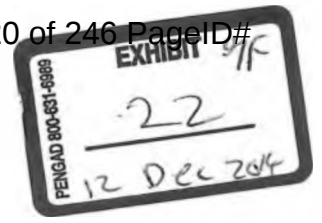




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# A randomized, double-blind comparison of duloxetine and venlafaxine in the treatment of patients with major depressive disorder ☆

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**Abstract**

*Background:* Clinical trials assessing antidepressant therapies typically include separate assessments of efficacy (benefit) and adverse events (risk). Global benefit–risk (GBR) assessment allows the simultaneous evaluation of both efficacy and adverse events. The objective was to compare the serotonin and norepinephrine reuptake inhibitors (SNRIs) duloxetine and venlafaxine using GBR assessment.
*Methods:* Data were combined from two similarly designed, multicenter, randomized, double-blind, parallel group studies in which patients with major depressive disorder were randomized to either duloxetine 60 mg/day or venlafaxine extended release (XR) 150 mg/day (75 mg/day for the first 2 weeks) for a 6-week fixed dosing period followed by an additional 6 weeks of treatment in which the dose could be increased up to 120 mg/day for duloxetine and 225 mg/day for venlafaxine. Patients completing the study (or receiving study drug for 2 weeks or more) were eligible to enter a taper period where the dose of study drug was gradually reduced over 1–2 weeks prior to drug discontinuation. The primary outcome measure (defined *a priori*) was the GBR comparison of duloxetine 60 mg/day and venlafaxine XR 150 mg/day after 6 weeks of treatment. In the GBR analysis, benefit was defined as remission at endpoint [17-item Hamilton Depression Rating Scale (HAMD17) $\leqslant 7$]. Risk was defined by four categories: patients having either no adverse events (AEs), AEs with no severity rating greater than moderate, AEs with at least one severity rating of severe, or having discontinued with a reason of self-reported adverse event (regardless of any AE severity). Additional efficacy measures included HAMD17 total score and subscales, HAMA, CGI-S, and PGI-I. Safety and tolerability were assessed via analysis of reasons for discontinuation, treatment-emergent adverse events (TEAEs), discontinuation-emergent adverse events, and changes in vital signs, weight, and laboratory analytes.
*Results:* There were no significant differences between duloxetine 60 mg/day and venlafaxine 150 mg/day as measured by GBR assessment at the end of 6 weeks ($-1.418$ vs. $-1.079$, $P = 0.217$) or 12 weeks ($-0.349$ vs. $-0.121$, $P = 0.440$), nor were there significant differences between treatment groups on the majority of efficacy measures. Significantly more venlafaxine-treated patients (74.5%) completed 12 weeks of treatment compared with duloxetine-treated patients (64.8%, $P = .006$). Nausea was the most common treat-

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ment-emergent adverse event (TEAE) for both drugs, and was significantly higher with duloxetine 60 mg/day compared to venlafaxine 150 mg/day during the first 6 weeks of treatment (43.6% vs. 35.0%, $P \leqslant 0.05$). During the taper period, significantly more venlafaxine-treated patients reported discontinuation-emergent adverse events (DEAEs) than duloxetine-treated patients. From a safety perspective, significantly more venlafaxine-treated patients ($n = 4$) than duloxetine-treated patients ($n = 0$, $P = .047$) experienced sustained elevations of systolic blood pressure during the fixed dosing period. Otherwise, there were few significant differences in safety measures found between treatment groups during 6 and 12 weeks of therapy.

*Conclusions:* Duloxetine 60 mg/day and venlafaxine XR 150 mg/day have similar benefit–risk profiles on the basis of a comparison utilizing GBR assessment. The implications of the more subtle differences between these drugs, as well as for interpreting the GBR assessment, are discussed.



*Keywords:* Duloxetine; Venlafaxine; Major depressive disorder; Global benefit–risk

## 1. Introduction

Selective serotonin reuptake inhibitors (SSRIs) increasingly have become the drug treatment of choice for major depressive disorder (MDD) since the introduction of fluoxetine in the late 1980s. Widespread use of SSRIs is primarily because of their greater ease of use and more favorable side effect profile when compared with older antidepressant classes such as tricyclics and monoamine oxidase inhibitors.

More recently, venlafaxine, a serotonin and norepinephrine reuptake inhibitor (SNRI) has been shown in a number of meta-analyses and reviews to be more efficacious than SSRIs in treating patients with MDD (Stahl et al., 2002; Smith et al., 2002; Thase et al., 2001), although the advantage for the "average" patient is modest (Stahl et al., 2005) and not all study results are in agreement (see, for example, Bielski et al., 2004 or Sir et al., 2005). In one review, tolerability was found to be similar between SNRIs and SSRIs, but a potential for increased risk of cardiovascular effects was noted for venlafaxine compared with the SSRIs (Stahl et al., 2005). Results of pharmacoepidemiologic studies (Kelly et al., 2004; Buckley and McManus, 2004; Cheeta et al., 2004) and one case control series (Whyte et al., 2003) suggest that venlafaxine also may be more toxic in overdose than the SSRIs.

At the time of writing this paper, results of trials directly comparing the safety and/or efficacy of venlafaxine with the two other newer SNRIs, milnacipran and duloxetine, have not been published. Duloxetine, a relatively balanced reuptake inhibitor of both serotonin (5HT) and norepinephrine (NE) with high binding affinity for the 5HT and NE reuptake transporters, has been shown to be a safe and efficacious treatment for patients with MDD (Detke et al., 2002, 2004; Goldstein et al., 2002, 2004; Nemeroff et al., 2002). For comparison, the affinity ($K_i$, nM) of duloxetine for the NE and 5HT reuptake transporters was shown to be 7.5 and 0.8 (NE/5HT ratio of 9), respectively, whereas the equivalent $K_i$ of venlafaxine was 2480 and 82 (NE/5HT ratio of 30) (Bymaster et al., 2001; Wong and Bymaster, 2002). A lower $K_i$ signifies tighter binding, thus duloxetine binds more tightly than venlafaxine to both the NE and 5HT reuptake transporters with a more balanced ratio of binding. In one preliminary meta-analysis of individual patient data from the first six comparative studies of duloxetine and various SSRIs, duloxetine – like venlafaxine – was found to have a significant efficacy advantage among the more depressed patients (Thase et al., 2003).

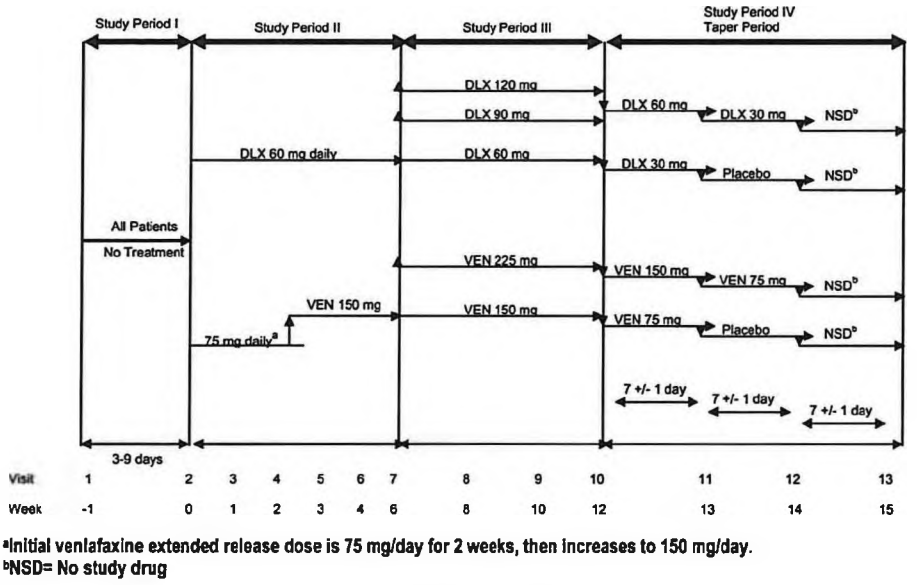
The present report concerns the first two studies that we are aware of which directly compare duloxetine with venlafaxine in patients with MDD. In order to evaluate the two therapies from efficacy and safety perspectives in a consolidated manner, the global benefit–risk (GBR) assessment was chosen as the primary outcome measure. This methodology has been used previously for comparisons of venlafaxine with SSRIs and placebo (Entsuah and Gao, 2002; Entsuah and Gorman, 2002).

The primary objective of the studies was to compare the GBR profiles of duloxetine 60 mg/day and venlafaxine extended release (venlafaxine) 150 mg/day (75 mg for 2 weeks) after 6 weeks of treatment in patients with MDD. In this approach, "benefit" was defined by remission status at endpoint, and "risk" was defined by the occurrence and severity of adverse events. Prespecified weights were applied to the benefit and risk categories defined by remission and adverse event status, and the GBR linear score was computed as the sum of the weighted estimated probability for each category. A positive difference between treatment groups in GBR linear scores implies greater benefit for one treatment with respect to the other. A GBR ratio score, defined as the ratio of the weighted sum of the categories related to remission status divided by those of the categories for non-remission status within each treatment group also was constructed. The treatment groups were compared by assessing the relative gain of one treatment over the other.

## 2. Methods

### 2.1. Study design

Studies 1 and 2 were virtually identical multicenter, randomized, double-blind, parallel studies of outpatients diagnosed with major depressive disorder (MDD). Both studies consisted of four Study Periods (Fig. 1). Study Period I was




[a]Initial venlafaxine extended release dose is 75 mg/day for 2 weeks, then increases to 150 mg/day.
[b]NSD= No study drug

Fig. 1. Study design.

a 3–9 day screening phase which was followed by randomization to either duloxetine or venlafaxine for a 6-week period of double-blind treatment (Study Period II). Patients completing Study Period II received six additional weeks of double-blind therapy (Study Period III) during which the drug dose could be increased at the discretion of the investigator. Study Period IV was a 3-week taper period during which study drug was tapered in a double-blind manner over 1–2 weeks depending on dose, followed by a 1–2 week period where patients received no active drug. The study protocols were approved by the ethics committee covering each site, in accordance with the principles of the Declaration of Helsinki. Patients provided written informed consent prior to participation in any study-related procedures.

### 2.2. Patients

Male and female outpatients of at least 18 years of age who met criteria for MDD as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) were recruited from 35 study centers in Austria, Australia, Germany, France, Spain, Italy, and the United Kingdom for Study 1, and from 32 study centers in the United States and Canada for Study 2. The diagnosis of MDD was confirmed via the use of the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Patients were required to have a 17-item Hamilton Depression Rating Scale ($HAMD_{17}$) total score $\geqslant 18$ at visit 1 of the screening phase, and to have had at least one prior episode of MDD. Exclusion criteria included having any current primary DSM-IV Axis I diagnosis other than MDD including dysthymia or any anxiety disorder as a primary diagnosis within the year preceding enrollment; any previous diagnosis of bipolar disorder, schizophrenia, or other psychotic disorders; lack of response of the current episode of MDD to at least two adequate courses of antidepressant therapy or if the investigator judged the patient to meet criteria for treatment-resistant depression; and history of lack of response to venlafaxine, venlafaxine extended release or any other SNRI (serotonin and norepinephrine reuptake inhibitor). Patients also were excluded if they were considered a serious suicide risk in the opinion of the investigator or had a $HAMD_{17}$ item 3 score $\geqslant 3$ indicative of suicidal ideas, gestures, or attempts, or had a DSM-IV history of substance abuse or dependence.

### 2.3. Treatments

In Study 1, patients were randomly assigned in a 1:1 ratio to duloxetine 60 mg/day or to venlafaxine 150 mg/day administered once daily. The venlafaxine group began treatment with venlafaxine 75 mg/day for the first 2 weeks as specified in the venlafaxine product labeling in a number of countries where the studies were being conducted prior to increasing to 150 mg/day for the remainder of Study Period II. During Study Period III, duloxetine could be increased up to a maximum of 120 mg/day (90 mg/day given as 30 mg in the morning and 60 mg in the evening, and 120 mg/day given as 60 mg in the morning and 60 mg in the evening). Venlafaxine could be increased to a maximum of 225 mg/day (once daily in the morning) at the discretion of the investigator and according to clinical response. The dose increases were conducted in a blinded manner. The dose of study medication could not be reduced at any time during Study Periods II and III. During Study Period IV, the dose of all study medication was tapered down in a double-blind manner (Fig. 1).

Study 2 was identical to Study 1 except for the inclusion of a third study arm where patients were commenced and maintained on venlafaxine 75 mg/day for the duration of Study Period II. This dose could be increased up to 150 mg/day and, if necessary, 225 mg/day during Study Period III.

### 2.4. Outcome measures

The primary outcome measure was the GBR linear score (Table 1), and the primary objective was to test the hypothesis that duloxetine 60 mg/day was statistically significantly superior to venlafaxine extended release 150 mg/day at the end of Study Period II using the GBR assessment. Data from Study 1 and Study 2 (excluding the subset randomized to the 75 mg/day arm of venlafaxine) were combined for this comparison, as specified *a priori* in the study protocols. Benefit was measured by remission status where remission was defined as a $HAMD_{17}$ total score of $\leqslant 7$ at the endpoint observation of Study Period II (Frank et al., 1991). Risk was defined by four mutually exclusive adverse event categories based on the Association for Methodology and Documentation in Psychiatry's (AMDP-5) standardized adverse event collection form. Patients were classified as having either no AEs, AEs with no severity rating greater than moderate, AEs with at least 1 severity rating of severe, or having discontinued with a reason of self-reported adverse event (regardless of any AE severity).

The primary efficacy measure was the $HAMD_{17}$ which was used to assess the severity of depression as well as improvement in symptomatology during the course of the study. Response and remission rates, the former defined as a $\geqslant 50\%$ reduction in the total score from baseline to endpoint, also were determined for each study period. Secondary efficacy measures included: $HAMD_{17}$ subscales (Anxiety/Somatization, Core Factor, Maier, Sleep, and Retardation) and the depressed mood item (Item 1), the Hamilton Anxiety Rating Scale (HAMA), (Hamilton, 1959) the Clinical Global Impression of Severity (CGI-S), (Guy, 1976) and Patient Global Impression of Improvement (PGI-I) rating scales (Guy, 1976).

### 2.5. Safety and tolerability assessments

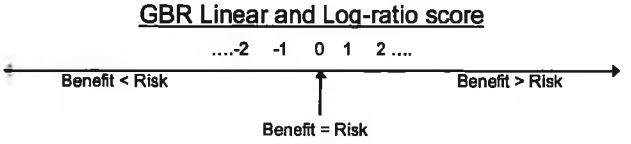
In addition to AMDP-5 adverse events (AMDPAEs) that were collected for the purpose of calculating GBR scores, spontaneously reported adverse events and vital signs were recorded at each visit prior to the collection of AMDPAE. An adverse event was considered treatment-emergent if it was new, or present, at baseline but increased in severity after randomization. Weight was recorded at screening and again at the end of Study Periods III and IV. Electrocardiograms (ECGs) were measured at screening and at the end of Study Periods II and III. Quantitative assessments of Fridericia's corrected QT intervals (QTcF) were conducted at the beginning and end of acute treatment, and once during the continuation phase. A potentially clinically significant (PCS) value was defined as an increase in QTcF of $\geqslant 30$ ms and any post-baseline value $\geqslant 450$ ms for males or $\geqslant 470$ ms for females.

Laboratory tests (hematology, clinical chemistry, and urinalysis) were conducted at screening and at the end of Study Periods II and III (except urinalysis at end of Study Period III). Sitting blood pressure and heart rate were recorded at each visit. A patient was considered to have sustained elevation in blood pressure if either: (1) systolic blood pressure was $\geqslant 140$ mm Hg and at least 10 mm Hg greater than baseline for three consecutive visits, and/or (2) diastolic pressure was $\geqslant 90$ mm Hg and at least 10 mm Hg greater than baseline for at least three consecutive visits. Baseline was defined as the highest value prior to randomization.

Table 1
Definition of GBR categories and weighting schemes

| | | AMDP-5 Elicited Adverse Events | | | |
|---|---|---|---|---|---|
| | | No AEs | Mild or moderate TEAEs | Severe TEAEs | AE reported as reasons for DC |
| Patients achieving remission ($HAMD_{17}$ total score $\leqslant 7$ at endpoint) | Category | I | II | III | IV |
| | Weighting | 5 | 4 | 3 | 1 |
| Patients not achieving remission | Category | V | VI | VII | VIII |
| | Weighting | −1 | −3 | −4 | −5 |

A weight function was applied (shown above) to the observed proportions within each category for the linear score. For the ratio score, all of the weights are positive. GBR scores were calculated for each treatment.



### 2.6. Statistical analysis

It was estimated that with 320 patients per arm in the pooled data set, there would be at least 80% power to detect a treatment group difference of 0.74 in the global benefit–risk linear score between duloxetine 60 mg/day and venlafaxine 150 mg/day in Study Period II. The sample size was determined assuming a common standard deviation of 3.16, a discontinuation rate of 10%, and based on the use of a two-sided test with $\alpha = 0.05$. An additional 160 patients were randomly assigned to venlafaxine 75 mg/day in Study 2.

Hypothesis testing for differences in the GBR linear and GBR ratio score between treatment groups was based on construction of a $Z$-score defined as the difference of the GBR score (either linear or ratio) divided by the estimated standard deviation of the difference.

All analyses were conducted on an intent-to-treat basis. Treatment effects were evaluated based on two-sided tests with an overall significance level of 0.05. Interactions were considered significant at the 0.10 level. Unless otherwise specified, when an analysis of variance (ANOVA) model was used to analyze a continuous efficacy variable, the model contained main effects for treatment and investigator. Treatment-by-investigator interactions were included when significant. Analysis of covariance (ANCOVA) modeling was implemented in the same manner as that for ANOVA with baseline score added as a covariate. Least-squares means were used for statistical comparisons of treatment group differences estimated from ANOVA or ANCOVA models. Continuous demographic and baseline disease severity measures and ranked changes in laboratory values were assessed using fixed effects ANOVA containing terms for treatment and investigator.

Unless otherwise specified, in all the comparisons where baseline and endpoint were used, baseline refers to the last non-missing observation at or before the randomization visit, and endpoint refers to the last non-missing observation after randomization (LOCF).

Changes over time were assessed using a mixed-effects repeated measures model (MMRM) containing fixed effects for treatment, investigator, study week, and treatment-by-week interaction with baseline value and baseline value-by-visit as covariates.

Non-inferiority based on mean change from baseline to endpoint in $HAMD_{17}$ total score was assessed after 6 and 12 weeks of treatment by comparing the upper bound of a one-sided 97.5% confidence interval for the difference between duloxetine and venlafaxine with a non-inferiority margin of 1.15, estimated to be 50% of the gain for venlafaxine over placebo (Rudolph and Feiger, 1999). Non-inferiority assessments were performed for the intent-to-treat (ITT) population and a Per Protocol (PP) subpopulation defined as those patients who did not have any protocol violations and remained on treatment for a minimum of 4 weeks.

Categorical measures were assessed using the Cochran–Mantel–Haenszel test for general association adjusted for study or Fisher's exact test when cell sizes were small, and onset of efficacy was compared using the log-rank test based on both time to first response and time to first remission as defined above.

## 3. Results

### 3.1. Patient characteristics

Study participants were predominantly Caucasian and approximately two-thirds were female (Table 2). The groups were relatively well matched with two exceptions: duloxetine-treated patients were statistically significantly older compared with venlafaxine-treated patients (44.3 vs. 41.6, $P = 0.007$) and were older at the time of their first depressive episode (30.9 vs. 28.8, $P = 0.036$). Importantly, the percentage of patients having previously been treated with an antidepressant for depression was similar between the patient groups (duloxetine, 57.9% vs. venlafaxine, 58.8%; $P = 0.792$).

Table 2
Patient characteristics

| Variable | Duloxetine 60QD ($N = 330$) | Venlafaxine 150QD ($N = 337$) | $P$-value |
|---|---|---|---|
| Age, years[a] | 44.3 (12.8) | 41.6 (12.3)* | .007 |
| Gender (%) | | | |
| Female | 69.7 | 65.3 | .230 |
| Male | 30.3 | 34.7 | |
| Ethnicity (%) | | | |
| African descent | 4.2 | 5.0 | .496 |
| Caucasian | 91.2 | 91.4 | |
| Hispanic | 2.7 | 2.4 | |
| Other | 1.8 | 1.2 | |
| Age at first episode[a] | 30.9 (13.4) | 28.8 (12.2) | .036 |
| Previous episodes[a] | 4.8 (10.7) | 4.8 (11.0) | .933 |
| Current episode (weeks)[a] | 33.0 (48.5) | 32.3 (41.6) | .782 |
| $HAMD_{17}$ total[a] | 22.7 (3.7) | 22.7 (3.4) | .970 |

[a] Mean (SD).

### 3.2. Patient disposition

Of the 667 patients that were randomized to duloxetine 60 mg/day or venlafaxine 150 mg/day, significantly fewer patients on duloxetine (76.1%) than venlafaxine (82.5%) completed Study Period II ($P = 0.038$; Table 3) and Study Periods II and III (64.8% vs. 74.5%; $P = 0.006$). Significantly more duloxetine-treated patients discontinued in Study Period II and in Study Periods II and III due to an adverse event or protocol violation compared with venlafaxine-treated patients. Rates of discontinuation for all other reasons were not significantly different between treatment groups for either Study Period.

### 3.3. Dosing

For patients who entered the flexible dose period of the study, Period III, the mean endpoint dose was 79.4 mg/day (SD = 22.7) for patients commenced at duloxetine 60 mg/day, and 189.7 mg/day (SD = 37.5) for patients in the venlafaxine 150 mg/day treatment group. The percentage of patients at each dose was as follows: duloxetine 60 mg/day (52.6%), duloxetine 90 mg/day (30.3%), duloxetine 120 mg/day (17.1%), venlafaxine 150 mg/day (47.1%), and venlafaxine 225 mg/day (52.9%). The percentage of patients having no dose increase during the 12 weeks of treatment was similar between therapy groups (duloxetine 60 mg/day group, 52.6%; venlafaxine 150 mg/day group 47.1%; $P = 0.205$).

### 3.4. Global benefit–risk

The distribution of patients within each GBR category is presented in Table 4. Neither the linear nor the log ratio GBR scores were significantly different between the duloxetine and venlafaxine treatment groups during either Study Period II or Study Periods II and III (Table 5). The comparisons of GBR linear scores between duloxetine and venlafaxine groups using standardized RIDIT scores yielded similar results to those using the protocol specified weights (Study Period II, −1.361 vs. −0.959, $P = 0.141$; Study Periods II and III, −0.393 vs. −0.142, $P = 0.285$).

### 3.5. Efficacy

Duloxetine 60 mg/day failed to meet the *a priori*-defined non-inferiority criteria for the comparison with venlafaxine 150 mg/day at Study Period II and Study Periods II and III. The upper bounds of the 1-sided 97.5% confidence intervals for the treatment group difference in mean change between the duloxetine and venlafaxine groups for Study Period II were 1.72 and 1.55 for the ITT and PP populations, respectively. Similarly, the upper bounds of the commensurate confidence intervals for Study Periods II and III were 1.91 and 1.77 for the ITT and PP populations, respectively. In all cases, the non-inferiority margin of 1.15 was exceeded.

Mean changes from baseline to endpoint in the $HAMD_{17}$ total scores were not different between the duloxetine and venlafaxine treatment groups in either Study Period II or Study Periods II and III (Fig. 2). Comparisons of mean change from baseline to endpoint on secondary efficacy measures including $HAMD_{17}$ item 1, $HAMD_{17}$ subscales (core, Maier, anxiety/somatization, retardation and sleep), HAMA total score, CGI-S, and PGI-I did not reveal significant differences between the treatment groups during either Study Period II or Study Periods II and III, using either LOCF or MMRM analysis.

Table 3
Patient disposition during Study Periods II and III

| Reason for discontinuation | Duloxetine $N = 330$ | | Venlafaxine $N = 337$ | | *P*-value |
|---|---|---|---|---|---|
| | *n* | % | *n* | % | |
| *Study Period II* | | | | | |
| Completed study period | 251 | 76.1 | 278 | 82.5 | .038 |
| Adverse event | 40 | 12.1 | 21 | 6.2 | .008 |
| Lost to follow-up | 9 | 2.7 | 15 | 4.5 | .243 |
| Patient decision | 16 | 4.8 | 13 | 3.9 | .524 |
| Protocol criteria not met | 2 | 0.6 | 1 | 0.3 | .555 |
| Sponsor decision | 1 | 0.3 | 0 | | .307 |
| Physician decision | 0 | | 2 | 0.6 | .162 |
| Protocol violation | 7 | 2.1 | 1 | 0.3 | .030 |
| Lack of efficacy | 4 | 1.2 | 6 | 1.8 | .532 |
| *Study Periods II/III* | | | | | |
| Completed study | 214 | 64.8 | 251 | 74.5 | .006 |
| Adverse event | 48 | 14.5 | 31 | 9.2 | .032 |
| Lost to follow-up | 17 | 5.2 | 18 | 5.3 | .950 |
| Patient decision | 27 | 8.2 | 23 | 6.8 | .492 |
| Protocol criteria not met | 2 | 0.6 | 1 | 0.3 | .555 |
| Sponsor decision | 1 | 0.3 | 0 | | .307 |
| Physician decision | 1 | 0.3 | 2 | 0.6 | .571 |
| Protocol violation | 9 | 2.7 | 2 | 0.6 | .029 |
| Lack of efficacy | 11 | 3.3 | 9 | 2.7 | .626 |

Table 4
Percentage of patients within GBR categories (pooled data)

| | No AEs | Mild to moderate AEs | Severe AEs | AE causing discontinuation | Total |
|---|---|---|---|---|---|
| *Study Period II* | | | | | |
| Remitter, *n* (%) | | | | | |
| DLX 60 mg QD | 3 (0.9) | 61 (19.2) | 33 (10.4) | 3 (0.9) | 100 (31.4) |
| VEN 150 mg QD | 1 (0.3) | 72 (21.8) | 41 (12.4) | 2 (0.6) | 116 (35.2) |
| Non-remitter, *n* (%) | | | | | |
| DLX 60 mg QD | 2 (0.6) | 87 (27.4) | 96 (30.2) | 33 (10.4) | 218 (68.6) |
| VEN 150 mg QD | 3 (0.9) | 90 (27.3) | 104 (31.5) | 17 (5.2) | 214 (64.8) |
| *Study Periods III/III* | | | | | |
| Remitter, *n* (%) | | | | | |
| DLX 60–120 mg QD | 2 (0.6) | 86 (27.0) | 62 (19.5) | 3 (0.9) | 153 (48.1) |
| VEN 150–225 mg QD | 2 (0.6) | 87 (26.4) | 72 (21.8) | 5 (1.5) | 166 (50.3) |
| Non-remitter, *n* (%) | | | | | |
| DLX 60–120 mg QD | 1 (0.3) | 44 (13.8) | 79 (24.8) | 41 (12.9) | 165 (51.9) |
| VEN 150–225 mg QD | 1 (0.3) | 58 (17.6) | 81 (24.5) | 24 (7.3) | 164 (49.7) |

Remission rates were not significantly different between treatment groups for both study periods.

Table 5
GBR estimates

| GBR | DLX 60QD ($N = 318$) | | VEN 150QD ($N = 330$) | | *P*-value |
|---|---|---|---|---|---|
| | Mean | SE | Mean | SE | |
| *Pooled: Period II* | | | | | |
| Linear score | −1.418 | 0.195 | −1.079 | 0.193 | .217 |
| Log ratio score | −0.811 | 0.123 | −0.616 | 0.117 | .252 |
| *Pooled: Periods III/III* | | | | | |
| Linear score | −0.349 | 0.214 | −0.121 | 0.203 | .440 |
| Log ratio score | −0.186 | 0.114 | −0.067 | 0.112 | .456 |

*N* is the number of patients with at least one post-baseline $HAMD_{17}$ total score.

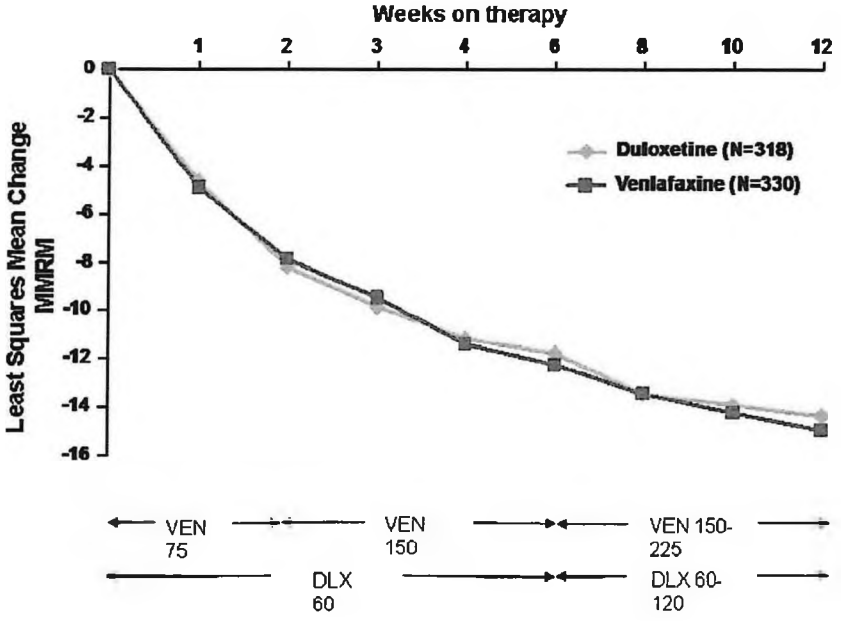



Fig. 2. Change from baseline in $HAMD_{17}$ total score.

Response and remission rates were not significantly different between duloxetine and venlafaxine at 6 weeks (response rate for duloxetine 51.6%, venlafaxine 54.5%; remission rate for duloxetine 31.4%, venlafaxine 35.2%) or 12 weeks (response rate for duloxetine 62.6%, venlafaxine 69.1%; remission rate for duloxetine 48.1%, venlafax-

ine, 50.3%). The percentage of duloxetine-treated patients entering Study Period III ($N = 251$) and remitting was 57.8% ($n = 145$). Of these, 96 (66.2%) remitted on the starting dose (60 mg/day). Venlafaxine-treated patients ($N = 278$) showed similar results; 158 (56.8%) remitting with 93 (58.9%) remitting on starting dose (150 mg/day).

Time to first response and time to first remission were similar between duloxetine- and venlafaxine-treated patients. Kaplan–Meier estimates of response rates at 2, 4, 8 and 12 weeks on treatment were 24.3%, 53.4%, 71.2% and 80.8% for the duloxetine-treated group and 22.8%, 52.3%, 70.0% and 80.6% for the venlafaxine-treated group, respectively ($P = 0.968$).

Similarly, estimates of remission rates at 2, 4, 8 and 12 weeks on treatment were 11.1%, 36.6%, 53.0% and 71.0% for the duloxetine-treated group and 10.4%, 32.1%, 51.7% and 67.4% for the venlafaxine-treated group, respectively ($P = 0.309$).

### 3.6. Efficacy: venlafaxine 75 mg treatment group

As previously stated, Study 2 had a venlafaxine 75 mg/day treatment group in addition to the duloxetine 60 mg/day and venlafaxine 150 mg/day treatment groups. Although this treatment group was underpowered for the purposes of a comparison with the pooled duloxetine 60 mg/day and venlafaxine 150 mg/day treatment groups, within-study comparisons were undertaken with the duloxetine 60 mg/day and venlafaxine 150 mg/day treatment groups from Study 2. A total of 81.7% and 72.2% of patients in the venlafaxine 75 mg/day treatment group completed Study Periods II and II and III respectively. The GBR linear score in Study Period II for venlafaxine 75 mg/day was −1.319 which was not significantly different than duloxetine 60 mg/day (−1.346, $P = 0.944$). The GBR linear scores also were not significantly different during Study Periods II and III (venlafaxine 75 mg/day, −0.313; duloxetine 60 mg/day, −0.031, $P = 0.499$). There were no significant differences between venlafaxine 75 mg/day and either duloxetine 60 mg/day or venlafaxine 150 mg/day on mean changes in the $HAMD_{17}$ total score and subscales in both study periods. Other secondary efficacy measures, as well as response and remission rates, also were not significantly different between treatment groups during both study periods.

### 3.7. Safety and tolerability (primary dose comparison)

#### 3.7.1. Adverse events

Four venlafaxine-treated patients experienced serious adverse events (bone pain, depression, diplopia, eye swelling, febrile infection, migraine, photophobia, papular rash, ruptured renal cyst) during the first 6 weeks of treatment compared with no reports in the duloxetine group. One additional venlafaxine patient had the serious adverse event of suicidal ideation during Study Period III and 1 duloxetine patient had a serious adverse event reported as syncope during the same period. There were no deaths or suicide attempts by any of the patients during these studies.

Nausea was the most commonly reported treatment-emergent adverse event (TEAE) with both drugs in both Study Periods. Nausea (43.6% vs. 35.0%, $P = 0.024$; Table 6) and dizziness (16.1% vs. 10.4%, $P = 0.029$) were reported significantly more often by duloxetine-treated patients compared with venlafaxine-treated patients in Study Period II. No other TEAEs having an incidence of $\geq 5\%$ were

Table 6
Treatment-emergent adverse events[a]

| Adverse event | Study Period II | | Study Periods II/III | |
|---|---|---|---|---|
| | Duloxetine (%) ($N = 330$) | Venlafaxine (%) ($N = 337$) | Duloxetine (%) ($N = 330$) | Venlafaxine (%) ($N = 337$) |
| Nausea | 43.6* | 35.0 | 43.9 | 36.5 |
| Headache | 19.7 | 20.5 | 21.2 | 23.4 |
| Dry mouth | 17.3 | 18.7 | 18.5 | 19.9 |
| Constipation | 13.0 | 14.8 | 14.5 | 16.0 |
| Hyperhidrosis | 13.6 | 13.1 | 14.8 | 15.4 |
| Dizziness | 16.1* | 10.4 | 16.1 | 13.6 |
| Diarrhea | 11.2 | 9.5 | 13.0 | 10.1 |
| Insomnia | 9.7 | 10.1 | 11.5 | 11.6 |
| Somnolence | 10.0 | 7.7 | 10.9 | 9.5 |
| Decreased appetite | 9.7 | 7.4 | 9.7 | 8.3 |
| Vomiting | 9.4 | 5.9 | 10.3 | 6.8 |
| Fatigue | 7.6 | 5.3 | 7.6 | 5.6 |
| Tremor | 6.4 | 5.9 | 6.7 | 6.2 |
| Abnormal dreams | 5.2 | 3.0 | 6.7 | 5.0 |
| Nasopharyngitis | 3.0 | 3.0 | 5.8 | 5.3 |
| Upper respiratory infection | 3.9 | 2.4 | 5.8 | 5.0 |
| Yawning | 6.7* | 3.0 | 6.7* | 3.3 |
| Vision blurred | 4.5 | 3.6 | 5.2 | 4.2 |

[a] TEAEs that were $\geq 5\%$ in either duloxetine or venlafaxine in either Study Period.
* $P \leq .05$.

reported significantly more frequently with one drug or the other in Study Period II and in Study Periods II and III. Treatment-emergent nausea was first reported almost exclusively in Study Period II for both duloxetine (99%) and venlafaxine (96%). The maximum reported severity of nausea was significantly higher with duloxetine (mild, 18.0%; moderate, 20.0%; severe, 6.1%) compared with venlafaxine (mild, 20.0%; moderate, 13.0%; severe, 2.7%; $P = 0.022$).

Discontinuation rates due to an adverse event were significantly higher in the duloxetine group compared with the venlafaxine group in Study Periods II (12.1% vs. 6.2%; $P = 0.008$) and II and III (14.5% vs. 9.2%; $P = 0.032$). Within the first 2 weeks on treatment, 64.6% of all discontinuations due to AEs had already occurred in the duloxetine group compared with 45.2% in the venlafaxine group, and by the end of period II, 83.3% of all discontinuations due to AEs had already occurred within the duloxetine group compared with 67.7% in the venlafaxine group, indicating overall that AE discontinuations tended to occur earlier in treatment with duloxetine compared with venlafaxine.

### 3.8. Vital signs

Significantly more venlafaxine-treated patients ($n = 4$ [1.2%]) experienced a sustained elevation of systolic blood pressure during Study Period II compared to duloxetine-treated patients ($n = 0$, $P = 0.047$; Table 7). There were no significant differences between treatment groups in mean changes [SD] for heart rate (Study Period II: duloxetine, 1.65 beats per minute (bpm) [9.82] vs. venlafaxine, 2.21 bpm [10.24], $P = 0.476$; Study Periods II and III: duloxetine, 2.80 bpm [9.92] vs. venlafaxine 2.88 bpm [10.25], $P = 0.922$), systolic blood pressure (Study Period II: duloxetine, 0.68 millimeters of mercury (mm Hg) [11.98] vs. venlafaxine, 1.23 mm Hg [12.12], $P = 0.561$; Study Periods II and III: duloxetine, 1.11 mm Hg [12.15] vs. venlafaxine 1.33 mm Hg [12.47], $P = 0.825$) diastolic blood pressure (Study Period II: duloxetine, 0.69 mm Hg [8.17] vs. venlafaxine, 0.60 mm Hg [8.88], $P = 0.898$; Study Periods II and III: duloxetine, 0.34 mm Hg [8.25] vs. venlafaxine 0.66 mm Hg [9.13], $P = 0.640$) and weight (Study Periods II and III: duloxetine, 0.05 kilograms (kg) [2.81] vs. venlafaxine −0.34 kg [3.05], $P = 0.114$). The mean change [SD] in the QTcF was not significantly different between duloxetine- and venlafaxine-treated patients during either Study Periods II (−2.12 milliseconds (ms) [15.16] vs. −2.72 ms [14.33], $P = 0.618$) or II and III (−3.99 ms [15.72] vs. −3.48 ms [15.36], $P = 0.696$).

Mean changes in several laboratory analytes were significantly different between duloxetine and venlafaxine during Study Period II and Study Periods II and III, but these differences were inconsistent between study periods and of dubious clinical significance. Apart from a significant difference between treatment groups in the percentage of patients having an abnormal low total bilirubin value at any time during Study Period II (duloxetine, 1.5% vs. venlafaxine, 6.5%, $P = 0.004$), there were no differences between treatment groups in the percentage of patients with abnormal high or low values for any laboratory analytes tested (including liver function tests) at any time during Study Period II or Study Periods II and II combined.

During the taper period (Study Period IV), more venlafaxine-treated patients reported discontinuation-emergent adverse events (DEAEs), with the rates of discontinuation-emergent insomnia, vomiting and fatigue being significantly higher in venlafaxine-treated patients than duloxetine-treated patients. Dizziness was the most commonly reported DEAE with both duloxetine (13.8%) and venlafaxine (19.1%) (Fig. 3).

### 3.9. Safety and tolerability: venlafaxine 75 mg treatment group

In Study 2, the 10 most common TEAEs for the venlafaxine 75 mg treatment group were similar to those seen in the venlafaxine 150 mg group with no TEAE being significantly different between the two treatment groups. Significant differences in TEAE reporting between duloxetine 60 mg/day and venlafaxine 75 mg/day during Study Period

Table 7
Sustained elevation in blood pressure

| | Duloxetine ($N = 319$) | | Venlafaxine ($N = 329$) | | $P$-value |
|---|---|---|---|---|---|
| | $n$ | (%) | $n$ | (%) | |
| *Study Period II* | | | | | |
| Systolic blood pressure | 0 | (0) | 4 | (1.2) | .047 |
| Diastolic blood pressure | 1 | (0.3) | 1 | (0.3) | .990 |
| Systolic or diastolic | 1 | (0.3) | 4 | (1.2) | .184 |
| *Study Periods II/III* | | | | | |
| Systolic blood pressure | 4 | (1.3) | 8 | (2.4) | .253 |
| Diastolic blood pressure | 3 | (0.9) | 3 | (0.9) | .982 |
| Systolic or diastolic | 6 | (1.9) | 8 | (2.4) | .610 |

A patient was considered to have sustained elevation in blood pressure if his or her blood pressure met the following criteria: (1) Supine diastolic blood pressure ≥90 mm Hg and an increase from baseline of ≥10 mm Hg for at least three consecutive visits, or (2) Supine systolic blood pressure ≥140 mm Hg and an increase from baseline of ≥10 mm Hg for at least three consecutive visits.

There were no statistical differences between treatment groups for baseline to endpoint changes in heart rate, systolic blood pressure, and diastolic blood pressure during both Study Period II and Study Periods II/III.

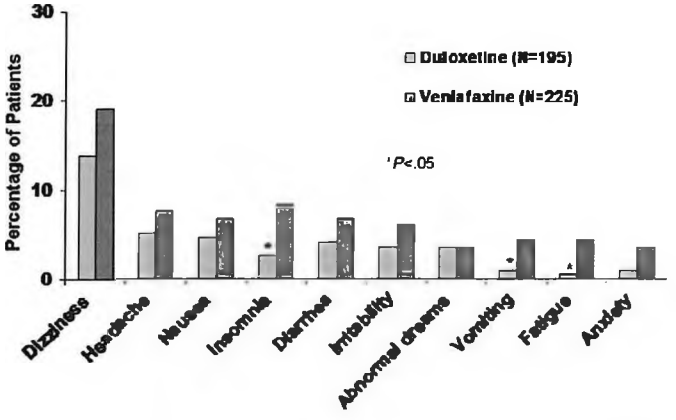



Fig. 3. Ten most common treatment-emergent adverse events during dose tapering: Study Period IV (pooled data).

II included nausea (duloxetine, 44.5%; venlafaxine, 29.0%, $P = .004$), decreased appetite (duloxetine, 15.9%; venlafaxine, 7.1%, $P = .015$), diarrhea (duloxetine, 11.6%; venlafaxine, 4.1%, $P = .014$), and yawning (duloxetine, 9.1%; venlafaxine, 1.8%, $P = 0.003$). During Study Periods II and III, nausea (duloxetine, 44.5%; venlafaxine, 31.4%, $P = .017$), decreased appetite (duloxetine, 15.9%; venlafaxine, 7.1%, $P = .015$), diarrhea (duloxetine, 14.6%; venlafaxine, 5.9%, $P = .011$), yawning (duloxetine, 9.1%; venlafaxine, 2.4%, $P = 0.009$), and middle insomnia (duloxetine, 4.9%; venlafaxine, 0.6%, $P = 0.018$) were significantly more common with duloxetine 60–120 mg/day compared with venlafaxine 75–225 mg/day whereas nervousness (duloxetine, 0.0%; venlafaxine, 3.6%, $P = 0.030$) was more common with venlafaxine 75–225 mg/day. Adverse events as reason for discontinuation in Study Periods II and II and III were 7.7% and 8.3% respectively in the venlafaxine 75 mg/day treatment arm.

Two venlafaxine 75 mg patients experienced a serious adverse event during Study Period II (nephrolithiasis and stress symptoms). In Study Period II, the only vital sign that was significantly different was a greater increase (mean [SD]) in diastolic blood pressure with venlafaxine 75 mg/day (2.43 mm Hg [7.39]) compared with duloxetine 60 mg/day (0.57 mm Hg [7.81], $P = .034$). Diastolic blood pressure also showed a significantly greater increase with venlafaxine 75–225 mg/day (2.25 mm Hg [7.70]) compared with duloxetine 60–120 mg/day (0.13 mm Hg [7.59], $P = .017$) during Study Periods II and III. One venlafaxine 75 mg/day patient in Study Period II and two 75–225 mg/day patients in Study Periods II and III experienced sustained elevation of systolic blood pressure. No duloxetine patients demonstrated a sustained elevation in blood pressure during either study period.

## 4. Discussion

Data from these studies indicate that duloxetine 60 mg/day and venlafaxine 150 mg/day have similar GBR profiles for the treatment of patients with MDD during 6 weeks of double-blind therapy. Treatment for six additional weeks, including upward dose adjustment if clinically indicated, resulted in a similar outcome.

From an efficacy perspective, the 60 mg/day dose of duloxetine and the 150 mg/day dose of venlafaxine were similar, with no significant differences observed between duloxetine and venlafaxine at these doses as measured by improvement on the $HAMD_{17}$ total score over 6 weeks of treatment, remission rates, response rates, and secondary efficacy measures. Again, extension of double-blind therapy and upward titration of study medications did not result in significant differences between treatments, and the onset of efficacy based on HAMD-defined response and remission criteria was similar for both treatments over the 12 week treatment period.

In this report, non-inferiority was assessed via comparisons of mean change from baseline to endpoint on the $HAMD_{17}$ total score. Despite the finding that mean changes in $HAMD_{17}$ total scores were virtually identical in the two treatment groups, our study failed to meet the *a priori*-defined statistical non-inferiority criteria for the comparison of duloxetine 60 mg/day and venlafaxine 150 mg/day. This finding was inconsistent with other study outcomes, and a number of difficulties associated with non-inferiority comparisons between antidepressants may have contributed to this. These difficulties include the lack of a consensus or guidance for the determination of clinically significant non-inferiority margins when comparing effective antidepressants. The estimation of the non-inferiority margin based on the standard statistical approach of using 50% of the treatment effect in the active comparator, coupled with the limited availability of information regarding $HAMD_{17}$-based estimates of the treatment effect of venlafaxine at the time of study design, may have resulted in the determination of an overly restrictive margin for non-inferiority testing and a consequent false negative result.

As was the case for efficacy, the safety and tolerability of duloxetine 60 mg/day and venlafaxine 150 mg/day were broadly similar, with the types of TEAEs and DEAEs reported by study patients being very much the same. A few differences did however emerge in the tolerability comparisons. Duloxetine 60 mg/day was associated with more

study discontinuations due to adverse events, as well as higher rates of treatment-emergent nausea and dizziness. Both the adverse events and study discontinuations due to adverse events tended to occur early in treatment compared with venlafaxine adverse event discontinuations which were more evenly distributed across Study Periods II and III. It might be that a subset of patients has difficulty tolerating a 60 mg starting dose of duloxetine; for such patients, a lower starting dose such as 30 mg/day may be better tolerated. Indeed, data from a recently published study of duloxetine suggest that this is the case, with patients starting duloxetine at a dose of 30 mg/day reporting nausea only half as often as those commencing the drug at 60 mg once a day (16.4% vs. 32.9%, $P = .03$) (Dunner et al., 2005).

During Study Period IV, patients withdrawn from double blind venlafaxine therapy (75–225 mg/day) were significantly more likely to experience discontinuation emergent adverse events (i.e., insomnia, vomiting and fatigue) than patients withdrawn from duloxetine therapy (60–120 mg/day). Whereas the rate of DEAEs seen in this analysis is consistent with published reports concerning venlafaxine (Sir et al., 2005; Campagne, 2005; Fava et al., 1997; Reeves et al., 2003; Agelink et al., 1997), the ability to directly compare DEAEs between venlafaxine and duloxetine provides new information. Blood pressure, heart rate, and ECG changes were generally similar between treatment groups during both 6 and 12 weeks of treatment, with no evidence of QTc prolongation with either drug, and only small changes in heart rate, systolic BP, diastolic BP and weight observed with either drug. Rates of sustained elevation of blood pressure were low overall, but the rate of sustained elevation of systolic blood pressure during the first 6 weeks of treatment was different (4 cases with venlafaxine compared with 0 cases with duloxetine) as was the increased mean change in diastolic blood pressure with venlafaxine. This suggests that despite their similar mechanism of action, duloxetine and venlafaxine might differ in their cardiovascular effects. The reason for this is not clear, although significant differences in the degree to which these two antidepressants are bound to plasma proteins (duloxetine, >90%; venlafaxine, 27%) and the consequent difference in the amount of free, unbound drug in plasma, might provide one possible explanation (Duloxetine [package insert], 2005; Venlafaxine [package insert], 2005).

In principle, the concept of comparing duloxetine and venlafaxine using a composite measure of efficacy and tolerability provided a scientifically sound means of weighing the benefit–risk of the two agents. Mean changes on a depression rating scale, or the incidence of certain adverse events, are, by themselves, not necessarily a good basis upon which to select an antidepressant, and the concept of an approach which would allow both efficacy and tolerability to be combined into one overall measure seemed clinically relevant and worth investigating. In any event, the use of the GBR to compare these two treatments did not show a significant difference between them. The absolute GBR scores for each treatment were difficult to interpret; use of the GBR in the form utilized by the current studies yielded negative GBR scores, which suggests that risks associated with both drugs outweigh the benefits. This is counterintuitive, contradicting both the assessments of regulatory authorities which have licensed both drugs for use in the United States, Europe, and elsewhere on the basis of a favorable benefit–risk ratio, and also experience from clinical practice where both drugs (particularly venlafaxine which has been available for more than 10 years) have been successfully used in the treatment of countless patients with MDD. It is the relationship between GBR for both treatment groups that is of importance when comparing overall benefit–risk. An explanation of this GBR aspect can be found in the weighting scheme employed in the calculation of the GBR score (Lu et al., 2004), where any outcome other than remission ($HAMD_{17}$ total score $\leqslant 7$) resulted in a negative GBR score. In hindsight, remission may have been too stringent a definition of benefit in these acute treatment trials, which consequently unduly penalized both treatments (e.g., a patient with a $HAMD_{17}$ score of 30 at baseline, falling to 8 at endpoint, would yield a negative GBR score in spite of what would generally be described as an excellent clinical response).

While the comparison of principle interest in the current studies was 60 mg/day duloxetine vs. 150 mg/day venlafaxine, Study 2 also included a treatment group where patients received a 75 mg dose of venlafaxine for 6 weeks, after which the investigator was permitted to dose flexibly up to a maximum of 225 mg/day according to clinical response. The 75 mg venlafaxine arm was included to provide some preliminary observations on the relative efficacy of duloxetine 60 mg/day vs. lower doses of venlafaxine. In fact, outcomes in patients treated with the 75 mg dose of venlafaxine were generally similar to those seen with venlafaxine 150 mg/day and duloxetine 60 mg/day. Although statistical power was limited, there was little evidence of a dose response relationship between the two doses of venlafaxine in terms of efficacy, TEAE reports, blood pressure or other variables. Although a dose–response relationship might have been expected, a failure to demonstrate this is unsurprising bearing in mind the well-documented challenges of conducting studies of antidepressants in MDD (Khan et al., 2003; Khan and Schwartz, 2005). Pooling of data from a number of similar studies would offer the best chance of seeing a relationship between dose and outcomes, if such a relationship exists (Kelsey, 1996; Rudolph et al., 1998; Berney, 2005).

The current studies have a number of limitations. The lack of a placebo arm means that assay sensitivity cannot be established, thereby limiting the conclusions that can be drawn from the data about the absolute efficacy of both compounds. The dose regimen for duloxetine in these studies was chosen before it was known that some patients may better tolerate a lower starting dose (such as 30 mg/day) increased as soon as tolerated to a therapeutic dose (such

as 60 mg/day) (Dunner et al., 2005). Similarly, the package insert for venlafaxine states that some patients may show improved tolerability if started on 37.5 mg/day for the first 4–7 days. Only one of the two studies included a venlafaxine 75 mg arm, so there was insufficient statistical power to draw firm conclusions about the comparison between this dose of venlafaxine and either the duloxetine 60 mg/day or the venlafaxine 150 mg/day arms.

To our knowledge, this is the first published direct comparison between two SNRIs in the treatment of MDD. The GBR assessment suggests that duloxetine 60 mg/day and venlafaxine 150 mg/day have a similar benefit–risk profile when treating patients with MDD for up to 12 weeks. Secondary efficacy measures also demonstrated little difference between the two drugs including response and remission rates. Duloxetine 60 mg/day was associated with more nausea and dizziness than venlafaxine during the first 6 weeks of the study, and the rate of discontinuation due to an adverse event was significantly higher in the duloxetine group than the venlafaxine group during both 6 weeks and 12 weeks of treatment. On the other hand, venlafaxine-treated patients experienced significantly more symptoms on discontinuation of treatment during the taper period. Additional head to head studies, including trials of longer duration, are warranted to determine if patients with MDD might have a better benefit–risk profile with one drug compared to the other.

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