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Safety and tolerability of edivoxetine as adjunctive treatment to selective serotonin reuptake inhibitor antidepressants for patients with major depressive disorder

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Abstract

Objective: The aim of this analysis was to assess the safety profile of edivoxetine as adjunctive treatment to selective serotonin reuptake inhibitor (SSRI) antidepressants.

Methods: A pooled analysis was conducted on data obtained from the integrated safety database of edivoxetine as adjunctive treatment to SSRIs. Safety and tolerability assessments included discontinuation rates, spontaneously reported treatment-emergent adverse events (TEAEs), clinical laboratory tests, blood pressure (BP) and pulse, and electrocardiograms (ECGs).

Results: The analysis included 1260 patients treated with adjunctive edivoxetine and 806 treated with adjunctive placebo. Study completion rates were 85.2% and 84.5% (p=0.994), respectively. Discontinuations due to adverse events were 4.9% and 3.5% (p=0.07), respectively. Significantly more patients in the adjunctive edivoxetine group compared with adjunctive placebo group reported at least one TEAE (56.8 *vs* 43.7%, p<0.001). The most common TEAEs (occurred ≥5% frequency) were hyperhidrosis, nausea, and tachycardia. Mean changes in sitting BP and pulse at the last visit were increased significantly in patients treated with adjunctive edivoxetine compared with adjunctive placebo (SBP: 2.7 *vs* 0.5 mm Hg, p<0.001; DBP: 4.1 *vs* 0.8 mm Hg, p<0.001; pulse: 8.8 *vs* –1.3 bpm, p<0.001). There were no clinically significant changes in laboratory measures.

Conclusions: The tolerability and safety profile of edivoxetine as adjunctive treatment to SSRI antidepressants was consistent with its norepinephrine reuptake inhibitor mechanism of action, and was comparable with edivoxetine monotherapy treatment in patients with major depressive disorder.

Keywords: norepinephrine reuptake inhibitor, serotonin reuptake inhibitor, second-generation antidepressive agent, major depressive disorder, adjunctive therapy, drug safety, drug tolerability.

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; ECG, electrocardiogram; MDD, major depressive disorder; SSRI, selective serotonin reuptake inhibitor; SBP, systolic blood pressure; TEAE, treatment-emergent adverse event.

Citation

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Introduction

Since the introduction of antidepressants with selective serotonin reuptake inhibition (SSRI) in late 1980s, SSRIs have replaced tricyclics as first-line antidepressants of choice due to their comparable efficacy and more acceptable safety profile [1]. While the use of SSRIs is widespread, less than one-half of patients respond to their SSRI treatment and less than one-third achieve remission [2]. One line of thinking suggests that the addition of another antidepressant with a different mode of action might improve outcomes [3]. Adjunctive therapy strategies were evaluated in level 2 of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, in which patients with major depressive disorder (MDD) who did not achieve remission on an initial trial of citalopram were randomized to receive adjunctive sustained-release bupropion or adjunctive buspirone [4]. In that trial, both groups had similar remission rates, but the adjunctive sustained-release bupropion group had greater reductions in depressive symptom severity scores. In a subsequent retrospective analysis that compared outcomes for medication augmentation compared with switching in the STAR*D trial, the authors concluded that patients who complete an initial treatment of 12 weeks or more and have a partial response with residual mild depressive severity may benefit more from augmentation relative to switching [5].

Although improving efficacy is the goal of adjunctive treatment, safety and tolerability are also important considerations. Edivoxetine, a potent and highly selective norepinephrine reuptake inhibitor (NRI), was investigated in one phase II [6] and three phase III acute placebo-controlled trials [7] as adjunctive therapy to ongoing treatment with SSRI antidepressants in patients with MDD who were partial responders to their SSRI treatment. Across these four studies, symptoms of depression assessed with the Montgomery–Åsberg Depression Rating Scale (MADRS) [8] total score improved, but there were no significant differences between adjunctive treatment groups in changes from baseline [6,7]. Herein, we present the tolerability and safety findings from those four trials.

Method

Data were obtained from the integrated safety database of edivoxetine (6–18 mg per day) as adjunctive therapy to SSRI antidepressant treatment in adult patients with MDD. Four studies were included in the analyses: one phase II study [6] and three phase III studies [7]. All four study protocols were approved by the Ethical Review Board for each study center. The studies were conducted in full accordance with the Good Clinical Practice: Consolidated Guidance approved by the International Conference on Harmonization and applicable laws or regulations. Written informed consent was obtained from each patient at study entry before commencement of any study procedures.

All four studies were double-blind, randomized, and placebo-controlled with three study periods: a screening period, a 2- to 3-week double-blind placebo lead-in followed by an 8-week randomized double-blind adjunctive treatment period, and an edivoxetine discontinuation period. All patients entered the studies taking a stable dose of SSRI antidepressant, and continued on this SSRI dose throughout the duration of the trial, including the discontinuation period.

Edivoxetine dosing differed across the trials. In the phase II study, edivoxetine was flexibly dosed (6–18 mg once daily (QD)). In the phase III studies, edivoxetine was fixed-dose (12 mg or 18 mg QD) in one study; flexible-dose (12–18 mg QD) or fixed-dose (6 mg QD) in another study; and flexibly dosed (12–18 mg QD) in a third study. For this analysis, data across all dosage arms were pooled.

The studies had similar inclusion criteria: adult outpatients who were between at least 18 years of age and who met the diagnostic criteria for MDD (defined by *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision) [9]; who had partial response to a course of ≥6 weeks of SSRI treatment; who were at a stable dose of SSRI for at least 4 weeks prior to study entry; and who had a GRID 17-item Hamilton Depression Rating Scale (GRID-HAMD) total score of ≥16 [10]. In the phase III studies, patients with less than 25% improvement and a score ≥14 on the MADRS total score during the adjunctive placebo lead-in period were randomized. In the phase II study, all patients were randomized. Baseline for all four studies was at the time of randomization to double-blind treatment.

The safety and tolerability results reported here are from the double-blind adjunctive treatment periods. Assessments included spontaneously reported treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), discontinuation rates, clinical laboratory tests (chemistry, hematology, and urinalysis), blood pressure (BP), pulse, electrocardiograms (ECGs), weight, suicidality, and sexual function.

TEAEs (defined as newly occurring events or events present during the baseline period that worsened post-baseline) were summarized according to preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA® version 16.1). Prior to the analysis of TEAEs, individual event terms were reviewed, and similar terms were combined together when possible.

Suicide-related events were assessed using the Columbia Suicide Severity Rating Scale (C-SSRS) [11]. The scale captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period to prospectively categorize suicide-related events. The scale includes suggested questions to solicit the type of information needed, to determine if a suicide-related thought or behavior occurred.

Sexual dysfunction was investigated using the patient-rated Arizona Sexual Experience Scale (ASEX) [12]. Patients with sexual dysfunction included those who met at least one of the following criteria: an ASEX total score ≥19; an individual ASEX item score ≥5; or a score ≥4 on three or more ASEX individual items.

Sitting BP was taken at each study visit in triplicate and the average value was used in the analysis, while sitting pulse was taken only once at each visit. The studies also included one supine and one standing BP and pulse measurement at select visits to assess orthostatic changes.

Treatment-emergent elevations in sitting BP and pulse were defined by the following criteria: systolic blood pressure (SBP) ≥140 mm Hg and ≥20 mm Hg increase from baseline; diastolic blood pressure (DBP) ≥90 mm Hg and ≥10 mm Hg increase from baseline; pulse >100 bpm and ≥15 bpm increase from baseline. Sustained elevations in BP and pulse were those measures that met treatment-emergent elevation criteria at three consecutive visits. Potentially clinically significant (PCS) elevations in BP were defined as SBP ≥180 mm Hg and ≥20 mm Hg increase from baseline; or DBP ≥105 mm Hg and ≥15 mm Hg increase from baseline. Treatment-emergent orthostatic changes from supine to standing were defined as an SBP decrease of ≥20 mm Hg; a DBP decrease of ≥10 mm Hg; or a pulse increase of ≥30 bpm. PCS changes in body weight were defined as a weight loss of ≥7% or weight gain of ≥7% from baseline.

Statistical methods

Randomized patients from all four studies were included in each of the safety analyses, except for changes in BP, pulse, and sexual dysfunction, which included only patients from the phase III studies, because these variables were collected differently in the phase II study. For categorical analyses, the Cochran–Mantel–Haenszel (CMH) test, stratified by study, was used for treatment comparisons of percentages, unless otherwise noted. For continuous numeric values, visit-wise changes from baseline were analyzed by mixed-model repeated measures (MMRM). The model included the fixed categorical effects of treatment, study, pooled investigative site nested within study, visit, and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline and baseline-by-visit interaction.

In addition, a subgroup analysis of visit-wise changes in BP and pulse was conducted to determine if there was a regional effect on the outcomes due to the ethnic diversity across the study sites. The geographic regions were the United States, Europe, Japan, and 'Other'. The European region included: Austria, Belgium, Croatia, Czech Republic, Finland, Hungary, Latvia, Poland, Romania, Slovakia, Sweden, and the UK. The 'Other' region included: Australia, Russian Federation, South Africa, and Ukraine. The MMRM analyses were repeated with the term 'geographical region' added to the model along with the 2- and 3-way interaction between region, treatment, and visit.

Results

Across the four studies, there were 1260 patients who were randomized to adjunctive edivoxetine and 806 patients who were randomized to adjunctive placebo. On average, patients had moderate to severe depression (MADRS total score of 25) and were 47 years of age, 78% were Caucasian, and 66% were female [6,7]. Most of the patients completed the randomized double-blind treatment period, and differences in completion rates between adjunctive treatment groups were not significant: adjunctive edivoxetine, 85.2%; adjunctive placebo, 84.5% (p=0.994). Discontinuation due to adverse events did not differ significantly between treatment groups: adjunctive edivoxetine, 4.9%; adjunctive placebo, 3.5% (p=0.07). Nausea was the only adverse event reported as a reason for discontinuation significantly more frequently by the adjunctive edivoxetine group (n=6, 0.5%) as compared with the adjunctive placebo group (n=0, 0%; p=0.046).

Significantly more patients in the adjunctive edivoxetine group reported at least one TEAE as compared with patients in the adjunctive placebo group (56.8 *vs* 43.7%, p<0.001). The TEAEs experienced by ≥2% of patients in the adjunctive edivoxetine group and that occurred significantly more frequently as compared with the adjunctive placebo group are summarized in Table 1. The most common TEAEs (occurred ≥5% frequency) were hyperhidrosis, nausea, and tachycardia. SAEs were spontaneously reported by 18 patients in the adjunctive edivoxetine group, and none of these events occurred at a significantly greater frequency than in the adjunctive placebo group (Table 2). The only event that occurred in more than one patient treated with adjunctive edivoxetine was depression (n=3).

Suicidal ideation was spontaneously reported by one patient treated with adjunctive edivoxetine and by three patients in the adjunctive placebo group (p=0.234). Three attempted

Table 1. Treatment-emergent adverse events that occurred with ≥2% of patients and significantly greater frequency in the adjunctive edivoxetine group as compared with the adjunctive placebo group.

Event	Adjunctive placebo (N=801) n (%)	Adjunctive edivoxetine (N=1254) n (%)	*p* value
Patients with at least one event	350 (43.7)	712 (56.8)	<0.001
Hyperhidrosis	9 (1.1)	95 (7.6)	<0.001
Nausea	20 (2.5)	79 (6.3)	<0.001
Tachycardia[a]	3 (0.4)	66 (5.3)	<0.001
Dizziness	17 (2.1)	53 (4.2)	0.007
Vomiting[a]	7 (0.9)	37 (3.0)	<0.001
Constipation	10 (1.3)	35 (2.8)	0.020
Palpitations	1 (0.1)	30 (2.4)	<0.001
Testicular pain[b]	0	10 (2.3)	0.010
Dry mouth	9 (1.1)	28 (2.2)	0.046
Increased heart rate	1 (0.1)	26 (2.1)	<0.001

[a]Combined terms: tachycardia = tachycardia and sinus tachycardia; vomiting = vomiting and retching.
[b]Number of males: adjunctive placebo, n=268; adjunctive edivoxetine, n=427.

Table 2. Serious adverse events.

Event	Adjunctive placebo (N=801) n (%)	Adjunctive edivoxetine (N=1254) n (%)
Patients with at least one event	12 (1.5)	18 (1.4)
Depression	0	3 (0.2)
Cervical dysplasia (f)	0	1 (0.1)
Angina pectoris	0	1 (0.1)
Appendicitis	0	1 (0.1)
Arteriosclerosis	0	1 (0.1)
Increased blood creatinine	1 (0.1)	1 (0.1)
Increased blood urea	0	1 (0.1)
Breast cancer	0	1 (0.1)
Food poisoning	0	1 (0.1)
Gastritis	0	1 (0.1)
Decreased hemoglobin	0	1 (0.1)
Inflammation	0	1 (0.1)
Major depression	0	1 (0.1)
Myocardial infarction	0	1 (0.1)
Esophageal achalasia	0	1 (0.1)
Paresthesia	0	1 (0.1)
Suicidal ideation	3 (0.4)	1 (0.1)
Adenocarcinoma of colon	1 (0.1)	0
Atrial fibrillation	2 (0.3)	0
Metrorrhagia (f)	1 (0.2)	0
Osteoarthritis	1 (0.1)	0
Rotator cuff syndrome	1 (0.1)	0
Suicide attempt	3 (0.4)*	0

(f) Event is gender specific and the denominator is based on the number of females: N=533 (adjunctive placebo), N=827 (adjunctive edivoxetine).
*This was the only SAE with a frequency of occurrence that was statistically significant (p=0.048).

suicides were also reported by patients in the adjunctive placebo group, but none were completed. Suicidal ideation (any new ideation or worsening in severity of ideation from the baseline screening period) was also assessed with the C-SSRS, and the frequency of these events was similar across the adjunctive treatment groups: 4.3% and 4.8% (p=0.716) for edivoxetine and placebo, respectively. In addition, there were no significant differences between adjunctive treatment groups in the rates of suicide-related behavior for patients with no prior history of suicidal behavior (adjunctive edivoxetine = 0.18%, adjunctive placebo = 0.28%, p=0.741). Rates of improvement from baseline in suicidal ideation were 72.7% and 74.0% (p=0.922) for adjunctive placebo and adjunctive edivoxetine, respectively.

Sexual dysfunction assessed by the ASEX is summarized in Table 3. Among the male and female patients who met the criteria for sexual dysfunction at baseline, there were no significant differences between adjunctive treatment groups in achieving resolution of sexual dysfunction at the last study visit. In addition, among patients who did not have sexual dysfunction at baseline, there were no significant differences between adjunctive treatment groups in the percentage of patients in either gender group who met the criteria for sexual dysfunction at the last study visit.

The cardiovascular responses to adjunctive treatment over 8 weeks are summarized in Figure 1. There were statistically significant increases in SBP in patients treated with adjunctive edivoxetine relative to adjunctive placebo after the first week of treatment, and at weeks 3–8. At the last visit, the mean changes from baseline were 2.7 mm Hg for adjunctive edivoxetine and were 0.5 mm Hg (p<0.001) for adjunctive placebo. Mean changes from baseline in sitting DBP were significantly increased with adjunctive edivoxetine relative to adjunctive placebo at each post-baseline visit; and at the last visit, mean changes were 4.1 mm Hg compared with 0.8 mm Hg (p<0.001), respectively. Sitting pulse was increased significantly from baseline at each post-baseline visit in the adjunctive edivoxetine group as compared with the adjunctive placebo group. At the last visit, mean changes in pulse were 8.8 bpm compared with –1.3 bpm (p<0.001) for adjunctive edivoxetine and adjunctive placebo, respectively.

The subgroup analysis of mean change to last post-baseline visit in BP and pulse by geographical region indicated a significant treatment-by-region interaction for DBP and pulse. At the last visit, patients in Japan and in the 'Other' group who were treated with adjunctive edivoxetine had larger mean increases relative to adjunctive placebo in DBP (Japan = 5.6 mm Hg; Other = 5.1 mm Hg) and pulse (Japan = 16.1 bpm; Other = 15.2 bpm) than was observed in patients from the United States (DBP = 3.5 mm Hg; pulse = 10.2 bpm) and Europe (DBP = 2.6 mm Hg; pulse = 8.1 bpm).

Categorical changes in BP and pulse are summarized in Table 4. Adjunctive edivoxetine was associated with significantly greater frequency relative to adjunctive placebo in treatment-emergent changes in SBP, DBP, and pulse that occurred at any time. Changes that were sustained over three consecutive visits were observed for DBP in 1 patient in both adjunctive treatment groups (p=0.78), and for pulse in 18 patients (1.7%, p<0.001) in the adjunctive edivoxetine group compared with none in the adjunctive placebo group. PCS changes in DBP were noted for four (0.4%) patients in the adjunctive edivoxetine group and none in the adjunctive placebo group. The percentage of patients with orthostatic changes was significantly greater in the adjunctive edivoxetine

Table 3. Sexual dysfunction[a] assessed by the Arizona Sexual Experience Scale.

Gender	Dysfunction at baseline	Adjunctive treatment	N	Dysfunction present at endpoint n (%)	Dysfunction absent at endpoint n (%)
Male					
	Present	Placebo	169	141 (83.4)	28 (16.6)
		Edivoxetine	292	239 (81.9)	53 (18.2)
	Absent	Placebo	63	8 (12.7)	55 (87.3)
		Edivoxetine	97	23 (23.7)	74 (76.3)
Female					
	Present	Placebo	388	349 (90.0)	39 (10.1)
		Edivoxetine	643	557 (86.6)	86 (13.4)
	Absent	Placebo	54	13 (24.1)	41 (75.9)
		Edivoxetine	88	15 (17.1)	73 (83.0)

Differences between adjunctive treatment groups were not significant.
[a]Sexual dysfunction was defined as an Arizona Sexual Experience Scale (ASEX) total score ≥19; an individual ASEX item score ≥5; or a score ≥4 on three or more ASEX individual items.

group for each measure (SBP, DBP, and pulse). However, only two patients in the adjunctive edivoxetine group discontinued from the study due to orthostatic changes such as hypotension.

There were significant differences between adjunctive treatment groups in ECG changes during the study that included mean decreases in PR interval at Week 4 (adjunctive edivoxetine = –4.6 milliseconds, adjunctive placebo = –0.3 milliseconds, $p \leq 0.001$) and at Week 8 (adjunctive edivoxetine = –5.6 milliseconds, adjunctive placebo = 0.3 milliseconds, $p \leq 0.001$). QRS changes for adjunctive edivoxetine and adjunctive placebo, respectively, at week 4 were –0.5 milliseconds compared with –0.2 milliseconds ($p=0.247$), and were –0.5 milliseconds compared with –0.3 milliseconds ($p=0.479$) at Week 8. There was a significant decrease in Fridericia's corrected QT interval (QTcF) at Week 4 of –3.2 milliseconds compared with –0.4 milliseconds ($p=<0.001$) in the adjunctive edivoxetine and adjunctive placebo group, and at Week 8 the QTcF changes were –1.4 milliseconds compared with 1.5 milliseconds ($p=<0.001$), respectively. Five (0.5%) patients treated with adjunctive edivoxetine had a QTcF interval increase of >30 milliseconds and ≤60 milliseconds compared with seven (1.0%, $p=0.383$) patients treated with adjunctive placebo. No patient in either treatment group had QTcF ≥500 milliseconds. There were significant differences in mean increases in heart rate with adjunctive edivoxetine at Week 4 (12.4 bpm) as compared with adjunctive placebo (0.5 bpm, $p<0.001$) and at Week 8 (11.9 *vs* 0.2 bpm, $p<0.001$).

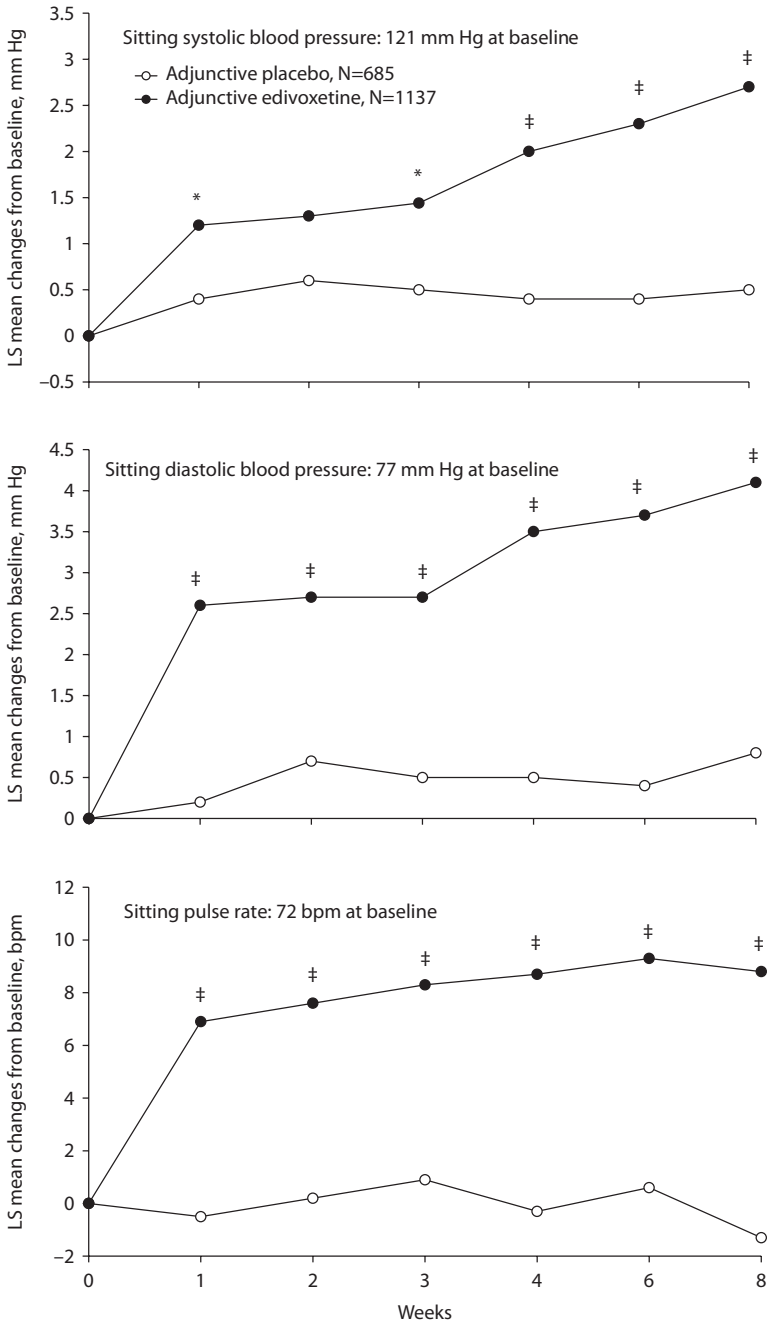
At baseline, the mean (SD) weight was 80.2 (20.1) kg in the adjunctive edivoxetine group and was 83.5 (21.7) kg in the adjunctive placebo group. Mean change (SE) from baseline at the last visit was –0.8 kg and 0.22 kg, respectively, in the adjunctive edivoxetine and adjunctive placebo group; the mean difference from adjunctive placebo was –1.0 kg ($p<0.001$). The percentage of patients with weight loss ≥7% was 1% in the adjunctive edivoxetine group and 0.8% in the adjunctive placebo group ($p=0.467$). The percentage of patients with weight gain ≥7% was 0.3% in the adjunctive edivoxetine group and 0.5% ($p=0.474$) in the adjunctive placebo group.

There were some statistically significant differences between adjunctive treatment groups in changes from baseline in clinical laboratory measures, but they were not judged to be clinically relevant. There were no significant differences between adjunctive treatment groups in the percentage of patients with treatment-emergent changes in hepatic measures such as alanine aminotransferase, aspartate aminotransferase, or bilirubin.

Discussion

Edivoxetine is one of three selective NRIs that have been investigated as adjunctive treatment to SSRI antidepressants in MDD patients. The other two are reboxetine and atomoxetine, and neither have an indication for adjunctive therapy in MDD. Reboxetine was studied as adjunctive treatment to SSRI antidepressants in a small (n=61) 6-week open-label trial [13]. The SSRIs included in that study were fluoxetine, paroxetine, sertraline, citalopram, and fluvoxamine. The safety outcomes of the adjunctive reboxetine study only included reporting the most common TEAEs (increased sweating, dry mouth, tremor, nervousness, insomnia, and urinary hesitancy), and there were no SAEs. Neither vital sign changes nor clinical

Figure 1. Least squares (LS) mean changes from baseline in sitting blood pressure and pulse.



*p<0.05; ‡p<0.001
bpm, beats per minute; LS, least squares; mm Hg, milliliters of mercury.

laboratory changes were reported, which limits tolerability and safety comparisons to adjunctive edivoxetine. Atomoxetine was studied as adjunctive treatment in patients with MDD who were partial responders to sertraline [14]. The most common TEAEs reported with adjunctive atomoxetine were dry mouth, insomnia, and constipation. There were no serious safety concerns or clinically meaningful changes in laboratory outcomes reported.

Adjunctive treatment to SSRI antidepressants with edivoxetine was generally well-tolerated as evidenced by high study completion rates (85.2%) and low rates of discontinuation due to adverse events (5.0%). The rates of discontinuation due to adverse events in this analysis were within the range reported in two acute placebo-controlled trials of edivoxetine monotherapy in patients with MDD: 1.5–9.2% [15,16]. In addition, TEAEs associated with adjunctive edivoxetine, with

Table 4. Treatment-emergent categorical elevations in blood pressure and pulse.

	Adjunctive placebo		Adjunctive edivoxetine		*p* value
Category	**N**	**n (%)**	**N**	**n (%)**	
Elevation at any time[a]					
Sitting SBP ≥140 mm Hg and ≥20 mm Hg increase from baseline	561	0	946	15 (1.6)	0.002
Sitting DBP ≥90 mm Hg and ≥10 mm Hg increase from baseline	555	11 (2.0)	945	57 (6.0)	<0.001
Sitting pulse >100 bpm and ≥15 bpm increase from baseline	677	4 (0.6)	1123	123 (11.0)	<0.001
Sustained elevation at three consecutive visits[b]					
Sitting SBP	534	0	903	0	NA
Sitting DBP	532	1 (0.2)	898	1 (0.1)	0.782
Sitting pulse	645	0	1062	18 (1.7)	0.001
Potentially clinically significant elevation at any time[a]					
Sitting SBP ≥180 mm Hg and ≥20 mm Hg increase from baseline	685	0	1132	0	NA
Sitting DBP ≥105 mm Hg and ≥15 mm Hg increase from baseline	681	0	1132	4 (0.4)	0.066
Orthostatic change at any time[a]					
SBP decrease of ≥20 mm Hg	662	27 (4.1)	1109	114 (10.3)	<0.001
DBP decrease of ≥10 mm Hg	658	28 (4.3)	1078	98 (9.1)	<0.001
Pulse increase of ≥30 bpm	669	9 (0.9)	1119	78 (7.0)	<0.001

[a]N = the number of patients who did do not meet criteria at baseline and had at least one post-baseline visit.
[b]N = the number of patients who met the criteria at baseline and had at least three post-baseline visit.
bpm, beats per minute; DBP, diastolic blood pressure; mm Hg, milliliters of mercury; SBP, systolic blood pressure.

the exception for tachycardia in this study, were comparable with those reported in the two placebo-controlled trials of edivoxetine monotherapy: constipation, dizziness, dry mouth, erectile dysfunction, headache, increased heart rate, hyperhidrosis, insomnia, and nausea. The similarity of TEAEs in the edivoxetine monotherapy and adjunctive treatment trials suggests that edivoxetine as adjunctive therapy to SSRI antidepressants does not impose a difference in tolerability as compared with edivoxetine taken alone.

Changes in sitting BP (SBP, mean increase of 2.7 mm Hg; DBP, mean increase of 4.1 mm Hg) and pulse (mean increase of 8.8 bpm) after 8 weeks of acute treatment with adjunctive edivoxetine were within the range of mean increases reported in the acute phase II adjunctive edivoxetine trial [6] and in the two acute edivoxetine monotherapy trials that assessed supine BP and pulse [15,16]: SBP, 1–3 mm Hg; DBP, 1–4 mm Hg; and pulse, 3–10 bpm. In addition, increases from baseline in vital signs have been reported in the acute treatment periods of two long-term trials of adjunctive edivoxetine. One was an open-label safety study of 54 weeks duration [17], and the other was a maintenance-of-effect study of 44 weeks duration [18]. With continued adjunctive edivoxetine treatment, vital sign changes increased relative to baseline but reached a plateau at approximately 12 weeks in both of the long-term studies [17,18]. In the long-term maintenance-of-effect study after 20 weeks of treatment with adjunctive edivoxetine, patients were randomized to 24 weeks of double-blind adjunctive treatment with placebo or were continued on adjunctive edivoxetine. Changes in BP and pulse appeared to be somewhat reversible upon discontinuation of adjunctive edivoxetine, as demonstrated by mean decreases in BP and pulse in the adjunctive placebo group over those 24 weeks [18].

Orthostatic changes were significantly more frequent with adjunctive edivoxetine and were within the range reported in

the two edivoxetine monotherapy studies (6.7–9.6%) [15,16]. There were statistically significant ECG changes for mean decreases in PR interval and QTcF with adjunctive edivoxetine treatment, but these changes may have been a result, at least in part, of increased heart rate, and were not considered clinically significant. The absence of clinically significant ECG abnormalities is consistent with what was observed in the acute edivoxetine monotherapy studies [15,16].

The significant treatment-by-geographic region interaction with adjunctive edivoxetine that was observed with DBP and pulse suggests that the hemodynamic response to NRIs as adjunctive treatment to SSRIs in Japanese patients may be different than in non-Japanese. However, a long-term (58 weeks) safety study of treatment with atomoxetine, which was conducted in adult Japanese patients with attention deficit hyperactivity disorder (ADHD) [19], reported treatment-emergent increases in pulse (9 bpm), and systolic and diastolic blood pressure (4 mm Hg and 5 mm Hg, respectively). Because the vital sign changes in the Japanese patients were similar to those reported in long-term studies in North American adults with ADHD [20–22], they were considered to be consistent with the known NRI mode of action.

Sexual dysfunction was present in the majority of patients at baseline, which may have been associated with SSRI treatment or depression itself [23]. However, the addition of adjunctive edivoxetine was not associated with much improvement in sexual functioning. Generally for those patients with sexual dysfunction at baseline, most continued to report dysfunction at study end. Similarly, for those patients without sexual dysfunction at baseline, most did not report sexual dysfunction at study end. The lack of a treatment effect with adjunctive edivoxetine in this study suggests that the addition of edivoxetine does not have a significant impact on sexual function.

One limitation to the results presented here is the pooling of data from studies that were not completely identical in design. However, this is an analysis of a large data set from placebo-controlled studies that allow quality assessment of the safety of adjunctive edivoxetine. The short duration of these studies may have limited the detection of adverse events that may occur with longer exposure to edivoxetine as adjunctive treatment to SSRI antidepressants. However, in a long-term open-label safety study of adjunctive edivoxetine, the profile of adverse events observed was consistent with the results presented here. In addition, most of the TEAEs in the long-term safety study had a median time of onset of approximately 2 weeks with the exception for upper respiratory tract infection that had a median time of onset of 50 days [17].

In conclusion, the tolerability and safety profile of edivoxetine as adjunctive treatment to SSRI antidepressants was consistent with an NRI mechanism of action. The cardiovascular responses to adjunctive edivoxetine treatment were expected due to this noradrenergic effect, but appear to be reversible when the drug is discontinued. Patients taking medications with an NRI mechanism of action should have their pulse and BP measured before treatment and periodically during treatment.

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