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Is lisdexamfetamine dimesylate safe and effective in reducing ADHD Symptoms?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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ABSTRACT

Objective: The purpose of this careful EBM review is to determine whether lisdexamfetamine dimesylate (LDX) is safe and effective in reducing attention-deficit/hyperactivity disorder (ADHD) symptoms.

Study Design: A systematic review of two randomized controlled studies and one double-blind, 2-arm, parallel-group placebo-controlled RWP published between 2011-2014, all in the English language.

Data Sources: Two randomized controlled trials and one double-blind, 2-arm, parallel-group placebo-controlled RWP published between 2011 and 2014 which were found using PubMed and Cochrane databases.

Outcomes Measured: ADHD global symptomatic improvement was measured using Clinical Global Impressions – Severity of Illness (CGI-S), Clinical Global Impression-Improvement (CGI-I) and ADHD Rating Scale-IV (ADHD-RS-IV). Safety was measured using treatment-emergent adverse events (TEAEs).

Results: Two randomized controlled trials and one double-blind, 2-arm, parallel-group placebo-controlled RWP revealed that using LDX helped reduce ADHD symptoms greater than the placebo it was compared against. The most common side effects caused by LDX were a headache, insomnia, and decreased appetite.

Conclusion: The literature utilized in this EBM project revealed that children and adolescents that used Vyvanse, demonstrated improvement in attention-deficit/hyperactivity disorder (ADHD) symptomatology. Additionally, it was found that LDX was safe for use as the side effects were benign.

Key Words: ADHD, Stimulant Therapy, Lisdexamfetamine Dimesylate

INTRODUCTION

ADHD is a disorder of the brain characterized by a continuous pattern of hyperactivity and impulsivity, or inattention which can impede development and functioning.¹ This paper evaluates two randomized control trials (RCTs) and one double-blind, two-arm, parallel-group, placebo controlled study to determine ADHD global symptomatic improvement/safety versus a placebo.

According to the Centers for Disease Control and Prevention (CDC) in 2011, 11% of United States children (approximately 6,400,000 children aged 4-17 years old) were diagnosed with ADHD.² It is estimated that \$42.5 billion are spent each year in the U.S.A. to treat this condition.³ The cost of lisdexamfetamine dimesylate (brand name: Vyvanse) for one diagnosed with ADHD is approximately \$885 for a 100 day supply, and no generic is available.⁴ Recently, the CDC estimated that there are 9 million health care visits each year in the United States which result in a primary diagnosis of ADHD.⁵

It is known that men develop ADHD more often compared to their female counterparts.¹ Scientific experts cannot pinpoint what causes ADHD. It is postulated that certain factors such as traumatic brain insults, exposure to environmental toxins and alcohol/drug usage during gestation contribute to the development of this disorder.¹ Although much is unknown about this disorder, there are many safe and effective treatment modalities.

Psychotherapy such as cognitive behavioral therapy (CBT) and family therapy are used to treat this condition in combination with medication.¹ Stimulant medications (like methylphenidate, dextroamphetamine saccharate, and lisdexamfetamine dimesylate) are the gold standard medications for treating symptoms of ADHD.¹ Finally, non-stimulant medications (i.e. atomoxetine) are only utilized if the stimulant medications are contraindicated.¹

All the treatment options that were presented in the previous paragraph have been shown to be safe and improve symptomatology in patients with ADHD. Lisdexamfetamine dimesylate may be used as a safe and effective alternative to older stimulant medications such as methylphenidate and dextroamphetamine saccharate.

OBJECTIVE

The purpose of this careful EBM review is to determine if lisdexamfetamine dimesylate is safe and effective in reducing ADHD symptoms.

METHODS

This review focused on children and adolescents (male and female) ages 6-17 with attention-deficit/hyperactivity disorder. In all three studies, the intervention studied was lisdexamfetamine dimesylate. The comparison group in Findling et al. and Coghill DR et al. was a placebo.^{6,7} In Coghill D, Banaschewski T, Lecendreux M, et al. the comparison group was osmotic-release oral system methylphenidate (OROS-MPH) and placebo.⁸ Although multiple outcomes were addressed in all three studies, this review focused on ADHD symptomatic improvement and safety. Two randomized controlled trials and one double-blind, 2-arm, parallel-group placebo-controlled RWP were included.

The keywords that were utilized to ascertain these articles were ADHD, stimulant therapy, and lisdexamfetamine dimesylate. All of the articles were published in English, were peer-reviewed, published and chosen from PubMed and Cochrane. Articles were selected based on the whether they were POEMs (patient oriented evidence that matters). Additionally, they were selected based on their relevance in regards to the chosen research question.

The inclusion criteria utilized for this review was based on whether the articles were relevant to the clinical question. Additional inclusion factors were experimental studies, RCTs,

POEMs, and published between 2011-present. Exclusion criteria were patients under the age of 6 or over the age of 17 and studies that did not have LDX and their intervention. Statistics that were utilized included *p*-values, relative risk reduction (RRR), Relative benefit increase (RBI), absolute risk reduction (ARR), and numbers needed to treat (NNT). Table 1 includes demographics and additional inclusion and exclusion criteria that were used in this review.

Table 1 – Demographics of included studies

Study	Type	Number of patients	Age (years old)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Coghill, D (8)	RCT	336	6-17	Kids 6-12 years old and adolescents 13-17 years old of both genders. With ADHD (moderate severity) age appropriate intelligence, able to swallow pills and blood pressure measurements within the 95 th percentile for sex, height, and age.	The presence of comorbid psychiatric diagnoses (with significant symptoms). BMI is greater than the 97 th percentile. Patients with specific diseases or conditions (i.e. Tourette's syndrome, smokers, and substance abusers). Finally, patients who were currently taking ADHD meds that adequately controlled their symptoms.	140 patients dropped out of the study	Lisdexamfetamine dimesylate (30,50,70 mg/d) vs. placebo vs. OROS-MPH. For 4 weeks study participants were randomly placed into one of three treatment categories. This was followed by a 3 week dose maintenance period.
Coghill, DR (7)	Double-blind, 2-arm, parallel-group, placebo-	276	6-17	Same criteria as above except patient had to complete 4 weeks of	Inability to respond to OROS-MPH. US patients who failed to	119 patients dropped out of the study	Lisdexamfetamine dimesylate (30,50,70 mg/d) vs. placebo for a 6 week randomized withdrawal

	controlled RWP			double-blind treatment and 1-week post-washout treatment without experiencing any clinically significant events. ADHD-RS-IV total score of 28 and above.	respond to more to more than 1 adequate course of amphetamine therapy. Patients with comorbid psychiatric diagnoses with significant symptoms.		period. Efficacy was measured using the proportion of patients meeting treatment failure criteria.
Finding, RL (6)	RCT	314	13-17	Ages 13 to 17 years old. They were required to meet the DSM-IV-TR diagnostic criteria for ADHD.	Same as above.	49 patients withdrew from the study	Lisdexamfetamine dimesylate (30,50,70 mg/d) vs. placebo.

OUTCOMES MEASURED

Reduction of ADHD symptoms using lisdexamfetamine dimesylate vs. placebo was measured using Clinical Global Impressions - Severity of Illness (CGI-S), Clinical Global Impression Improvement (CGI-I) and ADHD Rating Scale IV (ADHD-RS-IV). Safety was measured using treatment emergent adverse events (TEAEs) which were defined as drug reactions that began or got worse following the 1st administration of lisdexamfetamine dimesylate and 3 days after the patient stopped taking the medication.⁸

RESULTS

Findling et al. assessed whether or not lisdexamfetamine dimesylate was effective in treating ADHD symptomatology in 314 adolescents aged 13-17 years old.⁶ Of the original 314 adolescents 49 patients left before completing the study (276 patients finished the study).⁶ Outcomes were measured using CGI-I results were taken at baseline and each week after that for 4 weeks. It was shown that at endpoint 69.1% (EER) of patients who were taking LDX showed

symptomatic improvement regarding hyperactivity/impulsivity compared to the placebo which only showed a 39.5% (CER) improvement ($p\text{-value} < 0.0001$).⁶ Relative benefit increase (RBI) of 0.75, absolute benefit increase (ABI) of 29.65% and numbers needed to treat (NNT) 4. Refer to Table 2 for mathematical calculations.

Table 2

CER	EER	$\frac{\text{EER} - \text{CER}}{\text{CER}}$	EER - CER	1/ABI
39.5%	69.1%	$\frac{0.691 - 0.395}{0.395} = 0.75$	$69.1\% - 39.5\% = 29.65$	$1/29.6\% = 4 \text{ patients}$

In the study by Coghill D et al. the authors assessed whether LDX was safe and efficient in treating young adults and children diagnosed with ADHD.⁸ In this study, safety was reported as treatment emergent adverse (TEAEs). Only 3 out of 111 patients that took LDX experienced serious TEAEs even though the authors indicated it was not attributed to the medication usage.⁸ In the control group that was taking OROS-MPH, 1 patient had a serious TEAE (overdose) which required his removal from the study.⁸ Of the original 336 participants, 196 completed the study. Efficacy outcomes were measured via ADHD Rating Scale IV (ADHD-RS-IV) at the beginning of the study and following the completion of the participants. The confidence interval and $p\text{-value}$ for the efficacy of ADHD symptomatic improvement for those taking LDX were 95% and less than 0.001 respectively.⁸ It was shown that 78% (EER) of patients who were taking Vyvanse showed symptomatic improvement regarding hyperactivity and impulsivity.⁸ The placebo on the other hand only showed a 14% (CER) improvement.⁸ Relative benefit increase (RBI) of 4.75, absolute benefit increase (ABI) of 64% and a small numbers needed to treat (NNT) of 2. All calculations can be seen in Table 3.

Table 3

CER	EER	$\frac{EER - CER}{CER}$	EER - CER	1/ABI
14%	78%	$0.78 - 0.14 / 0.14 = 4.57$	$78\% - 14\% = 64\%$	$1/64\% = 2$ patients

In the randomized withdrawal study by Coghill DR et al. the author wanted to determine whether the discontinuation of LDX would cause a return of ADHD symptomatology based on a $\geq 50\%$ increase in ADHD Rating Scale IV (ADHD-RS-IV) from baseline.⁷ Of the 276 patients that began the study 119 dropped out.⁷ As seen in Table 4, patients randomly assigned to the LDX group had a lower treatment failure rate 15.8% versus those assigned to the placebo arm of which 67.5% met treatment failure criteria.⁷ This meant more people dropped out of the placebo group than LDX group at the end of the study. Relative risk reduction (RRR), absolute risk reduction (ARR) and numbers needed to treat (NNT) as seen in Table 4 were 3.27, 51.7%, and 2 patients respectively. A 95% confidence interval and a *p-value* of < 0.001 were reported by the authors of this study.⁷

Table 4

CER	EER	$\frac{EER - CER}{CER}$	EER - CER	1/ARR
15.8%	67.5%	$0.675 - 0.158 / 0.158 = 3.27$	$67.5\% - 15.8\% = 51.7\%$	$1/51.7\% = 2$ patients

DISCUSSION

One limitation of all three studies was that they looked at children and adolescents only (ages 6-17 years old). Another limitation was that two of the articles had authors that were employed by the pharmaceutical company which is the developer of LDX.^{7,8}

New literature published by a neutral party indicates that adults diagnosed with ADHD ages 18-55 experienced symptomatic relief and are more focused throughout the workday when

treated with LDX.⁹ Henceforth, LDX achieved similar results in children and adults alike.

Although LDX is effective, one issue with this medication is the cost.

Without insurance, LDX costs upwards of \$885 for a 100 day supply.⁴ Even those with insurance such as BlueCross Northeastern Pennsylvania may pay upwards of \$100 for a 90 day supply adding up to over \$400 each year.¹⁰ Additionally, it is important to note that some of the reported side effects of LDX are not trivial. Side effects included but were not limited to seizures, tremors, and mood swings have been reported.¹¹

CONCLUSION

Based on the systematic review of the three research articles LDX is safe and efficient in treating ADHD symptomatology when compared against OROS-MPH.⁸ Additionally, it is important to note that LDX is theorized to have a diminished abuse potential when compared to older medications like amphetamine sulfate.¹² One flaw of note, was approximately 140 people did not complete the Coghill D et al. study, so it was a small sample size.

Future research is warranted to see if LDX is more effective than other stimulant medications such as dextroamphetamine saccharate. Finally, subsequent research should focus on whether combined behavioral and LDX therapy is more effective at treating ADHD symptomatology compared to LDX monotherapy.

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