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

Madhukar H. Trivedi, MD; Andrew J. Cutler, MD; Cynthia Richards, MD; Robert Lasser, MD; Brooke B. Geibel, BA; Joseph Gao, PhD; Angelo Sambunaris, MD; and Ashwin A. Patkar, MD

ABSTRACT

Objective: Evaluate the efficacy and safety of lisdexamfetamine dimesylate augmentation for major depressive disorder (MDD) in escitalopram nonremitters.

Method: In this proof-of-concept study (conducted from July 2009–August 2010) with a prespecified critical α = .10, adults with nonpsychotic MDD (*DSM-IV-TR* criteria) and residual depressive symptoms (17-item Hamilton Depression Rating Scale score ≥ 4) after 8 weeks of open-label escitalopram were randomized to 6 weeks of lisdexamfetamine dimesylate (20–50 mg/d) or placebo augmentation. The primary endpoint, Montgomery-Asberg Depression Rating Scale (MADRS) total score change in escitalopram nonremitters (MADRS total score > 10) from week 8 (augmentation baseline) to week 14/end of study, was assessed using analysis of covariance, with last observation carried forward.

Results: For nonremitters (placebo, n = 64; lisdexamfetamine dimesylate, n = 65), the least squares (LS) mean (90% CI) treatment difference for MADRS total score reduction at week 14/end of study (–2.3 [–4.5 to –0.1]; *P* = .0902) met the prespecified criterion for lisdexamfetamine dimesylate superiority (adjusted effect size, –0.3); the number needed to treat for MADRS remission (MADRS total score ≤ 10) was 6.7. The LS mean treatment difference in remitters was not statistically significant (1.2 [–1.6 to 4.0]; *P* = .4726). Among randomized participants, 49.4% (42/85) receiving placebo and 60.2% (53/88) receiving lisdexamfetamine dimesylate had ≥ 1 treatment-emergent adverse event, the most frequent with lisdexamfetamine dimesylate being dry mouth and headache (both 11.4%). Mean (SD) vital sign and electrocardiogram changes (placebo vs lisdexamfetamine dimesylate) were 0.5 (8.98) versus 2.3 (9.04) mm Hg (systolic blood pressure), –1.0 (7.19) versus 0.9 (6.61) mm Hg (diastolic blood pressure), –0.4 (7.39) versus 4.8 (8.64) beats per minute (heart rate), and –1.6 (11.23) versus –4.9 (11.84) milliseconds (Fridericia-adjusted QTc).

Conclusions: Lisdexamfetamine dimesylate augmentation reduced depressive symptoms in participants with inadequate escitalopram response.

Trial Registration: ClinicalTrials.gov identifier: NCT00905424

J Clin Psychiatry 2013;74(8):802–809

Submitted: *January 9, 2013; accepted April 26, 2013 (doi:10.4088/JCP.13m08360).*
Corresponding author: *Madhukar H. Trivedi, MD, Department of Psychiatry, Comprehensive Center for Depression, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9119 (madhukar.trivedi@utsouthwestern.edu).*

Despite over 20 years of research, outcomes for individuals with major depressive disorder (MDD) remain modest. Initial treatment with antidepressant classes such as selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) leads to remission in approximately one-third or fewer individuals.[1,2] In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, over 60% of citalopram-treated individuals did not achieve remission[1]; only about 30% of those receiving second-step augmentation achieved remission.[3] These findings demonstrate a need for novel treatment approaches for MDD.

Depressive symptoms that persist following treatment with an SSRI or SNRI, medications primarily affecting serotonin, norepinephrine, or both may be amenable to augmentation therapy with medications affecting dopamine neurotransmission.[3,4] In support of this concept, evidence suggests atypical antipsychotics are effective augmentation agents; however, there are concerns regarding the adverse metabolic effects associated with some of these agents. Approaches using L-methylfolate,[5] modafinil,[6,7] *S*-adenosyl-L-methionine,[8] or methylphenidate[9] for augmentation provide additional support for achieving antidepressant effects through novel mechanisms, but the results have been inconsistent. A possible explanation for the lack of consistent results may be that previous augmentation trials have not been conducted with rigorous methodology and have largely employed relatively small samples without careful selection of a treatment population. For example, a small study of extended-release methylphenidate augmentation of antidepressant monotherapy (placebo, n = 30; methylphenidate, n = 30) reported numerical but not statistical superiority of methylphenidate over placebo for treatment-resistant depression.[9] Despite these mixed results, American Psychiatric Association treatment guidelines recommend augmenting an antidepressant with medications from different drug classes, including psychostimulants, for individuals with inadequate antidepressant responses.[10]

Lisdexamfetamine dimesylate, a prodrug of dextroamphetamine that is pharmacologically inactive until converted into dextroamphetamine, is approved for the treatment of attention-deficit/hyperactivity disorder in children (aged 6–12 years), adolescents (aged 13–17 years), and adults.[11] On

the basis of evidence supporting the role of dopaminergic agents in mitigating depressive symptoms, lisdexamfetamine dimesylate is being examined as augmentation therapy for MDD.

This proof-of-concept study examined the efficacy, safety, and tolerability of lisdexamfetamine dimesylate augmentation in individuals with MDD who inadequately responded to an 8-week period of escitalopram monotherapy.

Clinical Points

- Current treatment strategies for major depressive disorder are insufficient, with most individuals receiving antidepressant monotherapy not achieving remission.
- Augmentation therapy with a mechanistically distinct agent may offer clinical benefit in individuals with major depressive disorder who do not achieve full remission with antidepressant monotherapy.
- In this proof-of-concept study, lisdexamfetamine augmentation reduced depressive symptoms and was generally well tolerated in individuals with major depressive disorder who did not achieve full remission with escitalopram monotherapy.

METHOD

Study Design

This was a multicenter, randomized, double-blind, parallel-group, placebo-controlled study in participants with MDD conducted at 15 US sites (July 2009–August 2010). The study had 4 phases: screening and washout (if necessary); an 8-week lead-in phase consisting of treatment with open-label escitalopram and single-blind placebo capsules; a 6-week double-blind randomized treatment phase consisting of lisdexamfetamine dimesylate or placebo augmentation of escitalopram; and a safety follow-up phase (Figure 1).

The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice. After explanation of the study, voluntary written informed consent was obtained from participants. The study was registered on ClinicalTrials.gov (identifier: NCT00905424).

Study Participants

Eligible adults (18–55 years) had a primary diagnosis of nonpsychotic MDD according to the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders (SCID-I)[12]; diagnosis was confirmed using module A of the Mini-International Neuropsychiatric Interview.[13] Participants not receiving antidepressants at screening were required to have baseline 17-item Hamilton Depression Rating Scale (HDRS-17)[14] score ≥ 22. Those receiving antidepressants at screening had to have HDRS-17 scores ≥ 10 and could not have achieved remission based on investigator opinion following ≥ 6 weeks of treatment; the purpose of this criterion was to exclude participants who did not exhibit residual symptoms of depression on their current antidepressant therapy. Women of childbearing age were required to be nonpregnant/nonlactating and on adequate contraception. Permitted concomitant therapies included hormonal therapy, thyroid medication, antihypertensive monotherapy, bronchodilator inhalers, nonsedating antihistamines, antibiotics, and over-the-counter medications not affecting blood pressure, heart rate, or the central nervous system.

Exclusion criteria included a current MDD episode that had not responded to adequate treatment with escitalopram or 2 other antidepressants (≥ 6 weeks of treatment within the typical maximum adult therapeutic dosage range) or a lifetime history of treatment-resistant MDD (defined as inadequate response to at least 6 weeks of monotherapy with 3 or more antidepressants within the typical maximum adult therapeutic dosage range). Also excluded were those with a history of lack of response to escitalopram; those with comorbid ADHD; a comorbid psychiatric disorder (Axis I, Axis II, or other) assessed by SCID-I that, in the investigators' opinion, would contraindicate lisdexamfetamine dimesylate treatment or confound efficacy/safety assessments; a first-degree relative with bipolar I disorder; concurrent chronic or acute medical illness, disability, or condition that might increase the participant's risk; a history of or current suicide risk, suicide attempts, or suicidal ideations; a history of seizures (except infantile febrile seizures); Tourette's disorder; abnormal thyroid function or glaucoma; family history of sudden cardiac death or ventricular arrhythmias; history of symptomatic cardiovascular disease or structural cardiac abnormalities; moderate to severe hypertension (or resting systolic blood pressure > 139 mm Hg or diastolic blood pressure > 89 mm Hg); history (≤ 6 months prior) of substance abuse or dependence; or known hypersensitivity to amphetamine, escitalopram, or citalopram. Prohibited concomitant therapies included investigational compounds, antidepressants other than escitalopram, antipsychotics, anxiolytics, antihistamines, clonidine, electroconvulsive therapy, guanfacine, herbal preparations, monoamine oxidase inhibitors, multiple antihypertensive agents, norepinephrine reuptake inhibitors, oral corticosteroids, psychostimulants, sedatives, and triptans.

Treatment

After screening/washout, participants entered an 8-week lead-in phase and received open-label escitalopram (week 1: 10 mg/d; 20 mg/d thereafter) and single-blind lisdexamfetamine dimesylate–matched placebo capsules to minimize potential placebo effects during randomized augmentation treatment. At week 8 (augmentation baseline), those with a tolerable safety profile and residual MDD symptoms, defined as an HDRS-17 score ≥ 4, were randomized 1:1 to double-blind lisdexamfetamine dimesylate or placebo augmentation for 6 weeks. Randomization numbers and treatments were assigned using an interactive voice response system/interactive Web response system. Participants were stratified by augmentation baseline remission status (escitalopram remitters: Montgomery-Asberg Depression Rating Scale [MADRS][15] total score ≤ 10; escitalopram nonremitters:

MADRS total score > 10). Escitalopram remitters were randomized to minimize augmentation baseline score inflation. Lisdexamfetamine dimesylate treatment was initiated at 20 mg/d. The dose was increased weekly, first to 30 mg/d and then to 50 mg/d, during dose optimization. Investigators could increase the dose through study week 10 (week 2 of double-blind augmentation) and decrease the dose, once per participant, at any time; lisdexamfetamine dimesylate dose at study week 11 (week 3 of double-blind augmentation) was maintained through study week 14 (week 6 of double-blind augmentation)/end of study. Participants returned 7 to 9 days after last dose for adverse event and concomitant medication assessment.

Primary Efficacy Endpoint

The primary efficacy endpoint was change in MADRS total score from augmentation baseline to week 14/end of study in escitalopram nonremitters. The MADRS[15] is a 10-item, validated, semistructured clinician interview, with each item scored on a 7-point scale (0–6). The MADRS assessments were conducted at each visit.

Secondary Efficacy Endpoints

Remission on the MADRS was defined as a total score ≤ 10; response was defined as a 50% total score reduction from lead-in baseline.

The HDRS-17 is a 17-item, validated measurement[14]; 9 items are scored on a 5-point scale (0–4) and 8 are scored on a 3-point scale (0–2). The HDRS-17 assessments were conducted at each visit. Remission on the HDRS-17 was defined as a total score ≤ 7; response was defined as a 50% total score reduction from lead-in baseline.

The Clinical Global Impression-Severity of Illness scale (CGI-S),[16] a validated tool examining symptom severity on a 7-point scale (1 = normal; 7 = extremely ill), was assessed at weeks 0, 8, and 14/end of study. The CGI-Improvement scale (CGI-I)[16] assessed improvement on a 7-point scale (1 = very much improved; 7 = very much worse) at weeks 1–14/end of study, with improvement during the lead-in and randomized augmentation phases referenced to their respective baselines.

The Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR)[17] is a 16-item validated self-administered questionnaire; items are scored on a 4-point scale (0–3). Total scores range from 0 (no depression) to 27 (very severe depression). The QIDS-SR has shown high internal consistency and high correlation with the HDRS[17]; assessments were conducted at weeks 0, 8, and 14/end of study.

Safety Endpoints

Adverse events were collected and coded using the Medical Dictionary for Regulatory Activities, Version 11.1.[18] A *treatment-emergent adverse event* was defined as an adverse event starting or deteriorating on or after the first study drug dose during double-blind treatment and ≤ 3 days following the last dose. The frequency of treatment-emergent adverse events of special interest, including psychiatric (psychosis/mania, suicide, aggression, or other) and nonpsychiatric (weight, vital signs, clinical laboratory tests, and sexual dysfunction) treatment-emergent adverse events, was assessed. Vital signs (sitting systolic blood pressure and diastolic blood pressure, pulse, and sitting respiratory rate) and suicide-related thoughts and behaviors (according to the semistructured Columbia-Suicide Severity Rating Scale[16]) were measured at all visits. Laboratory assessments were conducted at screening, week 8, week 11, and week 14/end of study; physical examinations were conducted at screening, week 8, and week 14/end of study.

Statistical Analysis

The primary efficacy analysis set included all escitalopram nonremitters who had ≥ 1 MADRS assessment after receiving ≥ 1 randomized medication dose. The primary efficacy endpoint was analyzed using analysis of covariance (ANCOVA) with randomized augmentation treatment group as a factor and MADRS total score at augmentation baseline as a covariate; last observation carried forward (LOCF) accounted for missing data.

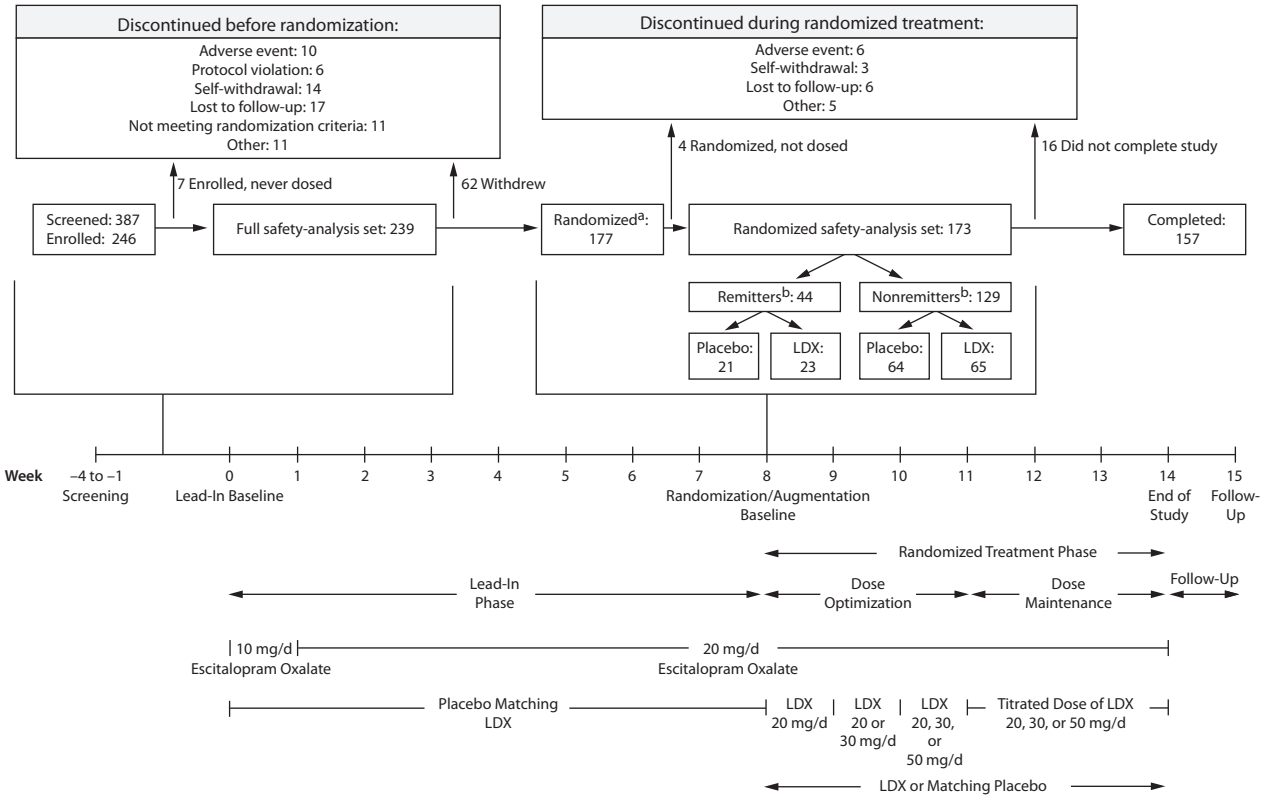
Secondary efficacy analyses used the full analysis set (all participants who took ≥ 1 randomized study drug dose and who had ≥ 1 postrandomization MADRS measurement) and escitalopram nonremitters. Analysis of covariance, with randomized augmentation treatment and augmentation baseline remission status as fixed effects and augmentation baseline score as a covariate, was used to assess HDRS-17 and QIDS-SR score changes (LOCF); ANCOVA analyses also assessed CGI-I scores (LOCF) using CGI-S augmentation baseline category score as a covariate. The percentage of participants achieving a 50% MADRS or HDRS-17 response (LOCF) was summarized by double-blind treatment visit, with treatment effects assessed using Cochran-Mantel-Haenszel tests stratified by augmentation baseline remission status for the full analysis set and Fisher exact tests for escitalopram nonremitters.

For the primary efficacy analysis set, adjusted effect size (lisdexamfetamine dimesylate vs placebo) was calculated post hoc using the primary ANCOVA model. Number needed to treat (NNT) for MADRS remission was calculated post hoc as the reciprocal of the difference in proportions of remitters between lisdexamfetamine dimesylate and placebo.

Primary and secondary efficacy analyses were performed at prespecified, 2-sided, critical $\alpha = .10$ for this exploratory proof-of-concept study.

The full safety analysis set included all participants who took ≥ 1 dose of lead-in phase treatment and had ≥ 1 safety assessment after treatment initiation. Safety analyses during double-blind treatment were performed on the randomized safety analysis set (all participants who took ≥ 1 dose of randomized augmentation treatment and had ≥ 1 safety assessment after treatment initiation, including escitalopram nonremitters and remitters). Adverse events, vital signs, weight and body mass index (BMI), electrocardiogram (ECG) findings, and laboratory and Columbia-Suicide Severity Rating Scale results were descriptively summarized.

Figure 1. Study Design and Disposition of Participants



[a]Randomization criterion: HDRS-17 score ≥ 4 at augmentation baseline.
[b]MADRS remission criteria: remitters, MADRS total score ≤ 10 at augmentation baseline; nonremitters, MADRS total score > 10 at augmentation baseline.
Abbreviations: HDRS-17 = 17-item Hamilton Depression Rating Scale, LDX = Lisdexamfetamine dimesylate, MADRS = Montgomery-Asberg Depression Rating Scale.

RESULTS

Disposition, Demographics, and Baseline Characteristics

A total of 239 of 246 enrolled participants received open-label escitalopram during the lead-in phase and were included in the full safety analysis set (Figure 1). The randomized treatment phase was completed by 79 of 88 (89.8%) and 78 of 89 (87.6%) randomized participants in the placebo and lisdexamfetamine dimesylate groups, respectively. Baseline clinical and demographic characteristics for the full safety analysis set, escitalopram nonremitters, and the randomized safety analysis set are presented in Table 1.

In the randomized safety analysis set (n = 173), mean (SD) MADRS and HDRS-17 total scores at lead-in baseline were 32.6 (4.90) and 25.1 (3.07), respectively, and 16.9 (8.59) and 13.7 (6.07), respectively, at augmentation baseline. Mean (SD) MADRS total score change from lead-in baseline to augmentation baseline with escitalopram (n = 237) was –15.6 (9.66).

Extent of exposure. The mean (SD) daily lisdexamfetamine dimesylate dose during double-blind treatment was 29.6 (9.69) mg. During double-blind treatment, all 88 participants in the lisdexamfetamine dimesylate group received the 20-mg dose; 75% (66/88) had the dose increased to 30 mg, and 42% (37/88) had the dose increased to 50 mg. The mean (SD) duration of exposure was 40.0 (6.60) days for placebo and 38.3 (9.56) days for lisdexamfetamine dimesylate.

Primary Efficacy Endpoint

Montgomery-Asberg Depression Rating Scale. The primary efficacy analysis in escitalopram nonremitters reported least squares (LS) mean (90% CI) MADRS total score reductions at week 14/end of study of –4.9 (–6.4 to –3.3) with placebo and –7.1 (–8.7 to –5.6) with lisdexamfetamine dimesylate; the LS mean (90% CI) treatment difference from augmentation baseline to week 14/end of study (–2.3 [–4.5 to –0.1]; $P = .0902$) met predefined signal detection criterion for superiority of lisdexamfetamine dimesylate over placebo.

Secondary Efficacy Endpoints

Montgomery-Asberg Depression Rating Scale. Escitalopram nonremitters in both treatment groups exhibited improvements in MADRS total score from augmentation baseline. Mean (SD) reductions were –1.8 (3.91) with placebo and –2.7 (5.04) with lisdexamfetamine dimesylate at week 9; –3.6 (5.50) and –4.2 (6.34) at week 10; –5.7 (6.92) and –5.5 (6.29) at week 11; –5.0 (7.90) and –5.7 (7.08) at week 12; and –4.9 (7.36) and –7.1 (8.04) at week 14. None

Table 1. Baseline Demographics and Clinical Characteristics

Variable	Full Safety Analysis Set (N = 239)	Randomized Augmentation Treatment Phase: Escitalopram Nonremitters Placebo (n = 64)	Escitalopram Nonremitters Lisdexamfetamine Dimesylate (n = 65)	Randomized Safety Analysis Set Placebo (n = 85)	Randomized Safety Analysis Set Lisdexamfetamine Dimesylate (n = 88)
Age, mean (SD), y	37.9 (10.21)	39.5 (10.40)	41.2 (9.60)	38.6 (10.38)	39.4 (9.65)
Sex, n (%)					
Male	97 (40.6)	22 (34.4)	28 (43.1)	31 (36.5)	35 (39.8)
Female	142 (59.4)	42 (65.6)	37 (56.9)	54 (63.5)	53 (60.2)
Race, n (%)					
White	177 (74.1)	47 (73.4)	51 (78.5)	66 (77.6)	67 (76.1)
Nonwhite	62 (25.9)	17 (26.6)	14 (21.5)	19 (22.4)	21 (23.9)
Ethnicity, n (%)					
Hispanic	15 (6.3)	4 (6.3)	3 (4.6)	6 (7.1)	3 (3.4)
Non-Hispanic	224 (93.7)	60 (93.8)	62 (95.4)	79 (92.9)	85 (96.6)
BMI (kg/m^2) category, n (%)					
Underweight, < 18.5	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Normal, 18.5–< 25.0	69 (28.9)	20 (31.3)	15 (23.1)	23 (27.1)	23 (26.1)
Overweight, 25.0–< 30.0	73 (30.5)	21 (32.8)	20 (30.8)	30 (35.3)	26 (29.5)
Obese, ≥ 30.0	97 (40.6)	23 (35.9)	30 (46.2)	32 (37.6)	39 (44.3)
MADRS total score, mean (SD)					
Lead-in baseline	32.8 (4.86)	33.3 (4.77)	32.9 (4.76)	33.2 (4.44)	32.1 (5.27)
Augmentation baseline	NA	20.8 (6.42)	20.3 (7.16)	17.3 (8.29)	16.6 (8.90)
HDRS-17 score, mean (SD)					
Lead-in baseline	25.1 (3.05)	25.7 (3.25)	25.1 (2.73)	25.5 (2.99)	24.6 (3.10)
Augmentation baseline	NA	16.3 (4.77)	15.8 (5.32)	13.9 (6.02)	13.4 (6.15)

Abbreviations: BMI = body mass index, HDRS-17 = 17-item Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, NA = not applicable.

Table 2. Change in Depressive Symptoms From Augmentation Baseline During Randomized Treatment

	Escitalopram Nonremitters Placebo (n = 64)	Escitalopram Nonremitters Lisdexamfetamine Dimesylate (n = 65)	*P* Value	Full Analysis Set Placebo (n = 85)	Full Analysis Set Lisdexamfetamine Dimesylate (n = 88)	*P* Value
MADRS total score						
Change from augmentation baseline at week 14/end of study, LS mean (90% CI)[a]	−4.9 (−6.4 to −3.3)	−7.1 (−8.7 to −5.6)	.0902	−3.5 (−4.9 to −2.0)	−4.8 (−6.3 to −3.4)	.2101
50% decrease at week 14/end of study, n (%)[b]	32 (50.0)	43 (66.2)	.0754	52 (61.2)	64 (72.7)	.1038
Total score ≤ 10 at week 14/end of study, n (%)[b]	22 (34.4)	32 (49.2)	.1088	40 (47.1)	52 (59.1)	.1049
HDRS-17 total score						
Change from augmentation baseline at week 14/end of study, LS mean (90% CI)[a]	−4.0 (−5.1 to −2.9)	−4.9 (−6.0 to −3.9)	.3091	−3.4 (−4.5 to −2.4)	−3.9 (−5.0 to −2.9)	.5109
50% decrease at week 14/end of study, n (%)[b]	35 (54.7)	41 (63.1)	.3736	55 (64.7)	62 (70.5)	.4376
Total score ≤ 7 at week 14/end of study, n (%)[b]	17 (26.6)	21 (32.3)	.5633	33 (38.8)	37 (42.0)	.7073
QIDS-SR total score change from augmentation baseline at week 14, LS mean (90% CI)[a,c]	−1.2 (−2.0 to −0.4)	−2.4 (−3.1 to −1.6)	.0774	−1.2 (−1.9 to −0.6)	−2.5 (−3.1 to −1.8)	.0203
CGI-I score at week 14/end of study, LS mean (90% CI)[d]	2.6 (2.4 to 2.8)	2.4 (2.2 to 2.6)	.3199	2.6 (2.3 to 2.8)	2.4 (2.1 to 2.6)	.2954

[a]Analysis of covariance with randomized augmentation treatment and augmentation baseline remission status as fixed effects and augmentation baseline score as a covariate.
[b]Cochran-Mantel-Haenszel tests stratified by augmentation baseline remission status for the full analysis set and Fisher exact test comparing treatment groups for nonremitters.
[c]Nonremitters (placebo, n = 62; lisdexamfetamine dimesylate, n = 63); all randomized (placebo, n = 83; lisdexamfetamine dimesylate, n = 85).
[d]Analysis of covariance with randomized augmentation treatment and augmentation baseline remission status as fixed effects and Clinical Global Impressions-Severity of Illness scale augmentation baseline category score as a covariate.
Abbreviations: CGI-I = Clinical Global Impression-Improvement scale, HDRS-17 = 17-item Hamilton Depression Rating Scale, LS=least squares, MADRS = Montgomery-Asberg Depression Rating Scale, QIDS-SR = Quick Inventory of Depressive Symptomatology–Self-Report.

of the LS mean treatment differences prior to week 14/end of study met the prespecified criterion for superiority of lisdexamfetamine dimesylate in escitalopram nonremitters.

Adjusted effect size (90% CI) for MADRS total score reduction (lisdexamfetamine dimesylate vs placebo) at week 14/end of study was –0.3 (–0.6 to 0.0) among escitalopram nonremitters. A significantly greater proportion of escitalopram nonremitters had a 50% decrease in MADRS total score with lisdexamfetamine dimesylate (66.2% vs 50.0% with placebo; $P = .0754$) at week 14/end of study (Table 2). A numerically greater, but not statistically different, proportion of escitalopram nonremitters achieved MADRS remission with lisdexamfetamine dimesylate (49.2% vs 34.4% with placebo; $P = .1088$) at week 14/end of study. The NNT for MADRS remission with lisdexamfetamine dimesylate augmentation was 6.7 for escitalopram nonremitters.

For the full analysis set, all MADRS endpoints exhibited numerically greater improvement with lisdexamfetamine dimesylate, but none reached the prespecified threshold for statistical significance (Table 2).

Table 3. Treatment-Emergent Adverse Events Reported During the Double-Blind Augmentation Phase in the Randomized Safety Analysis Set

Adverse Event, n (%)	Placebo (n = 85)	Lisdexamfetamine Dimesylate (n = 88)
Any treatment-emergent adverse event	42 (49.4)	53 (60.2)
Any treatment-emergent adverse event occurring at a frequency of ≥ 5% in either group		
Dry mouth	0	10 (11.4)
Headache	4 (4.7)	10 (11.4)
Decreased appetite	2 (2.4)	6 (6.8)
Nasopharyngitis	3 (3.5)	5 (5.7)
Insomnia	6 (7.1)	4 (4.5)

Other secondary endpoints. In this modest-sized sample, for escitalopram nonremitters and the full analysis set, all HDRS-17 endpoints exhibited numerically greater improvement with lisdexamfetamine dimesylate, but none reached the a priori threshold for statistical significance (Table 2).

Lisdexamfetamine dimesylate augmentation significantly reduced QIDS-SR total scores versus placebo for nonremitters ($P = .0774$) and the full analysis set ($P = .0203$) at week 14 (Table 2).

At augmentation baseline, 37.7% (83/220) of participants were rated as moderately or markedly ill according to the CGI-S. For escitalopram nonremitters and the full analysis set, LS mean CGI-I scores were similar with lisdexamfetamine dimesylate and placebo at week 14/end of study (Table 2).

Escitalopram Remitters

Among remitters at augmentation baseline and week 14/end of study, there were no significant treatment differences in primary (LS mean [90% CI] treatment difference for MADRS total score reduction at week 14/end of study: 1.2 [–1.6 to 4.0]; $P = .4726$) or secondary efficacy endpoints.

Safety

Adverse events. Safety and tolerability findings during the lead-in phase have been reported elsewhere.[20] During randomized augmentation, 42 participants (49.4%) receiving placebo experienced treatment-emergent adverse events, including 16 (18.8%), 22 (25.9%), and 4 (4.7%) participants reporting mild, moderate, and severe treatment-emergent adverse events, respectively; 53 participants (60.2%) receiving lisdexamfetamine dimesylate reported treatment-emergent adverse events, including 16 (18.2%), 27 (30.7%), and 10 (11.4%) participants reporting mild, moderate, and severe treatment-emergent adverse events, respectively. A serious treatment-emergent adverse event, severe rhabdomyolysis, which resolved after 20 days, was reported in 1 placebo participant. Discontinuation owing to treatment-emergent adverse events occurred in 3 participants (placebo, n = 1 [increased γ-glutamyltransferase]; lisdexamfetamine dimesylate, n = 2 [increased liver enzymes; ECG nonspecific T-wave abnormality]); no deaths were reported. Table 3 summarizes treatment-emergent adverse events occurring in ≥ 5% of participants during double-blind treatment.

Table 4. Change From Augmentation Baseline in Vital Signs and Electrocardiogram (ECG) Findings at Week 14 in the Randomized Safety Analysis Set

Variable	Placebo, Mean (SD)	Lisdexamfetamine Dimesylate, Mean (SD)
Vital signs		
Systolic blood pressure, mm Hg	0.5 (8.98)	2.3 (9.04)
Diastolic blood pressure, mm Hg	–1.0 (7.19)	0.9 (6.61)
Pulse, bpm	–0.4 (7.10)	3.3 (8.45)
Weight, kg	0.3 (2.05)	–1.2 (2.00)
BMI (kg/m^2)	0.1 (0.70)	–0.4 (0.70)
ECG findings		
Heart rate, bpm	–0.4 (7.39)	4.8 (8.64)
QTcF, ms	–1.6 (11.23)	–4.9 (11.84)

Abbreviations: BMI = body mass index, bpm = beats per minute, QTcF = Fridericia-adjusted QT interval.

Psychiatric treatment-emergent adverse events of special interest were experienced by 13 (15.3%) and 16 (18.2%) participants receiving placebo and lisdexamfetamine dimesylate, respectively. Psychiatric treatment-emergent adverse events occurring in ≥ 2 participants in either group (placebo vs lisdexamfetamine dimesylate) included feeling jittery (1 [1.2%] vs 2 [2.3%]), irritability (2 [2.4%] vs 3 [3.4%]), somnolence (3 [3.5%] vs 0), abnormal dreams (3 [3.5%] vs 1 [1.1%]), anxiety (1 [1.2%] vs 3 [3.4%]), and insomnia (6 [7.1%] vs 4 [4.5%]); no participant had a psychiatric treatment-emergent adverse event categorized as psychosis/mania, suicidal, or aggression. Nonpsychiatric treatment-emergent adverse events of special interest were experienced by 5 participants (5.9%) receiving placebo and 8 (9.1%) receiving lisdexamfetamine dimesylate. With placebo, 1 participant (1.2%) experienced increased weight, 3 (3.5%) had hepatic enzyme abnormalities, and 1 (1.2%) had decreased libido. With lisdexamfetamine dimesylate, 2 participants (2.3%) experienced decreased weight, 1 (1.1%) had abnormal hepatic enzymes, and 5 (5.7%) had vital sign–related treatment-emergent adverse events.

Columbia-Suicide Severity Rating Scale. At screening and lead-in baseline, 43 (18.0%) and 18 (7.5%) participants answered yes to the question "Have you wished you were dead or wished you could go to sleep and not wake up?" During double-blind treatment, an affirmative response was provided by 1 placebo participant each at weeks 9, 10, 12, and 14 and by 1 participant receiving lisdexamfetamine dimesylate at week 9, 2 at week 10, and 1 at week 14. As reported elsewhere,[20] a suicide attempt was reported by 1 participant at week 4 of open-label escitalopram; however, there were no reports of completed suicide. No participants exhibited suicidal behavior during augmentation treatment, and there were no reports of completed suicide at any time during the study.

Vital signs and electrocardiogram findings. Small mean changes from augmentation baseline were seen for blood pressure, pulse rate, and weight at week 14 (Table 4). Electrocardiogram findings indicated that heart rate tended to increase more and Fridericia-adjusted QT interval tended to decrease more with lisdexamfetamine dimesylate versus placebo (Table 4). Body mass index remained stable during

double-blind treatment, with the majority of participants in both groups (placebo: range, 89.7%–93.5%; lisdexamfetamine dimesylate: range, 76.9%–82.5%) remaining in the same BMI category at augmentation baseline and at week 14/end of study. For participants receiving lisdexamfetamine dimesylate, observed shifts were mostly to lower BMI categories.

There were no clinically significant changes in mean clinical laboratory values.

DISCUSSION

Three major findings emerged from this proof-of-concept study. First, among individuals with MDD who did not achieve remission of depressive symptoms after 8 weeks of escitalopram monotherapy, lisdexamfetamine dimesylate augmentation was superior to placebo for the primary endpoint of reduction of depressive symptoms (MADRS total score) and met prespecified signal-detection criteria. The adjusted effect size for MADRS total score reduction was –0.3, and NNT for MADRS remission was 6.7 with lisdexamfetamine dimesylate augmentation. Second, lisdexamfetamine dimesylate was numerically superior to placebo on multiple secondary endpoints, including response and remission rates. Interestingly, lisdexamfetamine dimesylate also improved self-reported depressive symptoms on the QIDS-SR in escitalopram nonremitters and the full analysis set, suggesting that self-perceived improvement in depressive symptoms accompanies clinician-rated improvement. Third, lisdexamfetamine dimesylate was generally well-tolerated as augmentation therapy. Furthermore, the antidepressant effects of lisdexamfetamine dimesylate suggest dopaminergic mechanisms may play a role in residual depressive symptoms in individuals with inadequate response to SSRI monotherapy; further investigation of these dopaminergic mechanisms is warranted for the development of new augmentation treatments.

These data support the findings from another exploratory study designed to assess the effects of lisdexamfetamine dimesylate augmentation of SSRI monotherapy on executive dysfunction in individuals with partially or fully remitted depressive symptoms of MDD. In that study, MADRS total score reductions also significantly favored lisdexamfetamine dimesylate over placebo (LS mean [95% CI] treatment difference = –1.9 [–3.7 to 0.0]; $P = .0465$) in participants with baseline MADRS total score ≤ 18.[21] Those findings in a population selected for being in full or partial remission of depressive symptoms complement the present findings in a population that excluded such individuals.

The mean reductions in MADRS total score after 6 weeks of lisdexamfetamine dimesylate augmentation versus placebo in the current study (–7.1 vs –4.9) are similar in magnitude to the mean reductions after 6 weeks of aripiprazole augmentation versus placebo reported in 2 studies (–8.8 vs –5.8 and –8.5 vs –5.7).[22,23] Similarly, adjusted effect size for MADRS total score reductions at week 14/end of study (–0.3) and NNT for MADRS remission (6.7) for lisdexamfetamine dimesylate in escitalopram nonremitters was roughly similar to reported effect sizes (0.35 and 0.39) and NNTs (both 10) for aripiprazole augmentation.[22,23] Differences between lisdexamfetamine dimesylate and aripiprazole across these measures may be partially related to MADRS total scores at the start of augmentation therapy. A meta-analysis of augmentation therapy for 4 atypical antipsychotics (olanzapine, risperidone, quetiapine, and aripiprazole) across 16 trials involving 3,480 patients reported an overall NNT of 9.[24]

Augmentation with other stimulants or wake-promoting agents has been assessed in several placebo-controlled trials.[6,9,25–27] In placebo-controlled augmentation trials of extended-release methylphenidate, statistically greater depressive symptom reductions on the 21-item HDRS[9] or the MADRS[25] were not observed for methylphenidate versus placebo. However, the population in one of these studies[9] specifically included treatment-resistant individuals, a population excluded from the current study. In 3 placebo-controlled trials, modafinil augmentation of antidepressant monotherapy did not produce statistically greater reductions on HDRS[6,26,27] or MADRS[6,27] total scores than placebo.

The main limitation of this exploratory, proof-of-concept study is the small sample size with limited statistical power; the primary efficacy endpoint was assessed in 129 escitalopram nonremitters, and 0.1 was the prespecified critical α that defined a between-group treatment difference. Additional limitations include the relatively short treatment duration, which precluded the ability to make conclusions regarding the long-term benefits of lisdexamfetamine dimesylate augmentation, and the exclusion of severely depressed individuals. Finally, since only escitalopram was used, the generalizability of these findings to other antidepressants is limited.

In conclusion, lisdexamfetamine dimesylate augmentation of escitalopram therapy reduced depressive symptoms in individuals with MDD who responded inadequately to escitalopram monotherapy. Lisdexamfetamine dimesylate was relatively well tolerated, with adverse events in the expected range based on previous research. Larger confirmatory and definitive trials are underway to confirm these findings.

Drug names: aripiprazole (Abilify), citalopram (Celexa and others), clonidine (Catapres, Duraclon, and others), escitalopram (Lexapro and others), guanfacine (Intuniv, Tenex, and others), lisdexamfetamine dimesylate (Vyvanse), methylphenidate (Daytrana, Ritalin, and others), modafinil (Provigil and others), olanzapine (Zyprexa and others), quetiapine (Seroquel and others), risperidone (Risperdal and others).

Author affiliations: Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas (Dr Trivedi); Florida Clinical Research Center, LLC, Bradenton (Dr Cutler); Global Clinical Development and Innovation (Dr Richards), Clinical Development Operations and Biometrics (Dr Gao and Ms Geibel), Shire Development LLC, Wayne, Pennsylvania; inVentiv Health Clinical, Princeton, New Jersey (Dr Lasser); Atlanta Institute of Medicine and Research, Atlanta, Georgia (Dr Sambunaris); and Department of Psychiatry, Duke University, Durham, North Carolina (Dr Patkar). Dr Lasser is now with inVentiv Health Clinical, Princeton, New Jersey.

Author contributions: Dr Trivedi served as the coordinating principal investigator during the design and conduct of this trial and worked closely with Dr Richards, Ms Geibel, and the investigator team at Shire Development LLC. UT Southwestern Medical Center (Dr Trivedi) was not a performing site for the clinical trial. Dr Trivedi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr Trivedi designed the initial draft of the manuscript with the coauthors. All the authors provided on-going feedback during the

development of the manuscript. Dr Trivedi was a paid consultant for Shire Development LLC.

Potential conflicts of interest: **Dr Trivedi** is or has been an advisor/consultant for Alkermes, AstraZeneca, Bristol-Myers Squibb, Cerecor, Concert, Eli Lilly, Forest, Janssen Global Services, Lundbeck, MedAvante, Merck, Mitsubishi Tanabe Pharma Development America, Naurex, Neuronetics, Otsuka, Pamlab, Ridge Diagnostics, Roche, Shire, Sunovion, and Takeda. **Dr Cutler** has received research grants from Abbott (including Solvay), AstraZeneca, Alkermes, Brain Cells, Bristol-Myers Squibb, Euthymics, Forest (including PGxHealth and Trovis), GlaxoSmithKline, Johnson & Johnson PRD, Lilly, Lundbeck, Merck (including Organon and Schering-Plough), Novartis, Ortho-McNeil-Janssen, Otsuka, Pamlab, Pfizer (including Wyeth), Sanofi, Shire, Sunovion (including DSP and Sepracor), Supernus, Takeda, Targacept, Teva (including Cephalon), and Vanda; has served as a consultant to Abbott (including Solvay), AstraZeneca, Alkermes, Bristol-Myers Squibb, CeNeRx, Euthymics, Forest (including PGxHealth and Trovis), GlaxoSmithKline, Johnson & Johnson PRD, Lilly, Lundbeck, Merck (including Organon and Schering-Plough), Novartis, Ortho-McNeil-Janssen, Otsuka, Pamlab, Pfizer (including Wyeth), Sanofi, Shire, Sunovion (including DSP and Sepracor), Supernus, Takeda, Targacept, and Vanda; and has been a speaker for Abbott (including Solvay), AstraZeneca, Bristol-Myers Squibb, Forest (including PGx Health and Trovis), GlaxoSmithKline, Lilly, Merck (including Organon and Schering-Plough), Novartis, Ortho-McNeil-Janssen, Otsuka, Pamlab, Pfizer (including Wyeth), Shire, Sunovion (including DSP and Sepracor), Takeda, and Vanda. **Drs Richards** and **Gao** and **Ms Geibel** are employees of Shire Development LLC and hold stock and/or stock options in Shire. **Dr Lasser** is a former employee of Shire Development LLC; he is currently employed by inVentiv Health Clinical. **Dr Sambunaris** has received research support from Shire. **Dr Patkar** is a consultant/advisory board member for Gilead, Forest, Dey, and TTK Pharma; is on the speakers bureau of Alkermes, Bristol-Myers Squibb, Dey, Merck, Sunovion, and Pfizer; and has received grant support from the National Institutes of Health (National Institute on Drug Abuse, National Institute on Alcohol Abuse and Alcoholism), Duke Endowment, Forest, Dey, Janssen, Envivo, Lundbeck, Merck, Pfizer, Sunovion, Shire, and Titan.

Funding/support: Clinical research was funded by Shire Development LLC (Wayne, Pennsylvania).

Role of sponsor: Although the sponsor was involved in the design, collection, analysis, interpretation, and fact checking of information, the content of the manuscript, its ultimate interpretation, and the decision to submit it for publication in the *Journal of Clinical Psychiatry* were made by the authors independently.

Previous presentations: These data have previously been presented at the American Psychiatric Association annual meeting; May 14–18, 2011; Honolulu, Hawaii ▪ American Psychiatric Association–Institute on Psychiatric Services annual meeting; October 27–30, 2011; San Francisco, California ▪ and at the annual meeting of the Collegium Internationale Neuro-Psychopharmacologicum; June 3–7, 2012; Stockholm, Sweden.

Acknowledgments: Under the direction of the authors, Michael Pucci, PhD, a full-time employee of SCI Scientific Communications & Information (Parsippany, New Jersey), provided writing assistance. Editorial assistance in the form of proofreading, copyediting, and fact checking was also provided by Maryann Travaglini, PharmD, and Craig Slawecki, PhD, full-time employees of Complete Healthcare Communications, Inc (Chadds Ford, PA), and by Elizabeth LaFlamme, PhD, formerly an employee of Complete Healthcare Communications, Inc. SCI Scientific Communications & Information and Complete Healthcare Communications, Inc were funded by Shire Development LLC for the development of this article. Brian Scheckner, PharmD, an employee of Shire Development LLC, and Joan Gu, MS, a contractor for Shire Development LLC, also reviewed and edited the manuscript for scientific accuracy. The authors also thank all the study investigators.

REFERENCES

1. Trivedi MH, Rush AJ, Wisniewski SR, et al; STAR*D Study Team. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry*. 2006;163(1):28–40.
2. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006;163(11):1905–1917.
3. Trivedi MH, Fava M, Wisniewski SR, et al; STAR*D Study Team. Medication augmentation after the failure of SSRIs for depression. *N Engl J Med*. 2006;354(12):1243–1252.
4. Nierenberg AA, Dougherty D, Rosenbaum JF. Dopaminergic agents and stimulants as antidepressant augmentation strategies. *J Clin Psychiatry*. 1998;59(suppl 5):60–63, discussion 64.
5. Fava M, Mischoulon D. Folate in depression: efficacy, safety, differences in formulations, and clinical issues. *J Clin Psychiatry*. 2009;70(suppl 5):12–17.
6. Fava M, Thase ME, DeBattista C. A multicenter, placebo-controlled study of modafinil augmentation in partial responders to selective serotonin reuptake inhibitors with persistent fatigue and sleepiness. *J Clin Psychiatry*. 2005;66(1):85–93.
7. Fava M, Thase ME, DeBattista C, et al. Modafinil augmentation of selective serotonin reuptake inhibitor therapy in MDD partial responders with persistent fatigue and sleepiness. *Ann Clin Psychiatry*. 2007;19(3):153–159.
8. Papakostas GI. Evidence for S-adenosyl-L-methionine (SAM-e) for the treatment of major depressive disorder. *J Clin Psychiatry*. 2009;70(suppl 5): 18–22.
9. Patkar AA, Masand PS, Pae CU, et al. 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*. 2006;26(6):653–656.
10. Gelenberg AJ, Freeman MP, Markowitz JC, et al. Practice guideline for the treatment of patients with major depressive disorder, third edition. http://guidelines.gov/content.aspx?id=24158. Accessed May 19, 2011.
11. Vyvanse (lisdexamfetamine dimesylate) [package insert]. Wayne, PA: Shire US Inc; 2012.
12. First MB, Williams JBW, Spitzer RL, et al. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Clinical Trials Version (SCID-CT)*. New York, NY: Biometrics Research, New York State Psychiatric Institute; 2007.
13. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for *DSM-IV* and *ICD-10*. *J Clin Psychiatry.* 1998;59(suppl 20):22–33, quiz 34–57.
14. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62.
15. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
16. Guy W. Clinical global improvement scale. *ECDEU Assessment Manual for Psychopharmacology*. US Department of Health, Education, and Welfare publication (ADM) 76-338; Rockville, MD: National Institute of Mental Health; 1976:218–222.
17. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry*. 2003;54(5):573–583.
18. Medical Dictionary for Regulatory Activities Terminology (MedDRA) version 11.1. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). http://meddramsso.com/index.asp. Accessed July 11, 2013.
19. Posner K, Brent D, Lucas C, et al. Columbia-Suicide Severity Rating Scale. http://www.maps.org/mdma/mt1_docs/c-ssrs1-14-09-baseline.pdf. Accessed May 14, 2013.
20. Geibel B, Cutler A, Richards C, et al. Demographics and open-label escitalopram therapy in adults with major depressive disorder: prior to adjunctive lisdexamfetamine dimesylate or placebo. In: 164th Annual Meeting of the American Psychiatric Association; May 14–18, 2011; Honolulu, HI.
21. Madhoo M, Keefe RSE, Roth RM, et al. Efficacy and safety of lisdexamfetamine dimesylate in adults with executive dysfunction and partial or full remission of major depressive disorder [abstract]. *Int J Neuropsychopharmacol.* 2012;15(suppl 1):189.
22. Berman RM, Marcus RN, Swanink R, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2007;68(6):843–853.
23. Marcus RN, McQuade RD, Carson WH, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol*. 2008;28(2):156–165.
24. Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. *Am J Psychiatry*. 2009;166(9):980–991.
25. Ravindran AV, Kennedy SH, O'Donovan MC, et al. 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*. 2008;69(1):87–94.
26. DeBattista C, Doghramji K, Menza MA, et al; Modafinil in Depression Study Group. Adjunct modafinil for the short-term treatment of fatigue and sleepiness in patients with major depressive disorder: a preliminary double-blind, placebo-controlled study. *J Clin Psychiatry*. 2003;64(9):1057–1064.
27. Dunlop BW, Crits-Christoph P, Evans DL, et al. Coadministration of modafinil and a selective serotonin reuptake inhibitor from the initiation of treatment of major depressive disorder with fatigue and sleepiness: a double-blind, placebo-controlled study. *J Clin Psychopharmacol*. 2007;27(6):614–619.