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Research paper

Lisdexamfetamine dimesylate augmentation for adults with major depressive disorder and inadequate response to antidepressant monotherapy: Results from 2 phase 3, multicenter, randomized, double-blind, placebo-controlled studies

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ABSTRACT

Background: The efficacy, safety, and tolerability of lisdexamfetamine dimesylate (LDX) augmentation of antidepressant monotherapy in adults with major depressive disorder (MDD) from two phase 3 studies are reported.

Methods: Across study 1 (placebo, n=201; LDX, n=201) and study 2 (placebo, n=213; LDX, n=211), most participants (placebo and LDX) in the safety analysis set were female (study 1: 66.2% and 64.2%; study 2: 67.1% and 66.8%); mean ± SD ages were 41.8 ± 12.04 with placebo and 42.2 ± 12.32 with LDX in study 1 and 42.6 ± 11.41 with placebo and 42.0 ± 11.63 with LDX in study 2. Participants (18–65 y) had *DSM-IV-TR*–diagnosed MDD and lead-in baseline Montgomery-Åsberg Depression Rating Scale (MADRS) total scores ≥ 24. Eight-week antidepressant lead-in phases prospectively assessed antidepressant response. Then, 8 weeks of randomized (1:1), double-blind treatment with dose-optimized LDX (20–70 mg) or placebo in participants exhibiting inadequate antidepressant monotherapy responses (augmentation baseline MADRS total scores ≥ 18 and < 50% MADRS total score reductions from lead-in baseline to augmentation baseline) was initiated. The primary endpoint was MADRS total score change from augmentation baseline to week 16. Safety and tolerability measures included the occurrence of treatment-emergent adverse events (TEAEs).

Results: Least squares mean (95% CI) treatment differences (LDX–placebo) for MADRS total score changes from augmentation baseline to week 16 were not statistically significant in study 1 (0.1 [–1.7, 2.0], $P=0.883$) or study 2 (–0.5 [–2.3, 1.3], $P=0.583$). The only TEAE reported by > 5% of LDX participants at twice the placebo rate in both studies was dry mouth.

Limitations: Limitations include the exclusion of participants with psychiatric comorbidities/active medical disorders, the inability to assess specific MDD symptom domains (eg, anhedonia, cognition) or subtypes, the use of telephone-based depression assessments, and the potential influence of placebo response.

Conclusion: Contrary to expectations, LDX augmentation was not superior to placebo in reducing

Abbreviations: ABAC-A, Abbreviated Brief Assessment of Cognition in Affective Disorders; ACSA, Amphetamine Cessation Symptom Assessment; ADHD, attention-deficit/hyperactivity disorder; BMI, body mass index; CGI-I, Clinical Global Impressions–Improvement; CMH, Cochran-Mantel-Haenszel; C-SSRS, Columbia-Suicide Severity Rating Scale; DBP, diastolic blood pressure; ECG, electrocardiogram; EOS, end of study; FAS, full analysis set; LDX, lisdexamfetamine dimesylate; MADRS, Montgomery-Åsberg Depression Rating Scale; MAF-GFI, global fatigue index of the Multidimensional Assessment of Fatigue; MDD, major depressive disorder; MMRM, mixed-effects model for repeated measures; QIDS-SR, Quick Inventory of Depressive Symptomatology–Self-Report; QTcF, Fridericia's corrected QTC interval; SCID-CT, Structured Clinical Interview for Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition–Text Revision, Clinical Trial Version; SBP, systolic blood pressure; SDS, Sheehan Disability Scale; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; STAR*D, Sequenced Treatment Alternatives to Relieve Depression; TEAEs, treatment-emergent adverse events

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depressive symptoms in individuals with MDD exhibiting inadequate responses to antidepressant monotherapy.

1. Introduction

Currently approved treatments for major depressive disorder (MDD), including selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), effectively reduce MDD symptoms (Arroll et al., 2005; Cipriani et al., 2009). Nevertheless, more than half of patients with MDD do not experience full remission with antidepressant monotherapy or with augmentation therapy (Rush et al., 2006; Trivedi et al., 2006a, 2006b). For example, in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, low remission rates (27.5% based on the 17-item Hamilton Depression Rating Scale, 32.9% based on the 16-item Quick Inventory of Depressive Symptomatology–Self-Report [QIDS-SR]) were observed with citalopram monotherapy (Trivedi et al., 2006b). In addition, only 29.7% to 39.0% of individuals receiving second-step augmentation with sustained-release bupropion or buspirone achieved remission (Trivedi et al., 2006a).

Despite the relatively high partial remission rates following antidepressant therapy, there are few medications approved by the US Food and Drug Administration for use as augmentation agents in MDD. Psychostimulants have been investigated for use as augmentation agents in MDD since the 1950s (Robin and Wiseberg, 1958). However, in 2 meta-analyses (Candy et al., 2008; Fleurence et al., 2009), mixed results were reported with respect to the efficacy of psychostimulants or eugorics (modafinil) as augmentation therapy in MDD.

Lisdexamfetamine dimesylate (LDX) is approved in the United States and in other countries for use in patients 6 years and older with attention-deficit/hyperactivity disorder (ADHD) and for use in adults with moderate to severe binge eating disorder only in the United States Vyvanse® [lisdexamfetamine dimesylate] 2015. The efficacy of LDX in MDD has been investigated in small, phase 2, randomized, double-blind, placebo-controlled studies in individuals with MDD who exhibited inadequate response to antidepressant monotherapy (Madhoo et al., 2014; Trivedi et al., 2013). In one study, LDX augmentation of escitalopram met signal-detection criteria (prespecified 2-sided significance level $\alpha = 0.10$) for significant reduction in mean Montgomery-Åsberg Depression Rating Scale (MADRS) total score versus placebo in escitalopram nonremitters (Trivedi et al., 2013). In a separate study that focused on treating executive dysfunction in individuals with fully or partially remitted MDD (defined as MADRS total scores ≤ 18), LDX augmentation of SSRI monotherapy produced significantly greater reductions in MADRS total score than placebo (Madhoo et al., 2014).

This report presents the findings of two phase 3 studies designed to assess the efficacy, safety, and tolerability of LDX augmentation in adults with MDD who exhibit inadequate response to an 8-week prospective course of antidepressant therapy. The primary objective of each study was to assess the efficacy of LDX augmentation, as measured by change in MADRS total score. Secondary objectives included assessment of LDX augmentation effects on the Sheehan Disability Scale (SDS; the key secondary endpoint), on other secondary efficacy endpoints, and on safety and tolerability.

2. Methods

2.1. Study design and treatment regimens

Study 1 (ClinicalTrials.gov identifier: NCT01436149) was conducted at 76 sites across Canada, Croatia, Mexico, Spain, and the United States. Study 2 (ClinicalTrials.gov identifier: NCT01436162) was conducted at 94 sites across the Czech Republic, Estonia, Finland, Germany, Hungary, Poland, Romania, South Africa, Sweden, and the United States. Both studies were conducted in accordance with guidelines from the International Conference on Harmonization Good Clinical Practice and the principles of the Declaration of Helsinki. All study protocols were approved by ethics committees and regulatory agencies before initiating the studies, and written informed consent was obtained before performing study-related procedures.

Each study employed a multicenter, randomized, double-blind, parallel-group, placebo-controlled, flexible-dose design. With the exception of differences in some of the secondary endpoints, the studies were identically designed and consisted of 4 phases (Fig. 1): a screening period of 1–4 weeks, an 8-week antidepressant lead-in phase (to prospectively confirm inadequate response to antidepressant monotherapy), an 8-week double-blind treatment phase (3 weeks of dose optimization followed by 5 weeks of dose maintenance), and a 7- to 9-day follow-up period.

After screening, eligible participants entered the 8-week single-blind antidepressant lead-in phase, which prospectively assessed response to antidepressant monotherapy and blinded participants to the time of randomization. During the antidepressant lead-in phase, participants were assigned by investigators to 1 of 4 commercially available antidepressant medications: an SSRI (escitalopram oxalate [10 or 20 mg] or sertraline hydrochloride [50–200 mg]) or an SNRI (venlafaxine hydrochloride extended release [37.5–375 mg] or duloxetine hydrochloride [30–120 mg]). Antidepressant assignment was unblinded to both investigators and participants and was based on clinical factors, including prior antidepressant use, response, and tolerability. Each individual investigator was asked to distribute antidepressant treatments equally at their site, attempting to not assign any 1 antidepressant to $>40\%$ of participants. Investigators managed antidepressant distribution at the site level and the study sponsor provided ongoing internal review of the overall distribution. No action from the sponsor was taken to ensure that the protocol-stated antidepressant distribution was attained. The initial antidepressant dose was taken after the lead-in baseline visit (week 0), with treatment titrated to the maximum tolerated approved dose by week 4; dose adjustments were not permitted after week 4. Weekly dose increases were made by the investigator according to product label guidelines. Antidepressant strength and doses varied based on commercial availability and country and were administered according to local guidelines. All participants also received LDX-matched placebo during this phase.

Following the lead-in phase, participants exhibiting an inadequate response to antidepressant monotherapy entered the double-blind treatment phase and were randomized (1:1) to LDX or placebo. Randomization criteria included having a MADRS total score of ≥ 18 at augmentation baseline (week 8), having a MADRS total score reduction of $<50\%$ from lead-in baseline to augmentation baseline, exhibiting improvement in depressive symptoms

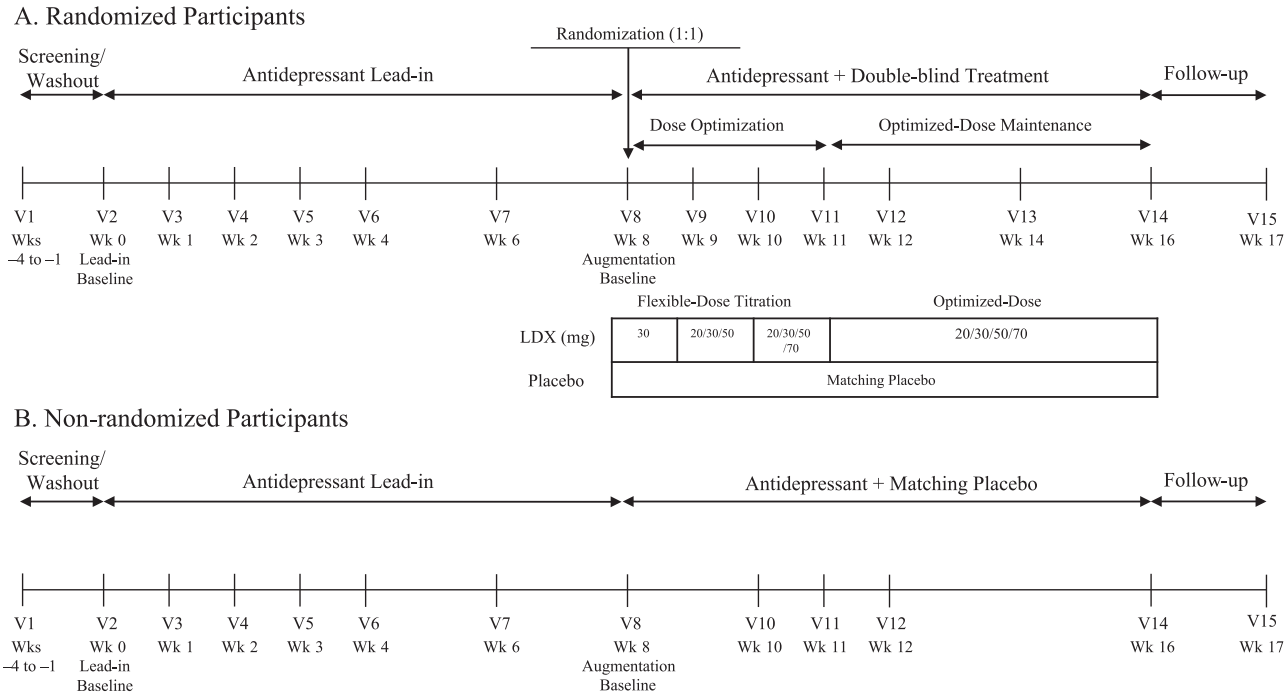

Fig. 1. Study designs for randomized participants (A) and non-randomized participants (B). LDX = lisdexamfetamine; V = visit; Wk = week.

from antidepressant lead-in baseline to augmentation baseline measured by MADRS total score, and having no changes since lead-in baseline in physical examination, clinical laboratories, electrocardiograms (ECGs), or vital signs that preclude LDX treatment. Participants whose depressive symptoms improved but who did not meet randomization criteria were not randomized (non-randomized participants); these participants continued on a modified schedule (visit 10 [week 10], 12 [week 12], and 14 [week 16]) and received single-blind placebo. Participants whose depressive symptoms did not improve or worsened (based on MADRS total score) on their assigned antidepressant were discontinued because LDX was not being assessed for efficacy as monotherapy and continuing a treatment with no demonstrated efficacy for the background antidepressant was considered to have an unfavorable risk/benefit balance. An interactive voice/web response system was used to generate a randomization number, stratified by sex and antidepressant type (SSRI vs SNRI), at augmentation baseline.

The double-blind treatment phase consisted of 3 weeks of dose optimization (weeks 8–11) followed by 5 weeks of dose maintenance (weeks 11–16). Study drug was taken each morning (7:00 a.m. [$\pm$ 2 h]); antidepressant treatment schedules were maintained from the lead-in phase. To maintain blinding, LDX capsules were over-encapsulated and appeared identical to placebo. During dose optimization, treatment was initiated with 30 mg LDX (or placebo). During weeks 9 and 10, the LDX dosage could be maintained, increased to 50 or 70 mg, or down-titrated to 20 mg (Fig. 1). Dosage could be reduced once by a single dose level at any time during dose optimization. Once reduced, the dosage was maintained for the remainder of the study. During dose maintenance, the dose being taken at week 11 was maintained until week 16 unless there was an emergent safety concern, in which case a single dose reduction was permitted. A vital signs assessment was to be taken at the time of this dose reduction. All participants returned for a safety follow-up visit approximately 7 to 9 days after the last study drug dose.

2.2. Study populations

Both studies enrolled adult (18 [or age of majority if $>$ 18 y by local regulation]-65 y at the time of consent) males or non-pregnant females. Eligible participants were also required to have a primary nonpsychotic MDD diagnosis (single or recurrent), as defined by the *Structured Clinical Interview for Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition–Text Revision, Clinical Trial Version* (SCID-CT), that had lasted for $\geq$ 8 weeks before screening and to have a MADRS total score of $\geq$ 24 at lead-in baseline.

Participants were excluded if they had a current MDD episode and did not sufficiently respond to adequate treatment ($\geq$ 6 weeks at the maximum tolerated dose) with $\geq$ 2 approved antidepressants or to an approved augmentation therapy; a lifetime history of treatment-resistant depression, defined as unresponsive to adequate treatment ($\geq$ 8 weeks at the maximum tolerated dose) with $\geq$ 2 treatments, including distinct classes of approved antidepressant monotherapy and adjunctive treatment; had been hospitalized within the past 12 months for the current MDD episode; had current comorbid psychiatric disorders (any significant Axis II disorder, ADHD, bipolar disorder, current or lifetime psychosis, posttraumatic stress disorder, obsessive compulsive disorder, pervasive development disorder, anorexia nervosa, bulimia nervosa) established by the SCID-CT and controlled with prohibited medications or uncontrolled and associated with significant symptoms; had symptoms (eg, agitated states) that contraindicated LDX treatment or could confound study assessments; or had a first-degree relative with bipolar I disorder (to ensure depressive symptoms were not related to undiagnosed bipolar disorder in a participant who had not yet experienced a manic episode).

Additional exclusion criteria included suspected substance abuse or dependence (except nicotine) within the past 6 months; considered a suicide risk in the opinion of the investigator, had made a suicide attempt within the past 3 years, or currently demonstrating active suicidal ideation; a history of symptomatic cardiovascular disease or other cardiovascular medical conditions;

a history of moderate to severe hypertension; systolic blood pressure (SBP) > 139 mmHg or diastolic blood pressure (DBP) > 89 mmHg or a body mass index (BMI) of < 18.5 or > 40 at screening or lead-in baseline; current use (within 30 days of screening) of any centrally acting medication that could affect the condition being studied or affect the action, absorption, or disposition of LDX; or participation in an LDX clinical trial or previous use of commercially available LDX.

2.3. Study endpoints

2.3.1. Efficacy

The primary efficacy endpoint was MADRS total score change from augmentation baseline to week 16. On the 10-item, clinician-rated MADRS (Montgomery and Asberg, 1979) each item is scored on a 7-point scale (0–6; higher scores indicate more severe symptoms). The MADRS was assessed at screening, antidepressant lead-in baseline (week 0), week 6, and augmentation baseline (week 8) for all participants; and at all double-blind treatment visits (weeks 8 through 16) for randomized participants. Although all participants visited the study site for each visit, the MADRS was completed by a central rater via telephone (MedAvante, Inc; Hamilton, NJ) who was blinded to study visit and entry criteria.

The prespecified key secondary endpoint was SDS total score change from augmentation baseline to week 16. The SDS (Sheehan et al., 1996) measures impairment of work/school, social life/leisure activity, and family life/home responsibilities on scales ranging from 0 to 10 (higher scores indicate more impairment; total score range: 0–30). The SDS was assessed at antidepressant lead-in baseline and augmentation baseline all participants and at all double-blind treatment visits (weeks 8 through 16/end of study [EOS]) for randomized participants.

Other secondary efficacy endpoints were the Clinical Global Impressions-Improvement (CGI-I) scale (Guy, 1976), the QIDS-SR (study 1 only) (Rush et al., 2003), the global fatigue index of the Multidimensional Assessment of Fatigue (MAF-GFI; study 2 only) scale (Basia, 2014), and the Abbreviated Brief Assessment of Cognition in Affective Disorders (ABAC-A; study 2 only), also referred to as the Brief Assessment of Cognition in Schizophrenia (Kaneda and Keefe, 2015). In both studies, CGI-I was assessed at all post-antidepressant lead-in baseline visits. The QIDS-SR (study 1 only), MAF (study 2 only), and the ABAC-A (study 2 only) were assessed at lead-in baseline, augmentation baseline, and week 16/EOS.

2.3.2. Safety and tolerability

Safety and tolerability included examination of adverse events (AEs), vital signs, clinical laboratory and ECG results, and responses on the Columbia-Suicide Severity Rating Scale (C-SSRS) and the Amphetamine Cessation Symptom Assessment (ACSA) scale. AEs were assessed at all visits from the time of informed consent through follow-up and were categorized based on severity, seriousness, and relatedness to treatment; treatment-emergent AEs (TEAEs) were defined as AEs that began or deteriorated on or after the date of the first randomized treatment dose and no later than 3 days after the final randomized treatment dose. Clinical laboratory tests were assessed at screening, lead-in and augmentation baselines, week 12, and week 16/EOS. Vital signs and weight were assessed at screening and all study visits through follow-up. Twelve-lead ECGs were recorded at screening, lead-in and augmentation baselines, and at week 16/EOS. The ACSA, a self-completed scale assessing amphetamine-related withdrawal symptoms (McGregor et al., 2008), was completed at follow-up. The C-SSRS, a semistructured interview measuring the occurrence, severity, and frequency of suicide-related thoughts and behaviors (Posner et al., 2009), was assessed at screening, all study visits, and follow-up.

2.4. Statistical analyses

Sample sizes in both studies were based on the primary efficacy endpoint (MADRS total score change from the augmentation baseline to week 16). Assuming a 3-point mean between-group difference (SD = 8.1), it was estimated that 155 participants per treatment would provide 90% power (2-sided 5% significance level). Based on an estimated 20% discontinuation rate during the double-blind treatment phase, approximately 388 participants (194 per treatment) were to be randomized.

MADRS total score change in randomized participants was assessed in the full analysis set (FAS: all participants taking ≥ 1 randomized study drug dose and having ≥ 1 post-augmentation baseline MADRS assessment). The primary efficacy analysis was conducted using a mixed-effects model for repeated measures (MMRM) analysis with treatment, visit, the treatment-by-visit interaction, sex, and antidepressant class included as factors, and augmentation baseline score as a covariate; the interaction of augmentation baseline score with visit was adjusted for in the model. Hypothesis testing was performed at the 2-sided 0.05 level of significance. Analysis of SDS total score change (the key secondary endpoint) was conducted using the same MMRM model described for the primary efficacy endpoint. The between-treatment comparisons at week 16 were of main interest for both the primary and key secondary endpoints.

Additional secondary efficacy endpoints were also assessed at week 16/EOS in the FAS. Percentages of participants demonstrating MADRS total score reductions from augmentation baseline of 25% or 50% and the percentage of participants achieving MADRS remission (defined by a MADRS total score ≤ 10) were assessed using Cochran-Mantel-Haenszel (CMH) tests stratified by sex and antidepressant class. Scores on the CGI-I were dichotomized as improved (very much improved or much improved) or not improved (minimally improved through very much worse) and assessed using CMH tests stratified by sex and antidepressant class. Changes from augmentation baseline for QIDS-SR total score (study 1 only), ABAC-A composite T-scores (study 2 only), and the MAF-GFI were assessed using an analysis of covariance model that included treatment, sex, and antidepressant class as factors and augmentation baseline score as a covariate.

Safety and tolerability were assessed in the safety analysis set, which included all randomized participants taking ≥ 1 randomized study drug dose and having ≥ 1 safety assessment during double-blind treatment. All safety and tolerability endpoints are presented using descriptive statistics.

3. Results

3.1. Participant disposition and demographics

Participant disposition and participant demographics and clinical characteristics are summarized in Fig. 2 and Table 1, respectively. Across studies, most randomized participants were female and were white (Table 1). Higher percentages of participants were assigned to SSRIs than SNRIs (Table 1). The most commonly assigned agent was escitalopram; the distribution of final lead-in antidepressant doses is summarized in Table 1. Mean ± SD MADRS total scores at antidepressant lead-in baseline and at augmentation baseline were comparable between treatment groups in both studies.

3.2. Prior MDD medication use

Before participation in the current studies, use of an MDD medication was captured in the safety analysis set prior to

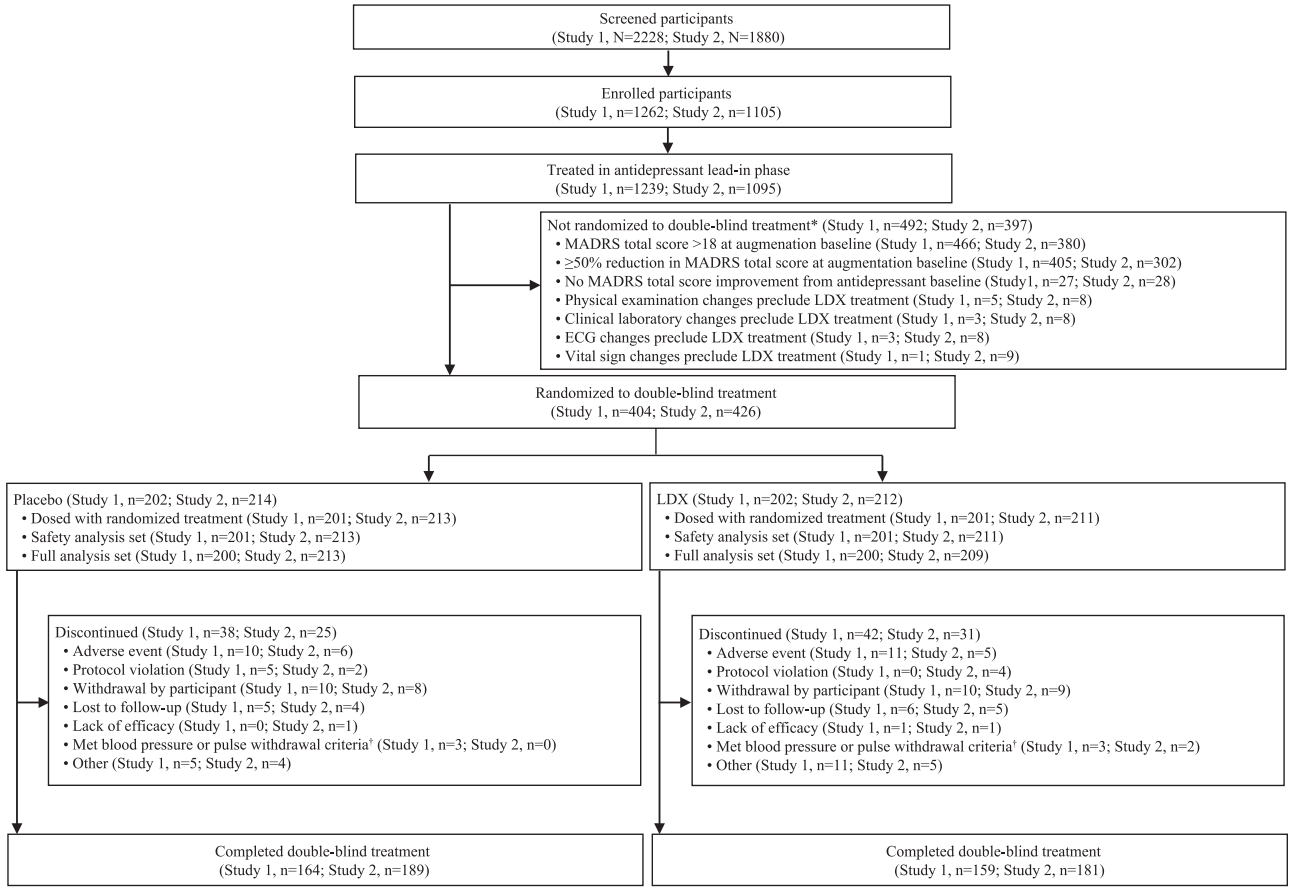

Fig. 2. Participant disposition. DBP=diastolic blood pressure; ECG=electrocardiogram; LDX=lisdexamfetamine dimesylate; MADRS=Montgomery-Åsberg Depression Rating Scale; SBP=systolic blood pressure. *Participants could have had multiple reasons for not being randomized to double-blind treatment. †Sustained elevations in average (of 3 readings) sitting SBP (an increase of ≥ 10 mmHg from lead-in baseline and an average value ≥ 140 mmHg on 2 consecutive visits), or sitting DBP (an increase of ≥ 10 mmHg from lead-in baseline and an average value ≥ 90 mmHg on 2 consecutive visits), or pulse rate (an increase of ≥ 20 bpm from lead-in baseline and an average value ≥ 100 bpm on 2 consecutive visits).

administration of the first randomized treatment dose (excluding the assigned background antidepressant in the current studies). Prior MDD medication use was reported by 57.0% (229/402) and 64.2% (272/424) of participants in studies 1 and 2, respectively. The most frequently used MDD medications (≥ 5% of participants) were escitalopram (16.4% [66/402]), sertraline (13.2% [53/402]), duloxetine (12.4% [50/402]), fluoxetine (11.7% [47/402]), citalopram (11.4% [46/402]), bupropion (10.9% [44/402]), paroxetine (9.0% [36/402]), and venlafaxine (7.7% [31/402]) in study 1 and citalopram (18.9% [80/424]), sertraline (18.6% [79/424]), venlafaxine (17.7% [75/424]), escitalopram (16.0% [68/424]), fluoxetine (11.6% [49/424]), bupropion (8.0% [34/424]), paroxetine (8.0% [34/424]), duloxetine (7.8% [33/424]), and any investigational drug (5.9% [25/424]) in study 2.

3.3. Extent of exposure and treatment compliance

During double-blind treatment, mean ± SD exposure days for placebo and LDX, respectively, were 49.5 ± 15.54 and 50.1 ± 14.76 in study 1 and 52.5 ± 12.33 and 51.5 ± 13.17 in study 2. During the double-blind treatment periods in studies 1 and 2, respectively, 74.1% (149/201) and 62.6% (132/211) of participants had their LDX dose increased to 50 mg and 39.3% (79/201) and 33.6% (71/211) had their dose increased to 70 mg; 6.0% (12/201) and 9.5% (20/211) had their dose down-titrated to 20 mg. The mean ± SD daily LDX dose during double-blind treatment was 46.5 ± 13.74 mg in study 1 and 43.4 ± 14.35 mg in study 2. Most participants (study 1 [placebo: 88.1% (177/201), LDX: 91.5% (184/201)]; study 2 [placebo: 96.2% (205/213), LDX: 98.1% (207/211)]) had compliance rates (defined as [total number of capsules taken × 100]/total planned days of dosing) in the range of 80% to 120%.

3.4. Efficacy

3.4.1. Primary endpoint – change in MADRS total score

In both studies, least squares (LS) mean MADRS total score decreases from augmentation baseline to week 16 were observed with placebo and LDX (Fig. 3). As reported in Table 2, the between-treatment difference (LDX – placebo) for mean change from augmentation baseline to week 16 in MADRS total score in the entire FAS was not statistically significant in either study (both $P > 0.05$). Findings were similar when assessed by sex or antidepressant class (Supplemental Fig. 1).

3.4.2. Secondary efficacy endpoints

Findings for the SDS (key secondary endpoint) and other secondary efficacy endpoints are presented in Table 2. In both studies, there were no statistically significant or clinically meaningful treatment differences for the change from augmentation baseline to week 16 between placebo and LDX for SDS total score (Table 2) or for the individual SDS domain scores (data not shown). Across most of the other secondary efficacy endpoints (dichotomized CGI-I, QIDS-SR, ABAC-A, MADRS remission rate, MADRS 50% response rate) similar findings were observed, with few nominally statistically significant treatment effects being observed between placebo and LDX at week 16/EOS (Table 2). However, because the primary

Table 1
Demographic and baseline clinical characteristics, safety analysis set.

	Study 1		Study 2	
	Placebo (n=201)	LDX (n=201)	Placebo (n=213)	LDX (n=211)
Mean ± SD age, years	41.8 ± 12.04	42.2 ± 12.32	42.6 ± 11.41	42.0 ± 11.63
Sex, n (%)				
Male	68 (33.8)	72 (35.8)	70 (32.9)	70 (33.2)
Female	133 (66.2)	129 (64.2)	143 (67.1)	141 (66.8)
Race, n (%)				
White	160 (79.6)	154 (76.6)	183 (85.9)	174 (82.5)
Black/African American	36 (17.9)	39 (19.4)	24 (11.3)	34 (16.1)
Native Hawaiian/Pacific Islander	0	0	1 (0.5)	1 (0.5)
Asian	5 (2.5)	5 (2.5)	3 (1.4)	1 (0.5)
American Indian/Alaska Native	0	1 (0.5)	0	0
Other	0	2 (1.0)	2 (0.9)	1 (0.5)
Mean ± SD weight, kg	82.4 ± 17.90	81.3 ± 18.34	80.8 ± 18.52	82.2 ± 17.66
Mean ± SD body mass index, kg/m^2	28.9 ± 5.43	28.5 ± 5.66	28.1 ± 5.47	28.4 ± 5.45
Mean ± SD MADRS total score				
Lead-in baseline	33.2 ± 4.63	33.8 ± 5.01	34.1 ± 5.21	33.4 ± 4.39
Augmentation baseline	25.2 ± 5.03	25.4 ± 4.75	25.7 ± 5.29	26.0 ± 5.15
Mean ± SD SDS scores at augmentation baseline[a]				
Total score	15.6 ± 5.65	15.9 ± 5.99	16.8 ± 5.75	16.8 ± 5.34
Disrupted family life score	5.2 ± 2.05	5.2 ± 2.19	5.5 ± 2.18	5.6 ± 1.98
Disrupted social life score	5.6 ± 2.16	5.7 ± 2.09	5.8 ± 2.14	5.8 ± 1.95
Disrupted work/school score	4.7 ± 2.26	5.0 ± 2.36	5.5 ± 2.23	5.3 ± 2.27
Lead-in baseline antidepressant, n (%)				
Venlafaxine HCl extended-release (SNRI)	25 (12.4)	21 (10.4)	52 (24.4)	48 (22.7)
Duloxetine HCl (SNRI)	62 (30.8)	65 (32.3)	46 (21.6)	48 (22.7)
Escitalopram oxalate (SSRI)	67 (33.3)	80 (39.8)	66 (31.0)	63 (29.9)
Sertraline HCl (SSRI)	47 (23.4)	35 (17.4)	49 (23.0)	52 (24.6)
Final antidepressant dose, n (%)				
Venlafaxine HCl extended-release (SNRI)				
37.5 mg	1 (0.5)	0	–	–
75 mg	0	1 (0.5)	7 (3.3)	7 (3.3)
150 mg	3 (1.5)	4 (2.0)	18 (8.5)	17 (8.1)
225 mg	21 (10.4)	16 (8.0)	22 (10.3)	20 (9.5)
300 mg	–	–	3 (1.4)	3 (1.4)
375 mg	–	–	2 (0.9)	1 (0.5)
Duloxetine HCl (SNRI)				
30 mg	1 (0.5)	2 (1.0)	0	2 (0.9)
40 mg	5 (2.5)	5 (2.5)	1 (0.5)	1 (0.5)
60 mg	48 (23.9)	44 (21.9)	31 (14.6)	37 (17.5)
90 mg	3 (1.5)	6 (3.0)	3 (1.4)	2 (0.9)
120 mg	5 (2.5)	8 (4.0)	11 (5.2)	6 (2.8)
Escitalopram oxalate (SSRI)				
10 mg	7 (3.5)	13 (6.5)	12 (5.6)	11 (5.2)
20 mg	60 (29.9)	67 (33.3)	54 (25.4)	52 (24.6)
Sertraline HCl (SSRI)				
50 mg	3 (1.5)	2 (1.0)	4 (1.9)	8 (3.8)
100 mg	8 (4.0)	7 (3.5)	13 (6.1)	18 (8.5)
150 mg	14 (7.0)	12 (6.0)	4 (1.9)	15 (7.1)
200 mg	22 (10.9)	14 (7.0)	28 (13.1)	11 (5.2)

LDX=lisdexamfetamine dimesylate; MADRS=Montgomery-Åsberg Depression Rating Scale; SDS=Sheehan Disability Scale; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor.

[a] Based on Full Analysis set: study 1 (total score [placebo, n=198; LDX, n=198], disrupted family life score [placebo, n=199; LDX, n=199], disrupted social life score [placebo, n=199; LDX, n=198], disrupted work/school score [placebo, n=198; LDX, n=199]); study 2 (placebo, n=213; LDX, n=209).

endpoint was not statistically significant, any nominal differences in secondary endpoints should not be considered statistically significant.

3.5. Safety and tolerability

3.5.1. Adverse events

Treatment-emergent AE (TEAEs) are summarized in Table 3. In both studies, higher percentages of TEAEs were reported with LDX than with placebo. Most TEAEs were mild or moderate in intensity; the frequency of severe TEAEs was low in both studies (see footnote to Table 3 for a complete listing). TEAEs leading to discontinuation were generally of mild to moderate intensity in both studies (see footnote to Table 3 for a complete listing of TEAEs leading to discontinuation), with the exception of 2 cases in study 1 (syncope in an LDX participant; suicide attempt in a placebo participant; both resolved) and 2 cases in study 2 (anxiety in an LDX participant; suicidal ideation in a placebo participant). The most frequently occurring TEAEs are summarized in Table 3. The TEAEs reported by ≥5% of participants treated with LDX and at twice the rate of placebo were dry mouth and nasopharyngitis in study 1 and dry mouth and decreased appetite in study 2. There were no instances of psychosis/mania or aggression reported as TEAEs or deaths in either study.

Few serious TEAEs were reported in either study (Table 3). In study 1, there were 3 serious TEAEs in the LDX group (nonsuicidal overdose of diphenhydramine, syncope, and appendicitis; none were considered treatment related by the investigator) and 7 serious TEAEs in the placebo group (suicide attempt, major depression, vertigo, syncope, appendectomy, laceration, and skin

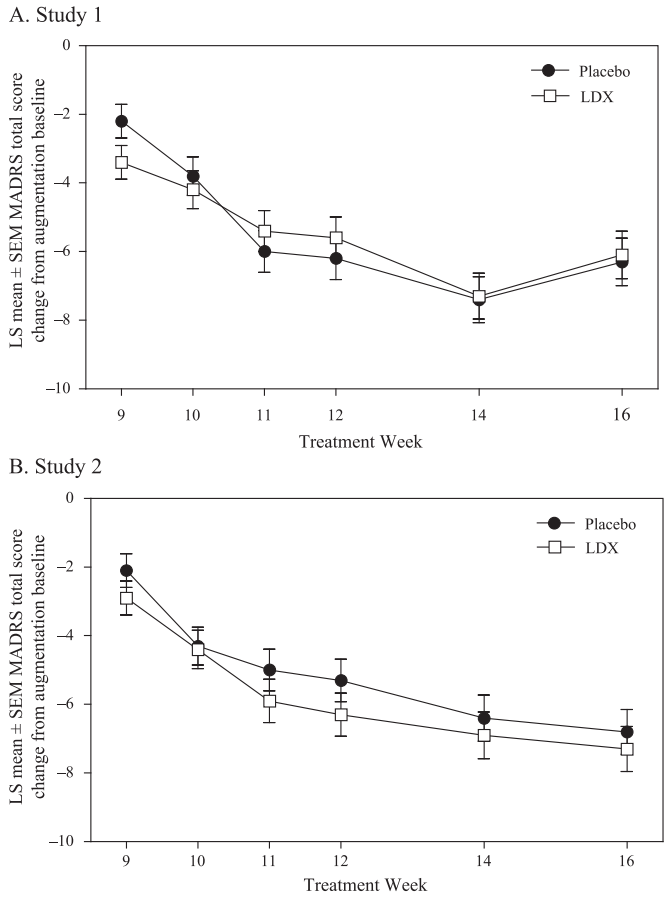

Fig. 3. Change in MADRS total score during double-blind treatment (full analysis set) for Study 1 (A) and Study 2 (B). LDX=lisdexamfetamine; dimesylate MADRS=Montgomery-Åsberg Depression Rating Scale.

infection). The suicide attempt and case of major depression were considered to be treatment related by the investigator. In study 2, the 2 serious TEAEs (suicidal ideation in a placebo participant and accelerated hypertension in an LDX participant) were both considered related to treatment; the suicidal ideation event resulted in study withdrawal but the case of accelerated hypertension did not.

3.5.2. *Vital signs and electrocardiogram*

At week 16/EOS, mean SBP and DBP decreased with placebo and increased with LDX in study 1. In study 2, increases in SBP and DBP at week 16/EOS were numerically larger with LDX than with placebo (Table 3). In both studies, mean increases in pulse with LDX were numerically larger than those observed for placebo (Table 3). The proportion of participants with potentially clinically important changes in SBP, DBP, and pulse was generally higher with LDX than with placebo (Table 3). Based on the ECG, mean heart rate increases and QT duration decreases were numerically larger with LDX than with placebo in both studies (Table 3). Fridericia-corrected QT interval decreases were comparable with placebo and LDX in study 1, but were numerically larger with LDX in study 2.

3.5.3. *Other safety and tolerability endpoints*

Mean weight and BMI increased with placebo and decreased with LDX in both studies (Table 3). Six LDX-treated participants (3.0%) in study 1 and 8 LDX-treated participants (3.8%) in study 2 exhibited $\geq 7\%$ decreases in body weight from the augmentation baseline; no placebo participants met this criterion in either study. Four placebo-treated participants (2.0%) in study 1 and 2 placebo-treated participants (0.9%) in study 2 had a $\geq 7\%$ increase in body weight from the augmentation baseline; no LDX participants met this criterion in either study. There were no differences of clinical concern between treatment groups regarding clinical laboratory findings in either study.

On the C-SSRS, ≥ 1 positive suicidal ideation occurred during double-blind treatment in 14 placebo (7.0%) and 14 LDX (7.0%) participants in study 1 and in 20 placebo (9.4%) and 19 LDX (9.0%) participants in study 2. At least 1 suicide attempt was reported on the C-SSRS during double-blind treatment in 1 (0.5%) placebo participant in each study; the suicide attempt in study 2 was also recorded as a TEAE of mild intensity.

At follow-up, mean $\pm$ SD ACSA total scores were 15.1 ± 10.71 with placebo (n=178) and 14.7 ± 10.94 with LDX (n=183) in study 1 and 17.2 ± 10.56 with placebo (n=199) and 17.0 ± 10.80 (n=194) with LDX in study 2.

4. Discussion

The primary finding of the current studies was that augmentation of antidepressant therapy with LDX was *not* associated with significantly different reductions in MADRS total score (the primary efficacy endpoint) than placebo augmentation in adults with inadequate responses to 8 weeks of standard antidepressant therapy. Similar findings were observed for the prespecified key secondary endpoint (SDS total score) and the other secondary efficacy endpoints.

These findings do not support previously published findings of LDX augmentation for MDD based on 2 small phase 2 studies (Madhoo et al., 2014; Trivedi et al., 2013), but they are generally consistent with published findings for psychostimulant (Patkar et al., 2006; Postolache et al., 1999; Ravindran et al., 2008) and modafinil augmentation studies for MDD (DeBattista et al., 2003; Dunlop et al., 2007; Fava et al., 2007) and with the conclusions of published meta-analyses (Candy et al., 2008; Fleurence et al., 2009). Discrepancies between the current phase 3 studies and previously published phase 2 studies might be attributed to study design differences. The phase 3 studies required that participants have MADRS total scores of ≥ 18 at augmentation baseline *and* MADRS total score reductions of $< 50\%$ from the antidepressant lead-in baseline to augmentation baseline, but the phase 2 studies included participants with 17-item Hamilton Depression Rating Scale scores ≥ 4 (Trivedi et al., 2013) or with executive dysfunction *and* MADRS total scores ≤ 18 (Madhoo et al., 2014). Second, both phase 2 studies included smaller study populations and used only SSRIs as the antidepressant medication (Madhoo et al., 2014; Trivedi et al., 2013). It has been suggested that using small, underpowered, proof-of-concept studies in the design of larger, randomized clinical trials may be problematic (Kraemer and Kupfer, 2006). Despite these potential explanations, it is important to note that the phase 3 studies described in this report were more rigorously designed and better powered than the published phase 2 studies (Madhoo et al., 2014; Trivedi et al., 2013). As such, these findings indicate that LDX was *not* superior to placebo in reducing the depressive symptoms of MDD.

The lack of efficacy observed in the current study may indicate that psychostimulants as a class are ineffective in treating undifferentiated residual depressive symptoms in individuals who exhibit an inadequate response to antidepressant monotherapy. Alternatively, it is possible that clinician-rated scales, such as MADRS, do not capture the true effects of psychostimulants or that psychostimulants do not provide multidimensional symptom relief. Rather, they may provide dimensional efficacy for individuals with symptoms related to anhedonia, fatigue, or cognitive dysfunction. The possibility that the failure to observe an effect of LDX

Table 2
Efficacy assessments at end of double-blind treatment, full analysis set.

	Study 1		Study 2	
	Placebo	**LDX**	**Placebo**	**LDX**
MADRS total score (primary endpoint)[a]				
Mean ± SD total score at augmentation baseline	25.2 ± 5.03	25.4 ± 4.77	25.7 ± 5.29	26.0 ± 5.16
Mean ± SD total score at week 16	18.9 ± 9.99	19.1 ± 9.10	18.9 ± 8.85	18.3 ± 9.58
LS mean (95% CI) change from augmentation baseline at week 16	−6.3 (−7.6, −4.9)	−6.1 (−7.5, −4.8)	−6.8 (−8.1, −5.5)	−7.3 (−8.6, −6.0)
LS mean (95% CI) treatment difference at week 16	0.1 (−1.7, 2.0); $P<0.883$		−0.5 (−2.3, 1.3); $P<0.583$	
SDS total score (key secondary endpoint)[b]				
Mean ± SD total score at augmentation baseline	15.6 ± 5.65	15.9 ± 5.99	16.8 ± 5.75	16.8 ± 5.34
Mean ± SD total score at week 16	11.5 ± 7.30	11.0 ± 6.86	12.1 ± 7.03	11.4 ± 7.23
LS mean (95% CI) change from augmentation baseline at week 16	−4.3 (−5.3, −3.3)	−4.7 (−5.6, −3.7)	−4.3 (−5.2, −3.4)	−4.9 (−5.8, −4.0)
LS mean (95% CI) treatment difference at week 16	−0.4 (−1.8, 1.0); $P=0.576$		−0.6 (−1.9, 0.7); $P=0.354$	
MAF-GFI (secondary endpoint)[c]				
Mean ± SD total score at augmentation baseline	–	–	32.3 ± 9.36	32.6 ± 8.77
Mean ± SD total score at week 16	–	–	27.8 ± 11.78	25.6 ± 11.16
LS mean (95% CI) change from augmentation baseline at week 16	–	–	−4.4 (−5.8, −3.0)	−6.6 (−8.0, −5.1)
LS mean (95% CI) treatment difference at week 16	–		−2.2 (−4.1, −0.2); nominal $P=0.031$	
QIDS-SR total score (secondary endpoint)[d]				
Mean ± SD total score at augmentation baseline	11.9 ± 3.74	11.8 ± 3.97	–	–
Mean ± SD total score at week 16	9.6 ± 4.66	9.6 ± 4.79	–	–
LS mean (95% CI) change from augmentation baseline at week 16	−2.6 (−3.2, −1.9)	−2.3 (−2.9, −1.7)	–	–
LS mean (95% CI) treatment difference at week 16	0.3 (−0.6, 1.1); nominal $P=0.500$		–	
ABAC-A T-composite score (secondary endpoint)[e]				
Mean ± SD total score at augmentation baseline	–	–	46.1 ± 13.18	45.0 ± 13.35
Mean ± SD total score at week 16	–	–	48.2 ± 12.96	47.7 ± 12.70
LS mean (95% CI) change from augmentation baseline at week 16	–	–	2.5 (1.5, 3.5)	3.0 (2.1, 4.0)
LS mean (95% CI) treatment difference at week 16	–		0.5 (−0.8, 1.9); nominal $P=0.435$	
25% MADRS response at week 16/EOS (secondary endpoint)				
n/N (%)	130/200 (65.0)	149/200 (74.5)	158/213 (74.2)	144/209 (68.9)
Nominal *P* value	0.039		0.234	
50% MADRS response at week 16/EOS (secondary endpoint)				
n/N (%)	77/200 (38.5)	82/200 (41.0)	79/213 (37.1)	87/209 (41.6)
Nominal *P* value	0.591		0.342	
MADRS remission at week 16/EOS (secondary endpoint)				
n/N (%)	45/200 (22.5)	37/200 (18.5)	38/213 (17.8)	48/209 (23.0)
Nominal *P* value	0.335		0.195	
CGI-I Improved at week 16/EOS (secondary endpoint)				
n/N (%)	106/199 (53.3)	110/199 (55.3)	114/213 (53.5)	119/209 (56.9)
Nominal *P* value	0.729		0.486	

ABAC-A=Abbreviated Brief Assessment of Cognition in Affective Disorders; CGI-I=Clinical Global Impressions-Improvement; EOS=end of study; MADRS=Montgomery-Åsberg Depression Rating Scale; MAF-GFI=global fatigue index of the Multidimensional Assessment of Fatigue; QIDS-SR=Quick Inventory of Depressive Symptomatology–Self-Report; SDS=Sheehan Disability Scale.

[a] MADRS sample sizes: augmentation baseline (study 1 [placebo (n=200), LDX (n=200)]; study 2 [placebo (n=213), LDX (n=209)]); week 16, LS mean change from augmentation baseline, and LS mean treatment difference at week 16 (study 1 [placebo (n=165), LDX (n=163)]; study 2 [placebo (n=189), LDX (n=181)]).

[b] SDS sample sizes: augmentation baseline (study 1 [placebo (n=198), LDX (n=198)]; study 2 [placebo (n=213), LDX (n=209)]); week 16 (study 1 [placebo (n=165), LDX (n=163)]; study 2 [placebo (n=189), LDX (n=180)]); LS mean change from augmentation baseline and LS mean treatment difference at week 16 (study 1 [placebo (n=164), LDX (n=162)]), study 2 (placebo [n=189], LDX [n=180]).

[c] MAF-GFI sample sizes: augmentation baseline (study 2 [placebo (n=212), LDX (n=209)]); week 16, LS mean change from augmentation baseline and LS mean treatment difference at week 16 (study 2 [placebo (n=205), LDX (n=197)]).

[d] QIDS-SR sample sizes: augmentation baseline (study 1 [placebo (n=197), LDX (n=199)]); week 16 (study 1 [placebo (n=189), LDX (n=186)]); LS mean change from augmentation baseline and LS mean treatment difference at week 16 (study 1 [placebo (n=186), LDX (n=185)]).

[e] ABAC-A sample sizes: augmentation baseline (study 2 [placebo (n=213), LDX (n=209)]); week 16, LS mean change from augmentation baseline and LS mean treatment difference at week 16 (study 2 [placebo (n=198), LDX (n=194)]).

was related to the use of the MADRS seems unlikely because of the consistent lack of effect observed across all study assessments, including the QIDS-SR. In support of the latter hypothesis, methylphenidate has been reported to be efficacious in reducing apathy in individuals with Alzheimer's disease (Rosenberg et al., 2013) and apathy and fatigue in individuals with MDD (Ravindran et al., 2008). Additionally, a previously published study reported LDX augmentation significantly improved self-reported and informant-reported executive dysfunction, as measured by the Behavior Rating Inventory of Executive Function-Adult Version, in participants with mild MDD (Madhoo et al., 2014). However, given the lack of effect of LDX on the ABAC-A in the current studies, this finding also needs to be cautiously considered. Nevertheless, the possibility that psychostimulants may effectively reduce apathy, inattention, or indifference (symptoms that may not be effectively captured by the MADRS or ABAC-A) remains. Additional studies are needed to understand the nuanced effects of psychostimulants and to further delineate the biological differences between symptoms of apathy and mood enhancement in individuals with MDD.

The overall safety and tolerability findings observed in these studies are consistent with previously published studies of LDX augmentation for MDD with other clinical studies of LDX for which LDX is approved for use (Adler et al., 2008; Madhoo et al., 2014; McElroy et al., 2016; Trivedi et al., 2013 Wigal et al., 2010). Insomnia, dry mouth, headache, decreased appetite, and nasopharyngitis were among the most frequently reported TEAEs with LDX. LDX was associated with greater mean increases in pulse rate and blood pressure than placebo and with decreases in weight and BMI.

These findings should be considered in light of several limitations. First, these studies used remote telephone assessment of the

Table 3
Summary of safety and tolerability during double-blind treatment, safety analysis set.

	Study 1			Study 2	
	Placebo (n=201)	LDX (n=201)		Placebo (n=213)	LDX (n=211)
Any TEAE, n (%)	118 (58.7)	131 (65.2)	Any TEAE, n (%)	108 (50.7)	139 (65.9)
Serious TEAEs	5 (2.5)	3 (1.5)	Serious TEAEs	1 (0.5)	1 (0.5)
Severe TEAEs[a]	6 (3.0)	4 (2.0)	Severe TEAEs[a]	3 (1.4)	7 (3.3)
Treatment-related TEAEs	56 (27.9)	75 (37.3)	Treatment-related TEAEs	43 (20.2)	85 (40.3)
TEAEs leading to discontinuation[b]	7 (3.5)	8 (4.0)	TEAEs leading to discontinuation[b]	1 (0.5)	2 (0.9)
TEAEs reported by ≥5% of participants in either treatment group			TEAEs reported by ≥5% of participants in either treatment group		
Insomnia	15 (7.5)	19 (9.5)	Headache	16 (7.5)	25 (11.8)
Dry mouth	6 (3.0)	19 (9.5)	Dry mouth	6 (2.8)	25 (11.8)
Decreased appetite	8 (4.0)	15 (7.5)	Nasopharyngitis	19 (8.9)	14 (6.6)
Headache	21 (10.4)	13 (6.5)	Decreased appetite	5 (2.3)	13 (6.2)
Nausea	10 (5.0)	13 (6.5)	Insomnia	7 (3.3)	11 (5.2)
Nasopharyngitis	4 (2.0)	11 (5.5)	Hyperhidrosis	1 (0.5)	11 (5.2)
Dizziness	10 (5.0)	9 (4.5)			
Changes (mean ± SD) from augmentation baseline at week 16/EOS			Changes (mean ± SD) from augmentation baseline at week 16/EOS		
Diastolic blood pressure, mmHg[c]	−0.4 ± 7.69	1.5 ± 8.60	Diastolic blood pressure, mmHg[c]	0.1 ± 6.55	2.6 ± 7.17
Systolic blood pressure, mmHg[c]	−0.4 ± 10.04	1.2 ± 9.70	Systolic blood pressure, mmHg[c]	0.3 ± 8.39	2.6 ± 9.79
Pulse, bpm[c]	0.7 ± 9.75	5.9 ± 10.64	Pulse, bpm[c]	0.5 ± 8.31	5.2 ± 10.34
ECG heart rate, bpm[d]	0.3 ± 8.84	6.1 ± 10.29	ECG heart rate, bpm[d]	0.5 ± 8.01	5.2 ± 10.67
ECG QT duration, ms[d]	−1.8 ± 21.67	−11.4 ± 23.57	ECG QT duration, ms[d]	−1.6 ± 19.80	−10.7 ± 25.23
ECG QTcF, ms[d]	−0.8 ± 11.30	−0.8 ± 12.80	ECG QTcF, ms[d]	0.0 ± 12.27	−1.7 ± 13.03
Weight, kg[c]	0.3 ± 1.90	−1.0 ± 2.16	Weight, kg[c]	0.2 ± 1.64	−1.0 ± 2.21
BMI, kg/m^2[c]	0.1 ± 0.67	−0.4 ± 0.77	BMI, kg/m^2[c]	0.1 ± 0.58	−0.3 ± 0.77
Potentially clinically important vital signs at 2 consecutive visits (of which 1 was the last visit)[c]			Potentially clinically important vital signs at 2 consecutive visits (of which 1 was the last visit)[c]		
Systolic blood pressure ≥ 140 mmHg[c]	2 (1.0)	0	Systolic blood pressure ≥ 140 mmHg[c]	0	3 (1.4)
Diastolic blood pressure ≥ 90 mmHg[c]	2 (1.0)	0	Diastolic blood pressure ≥ 90 mmHg[c]	0	5 (2.4)
Pulse ≥ 100 bpm[c]	0	0	Pulse ≥ 100 bpm[c]	0	3 (1.4)

BMI=body mass index; ECG=electrocardiogram; EOS=end of study; QTcF=Fridericia's corrected QTC interval; TEAE=treatment-emergent adverse event.

[a] Severe TEAEs: study 1 (placebo: gingivitis, wound infection, laceration, headache, insomnia, suicide attempt [n=1 for all]; LDX: fatigue, appendicitis, migraine, syncope, apathy [n=1 for all]); study 2 (placebo: seasonal allergy, sleep disorder, suicidal ideation [n=1 for all]; LDX: dental caries, dry mouth, dyspepsia, nasopharyngitis, anxiety, insomnia, restlessness, hot flush [n=1 for all]).

[b] TEAEs leading to discontinuation: study 1 (placebo: diarrhea, disturbance in attention, liver function test abnormal, syncope, suicide attempt, major depression, and rash [n=1 for all]; LDX: accidental overdose, sedation, systolic blood pressure increased, liver function test abnormal, musculoskeletal pain, pain in extremity, syncope, self-injurious behavior, and palpitations [n=1 for all]); study 2 (placebo: suicidal ideation [n=1]; LDX: headache and anxiety [both n=1]).

[c] Study 1 (placebo, n=200; LDX, n=201); study 2 (placebo, n=213; LDX, n=209).

[d] Study 1 (placebo, n=189; LDX, n=189); study 2 (placebo, n=202; LDX, n=196).

primary efficacy endpoint by a small pool of calibrated raters to reduce the overall number of raters and the potential for variability across raters. As inter-rater reliability was not assessed in the current studies, it is a limitation that variability across raters is unknown. The use of telephone measures is a method now being used in clinical trials to reduce bias (Kobak et al., 2008). Even though it may offer less specificity and more variability than a face-to-face clinical assessment, due in part to the inability to visually observe the participant, it is important to note that the validity of using standardized central rating via telephone correlates well with face-to-face interviews (Kobak et al., 2008) and that site- and participant-rated secondary assessments were consistent with the primary efficacy assessment. In addition, as alluded to above, it is possible that psychostimulants provide dimensional efficacy and that assessment of specific MADRS items or clusters may have revealed effects of LDX that were not apparent in the total score. However, a detailed assessment of MADRS domains was not performed because the primary and key secondary endpoints consistently failed in both studies, making such assessments statistically inappropriate and unreliable. Also, participants in the current studies lacked diversity in terms of race (most were White) and gender (most were female). Those with psychiatric comorbidities (including ADHD) and/or active medical disorders were excluded and executive functioning was not fully examined in these studies. Therefore, these findings are limited to a specific MDD population and do not extend to potential MDD subtypes. It should also be noted that the treatment duration in the current studies was relatively short. A longer duration antidepressant lead-in phase may have increased the number of participants exhibiting antidepressant responses, and a longer duration double-blind treatment phase may have increased the magnitude of LDX responses. Finally, clinical trials for MDD are susceptible to having high placebo responses (Walsh et al., 2002), which could mask a potential therapeutic effect.

In conclusion, in the 2 largest, randomized clinical trials of stimulant augmentation of antidepressant therapy completed to date, LDX was *not* superior to placebo in reducing the depressive symptoms of MDD in individuals with inadequate responses to standard antidepressant monotherapy. Although these studies did not show a treatment difference, the potential exists that stimulant augmentation may be appropriate in subgroups of individuals with MDD (eg, treatment-resistant MDD) or with a different stimulant augmentation.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi:10.1016/j.jad.2016.07.006.

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