Original Paper

Journal of Psychopharmacology
2017, Vol. 31(9) 1190–1203

DOI: 10.1177/0269881117722998
journals.sagepub.com/home/jop
SAGE

A randomized, double-blind, placebo-controlled, dose-ranging study of lisdexamfetamine dimesylate augmentation for major depressive disorder in adults with inadequate response to antidepressant therapy

Cynthia Richards[1], Dan V Iosifescu[2], Rajnish Mago[3], Elias Sarkis[4], James Reynolds[1], Brooke Geibel[1] and Matthew Dauphin[1]

Abstract

Background: This randomized, double-blind, placebo-controlled study evaluated dose-response relationships of lisdexamfetamine dimesylate when used as augmentation for major depressive disorder in individuals exhibiting inadequate responses to antidepressant monotherapy.

Methods: Eligible adults (18–65 years) were assigned to antidepressant monotherapy (escitalopram or venlafaxine extended-release) plus lisdexamfetamine dimesylate-matching placebo during an eight-week single-blind lead-in phase. Participants meeting randomization criteria were randomized (1:1:1:1:1) to eight weeks of lisdexamfetamine dimesylate (10, 30, 50, or 70 mg) or placebo while maintaining antidepressant therapy. Dose-responses for changes from augmentation baseline to week 16/early termination for Montgomery-Åsberg Depression Rating Scale total score (primary efficacy endpoint) and vital signs (systolic and diastolic blood pressure and pulse) were assessed using multiple comparisons procedures with modeling.

Results: For Montgomery-Åsberg Depression Rating Scale total score change, no significant dose-responses were observed for any candidate dose-response curve (all $p>0.10$). In the dose-response evaluable population, least squares mean (90% confidence interval) treatment differences versus placebo for Montgomery-Åsberg Depression Rating Scale total score change at week 16 were –1.4 (–3.9, 1.2), 0.1 (–2.5, 2.7), –0.7 (–3.4, 2.0), and –0.9 (–3.5, 1.6) with 10, 30, 50, and 70 mg lisdexamfetamine dimesylate, respectively. For all vital sign parameters, lisdexamfetamine dimesylate exhibited significant dose-responses for all candidate dose-response curves (all $p<0.10$), with increases observed as lisdexamfetamine dimesylate dose increased; a linear relationship provided the best fit. Mean±standard deviation changes from augmentation baseline for systolic and diastolic blood pressure and pulse at week 16/early termination were –0.7±9.90 and –0.3±7.24 mm Hg and 0.2±10.57 bpm with placebo and were 1.9±9.47 and 0.8±7.40 mm Hg and 3.6±9.74 bpm with lisdexamfetamine dimesylate (all doses combined). The safety and tolerability profile of lisdexamfetamine dimesylate was consistent with previous studies.

Conclusions: Lisdexamfetamine dimesylate augmentation did not provide benefit over placebo in adults with inadequate responses to antidepressant monotherapy based on the assessed efficacy measures.

Keywords

Major depressive disorder, lisdexamfetamine, augmentation, dose-response, multiple comparisons procedure with modeling

Introduction

Although medications indicated for major depressive disorder (MDD), including selective serotonin reuptake inhibitors (SSRIs), effectively reduce the depressive symptoms of MDD (Arroll et al., 2005; Cipriani et al., 2009), more than 60% of individuals with MDD do not experience full remission with monotherapy or second-step augmentation (Rush et al., 2006; Trivedi et al., 2006a; Trivedi et al., 2006b), which highlights the need for novel treatment approaches. For instance, in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, remission rates with citalopram monotherapy were only 27.5% (as measured by total scores ⩽7 on the 17-item Hamilton Depression Rating Scale) and 32.9% (as measured by total scores ⩽5 on the 16-item Quick Inventory of Depressive Symptomatology self-report) (Trivedi et al., 2006b). In addition, only 29.7–39.0% of those receiving second-step augmentation

[1]Formerly of Shire, Lexington, USA
[2]Department of Psychiatry, New York University School of Medicine, New York, USA
[3]Private Practice, Philadelphia, USA
[4]Sarkis Family Psychiatry, Gainesville, USA

Corresponding author:
James Reynolds (formerly of Shire), Abbvie, 1 Waukegan Road, Chicago, IL 60064, USA.
Email: jmr19438@gmail.com

with sustained-release bupropion or with buspirone achieved remission (Trivedi et al., 2006a).

Stimulants have long been considered possible treatment options for MDD, in part because of the role of dopamine in the pathophysiology of depression and its associated symptoms, such as anhedonia and lethargy (Dunlop and Nemeroff, 2007). Methylphenidate was first investigated for the treatment of MDD as early as the 1950s (Robin and Wiseberg, 1958). In addition, meta-analyses identified multiple trials from 2003 onward that investigated stimulants or modafinil as adjuncts for antidepressants (Candy et al., 2008; Fleurence et al., 2009).

Lisdexamfetamine dimesylate (LDX), a d-amphetamine prodrug (Pennick, 2010), is approved in the USA and in other countries for use in individuals aged six years and older with attention-deficit/hyperactivity disorder (ADHD) and in adults with moderate to severe binge eating disorder in the USA and Canada (Vyvanse® Product Monograph, 2016; Vyvanse® Product Monograph, 2017). The effects of LDX augmentation therapy on depressive symptoms in individuals with MDD have been examined in two small phase 2, randomized, double-blind, placebo-controlled, proof-of-concept studies (Madhoo et al., 2014; Trivedi et al., 2013) and in two large phase 3 randomized, double-blind, placebo-controlled studies (Richards et al., 2016). In the first phase 2 study, LDX augmentation of escitalopram oxalate (ESC) monotherapy met predefined signal-detection criteria (prespecified critical α=0.10) for significant reductions in Montgomery-Åsberg Depression Rating Scale (MADRS) total score versus placebo in patients whose depression had not remitted with escitalopram monotherapy (Trivedi et al., 2013). The second phase 2 study focused on executive dysfunction in participants with partially to fully remitted MDD (MADRS total score $\leqslant$18) and found that LDX augmentation of SSRI monotherapy produced significant MADRS total score reductions versus placebo (Madhoo et al., 2014). In contrast, LDX augmentation was not superior to placebo in reducing depressive symptoms in individuals with MDD exhibiting inadequate responses to antidepressant monotherapy in either of the phase 3 studies (Richards et al., 2016).

As the published LDX studies of augmentation therapy for MDD used flexible-dose designs, analyses of dose-response relationships for efficacy, safety, or tolerability were not performed. The primary objective of this study was to assess the efficacy dose-response relationship of LDX when used as augmentation therapy for MDD in individuals who exhibited inadequate MADRS total score responses to an eight-week course of antidepressant monotherapy. Secondary objectives included the evaluation of LDX dose-response relationships on systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse, and the assessment of the safety and tolerability of LDX based on the occurrence of treatment-emergent adverse events (TEAEs), responses to the Columbia-Suicide Severity Rating Scale (C-SSRS), clinical laboratory tests, and electrocardiogram (ECG) results.

Materials and methods

Participants

Eligible participants were men or nonpregnant/nonnursing women (18–65 years) with a primary diagnosis of nonpsychotic MDD, as defined by the Structured Clinical Interview for *DSM* Disorders–Clinical Trial version (SCID-CT), that had lasted for at least eight weeks before screening and who had a lead-in baseline MADRS total score $\geqslant$24. All eligible participants also had to be able to provide written informed consent before completing any study-related procedures and be willing and able to fully comply with study procedures.

Key exclusion criteria included nonresponse ($\geqslant$6 weeks of treatment at the maximum tolerated adult dose approved for MDD) to the current MDD episode with two or more antidepressant monotherapies or to an approved augmentation treatment; and a lifetime history of treatment-resistant depression, defined as having not responded to adequate treatment ($\geqslant$8 weeks of treatment at the maximum tolerated dose within the dose range approved for adults with MDD) with two or more treatment regimens, including distinct classes of approved antidepressant monotherapies and augmentation treatments. Participants were excluded if they had a history of treatment-resistant depression because the objective of the study was to assess the efficacy of LDX as augmentation therapy in participants with a minimal history of previous failed antidepressant treatments, and not to assess LDX as a possible therapy for treatment-resistant depression. As such, the inclusion of individuals with treatment-resistant depression was considered to have an unfavorable risk-benefit balance.

Participants were also excluded due to hospitalization within the last 12 months for the current MDD episode, having received electroshock therapy for the current depressive episode within three months of lead-in baseline or the need to initiate or modify the frequency of psychotherapy or to continue or initiate other treatments for depression; a current comorbid psychiatric disorder (established by a psychiatric interview that included the SCID-CT) either controlled with prohibited medications or uncontrolled and associated with significant symptoms; any symptom that contraindicated LDX treatment or could confound clinical assessments at screening; a current or lifetime history of ADHD; a first-degree relative with bipolar I disorder; a chronic or acute illness or unstable medical condition that could confound safety assessments or lead to increased risk to the participant or difficulty complying with study procedures; and being considered a suicide risk by the investigator, having attempted suicide within the past three years, or currently demonstrating active suicidal ideations (individuals with intermittent passive suicidal ideation were not necessarily excluded). Participants were also excluded if they had a history of symptomatic cardiovascular disease, advanced atherosclerosis, a cardiac abnormality, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or any condition affecting cardiac performance; a history of moderate to severe hypertension or resting average sitting SBP >139 mm Hg or average DBP >89 mm Hg at screening or lead-in baseline; a clinically significant ECG or laboratory abnormality at screening; family history of sudden cardiac death or ventricular arrhythmia; a history of seizures (excluding infantile febrile seizures), tic disorders, or a current diagnosis and/or family history of Tourette syndrome; a history ($\leqslant$6 months) of suspected abuse or dependence disorder (excluding nicotine); a lifetime history of amphetamine, cocaine, or other stimulant abuse and/or dependence; had used within 30 days of screening any other medication (including ADHD medication and over-the-counter herbal or homoeopathic preparations) with central nervous system effects that could affect the

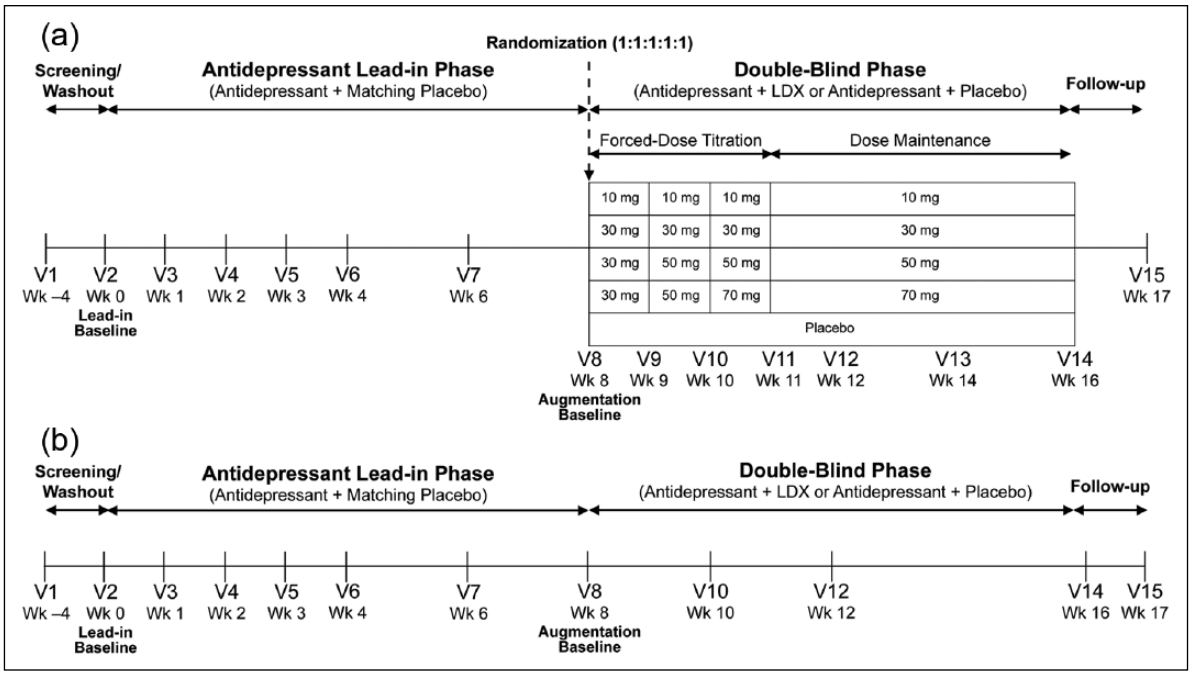

Figure 1. Study timeline and dose adjustment schedule for (a) randomized and (b) nonrandomized participants.
LDX: lisdexamfetamine dimesylate; V: visit; Wk: week.

condition being studied or the action, absorption, or disposition of LDX or the clinical laboratory assessments; or a known or suspected intolerance, hypersensitivity, or contraindication to LDX or the assigned antidepressant.

Study design and treatment

This randomized, placebo-controlled, double-blind, forced-dose titration, dose-finding study (ClinicalTrials.gov identifier: NCT01435759) was conducted at 76 sites across five countries (USA, Argentina, Chile, Australia, and the UK) between 31 May 2011–17 January 2014. The study included a screening and washout phase (1–4 weeks), an eight-week single-blind antidepressant lead-in phase, an eight-week double-blind treatment phase (three weeks of forced-dose titration followed by five weeks of dose maintenance), and a one-week follow-up phase (Figure 1).

During the lead-in antidepressant phase, which was designed to prospectively identify inadequate responders, investigators assigned unblinded antidepressant therapy (ESC or venlafaxine extended-release (VXR)) along with single-blind LDX-matching placebo to participants. Antidepressant treatment, which was based on investigator assessment of clinical factors (including prior antidepressant use, response, and tolerability), was initiated at the lowest dose allowed on the morning following the lead-in baseline visit if the participant was not already receiving the assigned antidepressant. If the participant was already taking one of the two background antidepressants (ESC or VXR) at study entry, the treatment regimen was maintained. Treatment assignment was monitored to ensure an adequate representation of each type of antidepressant in the overall study population. Participants already taking the assigned antidepressant started this phase at their current dose. Doses were subsequently titrated to the maximum tolerated dose over four weeks, after which time dose adjustments were not permitted. If a participant required a dose decrease or needed to be discontinued from treatment, the dose was tapered according to labeled guidelines. Assessments of vital signs, adverse events (AEs), and C-SSRS responses were made in conjunction with dose decreases.

At the end of the antidepressant lead-in phase (week 8; augmentation baseline), participants were randomized to augmentation with LDX or placebo if they met all of the following randomization criteria: (a) MADRS total score ⩾18 at augmentation baseline, (b) an improvement (reduction) in MADRS total score of less than 50% from week 0 (lead-in baseline) to augmentation baseline, and (c) no changes since lead-in baseline in physical examination, clinical laboratory parameters, ECG, or vital signs that would preclude LDX treatment. Participants whose depressive symptoms improved but who did not meet the randomization criteria were allocated to the nonrandomized study arm and continued to receive single-blind placebo in conjunction with their assigned antidepressant therapy on a modified visit schedule (i.e. weeks 10, 12, and 16). Participants not demonstrating improved depressive symptoms (defined as no change or a worsening of MADRS total score from the lead-in baseline) were discontinued from the study.

During the double-blind treatment phase, participants meeting all of the randomization criteria were randomized 1:1:1:1:1 to eight weeks of augmentation therapy with LDX (10, 30, 50, or 70 mg) or LDX-matching placebo (0 mg); all participants maintained their assigned antidepressant therapy. The LDX doses selected for use in this study were chosen based on two previously published phase 2 studies (Madhoo et al., 2014; Trivedi et al., 2013). Those studies reported that dose-optimized LDX

(over ranges of 20–50 mg and 20–70 mg, respectively) significantly improved depressive symptoms when used as an augmentation strategy in adults on antidepressant monotherapy. Treatment regimens for LDX or placebo were assigned using an interactive voice/web response system. A stratified randomization schedule was used, with each participant being assigned a randomization number. The stratified randomization schedule facilitated the balance between sex and the assigned background antidepressant. All treatments were administered completely at random within strata. The LDX capsule was over-encapsulated and appeared identical to the matching placebo.

During the forced-dose titration portion of double-blind treatment, doses were increased for participants randomized to LDX, and participants in the placebo group continued treatment as in the antidepressant lead-in phase. Participants randomized to 10 or 30 mg LDX started at 10 or 30 mg LDX, respectively, at week 8 and maintained these doses during weeks 9 and 10. Participants randomized to 50 mg LDX started at 30 mg at week 8 and increased to 50 mg during week 9. Participants randomized to 70 mg LDX started at 30 mg at week 8 and increased to 50 mg and 70 mg LDX during weeks 9 and 10, respectively. During the dose-maintenance portion of double-blind treatment, participants continued to receive the target doses being taken during week 10. Regardless of treatment group or treatment phase, LDX or placebo was taken once daily (at approximately 07:00 ±2 h) in conjunction with their assigned antidepressant.

One down-titration was permitted during double-blind treatment to manage increases in blood pressure or pulse; assessments of vital signs, AEs, MADRS scores, and C-SSRS responses were made in conjunction with any down-titration. Participants whose doses were decreased were permitted to continue the study at the lower dose; those requiring >1 dose reduction were discontinued from the study.

During the follow-up visit, which occurred 7–9 days after the last dose of study drug, participants returned to the study site for a final evaluation.

This study was conducted in accordance with International Conference on Harmonisation Good Clinical Practice and the principles of the Declaration of Helsinki. The protocol was approved by ethics committees and institutional review boards at each study site before study initiation.

Endpoints

Efficacy. The primary efficacy endpoint was change in MADRS (Montgomery and Asberg, 1979) total score from augmentation baseline at week 16 or early termination (ET), with assessments determined by central raters who were experienced clinicians and who were blinded to study visit and entry criteria. The central raters were trained on administration of the MADRS and were continuously calibrated to maintain the fidelity of ratings.

Exploratory efficacy endpoints included the Sheehan Disability Scale (SDS), a validated measure of functional impairments in work, family, and social life (Leon et al., 1997), and the EuroQoL 5-Dimension 5-Level Questionnaire (EQ-5D-5L), a validated measure of general health and quality of life (Shaw et al., 2005). On the SDS (assessed at lead-in and augmentation baseline and weeks 10, 12, 14, and 16/ET in randomized participants), participants rated the impact of their illness on work/school, social life, and family life/home responsibilities using an 11-point scale (0 (no impairment) to 10 (most severe)); total scores range from 0–30 (Sheehan and Sheehan, 2008). On EQ-5D-5L (assessed at lead-in and augmentation baseline and week 16/ET in randomized participants), participants designated their overall health status on a visual analog scale from 0 ("worst imaginable health status") to 100 ("best imaginable health status") (Shaw et al., 2005).

Safety and tolerability. Safety and tolerability examinations included assessment of AEs, vital signs, clinical laboratory and ECG results, and C-SSRS responses. Collection of AEs occurred at screening, every study visit during the antidepressant lead-in and double-blind phases, and at follow-up. All AEs were categorized based on severity and relatedness to study drug based on the opinion of investigators. TEAEs were defined as AEs that started or deteriorated on or after the date of the first randomized dose and no later than three days after the last dose of study drug. In addition, AEs defined a priori as being of special interest to this study included psychiatric events of aggression and violent behavior, psychosis/mania, suicidal ideation and behavior, and certain weight-related clinical laboratory or vital sign AEs.

Vital sign measures, including sitting SBP and DBP and pulse, were assessed in triplicate (⩾2 min between each assessment) at every study visit using automated machines. During the double-blind augmentation phase, blood pressure and pulse were collected at two time points (>1 hour separating each time point) at augmentation baseline, weeks 10 and 12, and week 16/ET in randomized participants only; the average of each set of three measurements was used to determine continued study participation. The 12-lead ECGs were assessed in triplicate at screening, augmentation baseline, and week 16/ET; if more than 30 days elapsed between screening and lead-in baseline, an ECG assessment was performed at lead-in baseline. Nonfasting, clinical laboratory evaluations were assessed at screening, augmentation baseline, week 12, and week 16/ET; if more than 30 days elapsed between screening and lead-in baseline, an ECG assessment was performed at lead-in baseline. Physical examinations were performed at screening, augmentation baseline, and week 16/ET; if more than 30 days had elapsed between screening and lead-in baseline, an abbreviated physical examination was performed at lead-in baseline. Height (screening and lead-in baseline) and weight (screening, every study visit during the antidepressant lead-in phase and double-blind treatment phase, and at follow-up) were also recorded. The C-SSRS, a semistructured interview assessing suicide-related thoughts and behaviors (Posner et al., 2009), was assessed at screening and every study visit.

Statistical methods and sample size

Dose-response relationships for the primary efficacy endpoint (change in MADRS total score from augmentation baseline to week 16/ET) and for vital signs (SBP, DBP, and pulse) were assessed using the multiple comparisons procedure with modeling (MCP-Mod) approach (Bretz et al., 2005; Pinheiro et al., 2006). Briefly, the MCP-Mod technique starts with a set of pre-specified candidate dose-response curves and uses a multiple-comparisons technique to test whether any of these curves fit the data significantly better than does a flat line (indicative of no dose response). If at least one of the pre-specified candidate models is significant, then this is indicative of a dose response. Any

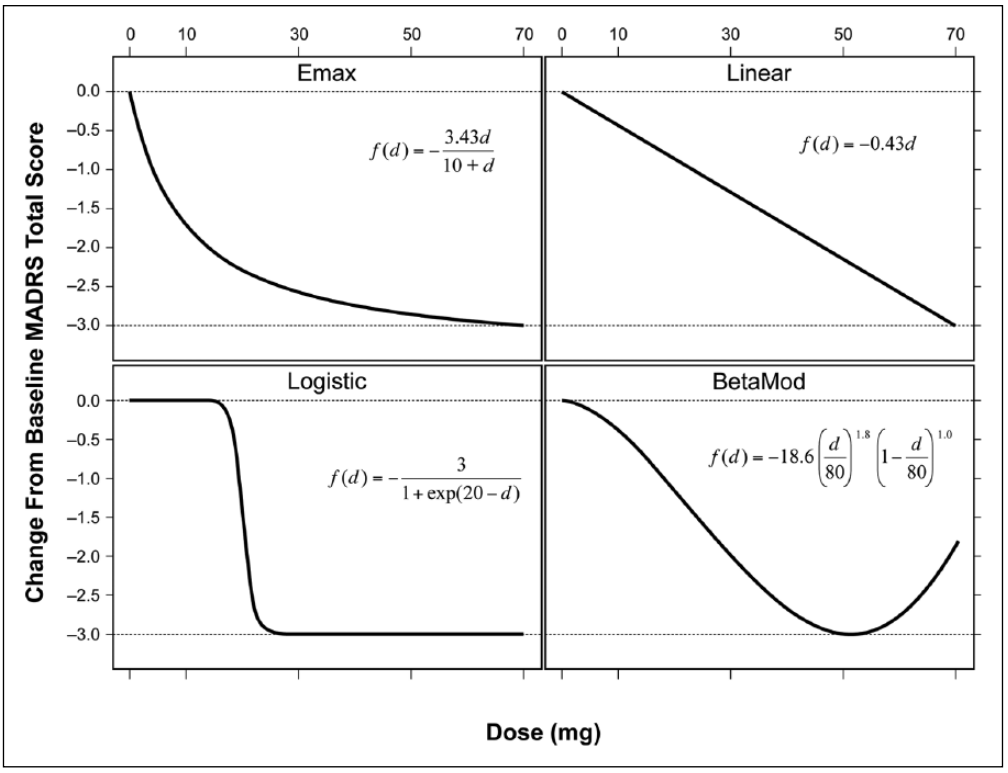

Figure 2. Prespecified candidate dose-response curves used for multiple comparisons procedure with modeling (MCP-Mod) assessment of Montgomery-Åsberg Depression Rating Scale (MADRS) total score.

significant curves are then used to develop inferences on adequate treatment doses and for estimating the minimum effective dose (Bretz et al., 2005). This method has been adopted by the Committee for Medicinal Products for Human Use of the European Medicines Agency as an efficient statistical methodology for the analysis of phase 2 dose-finding studies under dose-response uncertainty (European Medicines Agency Committee for Medicinal Products for Human Use, 2014). The pre-specified dose-response curves tested for MADRS total score change (Emax, logistic, linear, and betaMod) are depicted in Figure 2; dose-response curves tested for vital signs were Emax, exponential, linear, logistic 1, logistic 2. Placebo was considered 0 mg LDX.

The MADRS dose-response was assessed in the dose-response evaluable set (DRES), which included all randomized participants having ⩾1 primary efficacy assessment during the dose-maintenance portion of double-blind treatment (i.e. after the three-week forced-titration phase). The most recent MADRS score was carried forward for missing scores during the dose-maintenance phase. As such, a last observation carried forward analysis was effectively performed for the primary analysis. The results of the primary analysis, which used the dose-response evaluable set, were verified in the full analysis set using a mixed-effects model for repeated measures (MMRM) as a sensitivity analysis. Vital sign dose-responses were assessed based on the average of the three repeated vital sign measurements per visit in the vital signs evaluable set, which included all randomized participants having ⩾1 vital sign measurement during the dose-maintenance portion of double-blind treatment.

The null hypothesis was that the mean LDX response at each dose was the same as the placebo response. Dose-response curves were tested using appropriate contrast t statistics. If at least one candidate dose-response relationship reached a two-sided significance value of 0.10, proof of an LDX dose-response would be considered to have been established. Dose-response models included sex and antidepressant type as explanatory categorical variables; augmentation baseline MADRS total score or vital signs were included as explanatory continuous variables for their respective analyses.

Sample size was determined based on estimates of a 40% screening failure rate, 25% withdrawal from the antidepressant lead-in phase, 50% attrition due to participants not meeting randomization criteria, and 20% withdrawal of randomized participants during double-blind augmentation. Therefore, an estimated 1890 screened individuals were expected to yield 1134 enrolled participants, of which 425 (85 per treatment arm) would be randomized and 340 (68 per treatment arm) would complete the study. Assuming a mean±standard deviation (SD) maximum effect of 3.0±8.1 for MADRS total score change from augmentation baseline for each candidate dose-response curve, 68 participants per treatment arm would provide 80% power. Similarly, assuming mean±SD peak responses of 7±10 mm Hg, 5±10 mm Hg, and 10±10 bpm for SBP, DBP, and pulse, respectively, the power for identifying a dose-response relationships was approximately >95% for SBP and pulse and 62% for DBP. Due to a lower than anticipated drop-out rate, the number of randomized participants needed to obtain the necessary number of study completers was lower than expected. As a result, adequate statistical power was maintained when a lower number of participants were randomized.

In addition to MCP-Mod analyses, inferential and descriptive analyses were conducted. MADRS total score change from

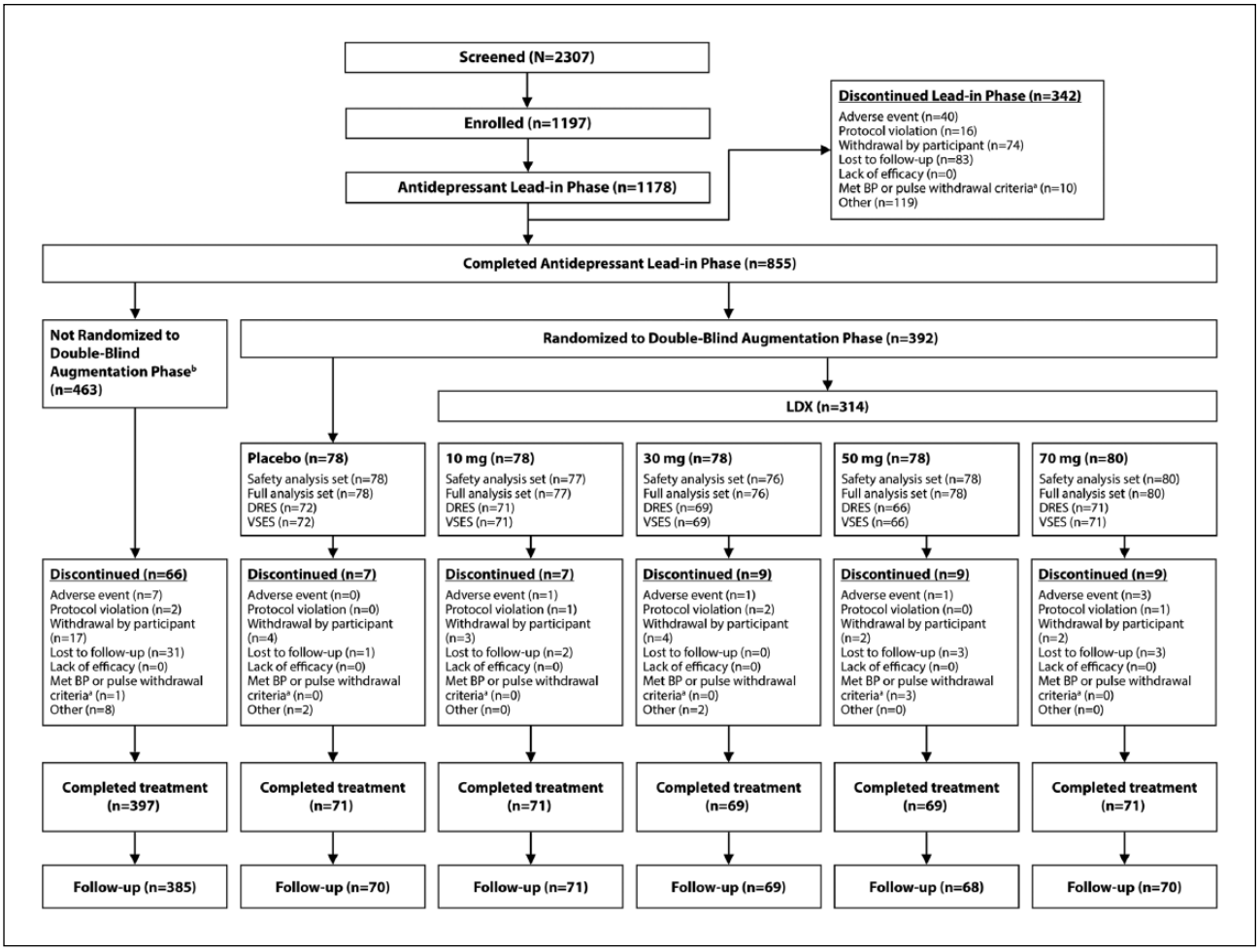

Figure 3. Participant disposition.

[a]Sustained elevations in average sitting systolic blood pressure (SBP) (increases of ⩾10 mm Hg from antidepressant lead-in baseline and an average value ⩾140 mm Hg on two consecutive visits), average sitting diastolic blood pressure (DBP) (increases of ⩾10 mm Hg from antidepressant lead-in baseline and an average value ⩾90 mm Hg on two consecutive visits), or average pulse (increase of ⩾20 bpm from antidepressant lead-in baseline and an average value ⩾100 bpm on two consecutive visits).

[b]Participants whose depressive symptoms improved but did not meet the randomization criteria; allocated to single-blind placebo in conjunction with the antidepressant therapy assigned during the antidepressant lead-in phase.

BP: blood pressure; DRES: dose-response evaluable set; LDX: lisdexamfetamine dimesylate; VSES: vital signs evaluable set.

augmentation baseline was analyzed in the DRES and the full-analysis set (FAS; all participants who took ⩾1 randomized study drug dose, had ⩾1 postaugmentation safety assessment, and had ⩾1 valid postaugmentation MADRS total score assessment) with MMRM using both double-blind augmentation phases. All MADRS data from the double-blind augmentation phase, including those taken after LDX down-titration, were included in the FAS analysis; DRES analyses did not include MADRS data collected after down-titration. Analyses were performed with treatment group, sex, antidepressant type, visit, and the interaction between treatment group and visit as fixed factors and augmentation baseline MADRS total score as a covariate; analyses also adjusted for the interaction between augmentation baseline score and visit. Least squares (LS) mean changes from augmentation baseline on the MADRS total score were calculated for each treatment group at each visit during the double-blind augmentation phase; treatment differences were estimated with two-sided 95% confidence intervals.

Safety and tolerability endpoints were assessed using descriptive statistics in the safety analysis set (all participants who took ⩾1 randomized study drug dose and had ⩾1 postaugmentation safety assessment).

Results

Participant disposition and demographics

Participant disposition is reported in Figure 3; most participants completed the study. Demographic and clinical characteristics are summarized in Table 1. Most participants in the safety analysis set were white (72.2% (281/389)), female (67.9% (264/389)), and allocated to receive ESC during the antidepressant lead-in phase (62.7% (244/389)). Mean±SD age and body mass index (BMI), respectively, were 42.3±11.61 years and 28.7±5.49 kg/m^2. Mean±SD MADRS total scores at lead-in and augmentation baseline were 33.9±4.89 and 25.7±5.12, respectively.

Table 1. Demographics and baseline clinical characteristics, safety analysis set (*n*=389).

	Placebo (*n*=78)	LDX			
		10 mg (*n*=77)	30 mg (*n*=76)	50 mg (*n*=78)	70 mg (*n*=80)
Mean±SD age, years	43.7±10.48	39.1±11.83	43.4±12.06	43.8±12.40	41.5±10.81
Sex, *n* (%)					
Male	25 (32.1)	24 (31.2)	24 (31.6)	25 (32.1)	27 (33.8)
Female	53 (67.9)	53 (68.8)	52 (68.4)	53 (67.9)	53 (66.3)
Ethnicity, *n* (%)					
Hispanic or Latino	10 (12.8)	21 (27.3)	20 (26.3)	21 (26.9)	22 (27.5)
Not Hispanic or Latino	68 (87.2)	56 (72.7)	56 (73.7)	57 (73.1)	58 (72.5)
Race, *n* (%)					
White	52 (66.7)	58 (75.3)	57 (75.0)	58 (74.4)	56 (70.0)
Black/African American	24 (30.8)	16 (20.8)	16 (21.1)	16 (20.5)	21 (26.3)
Asian	1 (1.3)	2 (2.6)	2 (2.6)	4 (5.1)	2 (2.5)
American Indian/Alaska Native	1 (1.3)	1 (1.3)	1 (1.3)	0	0
Other	0	0	0	0	1 (1.3)
Mean±SD weight, kg	82.1±20.78	83.5±20.38	80.9±18.39	81.8±19.20	81.9±19.62
Mean±SD BMI, kg/m^2	28.2±5.57	29.1±5.68	28.3±4.74	29.0±5.64	28.7±5.82
Mean±SD MADRS total score					
Antidepressant lead-in baseline	33.8±4.90	32.9±4.79	34.2±4.86	34.3±5.02	34.3±4.85
Double-blind augmentation baseline	25.4±5.03	25.2±5.08	26.3±5.27	25.5±4.92	25.9±5.32
Antidepressant type, *n* (%)					
Escitalopram oxalate	49 (62.8)	48 (62.3)	48 (63.2)	50 (64.1)	49 (61.3)
Venlafaxine extended-release	29 (37.2)	29 (37.7)	28 (36.8)	28 (35.9)	31 (38.8)
Final antidepressant dose, *n* (%)					
Escitalopram oxalate, mg					
10	9 (11.5)	8 (10.4)	9 (11.8)	5 (6.4)	5 (6.3)
20	40 (51.3)	40 (51.9)	39 (51.3)	45 (57.7)	44 (55.0)
Venlafaxine extended-release, mg					
75	6 (7.7)	2 (2.6)	10 (13.2)	4 (5.1)	6 (7.5)
150	8 (10.3)	7 (9.1)	7 (9.2)	13 (16.7)	12 (15.0)
225	15 (19.2)	20 (26.0)	11 (14.5)	11 (14.1)	13 (16.3)

BMI: body mass index; LDX: lisdexamfetamine dimesylate; MADRS: Montgomery-Åsberg Depression Rating Scale; SD: standard deviation.

Prior and concomitant medication use

Before the study, 52.7% (164/311) of the safety analysis set reported any use of antidepressant medications (placebo, 52.6% (41/78); 10 mg LDX, 53.2% (41/77); 30 mg LDX, 53.9% (41/76); 50 mg LDX, 50.0% (39/78); 70 mg LDX, 53.8% (43/80)). Antidepressant medications taken by ⩾5% of participants randomized to placebo or any LDX dose (placebo; LDX) were fluoxetine (15.4% (12/78); 15.8% (49/311)), sertraline (17.9% (14/78); 15.4% (48/311)), escitalopram (9.0% (7/78); 13.8% (43/311)), citalopram (11.5% (9/78); 11.9% (37/311)), venlafaxine (5.1% (4/78); 9.6% (30/311)), bupropion (9.0% (7/78); 8.0% (25/311)), paroxetine (3.8% (3/78); 7.4% (23/311)), or duloxetine (5.1% (4/78); 1.9% (6/311)).

During the study, most participants randomized to placebo or LDX reported concomitant medication use (placebo, 59.0% (46/78); 10 mg LDX, 64.9% (50/77); 30 mg LDX, 56.6% (43/76); 50 mg LDX, 47.4% (37/78); 70 mg LDX, 63.8% (51/80)).

Drug exposure

Final ESC or VXR doses at the end of the lead-in antidepressant phase in each treatment group are summarized in Table 1. All participants randomized to 10 and 30 mg LDX received those doses as the maximum dose during double-blind treatment. Four participants randomized to 50 mg LDX were down-titrated to 30 mg LDX; among participants randomized to 70 mg LDX, five were down-titrated to 50 mg LDX, and four were down-titrated to 30 mg LDX. The mean±SD daily LDX dose was 9.7±1.37 for 10 mg LDX, 29.4±2.72 for 30 mg LDX, 42.9±8.58 for 50 mg LDX, and 57.3±12.19 for 70 mg LDX. The mean±SD duration of exposure (in days) was 53.5±10.30 for placebo, 53.8±10.04 for 10 mg LDX, 52.2±11.86 for 30 mg LDX, 53.9±10.47 for 50 mg LDX, and 52.5±11.14 for 70 mg LDX.

Efficacy endpoints

Primary efficacy endpoint. No significant dose-response relationships were detected for the MADRS total score change from augmentation baseline for any of the candidate dose-response curves (Table 2).

Other efficacy analyses. Table 3 summarizes the descriptive and inferential analyses of MADRS total scores at augmentation

Table 2. Dose-response relationship for change in Montgomery-Åsberg Depression Rating Scale (MADRS) (dose-response evaluable set) and in vital signs (vital signs evaluable set) from augmentation baseline to week 16 using multiple comparisons procedure with modeling (MCP-Mod).

	Estimate±SE	*T* statistic	Adjusted *p* value
MADRS total score[a]			
betaMod	−0.11±1.07	0.10	1.000
Emax	0.43±1.06	0.41	0.942
Linear	0.21±1.06	0.20	0.995
Logistic	−0.32±1.07	0.30	0.978
Systolic blood pressure,[b] mm Hg			
Emax	3.16±1.01	3.14	0.004
Exponential	2.50±1.01	2.48	0.032
Linear	3.28±1.01	3.26	0.003
Logistic1	2.91±1.01	2.88	0.010
Logistic2	3.15±1.01	3.12	0.005
Diastolic blood pressure,[c] mm Hg			
Emax	2.16±0.75	2.86	0.011
Exponential	1.95±0.75	2.59	0.023
Linear	2.47±0.75	3.28	0.003
Logistic1	2.22±0.76	2.93	0.009
Logistic2	2.37±0.76	3.13	0.005
Pulse rate,[d] bpm			
Emax	4.45±1.05	4.24	<0.001
Exponential	3.52±1.05	3.36	0.002
Linear	4.30±1.05	4.10	<0.001
Logistic1	4.63±1.05	4.39	<0.001
Logistic2	4.63±1.05	4.39	<0.001

SE: standard error.

[a]MADRS total score change candidate dose-response curves: betaMod $[f(d) = -18.6\left(\frac{d}{80}\right)^{1.8}\left(1-\frac{d}{80}\right)^{1.0}]$, Emax $[f(d) = -\frac{3.43d}{10+d}]$, linear $[f(d) = -0.043d]$, logistic $[f(d) = -\frac{3}{1+e^{(20-d)}}]$.

[b]Systolic blood pressure candidate dose-response curves: Emax $[f(d) = 2+\frac{9.71d}{15+d}]$, exponential $[f(d) = 2+0.249e^{\left(\frac{d}{20}\right)}]$, linear $[f(d) = 2+0.114d]$, logistic 1 $[f(d) = 2+\frac{8}{1+e^{(20-d)}}]$, logistic 2 $[f(d) = 1.85+\frac{8.15}{1+e^{\left(\frac{20-d}{5}\right)}}]$.

[c]Diastolic blood pressure candidate dose-response curves: Emax $[f(d) = 2+\frac{8.5d}{15+d}]$, exponential $[f(d) = 2+0.218e^{\left(\frac{d}{20}\right)}]$, linear $[f(d) = 2+0.1d]$, logistic 1 $[f(d) = 2+\frac{7}{1+e^{(20-d)}}]$, logistic 2 $[f(d) = 1.87+\frac{7.13}{1+e^{\left(\frac{20-d}{5}\right)}}]$.

[d]Pulse rate candidate dose-response curves: Emax $[f(d) = 2+\frac{13.36d}{15+d}]$, exponential $[f(d) = 2+0.343e^{\left(\frac{d}{20}\right)}]$, linear $[f(d) = 2+0.157d]$, logistic 1 $[f(d) = 2+\frac{11}{1+e^{(20-d)}}]$, logistic 2 $[f(d) = 1.80+\frac{11.20}{1+e^{\left(\frac{20-d}{5}\right)}}]$.

baseline at week 16. Consistent with the MCP-Mod analysis, LS mean treatment differences between placebo and LDX were not statistically significant for the DRES or FAS. Mean MADRS total score changes from augmentation baseline at week 16 among the randomized treatment groups were similar regardless of antidepressant type or sex in the DRES, with no evidence of a dose response (data not shown).

Across treatment groups in the FAS, mean±SD SDS augmentation baseline total scores were 15.3±6.14 with placebo, 13.5±6.25 with 10 mg LDX, 16.6±6.04 with 30 mg LDX, 13.2±6.76 with 50 mg LDX, and 15.8±6.40 with 70 mg LDX. Mean±SD changes in SDS total score from augmentation baseline to week 16 were −3.9±7.01 with placebo,−3.3±5.54 with 10 mg LDX, −4.2±7.23 with 30 mg LDX, −4.6±6.42 with 50 mg LDX, and −4.2±8.00 with 70 mg LDX.

Across treatment groups in the FAS, mean±SD EQ-5D-5L augmentation baseline scores were 67.8±16.39 with placebo, 69.2±17.35 with 10 mg LDX, 62.0±18.39 with 30 mg LDX, 67.9±18.96 with 50 mg LDX, and 67.1±15.25 with 70 mg LDX. Mean±SD changes from augmentation baseline at week 16 were 2.3±17.09 with placebo, 2.5±15.41 with 10 mg LDX, 6.7±20.98 with 30 mg LDX, 4.5±15.72 with 50 mg LDX, and 6.7±15.09 with 70 mg LDX.

Safety and tolerability endpoints

MCP-Mod vital signs analyses. Statistically significant dose-response relationships between LDX dose and change from augmentation baseline in SBP, DBP, and pulse were observed (Table 2, Figure 4). All three vital sign parameters tended to increase as LDX dose increased; a linear relationship provided the best fit of the data.

Descriptive safety and tolerability analyses. Greater percentages of participants randomized to LDX than to placebo reported

Table 3. Summary of descriptive and inferential analyses of Montgomery-Åsberg Depression Rating Scale (MADRS) total scores at augmentation baseline and week 16.

	Placebo	LDX			
		10 mg	30 mg	50 mg	70 mg
Dose-response evaluable set					
Augmentation baseline					
n	72	71	69	66	71
Mean±SD MADRS total score	25.3±5.14	25.2±5.13	26.1±5.19	25.2±4.81	25.9±5.40
Week 16					
n	67	68	65	51	63
Mean±SD MADRS total score	20.0±10.62	18.7±10.02	20.5±10.31	19.6±9.88	19.5±8.28
LS mean (90% CI) change from augmentation baseline	−5.4 (−7.2, −3.5)	−6.7 (−8.6, −4.9)	−5.3 (−7.1, −3.4)	−6.1 (−8.1, −4.1)	−6.3 (−8.2, −4.4)
LS mean (90% CI) treatment difference vs placebo[a]	—	−1.4 (−3.9,1.2)	0.1 (−2.5,2.7)	−0.7 (−3.4,2.0)	−0.9 (−3.5,1.6)
p value[b]	—	0.375	0.940	0.652	0.551
Full analysis set					
Augmentation baseline					
n	78	77	76	78	80
Mean±SD MADRS total score	25.4±5.03	25.2±5.08	26.3±5.27	25.5±4.92	25.9±5.32
Week 16					
n	71	71	69	70	72
Mean±SD MADRS total score	19.8±10.37	18.3±9.96	20.6±10.41	18.6±10.09	18.8±8.84
LS mean (90% CI) change from augmentation baseline	−5.5 (−7.2, −3.7)	−7.1 (−8.8, −5.3)	−5.3 (−7.1, −3.5)	−6.6 (−8.3, −4.8)	−6.7 (−8.4, −5.0)
LS mean (90% CI) treatment difference vs placebo[a]	—	−1.6 (−4.1,0.9)	0.1 (−2.4,2.6)	−1.1 (−3.6,1.4)	−1.2 (−3.7,1.2)
p value[b]	—	0.288	0.923	0.468	0.410

CI: confidence interval; LDX: lisdexamfetamine dimesylate; LS: least squares; MADRS: Montgomery-Åsberg Depression Rating Scale; SD: standard deviation.
[a]Difference is LDX minus placebo.
[b]Based on mixed-effects model for repeated measures analysis over all postrandomization visits, with the change from augmentation baseline in MADRS total score as the outcome, treatment group, visit, their interaction, sex, and antidepressant type as factors; augmentation baseline MADRS total score was a covariate and its interaction with visit adjusted in the model. The model is based on the residual maximum likelihood method of estimation, with Kenward-Roger method for estimating degrees of freedom and an unstructured covariance matrix.

TEAEs (Table 4); most TEAEs in each treatment group were mild or moderate in severity. The most frequently reported TEAEs with LDX (reported by ⩾5% of participants and at twice the rate of placebo for any one LDX dose) are summarized in Table 4.

Severe TEAEs were reported in 18 participants randomized to LDX, with the frequency of severe TEAEs being higher with 70 mg LDX than all other LDX doses. There was no apparent dose response observed for any specific severe TEAE. Severe TEAEs reported by ⩾2 participants were insomnia (*n*=4; one for each LDX dose), anxiety (*n*=1 each with 30 and 50 mg), and lethargy and nephrolithiasis (*n*=1 each with 50 and 70 mg LDX). TEAEs led to discontinuation in five participants randomized to LDX (vomiting, *n*=1 with 30 mg LDX; blood pressure increased, *n*=1 each with 50 and 70 mg LDX; suicidal ideation and tachyphrenia (i.e. racing thoughts), *n*=1 each with 70 mg). There were no deaths during the trial. One serious treatment-emergent AE was reported. A case of cholecystitis was reported by a participant in the 70 mg LDX group. It occurred on day 29 of the double-blind augmentation phase (onset dose, 70 mg), resolved three days after onset, and was considered by the investigator not to be related to the study medication.

TEAEs of special interest (defined as aggression and violent behavior; psychosis/mania; suicidal ideation and behavior; and weight-related, clinical laboratory, or vital sign AEs) were reported by seven participants (9.0%) randomized to placebo and 77 (24.8%) randomized to LDX. TEAEs of special interest showed a dose-response relationship for LDX, with the frequency being lower with 10 mg LDX (15 (19.5%)) and 30 mg LDX (13 (17.1%)) than with 50 mg LDX (19 (24.4%)) and 70 mg LDX (30 (37.5%)). There were no instances of psychosis/mania. There was one suicidal ideation (nonlethal) in a male participant (onset at 10 mg LDX; considered related to study drug) and one instance of aggression event in a female participant (onset at 30 mg; not considered related to study drug); both participants had been randomized to 70 mg LDX. Non-psychiatric TEAEs of special interest for which an apparent dose response was observed were increased blood pressure (10 mg, one (1.3%); 30 mg, none; 50 mg, three (3.8%); 70 mg, four (5.0%)) and decreased weight (10 mg, none; 30 mg, none; 50 mg, one (1.3%); 70 mg, three (3.8%)).

Table 5 summarizes vital sign and physical examination changes from augmentation baseline at week 16/ET for the safety analysis population. At week 16/ET, mean increases in SBP and

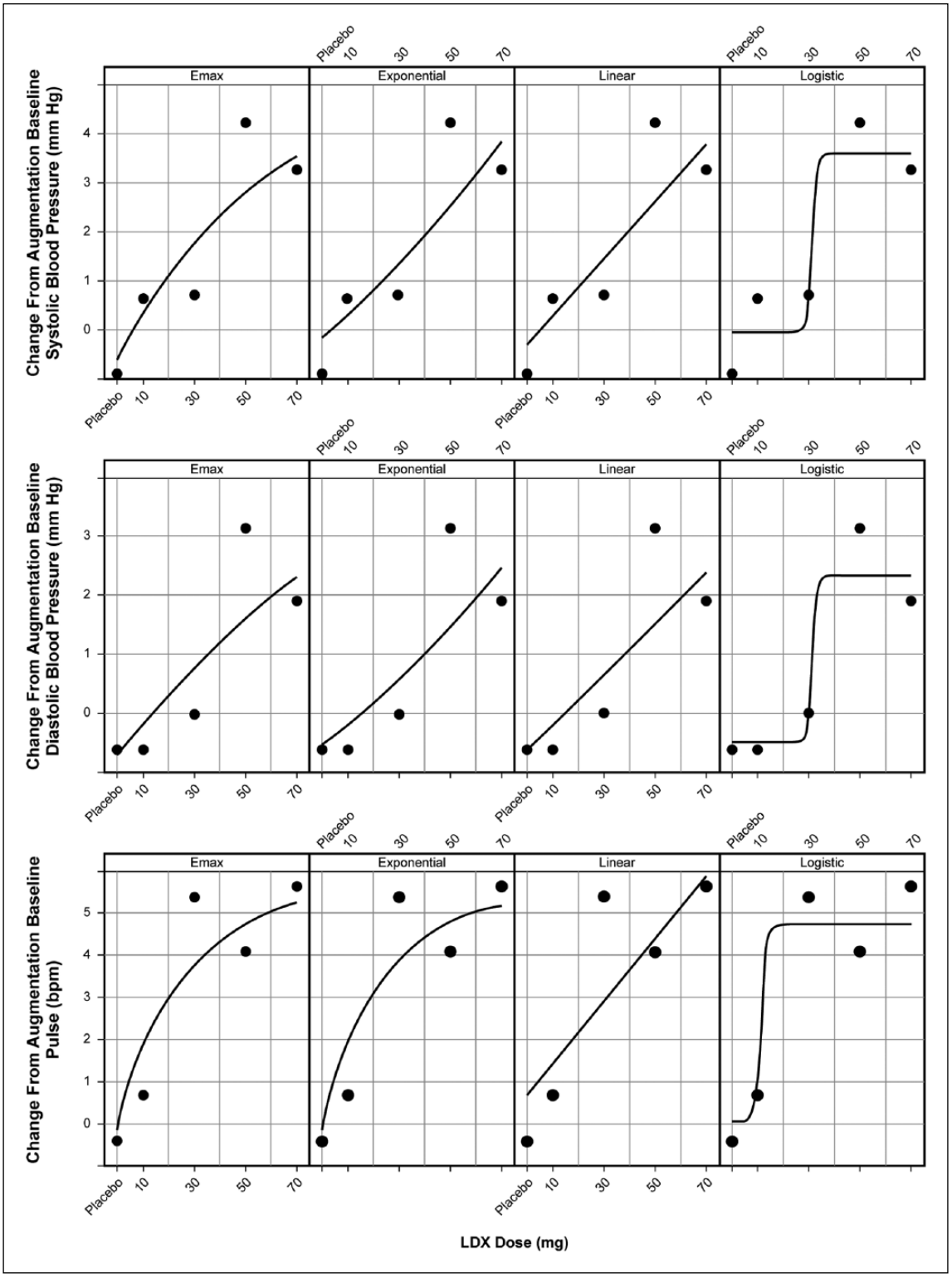

Figure 4. Dose-response relationship between the lisdexamfetamine dimesylate (LDX) dose test (10–70 mg/d) for (a) systolic blood pressure, (b) diastolic blood pressure, and (c) pulse rate.

DBP were observed with all LDX doses except the 30 mg dose, whereas decreases were observed with placebo; mean pulse increased more with all LDX doses than with placebo.

Mean body weight and BMI increased with placebo and decreased with LDX at week 16/ET, except for the 10 mg LDX group. Body weight decreases of ⩾7% from augmentation

Table 4. Summary of treatment-emergent adverse events (TEAEs), safety analysis set.

	Placebo (*n*=78)	LDX				
		10 mg (*n*=77)	30 mg (*n*=76)	50 mg (*n*=78)	70 mg (*n*=80)	All LDX (*n*=311)
Any TEAE, *n* (%)	35 (44.9)	45 (58.4)	42 (55.3)	48 (61.5)	62 (77.5)	197 (63.3)
Serious TEAEs	0	0	0	0	1 (1.3)[a]	1 (0.3)
TEAEs related to study drug	11 (14.1)	18 (23.4)	26 (34.2)	31 (39.7)	39 (48.8)	114 (36.7)
Severe TEAEs	0	3 (3.9)	2 (2.6)	4 (5.1)	9 (11.3)	18 (5.8)
TEAEs leading to discontinuation	0	0	1 (1.3)	1 (1.3)	3 (3.8)	5 (1.6)
TEAEs in ⩾5% of participants in any treatment group and twice the rate of placebo (for any one LDX dose), *n* (%)						
Insomnia	2 (2.6)	7 (9.1)	2 (2.6)	8 (10.3)	9 (11.3)	26 (8.4)
Dry mouth	1 (1.3)	2 (2.6)	2 (2.6)	10 (12.8)	10 (12.5)	24 (7.7)
Decreased appetite	1 (1.3)	4 (5.2)	5 (6.6)	5 (6.4)	4 (5.0)	18 (5.8)
Nausea	1 (1.3)	5 (6.5)	6 (7.9)	1 (1.3)	6 (7.5)	18 (5.8)
Nasopharyngitis	0	5 (6.5)	4 (5.3)	2 (2.6)	7 (8.8)	18 (5.8)
Upper respiratory tract infection	0	3 (3.9)	3 (3.9)	4 (5.1)	3 (3.8)	13 (4.2)
Bruxism	1 (1.3)	0	1 (1.3)	4 (5.1)	6 (7.5)	11 (3.5)
Influenza	2 (2.6)	1 (1.3)	4 (5.3)	4 (5.1)	1 (1.3)	10 (3.2)
Dizziness	2 (2.6)	2 (2.6)	2 (2.6)	5 (6.4)	1 (1.3)	10 (3.2)
Hyperhidrosis	1 (1.3)	4 (5.2)	0	1 (1.3)	3 (3.8)	8 (2.6)
Blood pressure increased	0	1 (1.3)	0	3 (3.8)	4 (5.0)	8 (2.6)
Fatigue	1 (1.3)	0	2 (2.6)	1 (1.3)	4 (5.0)	7 (2.3)

LDX: lisdexamfetamine dimesylate.
[a]Cholecystitis was reported by a participant in the 70 mg LDX group and occurred on day 29 of the double-blind augmentation phase (onset dose, 70 mg); it resolved three days after onset and was considered by the investigator not to be related to LDX.

Table 5. Change from augmentation baseline in vital signs and physical examinations at Week 16/ early termination (ET), safety analysis set.

	Placebo (*n*=78)	LDX				
		10 mg (*n*=77)	30 mg (*n*=76)	50 mg (*n*=78)	70 mg (*n*=80)	All LDX (*n*=311)
Vital signs, mean±SD						
SBP, mm Hg	−0.7±9.90	1.2±9.01	−0.1±8.98	3.4±8.85	3.0±10.62	1.9±9.47
DBP, mm Hg	−0.3±7.24	−0.5±6.65	−0.5±7.58	2.4±7.11	1.6±7.88	0.8±7.40
Pulse, bpm	0.2±10.57	1.1±7.51	4.6±8.14	3.4±9.67	5.0±12.44	3.6±9.74
Physical examinations, mean±SD						
Weight, kg	0.5±1.84	0.2±1.84	−0.3±1.85	−1.0±2.25	−1.5±2.90	−0.7±2.34
BMI, kg/m^2	0.2±0.61	0.1±0.63	−0.1±0.64	−0.4±0.79	−0.5±1.04	−0.2±0.83

BMI: body mass index; DBP: diastolic blood pressure; LDX: lisdexamfetamine dimesylate; SBP: systolic blood pressure; SD: standard deviation.

baseline were observed in three (3.9%) participants randomized to 50 mg LDX and 6 (7.5%) participants randomized to 70 mg LDX and in no participants randomized to placebo, 10 mg LDX, or 30 mg LDX.

Mean ECG changes from augmentation baseline were generally small, except for the RR interval, which decreased more with LDX (10 mg, −27.2±97.80 ms; 30 mg, −56.6±92.22 ms; 50 mg, −65.1±92.76 ms; 70 mg, −56.6±130.13 ms) than with placebo (−6.7±117.88 ms). No participant in any treatment group had a shift from a normal ECG at augmentation baseline to a clinically significant ECG at week 16/ET. Mean changes from augmentation baseline week 16/ET for clinical laboratory parameters were generally small in magnitude, similar between placebo and LDX, and not considered clinically meaningful.

During double-blind augmentation, ⩾1 positive suicidal ideation occurred in 11 (14.1%) participants in the placebo group and 30 (9.6%) participants across LDX groups (10 mg, seven (9.1%); 30 mg, six (7.9%); 50 mg, eight (10.3%); 70 mg, nine (11.3%)). No suicidal attempts were reported with placebo during double-blind augmentation; one (0.3%) suicide attempt was reported in a participant from the 70 mg LDX treatment group.

Discussion

In this phase 2 dose-ranging study, LDX augmentation of ESC or VXR was not statistically superior to placebo augmentation in adults with MDD who exhibited inadequate response to

antidepressant monotherapy, and no dose-response relationship for efficacy was identified. In contrast, changes in SBP, DBP, and pulse from augmentation baseline to week 16/ET exhibited significant dose-response relationships across the dose range studied. All vital sign endpoints tended to increase as LDX dose increased, with a linear relationship providing the best fit.

The lack of efficacy in the current study is consistent with the published literature describing the effects of stimulant augmentation for MDD in general (Candy et al., 2008; Fleurence et al., 2009; Patkar et al., 2006; Postolache et al., 1999; Ravindran et al., 2008) and with the phase 3 studies of LDX augmentation for MDD (Richards et al., 2016). Although individual studies provided some support for the efficacy of stimulant augmentation versus placebo for some aspects of depressive symptomatology (Madhoo et al., 2014; Trivedi et al., 2013), the weight of evidence based on meta-analyses suggests there is limited evidence for additional clinical benefit with stimulant augmentation of antidepressant monotherapy (Candy et al., 2008; Fleurence et al., 2009). Although these results are not consistent with previously reported findings of the phase 2 clinical trials of LDX augmentation in adults with MDD (Madhoo et al., 2014; Trivedi et al., 2013), it is important to note that these studies differed in important ways. This phase 2 study, and the published phase 3 studies (Trivedi et al., 2013), required that participants have MADRS total scores $\geqslant$18 at augmentation baseline *and* MADRS total score reductions <50% from the antidepressant lead-in baseline to augmentation baseline. In contrast, the previously published phase 2 studies had different inclusion criteria, using participants with 17-item Hamilton Depression Rating Scale scores $\geqslant$4 (Trivedi et al., 2013) or with executive dysfunction *and* MADRS total scores $\leqslant$18 (Madhoo et al., 2014). Additionally, one of the phase 2 studies used predefined signal-detection criteria with a critical α of 0.10 (Trivedi et al., 2013). The aforementioned two studies were also small proof-of-concept studies, which makes comparisons to the present larger dose-finding study difficult. It has been suggested that using small, underpowered proof-of-concept studies in the design of larger, randomized clinical trials may be problematic because small studies may provide inaccurate effect size estimates (Kraemer and Kupfer, 2006).

Significant dose-response relationships were observed for LDX on SBP, DBP, and pulse, with greater increases generally being observed at higher LDX doses. These findings of increased SBP, DBP, and pulse and decreased weight are consistent with previously published LDX augmentation studies for MDD (Madhoo et al., 2014; Trivedi et al., 2013) and with studies of LDX in adults diagnosed with ADHD (Adler et al., 2008) or binge eating disorder (McElroy et al., 2015a; McElroy et al., 2015b). These findings also align with the cardiovascular effects of stimulants in general (Duong et al., 2012; Santosh et al., 2011). When considered in light of the cardiovascular safety concerns associated with stimulant use (Panagiotou et al., 2011; Westover and Halm, 2012), these findings support the importance of regular cardiovascular monitoring when using stimulants in adults.

The overall TEAE profile of LDX in the current study is consistent with previously published studies of LDX augmentation for MDD (Madhoo et al., 2014; Richards et al., 2016; Trivedi et al., 2013). As in these previous studies, the most frequently reported TEAEs with LDX included insomnia, dry mouth, headache, decreased appetite, and nasopharyngitis (Madhoo et al., 2014; Trivedi et al., 2013). There were no clinically important mean changes in clinical laboratory parameters (Richards et al., 2016; Trivedi et al., 2013) or ECG (Madhoo et al., 2014; Trivedi et al., 2013) reported in previously published studies.

Potential limitations of these data related to the placebo effect and the use of the MADRS as the primary efficacy assessment instrument should be considered. Regarding the placebo effect, it has been reported that a greater probability of receiving placebo (based on the lower number of treatment arms and randomization schedule) is associated with greater separation between antidepressant treatment and placebo (Papakostas and Fava, 2009). This suggests that the probability of observing LDX treatment effects in the smaller two-arm dose-optimization studies (Madhoo et al., 2014; Trivedi et al., 2013) may have been higher than in this five-arm dose-ranging study in which there was only a 20% chance of being assigned to placebo.

In regard to the MADRS, it is possible that the benefits of stimulant augmentation are specifically related to improvement in symptoms associated with atypical depression, such as lethargy (Fava et al., 2007), or for cognitive symptoms (Madhoo et al., 2014). Improvement in these domains would not be discriminated using MADRS total score, but may be more adequately addressed on an instrument such as the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (Fava et al., 2009). Although an item analysis of the MADRS could provide insight into issues related to specific MADRS items or item clusters such as lassitude, concentration, or anhedonia, the current study was not powered to assess changes in individual MADRS items. It should also be noted that the MADRS assesses appetite as a separate item and that stimulant effects on appetite could confound the assessment of MDD symptoms. Future studies are needed to determine if the traditional outcomes used to measure depressive symptoms in the current study are adequate in terms of their specificity and sensitivity for assessing the efficacy of stimulant augmentation of antidepressant therapy in MDD. Additionally, it is possible that the use of a self-report scale, such as the 16-item Quick Inventory of Depressive Symptomatology-Self-Report, would provide benefit beyond that of the MADRS by capturing the individual's own perception of changes in their depressive symptoms. Finally, it should also be noted that in this study the MADRS was assessed using remote telephone interviews by a small number of trained raters to reduce the potential for inter-rater variability. However, inter-rater reliability was not assessed and this limitation should be considered when interpreting these data.

In conclusion, no significant dose response was detected for MADRS total score change from augmentation baseline using MCP-Mod analysis. LDX augmentation up to 70 mg did not provide clinical benefit over placebo based on the efficacy measures used in this study in adults with inadequate responses to antidepressant monotherapy.

Acknowledgements

Shire Development LLC (Lexington, MA, USA) provided funding to Complete Healthcare Communications, LLC (CHC; West Chester, Pennsylvania, USA), for support in writing and editing this manuscript. Under the direction of the authors, writing assistance was provided by Stefan Kolata, (a former employee of CHC), and Craig Slawecki (an employee of CHC). Editorial assistance in the form of proofreading, copyediting, and fact checking was also provided by CHC. Shailesh

Desai from Shire reviewed and edited the manuscript for scientific accuracy. The content of this manuscript, the ultimate interpretation, and the decision to submit it for publication in the *Journal of Psychopharmacology* were made by the authors. The authors would like to thank John Zajecka for his contributions to this manuscript.

Declaration of conflicting interest

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: C Richards, J Reynolds, M Dauphin, and B Geibel are former employees of Shire and hold stock and/or stock options in Shire. D Iosifescu, in the past three years, has consulted for Avanir, Axsome, CNS Response, INSYS Therapeutics, Lundbeck, Otsuka, Servier, and Sunovion and received research support through the Icahn School of Medicine at Mount Sinai from Alkermes, AstraZeneca, Brainsway, Euthymics, Neosync, Roche, and Shire. R Mago, in the past three years, has received research grants through Thomas Jefferson University from Alkermes, Forest Research Institute, Genomind, Shire Development, and has done consultations for Forest Laboratories, GuidePoint Global, Nestle Health Science, Otsuka America Pharmaceuticals, and Sunovion, and has received payment through Thomas Jefferson University from Shire US for live training. E Sarkis, in the past three years, has conducted clinical trials with Alkermes, Allergan, AstraZeneca, Auspex, Daiichi-Sankyo, Eli-Lilly, Forest, GlaxoSmithKline, Lundbeck, Neurim, Otsuka, Pfizer, Purdue, Shire, Sunovion, and Tonix.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This clinical research was funded by the sponsor, Shire Development LLC (Lexington, Massachusetts, USA). Clinical trials registration: This trial (NCT01435759) is registered at clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT01435759).

References

Adler LA, Goodman DW, Kollins SH, et al. (2008) Double-blind, placebo-controlled study of the efficacy and safety of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder. *J Clin Psychiatry* 69: 1364–1373.

Arroll B, Macgillivray S, Ogston S, et al. (2005) Efficacy and tolerability of tricyclic antidepressants and SSRIs compared with placebo for treatment of depression in primary care: A meta-analysis. *Ann Fam Med* 3: 449–456.

Bretz F, Pinheiro JC and Branson M (2005) Combining multiple comparisons and modeling techniques in dose-response studies. *Biometrics* 61: 738–748.

Candy M, Jones L, Williams R, et al. (2008) Psychostimulants for depression. *Cochrane Database of Systematic Reviews*: CD006722.

Cipriani A, Furukawa TA, Salanti G, et al. (2009) Comparative efficacy and acceptability of 12 new-generation antidepressants: A multiple-treatments meta-analysis. *Lancet* 373: 746–758.

Dunlop BW and Nemeroff CB (2007) The role of dopamine in the pathophysiology of depression. *Arch Gen Psychiatry* 64: 327–337.

Duong S, Chung K and Wigal SB (2012) Metabolic, toxicological, and safety considerations for drugs used to treat ADHD. *Expert Opin Drug Metab Toxicol* 8: 543–552.

European Medicines Agency Committee for Medicinal Products for Human Use (2014) *Qualification opinion of MCP-Mod as an efficient statistical methodology for model-based design and analysis of phase II dose finding studies under model uncertainty*. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2014/02/WC500161027.pdf

Fava M, Iosifescu DV, Pedrelli P, et al. (2009) Reliability and validity of the Massachusetts General Hospital Cognitive and Physical Functioning questionnaire. *Psychother Psychosom* 78: 91–97.

Fava M, Thase ME, DeBattista C, et al. (2007) Modafinil augmentation of selective serotonin reuptake inhibitor therapy in MDD partial responders with persistent fatigue and sleepiness. *Ann Clin Psychiatry* 19: 153–159.

Fleurence R, Williamson R, Jing Y, et al. (2009) A systematic review of augmentation strategies for patients with major depressive disorder. *Psychopharmacol Bull* 42: 57–90.

Kraemer HC and Kupfer DJ (2006) Size of treatment effects and their importance to clinical research and practice. *Biol Psychiatry* 59: 990–996.

Leon AC, Olfson M, Portera L, et al. (1997) Assessing psychiatric impairment in primary care with the Sheehan Disability Scale. *Int J Psychiatry Med* 27: 93–105.

Madhoo M, Keefe RS, Roth RM, et al. (2014) Lisdexamfetamine dimesylate augmentation in adults with persistent executive dysfunction after partial or full remission of major depressive disorder. *Neuropsychopharmacology* 39: 1388–1398.

McElroy SL, Hudson J, Ferreira-Cornwell MC, et al. (2015a) Lisdexamfetamine dimesylate for adults with moderate to severe binge eating disorder: Results of two pivotal phase 3 randomized controlled trials. *Neuropsychopharmacology* 41: 1251–1260.

McElroy SL, Hudson JI, Mitchell JE, et al. (2015b) Efficacy and safety of lisdexamfetamine for treatment of adults with moderate to severe binge-eating disorder: A randomized clinical trial. *JAMA Psychiatry* 72: 235–246.

Montgomery SA and Asberg M (1979) A new depression scale designed to be sensitive to change. *Br J Psychiatry* 134: 382–389.

Panagiotou OA, Contopoulos-Ioannidis DG, Papanikolaou PN, et al. (2011) Different black box warning labeling for same-class drugs. *J Gen Intern Med* 26: 603–610.

Papakostas GI and Fava M (2009) Does the probability of receiving placebo influence clinical trial outcome? A meta-regression of double-blind, randomized clinical trials in MDD. *Eur Neuropsychopharmacol* 19: 34–40.

Patkar AA, Masand PS, Pae CU, et al. (2006) A randomized, double-blind, placebo-controlled trial of augmentation with an extended release formulation of methylphenidate in outpatients with treatment-resistant depression. *J Clin Psychopharmacol* 26: 653–656.

Pennick M (2010) Absorption of lisdexamfetamine dimesylate and its enzymatic conversion to d-amphetamine. *Neuropsychiatr Dis Treat* 6: 317–327.

Pinheiro J, Bornkamp B and Bretz F (2006) Design and analysis of dose-finding studies combining multiple comparisons and modeling procedures. *J Biopharm Stat* 16: 639–656.

Posner K, Brent D, Lucas C, et al. (2009) *Columbia-Suicide Severity Rating Scale*. Available at: http://www.cssrs.columbia.edu/scale_versions.html.

Postolache TT, Rosenthal RN, Hellerstein DJ, et al. (1999) Early augmentation of sertraline with methylphenidate. *J Clin Psychiatry* 60: 123–124.

Ravindran AV, Kennedy SH, O'Donovan MC, et al. (2008) Osmotic-release oral system methylphenidate augmentation of antidepressant monotherapy in major depressive disorder: Results of a double-blind, randomized, placebo-controlled trial. *J Clin Psychiatry* 69: 87–94.

Richards C, McIntyre RS, Weisler R, et al. (2016) 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. *J Affect Disord* 206: 151–160.

Robin AA and Wiseberg S (1958) A controlled trial of methyl phenidate (ritalin) in the treatment of depressive states. *J Neurol Neurosurg Psychiatry* 21: 55–57.

Rush AJ, Trivedi MH, Wisniewski SR, et al. (2006) Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. *Am J Psychiatry* 163: 1905–1917.

Santosh PJ, Sattar S and Canagaratnam M (2011) Efficacy and tolerability of pharmacotherapies for attention-deficit hyperactivity disorder in adults. *CNS Drugs* 25: 737–763.

Shaw JW, Johnson JA and Coons SJ (2005) US valuation of the EQ-5D health states: Development and testing of the D1 valuation model. *Med Care* 43: 203–220.

Sheehan KH and Sheehan DV (2008) Assessing treatment effects in clinical trials with the discan metric of the Sheehan Disability Scale. *Int Clin Psychopharmacol* 23: 70–83.

Trivedi MH, Cutler AJ, Richards C, et al. (2013) A randomized controlled trial of the efficacy and safety of lisdexamfetamine dimesylate as augmentation therapy in adults with residual symptoms of major depressive disorder after treatment with escitalopram. *J Clin Psychiatry* 74: 802–809.

Trivedi MH, Fava M, Wisniewski SR, et al. (2006a) Medication augmentation after the failure of SSRIs for depression. *N Engl J Med* 354: 1243–1252.

Trivedi MH, Rush AJ, Wisniewski SR, et al. (2006b) Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: Implications for clinical practice. *Am J Psychiatry* 163: 28–40.

Vyvanse® Product Monograph (2016). *lisdexamfetamine dimesylate capsules*. Saint-Laurent, Québec: Shire Pharma Canada ULC.

Vyvanse® Product Monograph (2017). *lisdexamfetamine dimesylate*. Lexington, MA: Shire US Inc.

Westover AN and Halm EA (2012) Do prescription stimulants increase the risk of adverse cardiovascular events? A systematic review. *BMC Cardiovasc Disord* 12: 41.