

Effect of Lisdexamfetamine Dimesylate on Parent-Rated Measures of Oppositional Behavior in Children Aged 6 to 12 Years With Attention-Deficit/Hyperactivity Disorder: A Secondary Analysis

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ABSTRACT

Objective: To compare the effect of lisdexamfetamine dimesylate (LDX; Vyvanse™, Shire US Inc) versus placebo on parent-rated oppositional behavior in children aged 6 to 12 years with attention-deficit/hyperactivity disorder (ADHD).

Methods: The primary study was a phase 3, randomized, double-blind, parallel-group trial in 290 children aged 6 to 12 years with DSM-IV-TR®-defined ADHD. Subjects were randomized 1:1:1:1 to 4 weeks of treatment with placebo, 30, 50, or 70 mg/d LDX, with median daily dosing between 7:30 AM and 8 AM. The primary efficacy measure was the ADHD Rating Scale (ADHD-RS). Secondary efficacy measures included the Conners Parent Rating Scale-Revised Short Version Oppositional Subscale (CPRS oppositional), completed weekly at 10 AM, 2 PM, and 6 PM.

Results: At endpoint, least squares mean (±SE) percent changes from baseline in CPRS oppositional scores at 10 AM, 2 PM, and 6 PM were -35.6% (±6.2%), -30.1% (±5.7%), and -22.3% (±6.3%), respectively, for the 207 LDX-randomized subjects and -1.2% (±10.2%), 0.8% (±9.5%), and 0.2% (±10.5%), respectively, for the 72 placebo-randomized subjects. CPRS oppositional improvements for each LDX dose were numerically but not statistically greater than placebo at all 3 time points. Improvements started at the first postbaseline week and persisted throughout the study.

Conclusions: LDX significantly improved CPRS oppositional scores in children aged 6 to 12 years. Significant changes were especially observed for each dose in those subjects who were most severely ill (Clinical Global Impression-Severity scores of 5 to 7).

INTRODUCTION

- Attention-deficit/hyperactivity disorder (ADHD) is a common psychiatric disorder, affecting 8% to 12% of children worldwide¹
- Psychostimulants have been shown to be effective in improving symptoms of ADHD and are therefore commonly used to treat subjects with this condition.² Despite the availability of these agents, several therapeutic needs remain unmet, including the consistent delivery of medication throughout the day and adequate duration of action
- Parents of many children with ADHD, especially those aged 6 to 12 years, reported in online interviews that once-daily ADHD medications stop providing relief before 6 PM³
- Lisdexamfetamine dimesylate (LDX) is the first prodrug stimulant and is indicated for the treatment of ADHD. A therapeutically inactive prodrug in which d-amphetamine is covalently bound to l-lysine, LDX is converted to the pharmacologically active d-amphetamine by rate-limited hydrolysis. LDX was developed with the goal of providing an extended duration of effect that is consistent throughout the day, with a reduced potential for abuse, overdose toxicity, and drug tampering⁴
- LDX has been shown to have efficacy superior to placebo and a safety profile comparable to other stimulant medications in the treatment of school-aged children with ADHD^{4,5}:
 - Compared with placebo, LDX significantly reduced symptoms of ADHD
 - LDX is generally well tolerated, with an adverse-event (AE) profile similar to extended-release stimulant products
 - Improvements have been observed as early as the first week of treatment⁴
- This secondary analysis of a pivotal clinical trial evaluated the effect of LDX treatment on oppositional behavior in children with ADHD as evaluated by the oppositional subscale scores from the Conners Parent Rating Scale-Revised Short Version (CPRS)

MATERIALS AND METHODS

- This study was a phase 3, randomized, double-blind, multicenter, parallel-group, placebo-controlled, forced-dose titration trial in children aged 6 to 12 years with DSM-IV-TR® criteria diagnosis of ADHD (combined or hyperactive-impulsive subtypes) who may or may not have received prior ADHD treatment
- Following 1-week screening and 1-week washout periods, subjects were randomized 1:1:1:1 to placebo or once-daily doses of 30 mg, 50 mg, or 70 mg LDX for 4 weeks of treatment

- The CPRS was used to assess a cross-section of ADHD-related symptoms and problem behaviors⁶ (Table 1)

- The CPRS contains 27 items, grouped into 4 subscales: hyperactivity (6 items), oppositional (6 items), cognitive problems/inattention (6 items), and ADHD Index (12 items; contains items from other subscales)⁶
- The CPRS total score is the sum of scores on the 4 subscales

Table 1. CPRS Revised Short Version Oppositional Subscale Items⁶

- Angry and resentful
- Argues with adults
- Loses temper
- Irritable
- Actively defies or refuses to comply with adults' requests
- Deliberately does things that annoy other people

Conners CK. *Conners' Rating Scales-Revised Technical Manual*. North Tonawanda, NY: Multi-Health Systems Inc; 2001. © 2001 Multi-Health Systems Inc. 3770 Victoria Park Avenue, Toronto, ON, M2H 3M6. All rights reserved.

- Parents rated their child's behavior for the 2-hour period immediately preceding assessment times at 10 AM, 2 PM, and 6 PM
- At baseline, the investigator performed a Clinical Global Impression-Severity (CGI-S) assessment, rating severity on a scale of 1 (no symptoms) to 7 (very severe symptoms)
- Post hoc analysis was also conducted to compare the degree of improvement in CPRS oppositional scores with varying CGI-S assessments at baseline

RESULTS

Subject Demographics

- In the primary study, 290 subjects were randomized: 72 to placebo, 71 to 30 mg/d LDX, 74 to 50 mg/d LDX, and 73 to 70 mg/d LDX
- Of the 290 randomized subjects, 230 (79%) completed the trial
- <1% of LDX-treated subjects (2/218) discontinued for lack of efficacy, compared with 16.7% of placebo-treated subjects
- Demographics were similar across treatment groups (Table 2)

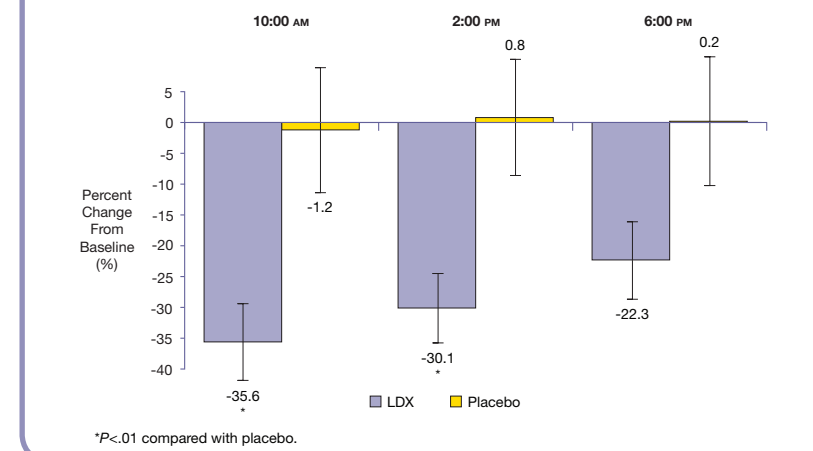
Efficacy

- For each of the 3 dose groups (30 mg/d, 50 mg/d, and 70 mg/d), improvement in CPRS total score at endpoint was significantly greater than placebo at 10 AM, 2 PM, and 6 PM ($P < .0001$)
- Least squares (LS) mean (±SE) percent changes in CPRS total scores from baseline to endpoint at 10 AM, 2 PM, and 6 PM were -51.9% (±3.0%), -50.9% (±3.3%), and -45.3% (±3.1%), respectively, for the LDX-treated group, and -4.5% (±4.8%), -3.3% (±5.3%), and -1.7% (±5.1%) for the placebo group

Characteristics	Placebo (n=72)	30 mg/d (n=71)	50 mg/d (n=74)	70 mg/d (n=73)
Age (y) Mean ± SD	9.4 ± 1.7	9.0 ± 1.9	8.9 ± 1.8	8.7 ± 1.8
Sex, n (%)				
Male	50 (69.4)	53 (74.6)	46 (62.2)	52 (71.2)
Female	22 (30.6)	18 (25.4)	28 (37.8)	21 (28.8)
Ethnicity, n (%)				
White	43 (59.7)	37 (52.1)	34 (45.9)	41 (56.2)
Black	16 (22.2)	18 (25.4)	19 (25.7)	17 (23.3)
Hispanic	9 (12.5)	10 (14.1)	17 (23.0)	12 (16.4)
Other	4 (5.6)	6 (8.5)	4 (5.4)	3 (4.1)
Weight (lb) Mean ± SD	82.6 ± 22.8	80.9 ± 27.2	80.7 ± 25.4	79.0 ± 23.7
CGI-S at Baseline, n (%)				
CGI-S 3 to 4	27 (37.5)	26 (36.6)	26 (35.2)	25 (34.2)
CGI-S 5 to 7	45 (62.5)	45 (63.4)	48 (64.9)	48 (65.8)

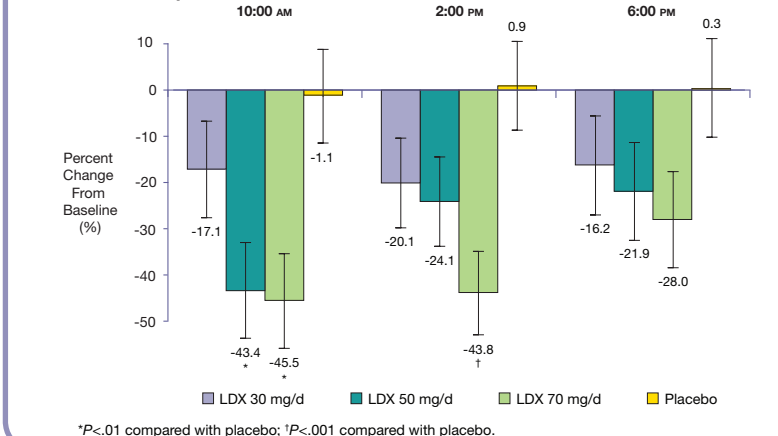
- The improvements in the CPRS total score in the LDX-treated group were statistically significantly greater than the placebo group at all 3 time points ($P < .0001$)
- LS mean (±SE) percent changes in CPRS oppositional scores from baseline to endpoint at 10 AM, 2 PM, and 6 PM were -35.6% (±6.2%), -30.1% (±5.7%), and -22.3% (±6.3%), respectively, for the LDX-treated group, and -1.2% (±10.2%), 0.8% (±9.5%), and 0.2% (±10.5%) for the placebo group (Figure 1)
- The improvements in CPRS oppositional score in the LDX-treated group were significantly greater than the placebo group at 10 AM and 2 PM

Figure 1. Percent change in CPRS oppositional score from baseline to endpoint.



- LS mean percent change from baseline CPRS oppositional score was significantly greater than placebo at 10 AM for the 50-mg/d and 70-mg/d dose groups ($P < .01$) and at 2 PM for the 70-mg/d dose group ($P < .001$) (Figure 2)

Figure 2. Percent change in CPRS oppositional score by dose throughout the day at endpoint.

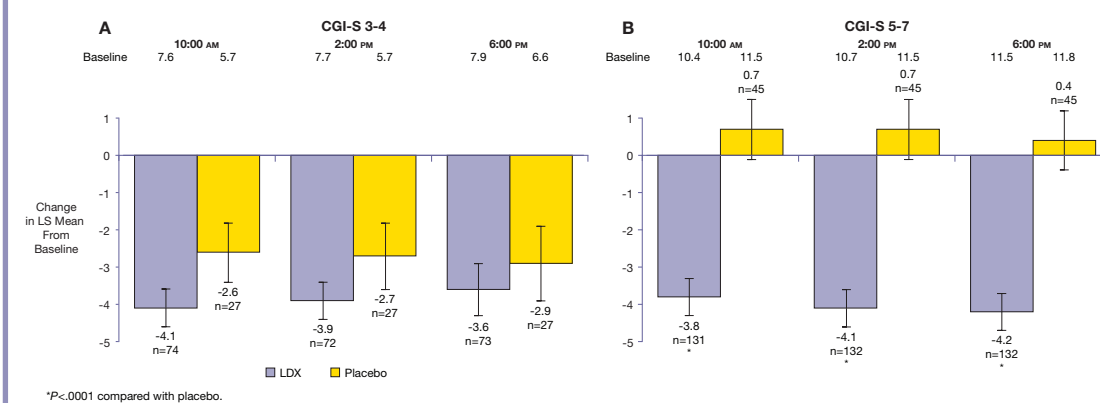


- When subjects were pooled according to baseline CGI-S, there was worsening from baseline in the more severely ill placebo group resulting in a more pronounced difference between LDX treatment and placebo treatment in improvement in CPRS oppositional score from baseline in subjects with a baseline CGI-S score of 5 to 7 (markedly to extremely ill) than in subjects with a baseline CGI-S score of 3 to 4 (mildly to moderately ill) at all time points (Figures 3A and 3B)
- Improvement in CPRS oppositional score was significantly greater with LDX treatment than with placebo in the CGI-S 5 to 7 group at all time points ($P < .0001$)
- Improvements started at the first postbaseline week and persisted throughout the study

Tolerability

- Overall, AEs were experienced by 72% of subjects in the 30-mg/d group, 68% in the 50-mg/d group, and 84% in the 70-mg/d group, compared with 47% in the placebo group (Table 3)

Figure 3. Mean change in CPRS oppositional score by baseline severity throughout the day at endpoint.



- The most frequently reported AEs among LDX subjects were typical side effects of stimulant products: decreased appetite (39% with active treatment vs 4% with placebo); insomnia (19% vs 3%), abdominal pain upper (12% vs 6%), headache (12% vs 10%), irritability (10% vs 0%), vomiting (9% vs 4%), weight decrease (9% vs 1%), and nausea (6% vs 3%)

- More than 95% of treatment-emergent AEs were mild or moderate in intensity
- A total of 21 randomized and treated subjects were withdrawn from the study due to AEs: 1 subject (1%) in the placebo group, 6 (9%) in the LDX 30-mg/d group, 4 (5%) in the 50-mg/d group, and 10 (14%) in the 70-mg/d group

Table 3. Treatment-Emergent Adverse Events With Subject Incidence Greater Than 5% in Any Dose Group

Adverse Events	No. (%) of Subjects Reporting				
	Placebo (n=72)	30 mg/d (n=71)	50 mg/d (n=74)	70 mg/d (n=73)	LDX Doses (n=218)
Any events, n (%)	34 (47)	51 (72)	50 (68)	61 (84)	162 (74)
Abdominal pain upper	4 (6)	10 (14)	5 (7)	11 (15)	26 (12)
Cough	4 (6)	2 (3)	1 (1)	0 (0)	3 (1)
Decreased appetite	3 (4)	26 (37)	23 (31)	36 (49)	85 (39)
Dizziness	0 (0)	5 (7)	4 (5)	2 (3)	11 (5)
Dry mouth	0 (0)	2 (3)	2 (3)	6 (8)	10 (5)
Headache	7 (10)	7 (10)	7 (10)	12 (16)	26 (12)
Irritability	0 (0)	8 (11)	6 (8)	7 (10)	21 (10)
Insomnia	2 (3)	11 (16)	12 (16)	18 (25)	41 (19)
Nasal congestion	4 (6)	3 (4)	0 (0)	0 (0)	3 (1)
Nasopharyngitis	4 (6)	4 (6)	3 (4)	4 (6)	11 (5)
Nausea	2 (3)	3 (4)	2 (3)	8 (11)	13 (6)
Vomiting	3 (4)	5 (7)	4 (5)	10 (14)	19 (9)
Weight loss	1 (1)	4 (6)	2 (3)	14 (19)	20 (9)

CONCLUSIONS

- Treatment with LDX significantly improved CPRS oppositional scores in children aged 6 to 12 with ADHD compared with placebo at 10 AM and 2 PM. Changes at 6 PM were numerically but not statistically different for LDX compared with placebo. Significant improvements were also observed for CPRS total scores
- Improvements in CPRS oppositional scores were observed at the first postbaseline week and persisted throughout the study
- Significant improvement in CPRS oppositional scores compared with placebo occurred in the baseline CGI-S 5 to 7 (markedly to extremely ill) group. Improvements were seen in LDX-treated subjects with a baseline CGI-S of 3 to 4, but the differences were not significant compared with placebo, possibly due to a large placebo effect
- LDX was generally well tolerated, with most AEs being mild to moderate in nature

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