ORIGINAL RESEARCH

Exploratory meta-analysis on lisdexamfetamine versus placebo in adult ADHD

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Background: Recent studies have promised that lisdexamfetamine (LDX) is effective in the treatment of adults with attention-deficit hyperactivity disorder (ADHD).

Objectives: This systematic review was undertaken to summarize LDX efficacy, acceptability, and tolerability in adult ADHD. All randomized controlled trials (RCTs) of lisdexamfetamine compared with placebo were included for synthesis. Clinical trials published between January 1991 and January 2014 were evaluated.

Methods: The database of MEDLINE®, EMBASE™, CINAHL®, PsycINFO® and Cochrane Controlled Trials Register were searched in January 2014. Studies were also searched in ClinicalTrials.gov and the EU Clinical Trials Register database. Study eligibility criteria, participants, and interventions were considered. All RCTs of LDX vs placebo reporting final results of: 1) severity of ADHD symptoms and executive function deficit, 2) response or remission rates, 3) overall discontinuation rate, or 4) discontinuation rate due to adverse events were included. The language of the papers was not restricted. All abstracts of studies gathered from the database were examined. After excluding irrelevant trials, the full text version of relevant studies were assessed and extracted for outcomes of interest. Examination of risks of bias, based on the Cochrane bias assessment, was carried out. The efficacy outcomes consisted of the mean end point or change scores for ADHD rating scales, the response rate, and the remission rate. The overall discontinuation rate and the discontinuation rate due to adverse events were measured for acceptability and tolerability, respectively. A random effect model was applied for the synthesis of relative risks (RRs), and weighted mean differences or standardized mean differences (SMDs) with 95% confidence intervals (CIs).

Results: A total of 806 final study or safety participants were included. The dosage of lisdexamfetamine was 30 to 70 mg/day. The pooled mean scores of mean change and mean end point scores between LDX- and placebo-treated groups also had a significant difference (SMD [95% CI] of -0.97 [-1.15, -0.78], $I^2=18\%$). The pooled response rates for adult ADHD between the two groups had a significant difference (RR [95% CI] of 1.99 [1.50, 2.63], $I^2=0\%$). Based on the Behavior Rating Inventory of Executive Function – Adult version (BRIEF-A), the pooled end point mean scores for the Global Executive Composite (GEC) for the LDX-treated groups was greater than that of placebo-treated groups (MD [95% CI] of -9.20 [-14.11, -4.29], $I^2=34\%$). The pooled overall discontinuation rates between the two groups had no significant difference (RR [95% CI] of 0.82 [0.59, 1.14], $I^2=0\%$). Similarly, the pooled discontinuation rates due to adverse events between the two groups was not significantly different (RR [95% CI] of 1.77 [0.71, 4.40], $I^2=0\%$).

Conclusion: The number of included studies was limited (five RCTs), but based on this meta-analysis, LDX is efficacious and well tolerated in the treatment of adult ADHD. Additionally, it also improved the executive function deficits in this population. However, its acceptability is no

higher than placebo. These findings should be carefully interpreted and considered as preliminary outcomes. To confirm these results, further studies are warranted. LDX is a viable alternative psychostimulant for adult ADHD.

Keywords: lisdexamfetamine, placebo, systematic review, adult ADHD, acceptability, tolerability

Background

Although its symptoms initially occur in early childhood and usually decline in adulthood, a symptom of inattention persisting through into adulthood is still common.[1,2] Recent evidence suggests that adult attention-deficit hyperactivity disorder (ADHD) prevalence ranges from 2.5% to 4.4%.[3,4] A previous study suggests that adult ADHD is associated with greater impairment in various areas of functioning.[5]

In addition to its inattention symptoms, frequently ADHD affects executive function.[6,7] Therefore, adult ADHD patients may encounter several difficulties, including on-task behavior, academic achievement, and social functioning[8,9] Recent evidence suggests that onset of ADHD in childhood may be associated with working disabilities in adults.[10]

Psychostimulants, including methylphenidate (MPH), dextroamphetamine, and mixed amphetamine salts are not only efficacious in the treatment of ADHD in children and adolescents but also, in adults.[11,12] The novel psychostimulant, lisdexamfetamine (LDX), is also efficacious in the treatment of ADHD. After oral administration, LDX, an originally inactive molecule, is rapidly absorbed from the gastrointestinal tract and converted to l-lysine, a naturally occurring essential amino acid, and dextroamphetamine, which therapeutically affects ADHD symptoms.[13] As a prodrug, LDX needs an enzyme in red blood cells to convert to the active form of amphetamine; therefore, it has less potential for abuse and diversion, and longer effect, as compared with other stimulants.[14,15]

The evidence suggests that LDX is an effective, safe, well-tolerated medication for children aged 6 to 12 years through to adulthood, with ADHD.[16,17] Although some randomized controlled trials (RCTs) of LDX demonstrated its efficacy and tolerability, compared with placebo, in the treatment of adult ADHD,[16,18–21] they had a limited sample size. Given small samples sizes in each trial, a systematic review, which is potentially more effective in calculating the true effect size, may be the method to determine the efficacy, acceptability, and tolerability of LDX.

The primary aim of this present meta-analysis was to examine the efficacy of LDX compared with placebo, in the treatment of adult ADHD. In addition, acceptability and tolerability of LDX were determined.

Methods

The first publication of LDX in the MEDLINE® search was in 2007; therefore, the related clinical trials were searched between January 2007 and January 2014.

Eligibility criteria

All RCTs of LDX compared with placebo performed regarding adult ADHD spectrum, and presenting scores of ADHD and executive function standard rating scales were included. In addition, response, remission, and discontinuation rates needed to be reported. ADHD may be viewed as a spectrum of disorders including ADHD, attention deficit disorder (ADD), hyperkinetic syndrome, and hyperkinetic reaction diagnosed by any set of criteria. The language of the papers was not an exclusion criterion.

Information sources

Searching, limited to "human", was mainly carried out in MEDLINE, EMBASE™, CINAHL®, PsycINFO®, and the Cochrane Controlled Trials Register databases in January 2014. The ClinicalTrials.gov and EU Clinical Trials Register databases were also searched. Additionally, any article reference collected by any means was also applied. The relevant studies gathered in this review were either RCTs or clinical controlled trials (CCTs).

Searches

For optimal identification of the RCTs and CCTs, a searching strategy applied a combination of the following words and phrases: ([lisdexamfetamine] OR [Vyvanse]) AND ([attention-deficit hyperactivity disorder] OR [ADHD] OR [attention-deficit disorder] OR [hyperkinetic syndrome] OR [hyperkinetic reaction]). This strategy was used for searching all databases.

Study selection

To determine which studies conformed to the eligibility criteria, the abstracts, identified from the databases, were examined by the authors (NM and BM) independently. When attaining the full-text version of relevant articles, the authors then separately evaluated those studies. When disagreements took place, they were solved by consensus.

Data collection process

The first author (NM) extracted the relevant results into the data extraction form. Then, the second reviewer (BM) revised the extracted outcomes. All author disputes were also resolved by means of consensus.

Data items

The important extracted data gathered from all trials consisted of the following: 1) the evaluated details of the study validity; 2) basic characteristics of included subjects, criteria used for diagnosis, design of each trial, and exclusion and inclusion criteria; 3) forms, doses, and time course for LDX treatment; and 4) relevent outcomes used for synthesis. Additionally, the intention-to-treat results were also gathered.

Risk of bias in individual studies

The internal validity (quality) was evaluated by the authors (NM and BM). According to the Cochrane Collaboration Handbook, risks of bias for individual study were assessed as follows: 1) the sequence of random generation; 2) allocation concealment, 3) blinding; 4) incomplete outcome; 5) selective reporting; 6) other sources of bias; and 7) baseline similarity.[22]

Summary measures

The essential criteria for inclusion in this analysis consisted of efficacy, acceptability and tolerability outcomes. The mean end point or mean change scores, based on the standardized ADHD measurement, and the rates of response and remission, evaluated by any set of criteria, were considered as efficacious outcomes. Acceptability and tolerability may be convertible terms; however, they individually have their specific definition. As in a previous meta-analysis, the acceptability in this review was assessed by the overall discontinuation rate,[23] and the discontinuation rate due to adverse events – fundamentally evaluating the side effects – was defined as tolerability.[24]

Statistical analysis

To synthesize each continuous outcome, either weighted mean differences (WMD) or standardized mean differences (SMD) with the 95% confidence interval (CI) are regularly applied. When the same outcome measure across studies is applied, it is able to compare or combine the outcomes, by using the WMD. In cases where different measurements are used, a standardized value, for which there is no unit,

is reasonably applied for those comparisons or combinations. In this review, therefore, either the WMDs or the SMDs were utilized for calculation, based on whether the included studies used the same or different rating scales. When the standard deviation (SD) of mean end point or mean change scores for ADHD rating scales in each study was not provided, it was estimated by performing direct substitution or any statistical method:[25] All pooled mean end point or mean change scores with 95% CIs were estimated by using the inverse variance approach, and the significance of those scores as an effect estimation was calculated by using the Z-test.

As a rule, the dichotomous results were synthesized by using relative risks (RRs) with 95% CIs. When an RR is one, it suggests that there is no difference between two groups. In the case of an RR being less than one, it indicates that such outcome is less likely to occur. For the present review, the RRs were applied in the comparison of the response rates, remission rates, overall discontinuation rates, and discontinuation rates due to adverse events between two groups. All pooled RRs of dichotomous data, with 95% CIs, were calculated by using the Mantel–Haenszel approach, and estimation of the significance of those RRs as an effect was calculated by using the Z-test.

Synthesis of results

In general, synthesis for outcomes applies either a fixed or random effect(s) approach. When all included studies are speculated to contribute a common effect size, it is reasonable to apply the fixed effect model. This approach, contrasted to a random effects model, ignores the variations across various studies. Although the eligible studies are a relative similarity, it is not able to assume that they are entirely same since one true effect size less plausibly exists. Hence, it is unlikely to assume that those studies are exactly identical. By this reason, synthesis of all outcomes in the present review applied a random effects model.

Statistical software

In this review, the RevMan 5.1 (The Nordic Cochrane Centre, Copenhagen, Denmark) computer program was used for data synthesis.

Risk of bias across studies

A funnel plot is applied for detecting the publication bias in meta-analysis. It is a simple graph of the intervention effect, calculating from each trial against some measure of each

trial's size or precision.[26] Consequently, we planned to use a funnel plot in this meta-analysis.

Test of heterogeneity

In general, use of a test of heterogeneity is necessary to determine the similarity of the study outcomes. We hypothesized that included study outcomes would not be the same effect due to the methodological quality in each trial. The extent of variation across the study outcomes was estimated. Based on the results outcomes presented by graphic display and the use of the test of heterogeneity, it was possible to estimate whether the study outcomes have greater differences than expected by chance alone. When an I^2 is 50% or greater, a significant heterogeneity of outcome is recognized.

Results

Study selection

According to the searches from those databases, 260 citations were gathered (MEDLINE =50 studies, EMBASE =59 studies, PsycINFO =47 studies, CINAHL =5 studies, Cochrane Controlled Trials Register =69 studies, ClinicalTrials. gov =25 studies, and EU Clinical Trials Register =5 studies) (Figure 1). After the duplicate articles were removed, 185 studies were taken into account. Based on assessment of the titles and abstracts of the remaining articles, 175 studies were excluded since they did not meet the eligibility criteria. Ten full articles were thoroughly examined. Five more articles were excluded, since three were the post hoc analysis using data from previous studies,[27–29] one had a randomized withdrawal study design,[30] and one did
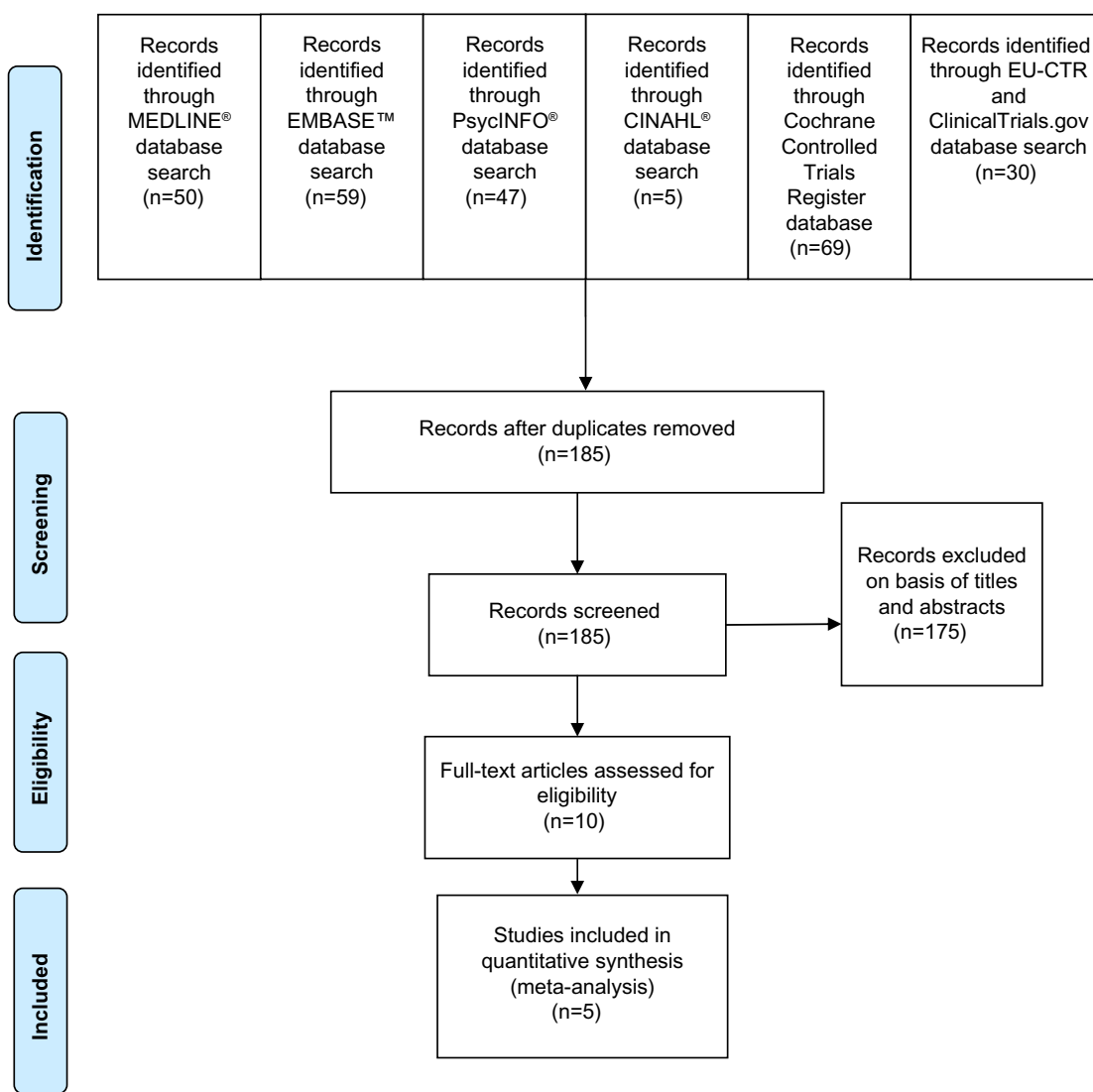

Figure 1 Flow diagram of study.
Abbreviation: EU-CTR, European Union Clinical Trials Register.

not report the outcomes of interest applied for this analysis.[9] Then, five studies were included in this review. There were no relevant and unpublished trials that met the eligibility criteria.

Study characteristics

The duration of the five included studies ranged from 4 to 14 weeks.[16,18–21] The washout periods were reported in three trials (1–6 weeks).[16,18,21] Of 806 final study or safety population participants, 56.08% were male. Mean ages (SDs) for the LDX and placebo groups were 32.70 (10.72) years and 30.83 (10.99) years, respectively. The dosage of LDX was 30 to 70 mg/day. The baseline characteristics of participants in the included studies are presented in Table 1.

The SMDs were applied for calculation and synthesis, since mean end point and change scores were assessed by using the different ADHD rating scales across the studies. Mean end point or mean change scores were found in four studies,[16,18,20,21] response rates were reported in two studies,[16,20] and remission rate was presented in one study.[16] However, overall discontinuation rates and discontinuation due to adverse events were found in four studies.[16,19–21]

Risk of bias within studies

The randomization, double-blind technique was applied in all eligible studies. Two trials used double-blind, crossover study designs.[18,20] An intention-to-treat analysis was applied in two studies.[16,18] A sequence generation of randomization was presented in one trial.[21] Additionally, allocation concealment was reported in two trials[18,21] and blinding of outcome assessment was reported in three trials.[16,20,21] The rest of the biases were reported in all studies (Table 2).

Results of individual studies

Since two studies used several doses of LDX (30, 50, and 70 mg), pooled mean change scores (SD) of those studies were used for this analysis and synthesis.[16,20] The mean end point or mean change scores of the ADHD Rating Scale version IV (ADHD-RS-IV) or Conners Adult ADHD Rating Scale (CAARS), short form in each study were significantly different between LDX- and placebo-treated groups (Figure 2). Similarly, the response rate of adult ADHD was significantly different between the two groups (Figure 3). The remission rate, gathered from only one study, showed a significant difference between the two groups (RR [95% CI] of 2.82 [1.58, 5.03]).

Table 1 Essential characteristics of controlled trials of lisdexamfetamine in adults with attention/deficit hyperactivity disorder

Study (author, year)	Number of enrolled patients	Age of subjects (years)	Study duration (weeks)	Drug/dose	Diagnostic criteria	Response criteria	Remission criteria	Outcome measures
Adler et al, 2008[16]	420	18–55	4	Lisdexamfetamine/ 30, 50, 70 mg/day	DSM IV-TR	CGI-I =1 or 2 and ≥30% reduction in ADHD-RS	ADHD-RS-IV ≤18 (average per-item score ≤1)	ADHD-RS-IV, CGI-I, CGI-S
Wigal et al, 2010[18]	142	18–55	12	Lisdexamfetamine/ 30, 50, 70 mg/day	DSM IV-TR	CGI-I =1 or 2 and ≥30% reduction in ADHD-RS	ADHD-RS ≤18	ADHD-RS-IV, CGI-I, CGI-S, PERMP
Biederman et al, 2012[19]	75	18–26	6	Lisdexamfetamine/ 30–70 mg/day	DSM IV	CGI-I =1 or 2 and ≥30% reduction in ADHD-RS	N/A	ADHD-RS-IV, CGI-I, DBQ
Dupaul et al, 2012[20]	24	18–23	4	Lisdexamfetamine/ 50, 70 mg/day	DSM IV-TR	RCI ≥1.96	N/A	CAARS-short form, BRIEF-A, CPT-II, CVLT-II, EESC, SAS-SR, SCL-90-R, Self-report instrument of study habits and organizational skills
Adler et al, 2013[21]	161	18–55	14	Lisdexamfetamine/ up to 70 mg/day	DSM IV-TR	N/A	N/A	ADHD-RS-IV, AIM-A, AAQoL, BRIEF-A, CGI-S

Abbreviations: AAQoL, Adult ADHD quality of life; ADHD, attention/deficit hyperactivity disorder; ADHD-RS-IV, ADHD Rating Scale version IV; AIM-A, Adult ADHD Impact Module; BRIEF-A GEC, Behavior Rating Inventory – Adult Version Global Executive Composite; CAARS, Conners Adult ADHD Rating Scales; CGI-I, Clinical Global Impression – Improvement; CGI-S, Clinical Global Impressions – Severity; CPT-II, Conners Continuous Performance Test; CVLT-II, California Verbal Learning Test–Second Edition; DBQ, Manchester Driving Behavior Questionnaire; DSM IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition – Text Revision; ESC, Expression and Emotion Scale; N/A, not available; PERMP, Permanent Product Measure of Performance; RCI, reliable change index; SAS-SR, Social Adjustment Scale Self-Report; SCL-90-R, Symptom Checklist 90 – Revised.

Table 2 Risk of bias summary of controlled trials of lisdexamfetamine in adult ADHD

Study	Issues of bias						
	1	2	3	4	5	6	7
Adler et al, 2008[16]	U	U	L	L	L	L	L
Wigal et al, 2010[18]	L	U	U	L	L	L	L
Biederman et al, 2012[19]	U	U	U	L	L	L	L
Dupaul et al, 2012[20]	U	U	L	L	L	L	L
Adler et al, 2013[21]	L	L	L	L	L	L	L

Notes: 1= adequate sequence generation; 2= allocation concealment; 3= blinding (subjective outcome); 4= dropout data addressed; 5= free of selective reporting; 6= free of other bias; 7= baseline similarity.
Abbreviation: ADHD, attention/deficit hyperactivity disorder; L, low risk of bias; U, unclear risk of bias.

Synthesis of results
Efficacy
A significant heterogeneity was not found in all efficacious outcomes, except for the Behavioral Regulation Index (BRI). The pooled mean change ADHD-RS-IV scores of adult ADHD between LDX- and placebo-treated groups had a significant difference (SMD [95% CI] of −0.85 [−1.07, −0.64], I^2=0%). In addition, the pooled end point mean ADHD-RS-IV and CAARS scores between the two groups were also significantly different (SMD [95% CI] of −1.14 [−1.41, −0.88], I^2=0%). The pooled mean score of mean change and mean end point scores between two groups had also a significant difference (SMD [95% CI] of −0.97 [−1.15, −0.78], I^2=18%) (Figure 2).

The pooled response rates for adult ADHD between LDX- and placebo-treated groups had a significant difference (RR [95% CI] of 1.99 [1.50, 2.63], I^2=0%) (Figure 3).

Based on its pooled response rates, the number need to treat (NNT) (95% CI) was 4 (2.2, 4.5). Unfortunately, only one study reported remission rates,[16] and its pooled remission rate could not be calculated.

The self-reported BRIEF-A consists of two subscales, including the BRI and Metacognition Index (MI). The summation of the BRI and MI provides an overall index, called the Global Executive Composite.[20,21] The pooled mean end point scores of the BRI and MI for the LDX-treated groups was greater than that of placebo-treated groups, with MD (95% CI) of −6.52 (−12.45, −0.60), I^2=56, and MD (95% CI) of −10.38 (−14.47, −6.28), I^2=0%, respectively. Finally, the pooled mean end point scores for the BRIEF-A Global Executive Composite for the LDX-treated groups was greater than that of placebo-treated groups, with MD (95% CI) of −9.20 (−14.11, −4.29), I^2=34%.

Discontinuation rates
The pooled overall discontinuation rates in adult ADHD between LDX- and placebo-treated groups did not show any significant differences (RR [95% CI] of 0.82 [0.59, 1.14], I^2=0%). Additionally, the pooled discontinuation rates due to adverse events in this population between the two groups was not significantly different (RR (95% CI) of 1.77 [0.71, 4.40], I^2=0%).
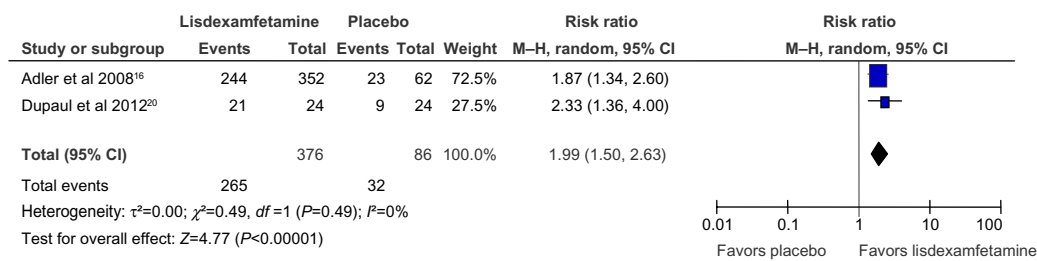
Risk of bias across studies
The funnel plot asymmetry is normally used to detect the publication bias in a meta-analysis that includes at least ten studies. In this review, only five trials were included, so it was
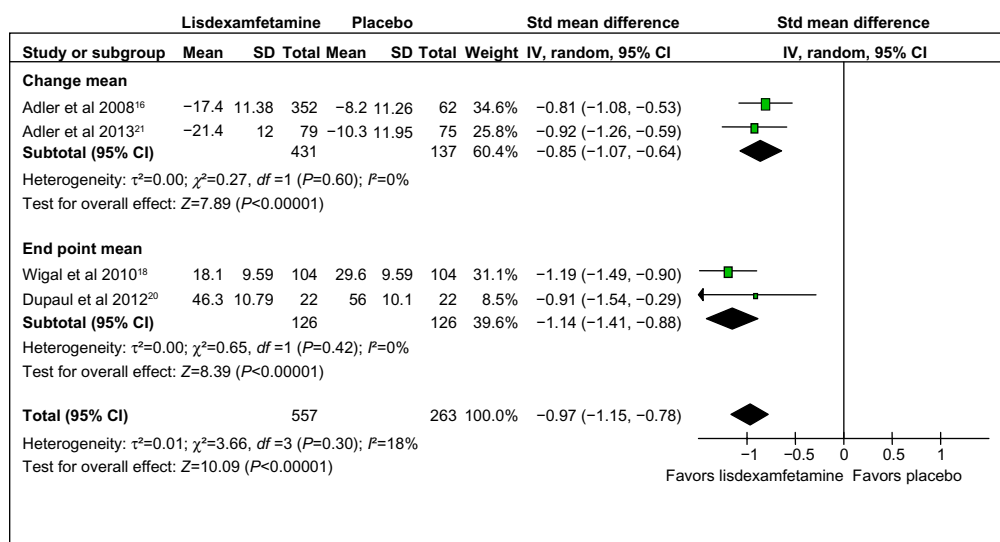
Figure 2 Comparison of the mean scores of ADHD rating scales (95% confidence interval) in adult ADHD: lisdexamfetamine vs placebo.
Abbreviations: ADHD, attention-deficit hyperactivity disorder; CI, confidence interval; df, degrees of freedom; IV, inverse variance; SD, standard deviation; Std, standard; vs, versus.

Study or subgroup	Lisdexamfetamine Events	Total	Placebo Events	Total	Weight	Risk ratio M–H, random, 95% CI	Risk ratio M–H, random, 95% CI
Adler et al 2008[16]	244	352	23	62	72.5%	1.87 (1.34, 2.60)	
Dupaul et al 2012[20]	21	24	9	24	27.5%	2.33 (1.36, 4.00)	
Total (95% CI)		376		86	100.0%	1.99 (1.50, 2.63)	
Total events	265		32				

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.49$, $df = 1$ ($P = 0.49$); $I^2 = 0\%$
Test for overall effect: $Z = 4.77$ ($P < 0.00001$)

0.01 0.1 1 10 100
Favors placebo   Favors lisdexamfetamine

Figure 3 Comparison of relative risk (95% confidence interval) for clinical response rates in adult ADHD: lisdexamfetamine vs placebo.
Abbreviations: CI, confidence interval; *df*, degrees of freedom; M–H, Mantel–Haenszel; ADHD, attention-deficit hyperactivity disorder; vs, versus.

difficult to distinguish the real chance asymmetry;[26] therefore, the funnel plot was not carried out in this meta-analysis.

Discussion

This meta-analysis found five RCTs of LDX compared with placebo, in the treatment of adult ADHD. This review suggests that LDX is effective in the treatment of adult ADHD. According to the pooled response rates, the NNT of 4 suggests that one in every four adult patients with ADHD will benefit from the LDX treatment. Additionally, this review also found that LDX improves executive function in those patients. The acceptability of LDX treatment, as measured by the pooled overall discontinuation rates, is comparable to placebo. In addition, its tolerability, based on the pooled rates of discontinuation due to adverse events, is also comparable. These outcomes may promise the efficacy, acceptability, and tolerability of LDX in adult ADHD.

Similar to present review, several stimulants are effective in the treatment of adult ADHD. For instance, recent evidence has shown the efficacy of the extended-release (ER) formulation of MPH[31] and osmotic-release oral system (OROS) MPH.[32,33] Previous studies have shown that the response rate of MPH ER treatment vs placebo (50% vs 18%)[31] and of OROS MPH treatment vs placebo (67% vs 37%)[32] in adult ADHD is comparable with the response rate in this review (LDX [70%] vs placebo [37%]). The efficacy of LDX in adult ADHD may be explained by its metabolite, dextroamphetamine, which blocks the reuptake of norepinephrine and dopamine into the presynaptic neuron and directly increases the release of these monoamines extraneuronally, similar to other psychostimulants.[15]

Based on the prospective study of ADHD in girls from childhood to young adulthood, it was found that both persistent and remitted adult ADHD evidently showed impairment of executive function. Executive function deficit is related to academic underachievement in children with ADHD,[34] and with both academic and occupational difficulties in adults with ADHD.[5] Based on the BRIEF-A, this review suggests

that LDX improves executive function in adult ADHD. This finding is similar to previous studies in adults with ADHD treated with psychostimulants, such as MPH,[35] and nonstimulants, such as atomoxetine.[36]

According to this review, the acceptability of LDX treatment in adult ADHD was not higher than that of placebo, which is similar to the findings for other psychostimulants. According to a recent meta-analysis, the acceptability of MPH treatment in adult ADHD was not greater than that of placebo (odds ratio [OR] 95% CI of 1.19 [0.82, 1.74]).[37] Unfortunately, the acceptability of OROS MPH in a recent review was worse than that of placebo.[37] These advantages of LDX may be explained by its prodrug formulation, which may reduce the side effects observed in several other psychostimulants, and by the LDX metabolite, dextroamphetamine, which is efficacious for ADHD treatment.

Although tolerability and acceptability of LDX are comparable with placebo, there is a concern of cardiomyopathy in LDX users. Recently, there was a report that three in 5,422 people reported adverse events when taking LDX had cardiomyopathy (one male adult and two male teenagers).[38] Although its incidence is rare, cardiomyopathy is serious, and more trials are needed to investigate this potential side effect.

In this review, there were numerous limitations. Firstly, the number of included studies was limited (five RCTs), which may undermine the potential impact of meta-analysis. Therefore, these findings should be cautiously interpreted. Secondly, all included trials were funded by a pharmaceutical company holding the patent of LDX; hence, their outcomes should be carefully considered. Thirdly, pooled discontinuation rate alone was not sufficient to determine the safety of LDX. Unfortunately, other safety data, for instance adverse events, laboratory testing, and vital signs, were not examined in this review; therefore, this agent should be used cautiously. Fourthly, analysis of statistical outliers and artifacts study are useful in meta-analysis, unfortunately, they were not performed in this review. Finally, as is well accepted, publication

bias should be examined in meta-analysis but was not assessed here due to the small number of included studies.[26]

Conclusion

Based on this meta-analysis, LDX is efficacious and well tolerated in the treatment of adult ADHD. Additionally, it also improves the executive function deficits in this population. However, its acceptability is no higher than that of placebo. These findings should be carefully interpreted and considered as preliminary outcomes. To confirm these results, further studies are warranted.

Author contributions

All authors conceived the idea, prepared the study protocol, analyzed the data and prepared the manuscript and approved the manuscript in its current form. NM and BM searched the databases, extracted the data.

Acknowledgment

Disclosure

NM has received travel reimbursement from Servier and Lundbeck. BM has received honoraria and/or travel reimbursement from Lundbeck. SS has received honoraria and/or research grants from Janssen-Cilag, Thai-Otsuka, Lundbeck, and AstraZeneca. MS has received honoraria, consultancy fees, research grants, and/or travel reimbursement from AstraZeneca, GlaxoSmithKline, Pfizer, Janssen-Cilag, Johnson & Johnson, Lundbeck, Thai-Otsuka, Sanofi-Aventis, and Servier. SDM has received honoraria, consultancy fees and research grants from Astra Zeneca, Eli Lilly, Janssen-Cilag, Sanofi-Aventis, Novartis and Wyeth. The authors report no other conflicts of interest.

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