Efficacy Outcomes From 3 Clinical Trials of Edivoxetine as Adjunctive Treatment for Patients With Major Depressive Disorder Who Are Partial Responders to Selective Serotonin Reuptake Inhibitor Treatment

Susan G. Ball, PhD[a,b,*]; Margaret B. Ferguson, PharmD[c]; James M. Martinez, MD[a]; Beth A. Pangallo, RN[a]; E. Serap Monkul Nery, MD[a]; Mary Anne Dellva, MS[a]; JonDavid Sparks, PhD[a]; Qi Zhang, PhD[a]; Peng Liu, PhD[a]; Mark Bangs, MD[a]; and Celine Goldberger, MD[a]

ABSTRACT

Objective: Three studies examined whether edivoxetine (a highly selective norepinephrine reuptake inhibitor) had efficacy as adjunctive therapy for patients with major depressive disorder (*DSM-IV-TR*) who were partial responders to selective serotonin reuptake inhibitor (SSRI) treatment of at least 6 weeks' duration.

Method: Studies were 8-week randomized, placebo-controlled trials with a 3-week double-blind placebo lead-in phase, conducted from December 16, 2010, to October 21, 2013. Patients entered the double-blind adjunctive treatment phase if they met randomization criteria (< 25% improvement on Montgomery-Asberg Depression Rating Scale [MADRS] and MADRS total score ≥ 14); patients not randomized remained on adjunctive placebo. Study 1 compared fixed-dose edivoxetine (12 or 18 mg daily) + SSRI (N = 231 and N = 230, respectively) with placebo + SSRI (N = 240); study 2 compared flexible-dose edivoxetine (12–18 mg daily) + SSRI (N = 232) and fixed-dose edivoxetine (6 mg daily) + SSRI (N = 226) with placebo + SSRI (N = 231); and study 3 compared flexible-dose edivoxetine (12–18 mg daily) + SSRI (N = 230) with placebo + SSRI (N = 219). The primary outcome was mean change from randomization baseline to week 8 in MADRS total score, analyzed using repeated measures analysis.

Results: Each trial failed to meet the primary and most of the secondary objectives. The least-squares mean changes in MADRS total score were as follows—study 1: −8.5 (edivoxetine 12 mg + SSRI), −8.7 (edivoxetine 18 mg + SSRI), and −7.8 (placebo + SSRI); study 2: −9.4 (edivoxetine 12–18 mg + SSRI), −9.6 (edivoxetine 6 mg + SSRI), and −9.4 (placebo + SSRI); and study 3: −8.7 (edivoxetine 12–18 mg + SSRI) and −8.5 (placebo + SSRI).

Conclusions: Adjunctive edivoxetine treatment for patients with major depressive disorder who were partial responders to SSRIs did not significantly improve efficacy outcomes.

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[a]Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana
[b]Department of Psychiatry, Indiana University School of Medicine, Indiana University, Indianapolis
[c]Eli Lilly Canada, Toronto, Ontario, Canada
**Corresponding author:* Susan G. Ball, PhD, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (ball_susan_G@lilly.com).

Current treatment guidelines for major depressive disorder (MDD) recommend selective serotonin reuptake inhibitors (SSRIs) as a first-line treatment.[1] While these medications have demonstrated efficacy, response to treatment varies, with only some patients achieving full remission. For example, in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) multicenter study, patients were initially treated with citalopram; after ≤ 14 weeks of treatment, the response rate (≥ 50% improvement) was 47%, and the remission rate was 28%.[2] Focus on remission as the primary treatment goal has increasingly occurred as evidence has accrued that residual symptoms, or partial treatment response, are associated with continued functional impairment and increased risk for subsequent relapse into a depressive episode.[3–7] Adjunctive treatment strategies, therefore, should be considered in the context of partial treatment response.

LY2216684 HCl (2-morpholinemethanol, α-[(5-fluoro-2-methoxyphenyl) methyl]-α-[tetrahydro-2H-pyran-4-yl]-, hydrochloride, [αR, 2S]) is a highly selective and potent norepinephrine reuptake inhibitor designated as edivoxetine hydrochloride (hereafter, edivoxetine). The efficacy of edivoxetine as adjunctive treatment for patients with MDD who were partial responders to an adequate course of treatment with an SSRI was evaluated in a phase 2 clinical study.[8] The results of this pilot study showed that compared with patients who received placebo adjunctive to an SSRI, patients who received adjunctive edivoxetine (SSRI + edivoxetine 6–18 mg once daily during an 8-week period) had numerically greater improvement in Montgomery-Asberg Depression Rating Scale (MADRS) total score and higher rates of remission along with statistically significantly greater improvement in overall role functioning and in the impact of fatigue on functioning. Thus, these findings from a pilot study supported further systematic study of edivoxetine for the adjunctive treatment of MDD.

Three phase 3 clinical trials have examined whether edivoxetine adjunctive to an SSRI would improve treatment outcomes and reduce residual symptoms and thereby address unmet medical needs of patients who experience partial response to SSRI therapy. The primary objective of each study was to determine whether edivoxetine was superior to placebo in adjunctive treatment of patients with MDD who were identified by their histories as partial responders to an adequate course of SSRI treatment. Efficacy results are reported here,

Table 1. Baseline Patient Demographics and Clinical Characteristics Pooled Across 3 Studies

Characteristic	Placebo + SSRI (N = 690)	Edivoxetine + SSRI (N = 1,149)
Age, mean (SD), y	44.6 (11.5)	46.6 (12.4)
Age group, n (%) < 65 y	658 (95.4)	1,089 (94.8)
Gender, n (%) female	456 (66.1)	751 (65.4)
Severity of illness (MADRS total), mean (SD)	25.2 (5.5)	25.1 (5.5)
Race, n (%)		
White	535 (77.5)	906 (78.9)
African American	68 (9.9)	86 (7.5)
Asian	77 (11.2)	141 (12.3)
Other	8 (1.2)	15 (1.3)
Geographical region,[a] n (%)		
Europe	321 (46.5)	531 (46.2)
Japan	72 (10.4)	134 (11.7)
United States	267 (38.7)	443 (38.6)
Other	30 (4.3)	41 (3.6)
SSRI therapy, n (%)		
Citalopram	168 (24.3)	242 (21.1)
Escitalopram	138 (20.0)	238 (20.7)
Fluoxetine	111 (16.1)	173 (15.1)
Fluvoxamine	17 (2.5)	38 (3.3)
Paroxetine	72 (10.4)	128 (11.1)
Sertraline	184 (26.7)	330 (28.7)
CGI-S, mean (SD)	4.2 (0.7)	4.2 (0.7)
HADS depression subscale, mean (SD)	11.6 (3.9)	11.6 (3.9)
HADS anxiety subscale, mean (SD)	9.6 (4.1)	9.6 (4.0)
FAsD average, mean (SD)	3.4 (0.7)	3.4 (0.7)
SDS global functional impairment score, mean (SD)	18.1 (6.1)	18.2 (5.8)
Q-LES-Q-SF, % total score, mean (SD)	40.2 (13.7)	40.6 (13.2)
VAS-F severity score, mean (SD)	67.7 (18.5)	68.3 (17.8)
Duration of current MDD episode[b]	26.9	24.9
Duration of current SSRI prior to visit 2[b]	20.9	19.4

[a]The countries that comprised Europe were Latvia and Poland (study 1); Croatia, Czech Republic, Finland, Hungary, Romania, and Slovakia (study 2); and Austria, Belgium, Germany, Sweden, and the United Kingdom (study 3). The countries that comprised "Other" were Russian Federation, South Africa, and Ukraine (study 1) and Australia (study 3).
[b]Median values (weeks) are presented.
Abbreviations: CGI-S = Clinical Global Impressions–Severity scale, FAsD = Fatigue Associated with Depression Questionnaire, HADS = Hospital Anxiety and Depression Scale, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form, SDS = Sheehan Disability Scale, SSRI = selective serotonin reuptake inhibitor, VAS-F = Visual Analog Scale for Fatigue.

whereas safety and tolerability outcomes from the studies will be reported elsewhere in a separate disclosure.

METHOD

Study Designs

All 3 studies were 8-week acute therapy, double-blind, randomized, placebo-controlled clinical trials conducted at multiple centers in various countries from December 16, 2010, to October 21, 2013 (Table 1). Several methodological design features were common across studies to mitigate investigators' and patients' expectancies and to confirm the partial response status of each patient. Each study included 3 periods: a screening period, an 11-week double-blind treatment period, and a discontinuation period (1 to 2 weeks per study). Throughout all study periods, patients continued their SSRI at their stable dose. During the acute

Clinical Points

- Adjunctive treatment of major depressive disorder for patients who have a partial response to selective serotonin reuptake inhibitor therapy with edivoxetine, a selective norepinephrine reuptake inhibitor, was not effective compared with placebo.
- A number of methodological features were incorporated in the study designs to address the challenge of placebo response in depression trials.
- Failure of edivoxetine to demonstrate efficacy has implications for the potential role of adjunctive norepinephrine as well as for study design innovations.

therapy phase, all patients received adjunctive placebo for the first 3 weeks. If patients had < 25% improvement on MADRS total score and a MADRS total score ≥ 14 at the end of this double-blind 3-week period, then they were randomly assigned to receive adjunctive edivoxetine or adjunctive placebo for an 8-week randomized adjunctive treatment period. Patients who did not meet randomization criteria were maintained with adjunctive placebo plus SSRI, remained in the study for blinding purposes, and experienced the same study assessments as the randomized patients. Patients and investigators therefore were blinded to the following: the presence of randomization criteria and a lead-in period, the absolute randomization ratio between edivoxetine and placebo, the timing of randomization (the study design suggested that randomization could occur at any visit between visit 2 and visit 9 even though it occurred at visit 5), and the fact that nonrandomized patients were maintained in the study with adjunctive placebo. After screening, patients were assessed weekly for the first 7 weeks and then every other week for the last 4 weeks.

In study 1 (NCT01173601), patients were randomly assigned to receive 1 of 2 fixed doses of adjunctive edivoxetine (12 or 18 mg daily) or adjunctive placebo; in study 2 (NCT01187407), patients were randomly assigned to receive flexible-dose adjunctive edivoxetine (12–18 mg daily), fixed-dose adjunctive edivoxetine (6 mg), or adjunctive placebo; and, in study 3 (NCT01185340), patients were randomly assigned to receive either flexible-dose adjunctive edivoxetine (12–18 mg daily) or adjunctive placebo.

The study protocols were approved by the Ethical Review Board at each study center. The studies were conducted in full accordance with the Good Clinical Practice: Consolidated Guideline that was approved by the International Conference on Harmonization and applicable laws or regulations. Written, informed consent was obtained from each patient at study entry before any study procedures took place.

Patients

Eligible patients were outpatients ≥ 18 years of age who met diagnostic criteria for primary MDD, defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*)[1] and were assessed by the Mini-International Neuropsychiatric Interview

(MINI)[9] at visit 1, with the primary diagnosis confirmed by a physician. Patients must have been taking an SSRI that had been approved for MDD at a dose within the labeling guidelines for the participating country. Duration of SSRI treatment had to be ≥ 6 weeks before visit 2, with at least the last 4 weeks at a stable, optimized dose as determined by the investigator. Eligible patients were required to meet criteria for partial response at visits 1 and 2, as defined by the investigator's opinion that the patient had experienced at least a minimally clinically meaningful improvement with the SSRI treatment. Additionally, patients had to score ≥ 16 on the GRID 17-item Hamilton Depression Rating Scale total score (GRID-$HDRS_{17}$)[10] and to rate ≤ 75% improvement for their current SSRI by using the patient-rated Massachusetts General Hospital Antidepressant Treatment Response Questionnaire-modified version[11] at visit 1. The GRID-$HDRS_{17}$ rating was administered remotely via telephone by independent clinicians who were blinded to the entry criteria and study details.

Key exclusion criteria were *DSM-IV-TR* Axis I conditions other than MDD that were considered a primary diagnosis within 1 year of visit 1; any current or previous diagnosis of bipolar disorder, schizophrenia, or other psychotic disorder; and treatment resistant (defined as a failure to respond to 2 prior treatments in current episode or by investigator opinion). Patients were also excluded from the studies if they had a serious or unstable medical illness or had any diagnosed medical condition that could be exacerbated by noradrenergic agents (eg, unstable hypertension, unstable heart disease, tachycardia or tachyarrhythmia, narrow angle glaucoma, or history of urinary hesitation or retention). Women who were pregnant and/or breastfeeding were also excluded.

Study Assessments

The primary efficacy outcome measure for all studies was the change from baseline of the MADRS total score to the last study visit of the adjunctive treatment phase (week 8 of randomized treatment). Key secondary efficacy measures that were gated statistically to control for multiple comparisons were the Sheehan Disability Scale global functional impairment score,[12] remission rate (MADRS total score ≤ 10) at the last visit and at least the patient's last 2 consecutive visits in the adjunctive treatment phase, and the Hospital Anxiety and Depression Scale (HADS) anxiety subscale score.[13] Other secondary efficacy measures included response rates (*response* was defined as ≥ 50% decrease from baseline in MADRS total score), HADS depression subscale score, MADRS individual item scores, Clinical Global Impressions-Severity score,[14] and the Fatigue Associated With Depression Questionnaire average score.[15]

Statistical Analyses

Unless otherwise specified, all analyses were conducted on an intent-to-treat basis. For continuous measures, analyses included patients who were randomized and who had baseline and postbaseline measurements. Comparisons of primary efficacy parameters between treatment groups were evaluated at a 2-sided .05 significance level, except for study 1 in which the significance level was a priori equally split (2-sided .025) for the 2 edivoxetine dose versus placebo comparisons. The primary comparison for study 2 was edivoxetine 12–18 mg versus placebo. Changes from baseline to all postbaseline visits in the active treatment period were analyzed by using a restricted maximum likelihood-based mixed-model repeated measures (MMRM) analysis. Model terms included the fixed, categorical effects of treatment; pooled investigative site, visit, and treatment-by-visit interaction; and the continuous, fixed covariates of baseline MADRS total score and baseline MADRS total score-by-visit interaction. For the key secondary outcomes of the Sheehan Disability Scale global functional impairment score, remission rate at last visit, remission rate at the patient's last 2 consecutive visits, and HADS anxiety subscale score, a sequential gatekeeper method was used to control for multiple comparisons. These secondary outcomes were listed in the above hierarchical order with the prespecification that each objective would be tested only if the primary analysis and the prior hierarchical analyses were statistically significantly different between treatment groups. Other secondary outcomes were analyzed without adjustment for multiple comparisons.

Numeric secondary outcomes were analyzed by using an MMRM model similar to that of the primary analysis. Treatment differences in the proportions of patients meeting criteria for remission using the last observation carried forward (LOCF) endpoint and for remission at the patient's last 2 consecutive visits in the adjunctive treatment phase were analyzed by using Koch nonparametric randomization-based analysis of covariance method.[16] This method adjusted for pooled investigative site and for the continuous covariate of baseline MADRS total score.

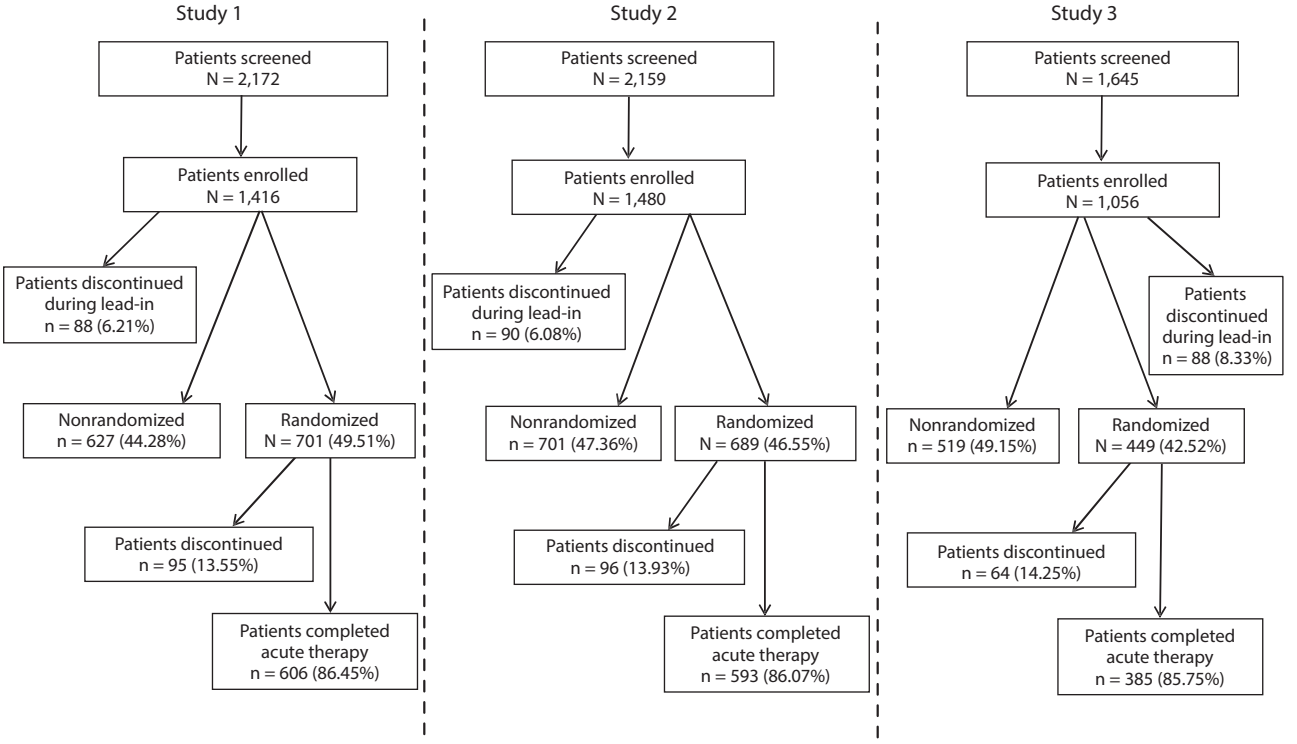
Prespecified subgroup analyses including the subgroups of gender, race, SSRI therapy, pooled investigative site, country, and region were performed for the change from baseline in MADRS total score. Subgroup analyses used an MMRM model similar to that of the primary analysis with relevant subgroup, subgroup-by-treatment, subgroup-by-visit, and subgroup-by-treatment-by-visit interactions added to the model.

RESULTS

Patient Characteristics

Pooled patient demographics and clinical characteristics across the 3 studies are shown in Table 1. Approximately 50% of enrolled patients did not meet randomization criteria and continued in the studies on SSRI and double-blind adjunctive placebo. The numbers of patients randomized per specific adjunctive treatment arm per study were as follows—study 1: placebo + SSRI (N = 240), 12-mg fixed-dose edivoxetine + SSRI (N = 231), 18-mg fixed-dose edivoxetine + SSRI (N = 230); study 2: placebo + SSRI (N = 231), 12- to 18-mg flexible-dose edivoxetine + SSRI

Figure 1. Patient Flow Through Screening, Double-Blind Lead-In, and Acute Therapy Phase by Study



(N = 232), 6-mg fixed-dose edivoxetine + SSRI (N = 226); and study 3: placebo + SSRI (N = 219), 12- to 18-mg flexible-dose edivoxetine + SSRI (N = 230). Figure 1 illustrates a high-level overview of the patient flow for each study, which had high completion rates for the acute therapy (range, 85.8%–86.5%), with the most frequent reason for study discontinuation being adverse event (range, 2.7%–6.5%). There were no deaths in any of the 3 studies.

Primary Efficacy Measure

In each of the 3 studies, patients treated with adjunctive edivoxetine (12- to 18-mg flexible dose daily; 6-, 12-, and 18-mg fixed dose daily) failed to demonstrate a statistically significant improvement compared to patients treated with adjunctive placebo on MADRS total score (primary efficacy endpoint) at week 8 (Figure 2). The least-squares mean changes in MADRS total score from baseline to week 8 were not significantly different between treatment groups, with the values as follows—study 1: −8.5 (edivoxetine 12 mg + SSRI), −8.7 (edivoxetine 18 mg + SSRI), and −7.8 (placebo + SSRI); study 2: −9.4 (edivoxetine 12–18 mg + SSRI), −9.6 (edivoxetine 6 mg + SSRI), and −9.4 (placebo + SSRI); and study 3: −8.7 (edivoxetine 12–18 mg + SSRI) and −8.5 (placebo + SSRI).

Secondary Efficacy Measures

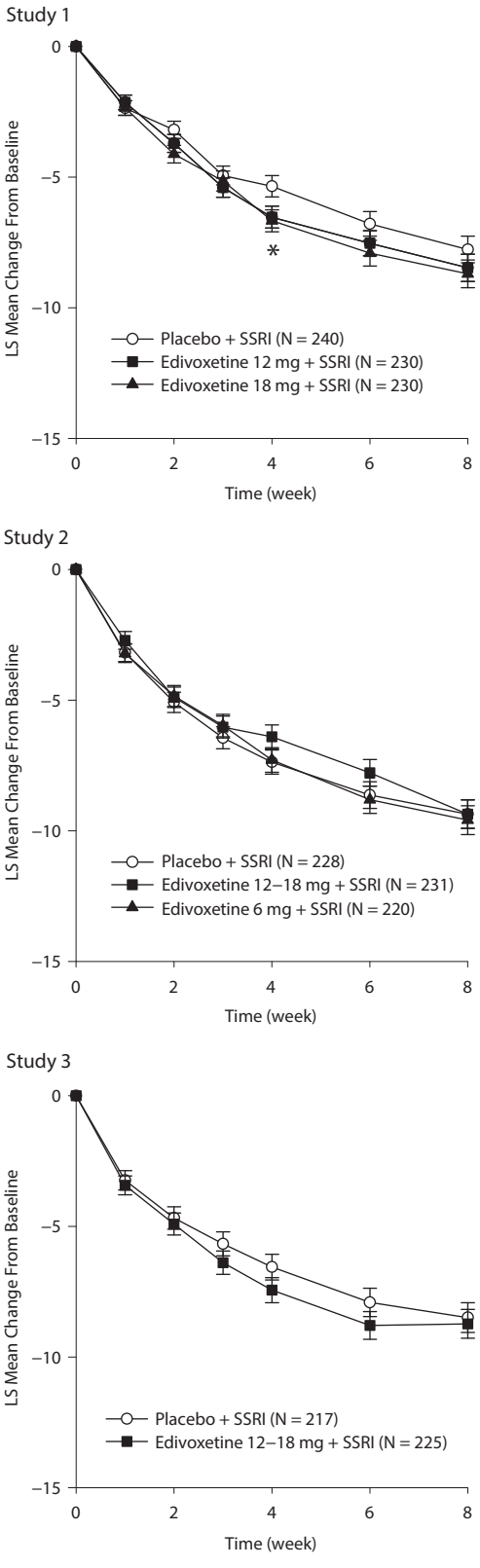
Each study failed to meet most secondary efficacy endpoints at 8 weeks. Response and remission rates at endpoint are presented in Figure 3. Across all 3 studies, there were no statistically significant differences between adjunctive edivoxetine and adjunctive placebo in response or remission rates at LOCF endpoint (Figure 3). Additional secondary efficacy measures and corresponding mean changes from baseline are summarized in Table 2. Across the studies, there were no significant treatment differences on a secondary outcome that replicated in a second study. Subgroup analyses performed in each study found no differential treatment effect for the subgroups of gender, race, SSRI therapy, pooled investigative site, country, or region (data not shown).

DISCUSSION

In each of the 3 studies, adjunctive edivoxetine failed to meet its primary objective for efficacy compared with placebo. Additionally, most secondary outcomes that assessed disease symptom severity and functional improvement were not statistically significantly different between adjunctive edivoxetine and adjunctive placebo groups; any significant treatment differences on a specific outcome were not independently replicated. These findings support the lack of a clinical effect, or a weak clinical effect, of adjunctive edivoxetine treatment for patients with MDD who are partial responders to an SSRI therapy.

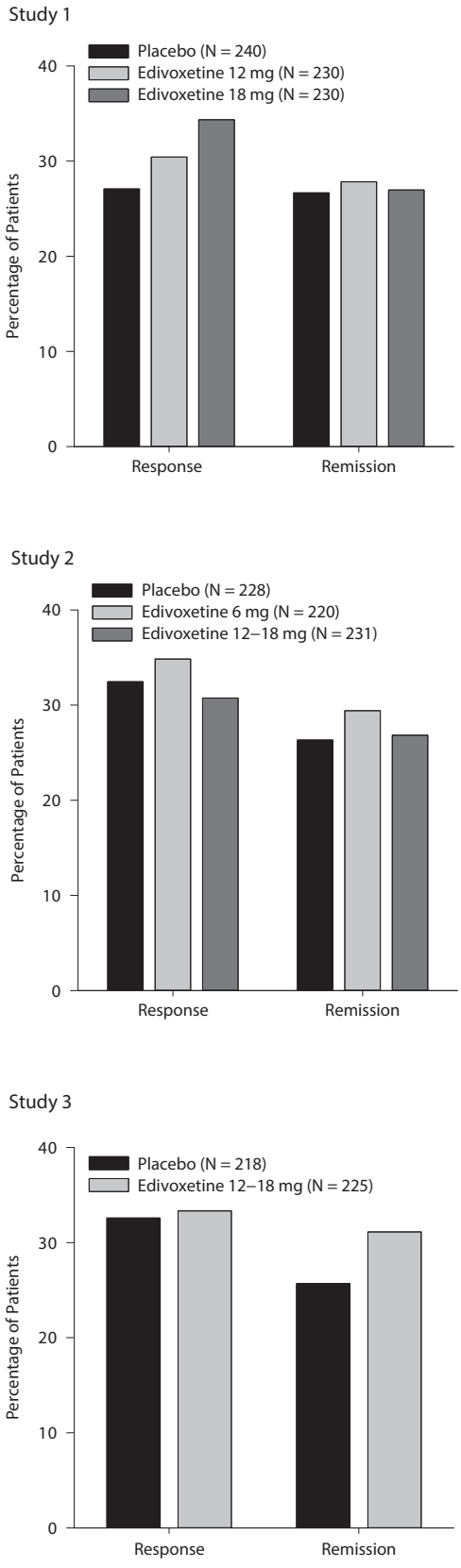
Previously, edivoxetine did demonstrate efficacy compared with placebo in a clinical trial for monotherapy of MDD,[17] although another monotherapy trial in patients with MDD with lower doses and higher discontinuation rates was more equivocal.[18] Furthermore, norepinephrine transmission has an established role in the pathogenesis and treatment of depression[19,20]; thus, the null finding from

Figure 2. Montgomery-Asberg Depression Rating Scale Total Score Mean Change From Baseline (MMRM)[a]



[a]N = number of patients who have nonmissing values at visit 3.
*$P \leq .025$.
Abbreviations: LS mean = least-squares mean, MMRM = mixed-model repeated measures, SSRI = selective serotonin reuptake inhibitor.

Figure 3. Response and Remission Rates at Last-Observation-Carried-Forward Endpoint[a]



[a]N = number of patients with a baseline and at least 1 postbaseline Montgomery-Asberg Depression Rating Scale observation.

Table 2. Mean Changes in Secondary Efficacy Measures From Baseline to Week 8 (repeated measures analysis)

	Study 1			Study 2			Study 3	
Characteristic	Placebo + SSRI (N = 240)	Edivoxetine (12 mg) + SSRI (N = 231)	Edivoxetine (18 mg) + SSRI (N = 230)	Placebo + SSRI (N = 231)	Edivoxetine (12–18 mg) + SSRI (N = 232)	Edivoxetine (6 mg) + SSRI (N = 226)	Placebo + SSRI (N = 219)	Edivoxetine (12–18 mg) + SSRI (N = 230)
CGI-S, LS mean (SE)	−0.95 (0.07)	−1.01 (0.07)	−1.08 (0.07)	−1.14 (0.07)	−1.20 (0.08)	−1.21 (0.08)	−1.02 (0.08)	−1.08 (0.08)
HADS depression subscale score, LS mean (SE)	−2.76 (0.26)	−3.19 (0.26)	−3.38 (0.27)	−2.55 (0.26)	−3.40* (0.27)	−3.62* (0.27)	−2.64 (0.27)	−2.82 (0.27)
HADS anxiety subscale score, LS mean (SE)	−1.85 (0.22)	−1.97 (0.22)	−2.05 (0.22)	−2.05 (0.24)	−2.24 (0.24)	−2.64 (0.24)	−1.78 (0.23)	−2.20 (0.22)
SDS global functional impairment score, LS mean (SE)	−4.47 (0.43)	−5.36 (0.44)	−5.27 (0.44)	−4.30 (0.43)	−5.30 (0.43)	−6.29* (0.44)	−4.38 (0.48)	−4.50 (0.47)
MADRS individual items, LS mean (SE)								
Apparent sadness	−1.01 (0.08)	−1.18 (0.08)	−1.04 (0.08)	−1.26 (0.08)	−1.34 (0.08)	−1.25 (0.08)	−1.26 (0.09)	−1.10 (0.09)
Reported sadness	−1.00 (0.08)	−1.21 (0.08)	−1.20 (0.08)	−1.26 (0.09)	−1.41 (0.09)	−1.31 (0.09)	−1.19 (0.09)	−1.17 (0.09)
Inner tension	−0.65 (0.07)	−0.71 (0.07)	−0.74 (0.07)	−0.87 (0.08)	−0.96 (0.08)	−0.91 (0.08)	−0.71 (0.09)	−0.72 (0.08)
Reduced sleep	−0.83 (0.08)	−0.97 (0.09)	−0.94 (0.09)	−0.92 (0.09)	−0.82 (0.09)	−0.96 (0.09)	−0.76 (0.10)	−0.83 (0.09)
Reduced appetite	−0.75 (0.08)	−0.82 (0.08)	−0.74 (0.08)	−0.71 (0.08)	−0.57 (0.08)	−0.67 (0.08)	−0.72 (0.08)	−0.54 (0.08)
Concentration difficulties	−0.94 (0.08)	−0.88 (0.08)	−1.01 (0.08)	−0.98 (0.08)	−1.13 (0.08)	−1.14 (0.08)	−0.82 (0.09)	−1.07 (0.09)
Lassitude	−0.89 (0.08)	−1.04 (0.08)	−1.12* (0.08)	−1.16 (0.09)	−1.15 (0.09)	−1.07 (0.09)	−0.98 (0.09)	−1.11 (0.09)
Inability to feel	−0.90 (0.08)	−1.05 (0.08)	−1.07 (0.08)	−1.14 (0.09)	−1.11 (0.09)	−1.30 (0.09)	−1.08 (0.09)	−1.17 (0.09)
Pessimistic thoughts	−0.74 (0.07)	−0.77 (0.07)	−0.74 (0.07)	−0.91 (0.07)	−0.84 (0.07)	−0.82 (0.07)	−0.77 (0.08)	−0.88 (0.08)
Suicidal thoughts	−0.15 (0.03)	−0.09 (0.03)	−0.13 (0.03)	−0.17 (0.03)	−0.17 (0.03)	−0.19 (0.03)	−0.24 (0.05)	−0.23 (0.05)
FAsD average score, LS mean (SE)	−0.57 (0.05)	−0.69 (0.05)	−0.67 (0.05)	−0.53 (0.05)	−0.67 (0.05)	−0.68 (0.06)	−0.55 (0.06)	−0.62 (0.06)

*$P \leq .05$ (adjunctive edivoxetine compared with adjunctive placebo).
Abbreviations: CGI-S = Clinical Global Impressions-Severity scale, FAsD = Fatigue Associated with Depression Questionnaire, HADS = Hospital Anxiety and Depression Scale, LS mean = least-squares mean, MADRS = Montgomery-Asberg Depression Rating Scale, SDS = Sheehan Disability Scale, SE = standard error.

the 3 studies was surprising. The contextual interpretation of these results should consider the neurobiology of depression, the patient population, and the design features of the study.

Regarding the neurobiology of depression, these findings suggest that adding norepinephrine to a system that has already been desensitized with ongoing serotonergic reuptake inhibition may not have the same effect of normalizing depression compared with a system in which serotonergic and noradrenergic activation are initiated at the same time. Meta-analysis of treatment outcomes with serotonergic noradrenergic reuptake inhibitor monotherapy has clearly demonstrated that these medications are effective.[21] While norepinephrine therapies such as tricyclic antidepressants and reboxetine have shown efficacy as monotherapies, these medications have not been studied for their efficacy in controlled studies as adjunctive therapies in the MDD partial-responder population. Thus, the dynamic nature of norepinephrine down-regulation may be such that timing of the intervention determines when activation of this system can enhance outcome.

Others have suggested that effectiveness of noradrenergic agents may relate to specific behavioral dimensions, such as arousal and executive functioning, rather than to the entire syndrome of depression.[22] In the adjunctive edivoxetine trials, individual items on the MADRS related to cognitive functioning and arousal did not show statistically significant differences, but this instrument may not have been sufficiently sensitive to detect these types of symptomatic outcomes. For some pharmacologic interventions, traditional assessment instruments may not be sufficient to detect improvements as the original "gold standards" were developed in the context of tricyclic antidepressant interventions. Thus, alternative methods or instruments may need to be considered for assessment of specific symptoms of depression within the context of adjunctive treatment.

A second consideration for interpreting results from the adjunctive edivoxetine trials is the heterogeneity of MDD and of the definition of a "partial responder" patient population. Patients were naturalistically selected for the edivoxetine studies in that they were determined to be a partial responder based on their response to SSRI by investigator opinion instead of a prospective observational period; thus, the partial responder patient enrolled within the trials could have been quite heterogeneous. For example, the enrolled sample could have included patients who experienced a wide response ranging from at least minimally responsive to near remission. Additionally, patients may have been in remission with the current SSRI at some point during their treatment but then worsened into a partial response status. While the definition of partial responder used in these studies is generalizable to how patients often present within clinical settings, it is unknown whether this heterogeneity precludes different responses to adjunctive treatment since there have not been direct comparisons of different methodologies for determination of the partial responder population. Among atypical antipsychotic studies, efficacy was established with both prospectively defined inadequate response population and historical report. However, a meta-analysis of these studies did not suggest that the method of defining the population was related to degree of response.[23] Overall, these considerations suggest that the partial responder population is distinct from the patients with MDD who participate in monotherapy clinical trials.

A third consideration is the methodology of the study designs and its potential impact on placebo response. Several methodological features were included in the studies to mitigate placebo response, such as blinded, independent clinicians for severity ratings to determine study entry, the confirmation of the partial response during a 3-week double-blind adjunctive placebo lead-in phase, the use of blinded randomization criteria for patients after this lead-in phase, and the use of blinded timing of randomization. Noteworthy, in each of the studies, across hundreds of different sites and over 20 countries, approximately half of the patients within each trial experienced sufficient improvement from baseline so that they failed to meet randomization criteria and were maintained in the study on blinded placebo. The improvement during this lead-in period represents not only response to nonpharmacological therapeutic effects (eg, interactions with clinical staff), but also may represent continued response to SSRI treatment.

Despite steps that were taken to reduce the influence of patients who were placebo responders or late SSRI monotherapy responders, the degree of improvement in patients who were randomized to placebo in the acute therapy trial was commensurate with the adjunctive edivoxetine rates. Without an active comparator, the magnitude of placebo response in comparison with a known effective drug cannot be directly compared, and the overall effectiveness of the double-blind lead-in period cannot be ascertained. However, the mean change in the MADRS total score for the placebo group (approximately 8 points across trials) was similar to the mean change observed in the published literature, suggesting that the placebo response within the randomized population was not exceedingly high. The consistency in the findings across the 3 independent trials favors an interpretation of a weak clinical effect for adjunctive edivoxetine or a partial responder population that may be particularly responsive to the psychosocial aspects of clinical trial participation and associated expectancies.[24] This potential reactivity leads to a further conundrum for determining whether the double-blind placebo lead-in is an optimal design to study adjunctive therapy in patients with MDD. Studies with other experimental antidepressants, outside of the atypical antipsychotics, that have not included these design features have also struggled to demonstrate greater efficacy compared with placebo.[25,26]

The strengths of the edivoxetine program include consistent implementation of 3 large trials of similar design; a global program involving over 20 countries; and the use of state-of-the-art methodology that standardized patient selection, assessment, and mitigation of expectancies. Limitations of the study program include potential effects of patient population, design, and lack of active comparator. In summary, edivoxetine as a selective norepinephrine reuptake inhibitor failed to demonstrate efficacy as an adjunctive treatment for patients with MDD who were partial responders to SSRI therapy, which therefore precludes further development of this drug for this indication.

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Drug names: citalopram (Celexa and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others).

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REFERENCES

1. Gelenberg AJ, Freeman MP, Markowitz JC, et al; Work Group on Major Depressive Disorder. *Practice Guideline for the Treatment of Patients With Major Depressive Disorder*. 3rd ed. Arlington, VA: American Psychiatric Association; 2010.
2. 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.
3. Judd LL, Paulus MJ, Schettler PJ, et al. Does incomplete recovery from first lifetime major depressive episode herald a chronic course of illness? *Am J Psychiatry*. 2000;157(9):1501–1504.
4. Paykel ES, Ramana R, Cooper Z, et al. Residual symptoms after partial remission: an important outcome in depression. *Psychol Med*. 1995;25(6):1171–1180.
5. Thase ME, Simons AD, McGeary J, et al. Relapse after cognitive behavior therapy of depression: potential implications for longer courses of treatment. *Am J Psychiatry*. 1992;149(8):1046–1052.
6. Tranter R, O'Donovan C, Chandarana P, et al. Prevalence and outcome of partial remission in depression. *J Psychiatry Neurosci*. 2002;27(4):241–247.
7. Trivedi MH, Thase ME, Osuntokun O, et al. An integrated analysis of olanzapine/fluoxetine combination in clinical trials of treatment-resistant depression. *J Clin Psychiatry*. 2009;70(3):387–396.
8. Ball S, Dellva MA, D'Souza DN, et al. A double-blind, placebo-controlled study of edivoxetine as an adjunctive treatment for patients with major depressive disorder who are partial responders to selective serotonin reuptake inhibitor treatment. *J Affect Disord*. 2014;167:215–223.
9. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (MINI): 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.
10. Williams JB, Kobak KA, Bech P, et al. The GRID-HAMD: standardization of the Hamilton Depression Rating Scale. *Int Clin Psychopharmacol*. 2008;23(3):120–129.
11. Chandler GM, Iosifescu DV, Pollack MH, et al. RESEARCH: validation of the Massachusetts General Hospital Antidepressant Treatment History Questionnaire (ATRQ). *CNS Neurosci Ther*. 2010;16(5):322–325.
12. Sheehan DV. *The Anxiety Disease*. New York, NY: Charles Scribner & Sons; 1983.
13. Snaith RP, Zigmond AS. The Hospital Anxiety and Depression Scale. *Br Med J (Clin Res Ed)*. 1986;292(6516):344.
14. Guy W. *ECDEU Assessment Manual for Psychopharmacology*. Revised Edition. Rockville, MD: US Department of Health, Education, and Welfare; 1976.
15. Matza LS, Wyrwich KW, Phillips GA, et al. The Fatigue Associated with Depression Questionnaire (FAsD): responsiveness and responder definition. *Qual Life Res*. 2013;22(2):351–360.
16. Koch GG, Tangen CM, Jung JW, et al. Issues for covariance analysis of dichotomous and ordered categorical data from randomized clinical trials and non-parametric strategies for

addressing them. *Stat Med*. 1998;17(15–16):1863–1892.
17. Pangallo B, Dellva MA, D'Souza DN, et al. A randomized, double-blind study comparing LY2216684 and placebo in the treatment of major depressive disorder. *J Psychiatr Res*. 2011;45(6):748–755.
18. Dubé S, Dellva MA, Jones M, et al. A study of the effects of LY2216684, a selective norepinephrine reuptake inhibitor, in the treatment of major depression. *J Psychiatr Res*. 2010;44(6):356–363.
19. Moret C, Briley M. The importance of norepinephrine in depression. *Neuropsychiatr Dis Treat*. 2011;7(suppl 1):9–13.
20. Gorman JM, Sullivan G. Noradrenergic approaches to antidepressant therapy. *J Clin Psychiatry*. 2000;61(suppl 1):13–16.
21. Papakostas GI, Thase ME, Fava M, et al. Are antidepressant drugs that combine serotonergic and noradrenergic mechanisms of action more effective than the selective serotonin reuptake inhibitors in treating major depressive disorder? a meta-analysis of studies of newer agents. *Biol Psychiatry*. 2007;62(11):1217–1227.
22. Dell'Osso B, Palazzo MC, Oldani L, et al. The noradrenergic action in antidepressant treatments: pharmacological and clinical aspects. *CNS Neurosci Ther*. 2011;17(6):723–732.
23. 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.
24. Rutherford BR, Roose SP. A model of placebo response in antidepressant clinical trials. *Am J Psychiatry*. 2013;170(7):723–733.
25. AstraZeneca and Targacept Announce Remaining TC-5214 Phase 3 Efficacy Studies Do Not Meet Primary Endpoint, Regulatory Filing Will Not Be Pursued [Press Release]. http://phx.corporate-ir.net/phoenix.zhtml?c=178332&p=irol-newsArticle&ID=1373490&highlight=. 2012.
26. Shire Reports Top-line Results from Two Phase 3 Studies for Vyvanse (lisdexamfetamine dimesylate) Capsules (CII) as an Adjunctive Treatment for Adults with Major Depressive Disorder [Press Release]. http://www.prnewswire.com/news-releases/shire-reports-top-line-results-from-two-phase-3-studies-for-vyvanse-lisdexamfetamine-dimesylate-capsules-cii-as-an-adjunctive-treatment-for-adults-with-major-depressive-disorder-244043531.html. 2014.

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