companies in mind.

Efficacy

The reviewed efficacy of LDX showed significant clinical improvement in ADHD symptoms when compared to placebo in children 6-12. Biederman et al (study A) showed improvement not only in the first week of treatment but the primary benefits
were continued on throughout the length of the study (6 weeks) as concluded from the ADHD-RS-IV score. Biederman et al (Study B), primary efficacy improvements were shown in SKAMP, PERMP and CGI scores (see table III) with the LDX group over 12 hours post-dose when compared with placebo. Wigal et al (Study C), demonstrated the onset of action for LDX at 1.5 hours and duration of efficacy up to 13 hours post dose compared to placebo. This study also showed the distinct improvement and continuous effect on attention, behavior and math scores. Secondary efficacy showed parents/guardians noticing considerable improvement in their child’s ADHD symptoms, throughout the day with single dosing when compared to placebo. Overall these studies showed improvement on the various ADHD symptoms assessment scales when measured throughout the day at home and at school.

This improvement of ADHD symptoms throughout the day supports the idea that the gradual release of d-amphetamine from LDX after a single dose provides an extended duration of action that would be sufficient for once daily dosing. This once daily dosing is a critical advantage for the management of children ages 6-12 with ADHD because of their forgetfulness and distractibility which can make it difficult to remember to take multiple doses daily. The consistency in efficacy over 13 hours was shown to avoid peaks and troughs throughout the day which is common with other stimulant medications. This consistency in medication may help relieve the frustration that comes with multiple dosing, peaks and troughs in medication release, not only for the patient, but for family and teachers. Well controlled ADHD symptoms will help children build normal, healthy, relationships; avoid struggles in the classroom and at home due to inattention, hyperactivity and impulsivity.
Tolerability

The tolerability profile across these studies are very similar and most reported treatment related adverse effects happened in the first week of treatment with dose titration, improved with time and were classified as mild to moderate. Study A escalated the doses of LDX faster than clinically recommended during dose titration. This escalation to most effective dose over a short period of time could have contributed to the amount (LDX 30mg = 72%, LDX 50mg = 68%, LDX = 84% and placebo = 47%) of adverse effects. More than 95% of these symptoms were mild to moderate, which is characteristic of stimulants. In Study B, regarding tolerability the open label dose optimization of MAS XR may have resulted in improved tolerability due to exposure to a stimulant prior to treatment. Therefore, the doses of MAS-XR may limit the conclusions regarding tolerability of LDX. The most common adverse effects across the studies were: anorexia, headache, insomnia, irritability and abdominal pain (Table IV). Each article notes that the adverse effect profile among these studies is similar and consistent with other currently marketed stimulants. Although, there is no direct comparisons shown in any of the literature. Further statistical comparison of these “similar adverse effects” and occurrences would be helpful when deciding which stimulant to prescribe and to possibly show one stimulant or class of ADHD medication to be more tolerable.

Compliance can be an issue with regards to tolerability. In study A, only 84% of participants were compliant for 4 weeks.\(^1\) With children ages 6-12 you are likely to have parents/guardians or the school faculty administering the medication, rather than child. This makes compliance measurements difficult by adding a second party to administer the medication and can affect tolerability if doses are being missed, skipped or given late.
in the day. Also a child may say they took the medication when they didn’t and parents may not admit to missing a dose due to being labeled as negligent. This compliance issue can affect the tolerability results especially with a once daily dosing that is designed as an extended release.

The class of medication that LDX is assigned to, has a warning of serious cardiovascular adverse effects, precaution and proper judgment should be used when treating children with stimulants for ADHD. It should be well understood that LDX has not been proven to cause serious cardiovascular adverse effects, but there is lack of an appropriate study to evaluate this. Cardiac disorders were exclusion criteria for all four studies. Therefore, any child with a cardiovascular condition should not take LDX. It would seem that it would have been important to address this serious risk directly which one study (study D) did. The other three studies were content to rely on a more mere mention under exclusion criteria.

Study D claimed a consistency with the other medications in its class that there was a slowing in growth rate measured by body weight when compared to appropriate age and sex controls. Since this is a primary concern of parents and providers, it would be beneficial if LDX and slowing growth rate was analyzed further. Perhaps in regards to why pharmacologically LDX causes slow growth, at what doses is there a greater risk, clear comparison of children taking LDX and children of same age growth, and a clear comparison of slow growth rates with LDX use vs. other stimulant use.

Additionally, anorexia is a common adverse effect of LDX which is classified as a mild to moderate effect. If a child develops anorexia from LDX this will most likely slow their growth, and lead to discontinuation of the medication. Should anorexia really be
considered a mild to moderate adverse effect if it can lead to slowing in growth rate and discontinuation of the medication? The impact, severity and comparison between long term ADHD medications regarding slowing of growth rate is difficult to study due to the population being studied, population size and avoidance of exposure to harm. There seems to be a lack of data regarding LDX and slowing growth rate. Therefore, growth should always be measured routinely among patients taking stimulants. Only one study (study D) compared growth rates based on the Centers for Disease Control and Prevention Growth Chart of height, weight and gender to evaluate the problem.

*Long term efficacy and tolerability*

The long term efficacies of medications in children are difficult to assess. In this case evaluating long term effects of LDX compared to placebo in children ages 6-12 was a challenge and revealed several limitations. Findling et al (study D), was the first long term study of LDX in children ages 6-12 versus placebo. This study showed that LDX treatment resulted in statistically and clinically significant improvements in the ADHD-RS total score during the titration period and the 11 month maintenance period. LDX was shown to be well tolerated long term, with only mild to moderate adverse effects for up to 12 months of treatment.

Two very important factors of limitation in this study should be considered when interpreting the results. The side effect profile used in study D did not use a structured adverse effect assessment, they used and open ended inquiry and observation which can limit the validity of the adverse effects or include unrelated effects. Also, the majority of participants had received LDX in recent previous studies which added a bias to the long term tolerability. It is likely that those who had adverse events in previous treatments had
discontinued and were not included in the long term study. This can cause a bias in the low rates of adverse effects reported in Study C, resulting in a bias toward the use of LDX in individuals with acceptable levels of known tolerability. This could possibly conclude there is an unknown tolerability of patients who have never been exposed to LDX. Since this is a new drug and there has not been much exposure the majority of your population is going to be unexposed to LDX. This bias may cause hesitation when prescribing the medication because tolerability is such a large factor when considering long term use.

Long term treatment for ADHD in children ages 6-12 with LDX will need to be further studied and evaluated in precise detail. LDX is lacking solid information regarding long term efficacy and adverse effects which may make this medication difficult to prescribe because of the unknown tolerability of the actual populations being treated.

Limitations

A major limitation to these studies is when evaluating efficacy of LDX researchers have excluded children with psychiatric comorbidities. Children with ADHD are more common to have a comorbid psychiatric condition, diagnosed or undiagnosed. Also, a comorbid condition is present in as many as two thirds of clinically referred children with ADHD; these studies have excluded a extremely large patient population in the evaluation of efficacy and tolerability of LDX. This exclusion does pose a problem when prescribing LDX to those patients with comorbid diagnoses or possibly undiagnosed comorbidities. It would be helpful to clinicians if studies included children with comorbid conditions and evaluate efficacy and tolerability of LDX. This would be a
serve as a more realistic approach to what clinicians are seeing and treating in their offices. The current studies will most likely serve as a backbone to researchers when they branch out and include a wider population into their further studies of LDX.

There are no studies in children ages 6-12 that evaluate the possibility of future addiction or abuse in children who take LDX. Addiction is a main concern for parents considering putting their children on stimulants, especially long term. Although, there have been studies in adults concerning addiction there have been no studies in children. Again this is a disadvantage of LDX being such a new drug on the market and there are difficulties following up with children exposed to LDX and deciphering if the factors that lead to addiction or abuse were potentiated by LDX.

Limitations of Biederman et al (Study A), include the 4 week duration which limits the evidence of efficacy and tolerability that is generally required in the treatment of ADHD. In addition several of the findings were based on parental assessments (CPRS rating) which can be biased or subjective. There was no study of children in a classroom environment. Again, doses were escalated too quickly during titration which is unlike clinical practice, therefore, contributing to adverse effects and possibly affecting efficacy.¹

Regarding limitations of Biederman et al (Study B), the short duration of the study did not help provide results regarding long term efficacy and tolerability of LDX at home or in the classroom. The children studied all had been previously exposed and responsive to stimulants. Therefore, this study’s conclusions exclude the patients who have not been treated with stimulants in the past. The prior stimulant use also causes a bias regarding the tolerability profile of LDX in this study. The open label dose
optimization use of MAS XR may have resulted in improved tolerability in the double blind period in this study. The use of MAX-XR limited the conclusions regarding tolerability of LDX. Finally, due to study size, researchers cannot determine the benefit concerning gender, race or age.²

Limitations of Wigal et al (Study C) were consistent with laboratory school study designs, in that the short treatment duration and assessment phases provide an underestimation of the number and severity of adverse effects seen with lengthier studies and under long term use. Also, the results were only measured for 13 hours a day and no measurements 13 hours post dose were taken to assess for change in symptoms post dose.³

Studies in the future should contain evaluation of LDX efficacy in relieving ADHD symptoms past 13 hours. They need to include patients with psychiatric comorbidities to better represent the ADHD populations being treated. The short and long term efficacy and tolerability of LDX need to be further assessed among those patients who have not taken stimulants in the past. Also long term studies that appropriately evaluate tolerability without bias are needed.

Conclusion

The symptoms of ADHD are unpredictable; they can extend beyond the school day and continue into afterschool activities and family interactions. The successful management of ADHD requires several combinations of treatment to be most successful. The first prodrug stimulant, Lisdexamfetamine Dimesylate (LDX) is another step forward in improving medication treatment for children with ADHD. The benefits of once daily dosing and suggested efficacy over the course of a school day and into the early evening
are areas that have been a challenge among other ADHD medications. This makes LDX a positive step forward in the treatment of ADHD for patients and their families.

Since ADHD is generally controlled with long term medication management, further long term studies will be valuable to confirm the therapeutic success of LDX. Studies should be broadened to cover a more representative population for example, children with psychiatric comorbidities or children with no prior exposure to stimulants. A better analysis should be done regarding growth and weight rates while on LDX and LDX should ultimately be compared to drugs both within and outside its class. While the studies address adverse effects as similar to those of the other stimulants, they do not outline what the adverse effects actually are. The latter may be due to the fact that these studies may have an interest in the outcome due to the inherent bias from pharmaceutical companies and too much attention to adverse effects would weaken the case for their drug. Future studies should be conducted by objective parties. Although, further evaluation and long term assessment needs to be done, these studies suggest that LDX is a promising prodrug stimulant when compared to placebo for the treatment of ADHD.
Table I

**DSM-IV criteria for attention deficit hyperactivity disorder**

1. Six (or more) of the following symptoms of inattention have persisted for at least six months to a degree that is maladaptive and inconsistent with developmental level:
   - **Inattention**
     - Often fails to give close attention to details or makes careless mistakes in schoolwork, work or other activities
     - Often has difficulty sustaining attention in tasks or play activities
     - Often does not seem to listen when spoken to directly
     - Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
     - Often has difficulty organizing tasks and activities
     - Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
     - Often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)
     - Is often easily distracted by extraneous stimuli
     - Is often forgetful in daily activities

2. Six (or more) of the following symptoms of hyperactivity-impulsivity have persisted for at least six months to a degree that is maladaptive and inconsistent with developmental level:
   - **Hyperactivity**
     - Often fidgets with hands or feet or squirms in seat
     - Often leaves seat in classroom or in other situations in which remaining seated is expected
     - Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents, or adults, may be limited to subjective feelings of restlessness)
     - Often has difficulty playing or engaging in leisure activities quietly
     - Is often "on the go" or often acts as if "driven by a motor"
     - Often talks excessively
   - **Impulsivity**
     - Often blurts out answers before questions have been completed
     - Often has difficulty awaiting turn
     - Often interrupts or intrudes on others (e.g., butts into conversations or games)
   - **Additional criteria**
     - Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age seven years.
     - Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).
     - There must be clear evidence of clinically significant impairment in social, academic or occupational functioning.
Table II
Selected Studies of Lisdexamfetamine Dimesylate for attention deficit hyperactivity disorder in children ages 6-12

<table>
<thead>
<tr>
<th>Authors, Title, Publication</th>
<th># Subjects</th>
<th>Regime</th>
<th>Study Type</th>
<th>Validity (Jadad score)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study A</strong> Biederman, J. et al. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: a phase III, multicenter, randomized, double-blind, forced-dose, parallel-group study. 2007</td>
<td>N=290 LDX 30mg=71 LDX50mg=74 LDX 70mg=73 Placebo=72</td>
<td>LDX Vs. Placebo</td>
<td>A phase III, multicenter, randomized, double-blind, forced-dose, parallel-group study</td>
<td>Score:5</td>
<td>Treatment once daily with 30 to 70 mg of the prodrug LDX appeared to be effective and had a tolerability profile similar to those of currently marketed extended-release stimulants.1</td>
</tr>
<tr>
<td><strong>Study B</strong> Biederman, J. et al. Lisdexamfetamine dimesylate and mixed amphetamine salts extended-release in children with ADHD. 2007</td>
<td>N=52 Cohort A=10 Cohort B=17 Cohort C=25</td>
<td>LDX Vs. Placebo</td>
<td>A double-blind, placebo-controlled, crossover analog classroom study</td>
<td>Score:4</td>
<td>In a laboratory classroom environment, LDX significantly improved ADHD symptoms versus placebo in school-age children with ADHD.2</td>
</tr>
<tr>
<td><strong>Study C</strong> Wigal, S.B. et al. A 13-hour laboratory school study of Lisdexamfetamine dimesylate in school-aged children with attention-deficit/hyperactivity disorder. 2009</td>
<td>N=129 LDX 30mg=58 LDX50mg=50 LDX 70mg=21</td>
<td>LDX Vs. Placebo</td>
<td>A Phase IIIb, Randomized, Double-Blind, Multi-Center, Placebo-Controlled, Dose-Optimization, Cross-Over, Analog Classroom Study</td>
<td>Score:4</td>
<td>In children (6 to 12 years) with ADHD, efficacy of LDX was maintained from 1.5 hours up to 13.0 hours. LDX was generally well tolerated, resulting in typical stimulant AEs.3</td>
</tr>
<tr>
<td><strong>Study D</strong> Findling, R.L. et al. Long-term effectiveness and safety of lisdexamfetamine dimesylate in school-aged children with ADHD. 2008</td>
<td>N=272</td>
<td>LDX</td>
<td>A open-label, multicenter, single-arm study</td>
<td>Long-term 30, 50, and 70 mg/day LDX was generally well tolerated and effective in children with ADHD.4</td>
<td></td>
</tr>
</tbody>
</table>
### Table III
ADHD rating scales used to evaluate LDX

<table>
<thead>
<tr>
<th>ADHD rating scales used in studies A-D</th>
<th>Appropriateness for</th>
<th>Administered by</th>
<th>Assessing</th>
<th>Measurement scale</th>
<th>Completion time</th>
<th>Evaluated in study</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD-RS-IV Attention deficit hyperactivity disorder-rating scale-fourth edition</td>
<td>Children and adolescence ages 3-17</td>
<td>Parents (home version), Teachers (school version)</td>
<td>Treatment response based on DSM-IV criteria</td>
<td>18 items scored. Total score range: 0-54 No symptoms (0) – The most severe symptoms (54).</td>
<td>5-10 minutes</td>
<td>A, C &amp; D</td>
</tr>
<tr>
<td>CGI Severity Clinical Global Impression</td>
<td>All patients</td>
<td>Clinicians</td>
<td>Treatment response relative to baseline</td>
<td>Scale 1-7 Normal, not ill at all (1) - the most extremely ill patients (7)</td>
<td>5 minutes</td>
<td>A, B, C &amp; D</td>
</tr>
<tr>
<td>CGI Improvement Clinical Global Impression</td>
<td>All patients</td>
<td>Clinicians</td>
<td>Treatment response relative to baseline</td>
<td>Scale 1-7 Very much improved (1) - Very much worse (7)</td>
<td>5 minutes</td>
<td>A, B, C &amp; D</td>
</tr>
<tr>
<td>CPRS-R (short version) Conners’ parent rating scale revised</td>
<td>Children and adolescents ages 3–17</td>
<td>Parents, teachers or self assessment</td>
<td>ADHD-severity: oppositional, cognitive problems, inattention, hyperactivity</td>
<td>Scale 0-4, Not true at all (0) - Very true (4)</td>
<td>Short version 5-10 minutes</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Long version 15-20 minutes</td>
<td></td>
</tr>
<tr>
<td>PERMP Attempted and Completed Permanent Product Measure of Performance</td>
<td>Children and adolescents ages 3–17</td>
<td>Teachers (math test)</td>
<td>Rate of behavior and response to stimulant, dose and duration.</td>
<td>(# of times behavior occurred) / (# of opportunities) = % of behavior occurrences</td>
<td>10 minutes</td>
<td>B &amp; C</td>
</tr>
<tr>
<td>SKAMP Deportment and Attention Swanson, Kotkin, Agler, M-Flynn, and Pelham</td>
<td>All patients</td>
<td>Teachers</td>
<td>Primary efficacy of medication and impairment in classroom behavior</td>
<td>Scale 0-6 No symptoms (0) – Severe symptoms (6)</td>
<td>5-10 minutes</td>
<td>B &amp; C</td>
</tr>
</tbody>
</table>
Table IV
Adverse effects of all LDX doses in each study group

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Study A All LDX Doses (n = 218)</th>
<th>Study B All LDX Doses (n = 50)</th>
<th>Study C All LDX Doses (n = 129)</th>
<th>Study D All LDX Doses (n = 272)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any events, No. % AE</td>
<td>162 (74.3)</td>
<td>9 (18.0)</td>
<td>110 (85.3)</td>
<td>213 (78)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>85 (39.0)</td>
<td>3 (6.0)</td>
<td>61 (47.3)</td>
<td>90 (33)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>41 (18.8)</td>
<td>4 (8.0)</td>
<td>35 (27.1)</td>
<td>47 (17)</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>26 (11.9)</td>
<td>0 (0.0)</td>
<td>20 (15.5)</td>
<td>29 (11)</td>
</tr>
<tr>
<td>Irritability</td>
<td>21 (9.6)</td>
<td>0 (0.0)</td>
<td>21 (16.3)</td>
<td>28 (10)</td>
</tr>
<tr>
<td>Headache</td>
<td>26 (11.9)</td>
<td>NR</td>
<td>22 (17.1)</td>
<td>48 (18)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11 (5.0)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19 (8.7)</td>
<td>0 (0.0)</td>
<td>NR</td>
<td>23 (9)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>11 (5.0)</td>
<td>NR</td>
<td>NR</td>
<td>26 (10)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>20 (9.2)</td>
<td>2 (4.0)</td>
<td>NR</td>
<td>48 (18)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>3 (1.4)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Nausea</td>
<td>13 (6.0)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Cough</td>
<td>3 (1.4)</td>
<td>NR</td>
<td>NR</td>
<td>19 (7)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>10 (4.6)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>NR</td>
<td>1 (2.0)</td>
<td>NR</td>
<td>29 (11)</td>
</tr>
</tbody>
</table>

NR = not reported
LDX = Lisdexamfetamine Dimesylate
References


